Use of technological platforms and big data to enhance phenotypic understanding in adult-onset primary dystonia

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Abstract

In this thesis, I make use of technological platforms in order to evaluate epidemiological characteristics and further our understanding of the non-motor symptoms in dystonia. I have determined the prevalence and incidence of dystonia over a 24-year period, and examined social deprivation status and mortality. Further, I explore the psychiatric symptoms and sleep patterns in detail.

I have developed a validated algorithm to identify individuals with dystonia using anonymised healthcare records. The optimised algorithm had a sensitivity of 79% and was employed to form the dystonia cohort within the Secure Anonymised Information Linkage (SAIL) databank. The validated algorithm identified a total of 54,966 individuals with dystonia, suggesting an overall prevalence of 1220/100,000/year (1.2%) amongst the Welsh population. Interestingly, a diagnosis of dystonia did not impact social deprivation, with no change in social deprivation status before or following diagnosis. Comparable causes of death were noted amongst dystonia and the general population, with respiratory disorders, circulatory disorders and cancer leading causes of death.

Psychiatric diagnoses and prescriptions were increased amongst those with idiopathic dystonia compared to a matched control cohort, depression and anxiety being most common. Psychiatric diagnoses predominantly pre-dated dystonia diagnosis, particularly in the 12-months leading up to diagnosis, however there was an elevated rate of most diagnoses throughout the study period. These findings suggest a bidirectional relationship between psychiatric disorders and dystonia potentially owing to common aetiological mechanisms.

Wrist-worn accelerometer data available as part of the UK Biobank demonstrated later bedtimes, less time in bed and suboptimal sleep duration in those with dystonia compared to matched controls. To address the lack of concurrent self-reported sleep, our own dystonia cohort was recruited. Detailed examination of sleep architecture showed increased non-rapid eye movement sleep and increased total sleep time compared to controls, although self-reported sleep and objective-derived sleep measures were not associated.

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Sleep disturbance in movement disorders: insights, treatments and challenges

Bailey GA, Hubbard EK, Fasano A, Tijssen, MAJ, Lynch, T, Anderson KN, Peall KJ. J Neurol Neurosurg Psychiatry 2021; doi:10.1136/jnnp-2020- 325546

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Adult-onset idiopathic dystonia: A national data-linkage study to determine epidemiological, social deprivation, and mortality characteristics

Bailey GA, Rawlings A, Torabi F, Pickrell WO, Peall KJ. European Journal of Neurology 2021; DOI: 10.1111/ene.15114

Formed Chapter 3 of this thesis

Longitudinal analysis of the relationship between motor and psychiatric symptoms in idiopathic dystonia

Bailey GA, Rawlings A, Torabi F, Pickrell WO, Peall KJ. European Journal of Neurology 2022; DOI: 10.1111/ene.15530

Formed Chapter 4 of this thesis

List of abbreviations

5-HT	Serotonin
ACh	Acetylcholine
AD	Axial diffusivity
ADDE	Annual District Death Extract
ADHD	Attention deficit hyperactive disorder
AHI	Apnea-hypopnea indices
ALF	Anonymous Linking Field
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AOIFCD	Adult-onset idiopathic, isolated focal cervical dystonia
ASD	Autism spectrum disorder
AUC	Area under curve
BHC	Benign Hereditary Chorea
BoNT	Botulinum toxin
BPAN	Beta-propeller protein associated neurodegeneration
BSP	Blepharospasm
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBS	Corticobasal Syndrome
CBT	Cognitive behavioural therapy
CD	Cervical dystonia
ChAc	Chorea-acanthocytosis
CPAP	Continuous positive airways pressure
CSA	Central sleep apnea
CSF	Cerebral spinal fluid
CWA	Continuous Wave Accelerometer
D1	Dopamine 1 receptor
D2	Dopamine 2 receptor
D3	Dopamine 3 receptor
DA	Dopamine
DAT	Dopamine transporter
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies

DNMSQuest	Dystonia non-motor symptoms questionnaire
DRD	Dopa-responsive dystonia
DRL	Deterministic record linkage
DRPLA	Dentatorubral-pallidoluysian Atrophy
DTI	Diffusion tenor imaging
ECG	Electrocardiography
EEG	Electroencephalography
ED	Embouchure dystonia
EMG	Electromyography
ENMO	Euclidean norm minus one
EOG	Electrooculogram
ER	Endoplasmic reticulum
ESS	Epworth Sleepiness Scale
ET	Essential tremor
FA	Fractional anisotropy
FAHN	Fatty acid hydroxylase-associated neurodegeneration
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GM	Grey matter
GP	General practice
GPe	External globus pallidus
GPi	Internal globus pallidus
GWAS	Genome-wide association study
HD	Huntington’s Disease
HDCZA	Distribution of Change in Z-Angle
HIRU	Health Information Research Unit
hNI	Head neural integrator
HR	Heart rate
HRV	Heart rate variability
Hz	Hertz
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases version 10
ICSD-3	International Classification of Sleep Disorders
IgLON5	Immunoglobulin-like cell adhesion molecule 5

IGRP	Information Governance Review Panel
iPSC	Induced pluripotent stem cell
IQ	Intelligence Quotient
LDT	Laterodorsal tegmental nuclei
LICI	Long interval intracortical inhibition
LH	Lateral hypothalamus
LSOA	Lower Super Output Area
MACRAL	Matching Algorithm for Consistent Results in Anonymised Linkage
MBCT	Mindfulness-based cognitive therapy
MCH	Melanin-concentrating neuron system
MD	Mean diffusivity
MEMS	Microelectromechanical systems
MESA	Multi-ethnic Study of Atherosclerosis
mg	Milli-gravity
M.I.N.I	Mini-International Neuropsychiatric Interview
MLS	McLeod Syndrome
MPAN	Mitochondrial membrane protein-associated neurodegeneration
MRI	Magnetic resonance imaging
MREC	Multi-centre Research Ethics Committee
MSLT	Multiple sleep latency test
MSA	Multiple System Atrophy
MSN	Medium spiny neurons
MWT	Maintenance of Wakefulness test
NA	Neuroacanthocytosis
NART	National Adult Reading Test
NBIA	Neurodegeneration with Brain Iron Accumulation
NBIS	Non-invasive brain stimulation
NHS	National Health Service
NHSAR	National Health Service Administrative Register
NMS	Non-motor symptoms
NREM	Non-rapid eye movement
NPC	Niemann-Pick disease Type C
NWIS	National Health Service Wales Informatics Service
OCD	Obsessive-compulsive disorder

OMD	Oromandibular dystonia
OPD	Outpatient Dataset
OSA	Obstructive sleep apnoea
OT	Occupational therapy
PAS	Paired associated simulation
PD	Parkinson’s disease
PEDW	Patient Episode Database
PET	Positron emission tomography
PKAN	Pantothenate kinase-associated neurodegeneration
PLAN	PLA2G6-associated neurodegeneration
PLMS	Periodic limb movement during sleep
PPG	Photoplethysmography
PPN	Pedunculopontine nucleus
PPT	Pedunculopontine
PPV	Positive predictive value
PRL	Probabilistic record linkage
PSQI	Pittsburgh Sleep Quality Index
PRO	Patient reported outcome
PSG	Polysomnography
PSP	Progressive Supranuclear Palsy
QoL	Quality of life
RBD	Rapid eye movement (REM) sleep behavioural disorder
RDP	Rapid-onset dystonia-Parkinsonism
RCT	Random control trial
REM	Rapid eye movement
RLS	Restless leg syndrome
RWA	Rapid eye movement sleep without atonia
ROC	Receiver operating characteristics
SAIL	Secure Anonymised Information Linkage
SAS	Sleep apnea syndromes
SCA	Spinocerebellar Ataxia
SCN	Suprachiasmatic nucleus
SCP	Superior cerebellar peduncle
SE	Sleep efficiency

SeRP	Secure Research Platform
SERT	Serotonin transporter
SICI	Short interval intracortical inhibition
SLD	Sublaterodorsal nucleus
SMA	Supplementary motor areas
SMI	Severe mental illness
SN	Substantia nigra
SNr	Substantia nigra reticulata
SOL	Sleep onset latency
SPECT	Single-photon emission computed tomography
SQL	Structured Query Language
SSRI	Selective serotonin re-uptake inhibitor
STN	Subthalamic nucleus
SUD	Substance use disorder
TD	Torsion dystonia
tDCS	Transcranial direct current stimulation
TDT	Temporal discrimination thresholds
TIB	Time in bed
TMS	Transcranial magnetic stimulation
TS	Tourette's syndrome
TST	Total sleep time
UKBB	United Kingdom Biobank
VBM	Voxel-based morphometry
vPAG	Ventral periaqueductal grey
VPLO	Ventrolateral preoptic area
VPN	Virtual Private Network
WASO	Wake after sleep onset
WCDS	Writer's cramp Disability Scale
WD	Wilson's Disease
WDS	Welsh Demographic Service
WIMD	Welsh Index of Multiple Deprivation
WLGP	Welsh Longitudinal General Practice
WMDRN	Welsh Movement Disorder Research Network
XDP	X-linked dystonia-parkinsonism

1 Introduction

1.1 Introduction

This thesis makes use of modern large data handling technologies to provide greater understanding of the phenotypes, notably non-motor symptoms and in particular sleep, associated with adult-onset idiopathic, isolated focal cervical dystonia (AOIFCD). In this chapter I will outline the classification and clinical features of the different forms of dystonia, while discussing treatment options and current models of pathogenesis. Finally, I will explore the clinical features and aetiology of AOIFCD, together with our current understanding of its associated non-motor phenotype.

1.2 Overview

Dystonia is a hyperkinetic movement disorder characterised by sustained muscle contractions, producing repetitive movements and abnormal postures, often initiated or worsened by voluntary action. The first description of dystonia dates back to the 19th century, although its clinical recognition has come much later. In 1911, the term *dystonia muscularum deformans* was introduced by Oppenheim (later renamed early-onset generalised torsion dystonia) and used to describe abnormal posturing in unrelated Jewish children.

Historically, dystonia was considered a manifestation of psychiatric disorders, with the bizarre and infrequent appearance of symptoms, which are often exacerbated by social and mental stress, believed to be indicative of a psychogenic aetiology.[1] Patients were diagnosed as suffering from 'hysteria', and consequently treated with psychological and surgical treatments typically used in psychiatric disorders. In the mid 1970's the late Professor David Marsden (Institute of Neurology, London) and Professor Stanley Fahn (Mount Sinai Hospital, New York) proposed that dystonia was an organic disorder, citing its heritable traits and association with lesions of the nervous system. The last three decades have seen a remarkable growth of research in dystonia, Figure 1.1 shows a brief timeline of this progression.

Dystonia is the third most common movement disorder however, despite this its true prevalence remains unknown. There is notable variation of reported rates worldwide, dependent on the form of this disorder and cohort ethnicity. Rates as high as 152 per million have been reported across Europe[2] and 295 per million in North America.[3]

Lower rates have been identified in Asia, with 6.8-144 per million in a Japanese cohort[4,5] and 27 per million in a Chinese study.[6] An Italian population study of those >50 years estimated substantially higher rates of 7,320 per million.[7] A more recent meta-analysis of available literature estimated an overall global prevalence of 160 per million, and suggested that age of onset is ethnically related.[8] However, these are likely to be underestimates due to lack of recognition, underdiagnosis and the limited number of patients seeking treatment.

1.3 Diagnosis

Dystonia remains a clinical diagnosis, although it is considered one of the most poorly recognised movement disorders owing to its phenotypic variability. Occasionally, electromyography (EMG) can be a useful complementary diagnostic tool, mapping muscle co-contraction, as well as facilitating differentiation from other movement disorders. In the majority of cases, dystonia combines sustained postures and intermittent movements, sometimes presenting with dystonic tremor. These are usually repetitive and predictable, involving the same body region and directionality. Some dystonia can be triggered by voluntary actions, and others only occur while performing a specific motor task, termed 'task-specific dystonia'. Symptoms may temporarily resolve when the body is positioned in the direction of the movement or may be transiently alleviated by sensory tricks ('*gestes antagonistes'*).

Clinical features that support a diagnosis include sensory tricks, mirroring, and overflow. These are summarised in Table 1.1.

Table 1.1 Clinical features of dystonia

Clinical Feature	Description
Dystonic movements and posture	Muscle contractions are predictable and patterned. Movements are usually twisting or pull in a direction and posture is flexed or twisted
Dystonic tremor	Patterned and rhythmic oscillation though often inconsistent dystonic movements. Exacerbated by positioning the affected area against the maximum direction of pull
Patterning	Repetitive and predictable movements involving the same body region
Overflow	An unintentional muscle contraction which is distinct from the initial site, but accompanies the dystonic movement
Mirror dystonia	Muscle contractions can be triggered by motor tasks performed by the unaffected contralateral side. Commonly seen in writer's cramp while writing with the unaffected hand
Alleviating manoeuvres ('*gestes anatonistes*')	One or more specific movements, often tactile stimuli without the use of force that transiently relieve the dystonic movement

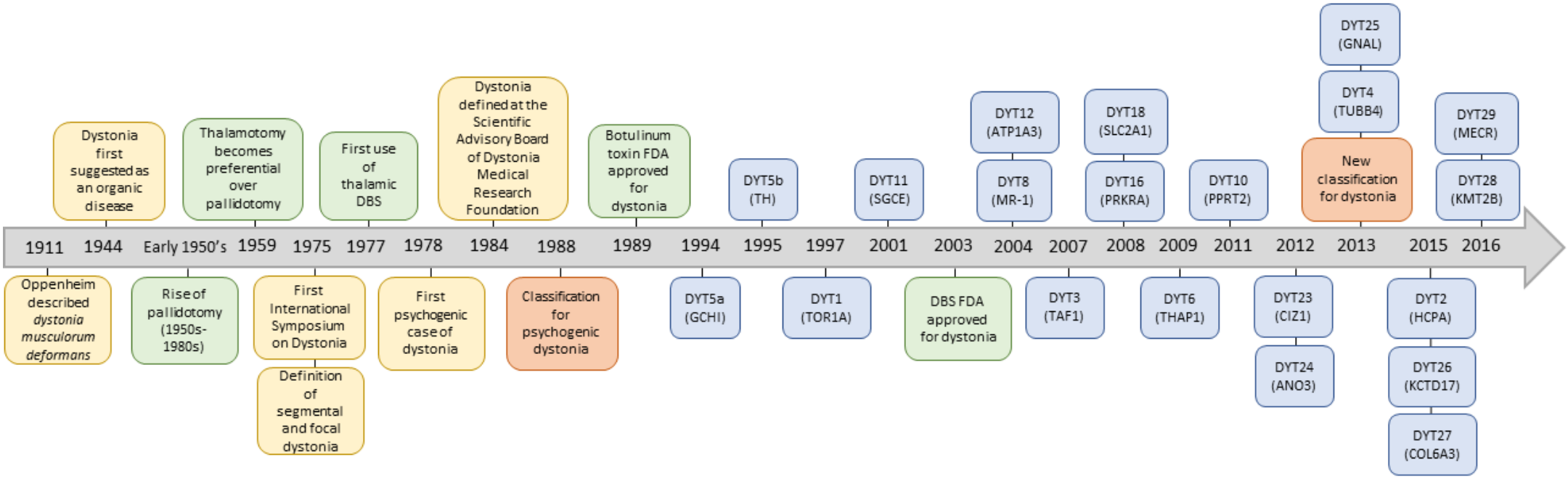

Figure 1.1 A brief timeline of the history of dystonia

Key: yellow boxes: nomenclature, green boxes: treatments, orange boxes: classification, blue boxes: identification of novel disease-causing genes

1.4 Classification

Given the clinical heterogeneity and growing number of causes of dystonia, diagnosis can be challenging, often resulting in misdiagnosis. To aid this process, the classification of dystonia has recently been revised. Initially categorised as primary, secondary or psychological dystonia, this classification was unable to distinguish symptomatology from aetiology. To address these concerns, a classification based on two axes was proposed.[9] Axis 1 consists of clinical features including age at onset, body distribution (Table 1.2), temporal pattern, and associated features. Axis 2 depicts aetiology including known causative genes. Figure 1.2 depicts the current classification, subdivided into Axis 1 and 2. A key component is the distribution of affected body parts, with age at onset closely linked to distribution; early disease onset is more likely to involve initial symptoms in the lower limbs, typically progressing to become generalised, while cranio-cervical involvement is usually associated with later-onset and often remains focal.

Table 1.2 Terms used to describe body regions affected in dystonia

Distribution	Body part affected
Focal	One body region
Segmental	Two or more contiguous regions
Multifocal	Two non-contiguous regions
Generalised	Trunk and at least two other sites
Hemidystonia	Restricted to one body side

1.5 Genetic forms of dystonia

Over the past 30 years, increasing evidence suggests that gene alterations may contribute to dystonia. To date, 28 monogenic dystonia loci (named DYT1 to 29) have been mapped in families with distinct forms of dystonia with differing modes of inheritance, including autosomal dominant transmission (21 loci), autosomal recessive transmission (6 loci), and recessive X-linked (1 locus) (See Table 1.3).

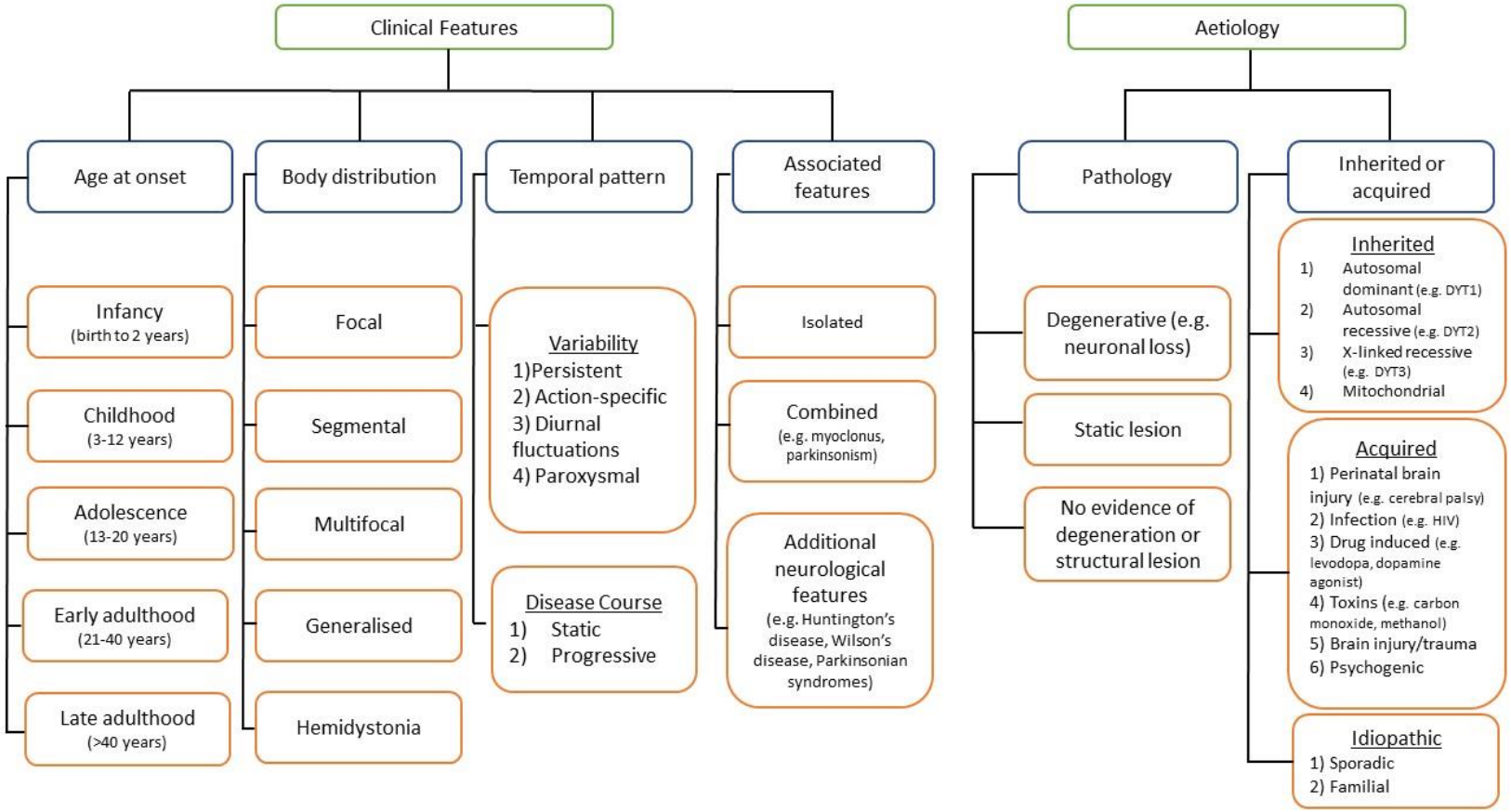

Figure 1.2 Diagram of the current classification of dystonia

Adapted diagrammatic representation of Albanese *et al* classification of dystonia[9]

Table 1.3 Monogenic forms of dystonia

Category	Locus	Clinical Description	Clinical Characteristics	Chromosome	Gene	Inheritance	Penetrance	Types of Mutation
Isolated Dystonia								
	DYT1	Early-onset generalised dystonia	• Childhood or adolescent onset (mean age 13, between 1 and 28 years), most present by 26 years • Presents in limbs, mainly the legs • Symptoms later progress to other body regions, typically to involve the trunk and other limbs[10]	9q34	*TOR1A*	AD	30%[11]	GAG deletion (c.904_ 906del)
	DYT2	Autosomal recessive idiopathic generalised dystonia	• Rare early-onset dystonia, (mean age 15 years) • Initiates in the lower extremities • Gradually worsens to become generalised[12,13] • Resembles DYT1	1q35-p34.2[14,15]	*HCPA*	AR	Incomplete	Missense mutations (N75K, T71N, A190T)
	DYT4	Primary torsion dystonia with whispering dysphonia	• Onset between 13-37 years, often before 20 years of age • Initially presents with whispering dysphonia • Phenotypic expression is variable, ranging from focal to generalised dystonia with an unusual "hobby horse" ataxic gait • Alcohol, caffeine and stress ameliorating symptoms during early manifestation[16,17]	19p13.12-13	*TUBBA4*[18,19]	AD	100%	Missense mutation c.2297C>G, p.T766R and splice site mutation IVS5+1G>T
	DYT6	Adult-onset mixed dystonia	• Late childhood or adolescent onset (mean: 16 years, ranging 5-38 years) • Presenting with prominent arm (46%) and cranio-cervical (25%) distribution • Progresses to become segmental or generalised[20,21] • Dysphonia is common, although clinical features are highly variable across ethnicities with laryngeal or oromandibular dystonia reported[22]	8p21-q22[23]	*THAP1*	AD	60% independent of sex[20]	Over 100 missense, nonsense and frameshift mutations. Two-thirds are missense

	DYT7	Adult-onset focal dystonia	• Mean age of onset 43 years • Primarily presents as cervical dystonia • Described in a single family of German origin[24]	18p More recent exome sequencing of candidate genes in the short arm of chromosome 18 could not detect any potential disease-causing variant[25]	Unknown	AD	Incomplete	Unknown
	DYT13	Early-onset primary segmental craniocervical dystonia	• Mean age of onset is 15 years of age • Characterised by torsion dystonia with prominent cranial-cervical involvement • Symptoms slowly progress to other body regions[26]	1p36.13-36.32	Unknown	AD	58%	Unknown
	DYT17	Idiopathic autosomal recessive primary dystonia	• Initially manifests as cervical dystonia • Progresses to segmental or generalised dystonia within two to three years • Additional clinical symptoms include dysphonia and dysarthria[27]	20p11.22-q13.12	Unknown	AR	Unknown	Unknown
	DYT21	Late-onset autosomal dominant focal dystonia	• Age of onset ranges between 13 and 50 years (mean age 25 years)[28] • Blepharospasm, cervical dystonia and upper-limb dystonia are prevalent • Occasionally presenting with spasmodic dysphonia[29]	2q14.3-21.3	Unknown	AD	90%[28]	Unknown
	DYT23	Adult-onset primary cervical dystonia	• Presents in fourth or fifth decade of life • Characterised by adult-onset cervical dystonia[30] • Prominent head, voice, or arm tremor	9q34.11	*CIZ1*	AD	Unknown	Missense mutation c.790A > G, p.S264G
	DYT24	Autosomal craniocervical dystonia	• Age at onset varies from early childhood to the fourth decade[31] • Typically presents as tremulous cervical dystonia, with slow progression to segmental dystonia[32] • Other sites of onset include cranial dystonia and laryngeal dystonia[33]	11p14.2	*ANO3*	AD	50%	Six missense mutations

	DYT25	Adult-onset cervical dystonia	• Clinical presentation is of a later onset (mean age at onset 31 years, range 7-54 years) • Usually begins in the neck (82%), before progressing to involve the cranial (57%) and speech (44%)[34]	18p.11	*GNAL*	AD	Incomplete	About 30 missense and nonsense mutations
	DYT27	Early-onset isolated segmental dystonia	• A childhood-onset segmental isolated dystonia • Affects the craniocervical, oromandibular regions or upper limbs • Loss-of-function mutations in the C-terminus of the α3 (VI) collagen gene (*COL6A3*) • Speculated perturbation of the brain extracellular matrix may contribute to irregular sensorimotor formation[35,36]	2q37.3	*COL6A3*	AR	Incomplete	Biallelic mutations, loss-of-function mutations in the C-terminus of the α3 (VI) collagen gene
	DYT28	Early-onset generalised dystonia	• Childhood-onset dystonia • Presents in the lower limbs • Progresses to the upper limbs, neck and orofacial region. • Other clinical features include gait difficulties, elongated face with bulbous nose, abnormal eye movements, psychiatric comorbidity and delayed motor and/or cognitive development	19p13.12	*KMT2B*[37]	AD	Unknown	Four heterozygous loss-of-function mutations (three de novo and one inherited)
Dystonia-plus syndrome								
	DYT3	X-linked dystonia-parkinsonism or Lubag	• Onset is typically in the third or fourth decade (mean age 38 years), ranging between 12 and 52 years • Initially characterised by focal dystonia in almost any part of the body • Progresses to become segmental or generalised within 5 years • Parkinsonism develops in more than 50% of cases, usually after the 10th year of illness, and becomes a prominent feature[38]	Xq13.1[39]	*TAF1*	X-linked	100%	Disease-specific single-nucleotide changes

	DYT5a/DYT14	Dopa-responsive dystonia or Segawa dystonia	• Childhood-onset of limb dystonia (mainly the legs) • Sometimes progresses to segmental or generalised dystonia • Marked diurnal fluctuation of symptoms, worsening throughout the day and after exercise, but improving after sleep and with levodopa therapy[40] • Additional clinical features include adult-onset parkinsonism[41], myoclonus[42], oromandibular dystonia[43], scoliosis[44], spasticity mimicking cerebral palsy[45], generalised hypotonia with proximal weakness[46] and psychiatric disorders[47]	14q22.1-q22.2[48]	*GCH1*	AD	50% in males and 80% in females[49]	More than 100 mutations
	DYT5b	Dopa-responsive dystonia or Segawa dystonia	• Onset often occurs before the first year (2 months to 5 years) • Initially presenting with dystonia in one leg, which progresses to involve the upper limbs, trunk, face and oropharyngeal muscles[50] • Additional features include rigidity of limbs, myoclonic jerks[51], hypotonia, progressive motor retardation, tremor[52], ptosis, spasticity and intellectual disability[50], infantile parkinsonism[53], progressive encephalopathy[54]	11p15.5	*TH*	AR	Unknown	Around 5 different mutations
	DYT11	Myoclonus-dystonia	• Onset is usually in childhood or adolescence • Characterised by coexistent dystonia and myoclonus mainly affecting the neck and upper limbs, cervical dystonia and writer's cramp are common manifestations • Jerks have a characteristic shock-like appearance often alcohol responsive[55] • Co-morbid psychiatric disorders, substance abuse and cognitive deficits are associated with myoclonus dystonia[56]	7p21[57]	*SGCE*[58]	AD	50% due to maternal imprinting	Around 80 different mutations

	DYT12	Rapid-onset dystonia parkinsonism	• Onset of symptoms is in adolescence or young adulthood (76% of cases present by 25 years) • Usually manifesting over hours to weeks, followed by slow or no progression • Characterised by sudden onset of orofacial dystonia, dysarthria, dysphagia, dystonic spasms of the upper limbs, as well as features of parkinsonism. • Presents with an anatomical distribution following a rostrocaudal gradient (face>arm>leg), in association with predominant bulbar[59]. • Seizures, paroxysmal dystonia, psychiatric symptoms and cognitive impairment are also observed[60]. • Attacks may be precipitated by alcohol or stressful events, e.g. physical exertion, fever, childbirth or emotional stress[61]	19q12-q13.2[62]	*ATP1A3*	AD	90%	Around 20 different mutations
	DYT15	Myoclonus-dystonia	• Characteristics are identical to DYT11: an alcohol-responsive myoclonic dystonia, characterised by jerky movements of the upper limbs, hands and axial muscles[63]	18p11	Unknown	AD	Incomplete	Unknown
	DYT16	Adolescent-onset dystonia parkinsonism	• Initial clinical features include gait abnormalities and leg pain, followed by dysphagia, progressive generalised dystonia affecting the face, neck, trunk and limbs and symptoms of parkinsonism[64] • Additional characteristics include bradykinesia, speech and language impairment, and some evidence of severe cognitive impairment[65] • Symptoms are unresponsive to levodopa	2q31	*PRKRA*	AR	Unknown	Most frequent variant is c.C665T, p.P222L

	DYT26	Myoclonus dystonia unresponsive to alcohol	• Symptoms present during the first or second decade of life • Characterised by myoclonic jerks affecting the upper limbs • Symptoms spread to involve the cranio-cervical, trunk and lower limbs[66]	22q12.3	*KCTD17*	AD	Unknown	Missense mutation (Arg145His)
	DYT29	Early-onset dystonia with optic atrophy and basal ganglia abnormalities	• Clinical presentation is of an early-onset, facial dystonia with myoclonus. • Additional features may include lower limb spasticity with hyperreflexia, chorea, dyskinesia, dysarthria and dysphagia[67]	1p35.3	*MECR*	AR	Unknown	Six mutations (missense, nonsense, splice site)
Paroxysmal Dystonia								
	DYT8	Paroxysmal nonkinesigenic dyskinesia 1	• Episodes first become evident during childhood or adolescence (mean age of onset 5) • Characterised by chorea, athetosis, ballismus and/or dystonia involving the face, trunk and limbs, movements are initially unilateral and spread or generalise • Episodes can last a few minutes to several hours • Frequency of attacks are highly variable and intermittent (usually once a week) • Attacks may cccur spontaneously but are often triggered by alcohol, caffeine or heightened emotion and alleviated by sleep[68]	2q33-2q35[69,70]	*MR-1*	AD	95%[71]	Two mutations (p.Ala7Val, p.Ala9Val)
	DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity	• Characterised by dystonia, choreoathetosis, with episodic ataxia, spasticity, seizures and mild-to-moderate cognitive impairments • Attacks are provoked by physical exercise, emotional stress, lack of sleep and alcohol[72,73]	1p21-p13.3	*SLC2A1*	AD	Unknown	Heterozygous mutation (R232C, R126C)

	DYT10	Paroxsymal kinesigenic dyskinesia 1	• Onset is typically in childhood or adolescence (mean age of onset 5-15 years) • Triggered by sudden movements, these brief (<1 minute) and episodic (on average 1-20 attacks per day) attacks consist of dystonia and/or choreoathetosis affecting the moving limb[74]	16p11.2[75]	*PRRT2*	AD	60-90%	Around 5 mutations, the majority causing truncation
	DYT18	Exercise-induced paroxysmal dyskinesia	• Onset is typically in childhood, and manifests in the lower limbs[76] • Attacks are characterised by involuntary flexing, extended movements, and twisting of the upper and lower limbs • These attacks can be induced by exercise, stress, and hunger • Additional clinical symptoms can include seizures, epilepsy, mild learning disabilities, irritable behaviour[77], spasticity, anaemia, migraine and developmental delay[78]	1p21-p13.3	*SLC2A1*	AD	Incomplete	>100 mutations
	DYT19	Paroxsymal kinesigenic dyskinesia 2	• Clinical phenotype is similar to DYT10: short attacks (lasting around two minutes), involving dystonic or choreic movements induced by sudden movements[79]	16q13-q22.1	Unknown	AD	75%	Unknown
	DYT20	Paroxysmal nonkinesigenic dyskinesia 2	• Age of onset ranged from childhood to 50 years of age • Episodic dystonia primarily affecting the hands and feet • Attacks last between two to five minutes, and occurring daily or several times per month[80]	2q31	Unknown, proposed genes *GAD-1* and *DLX1/DLX2*[80]	AD	89%	Unknown

1.6 Idiopathic, isolated, focal dystonias

The clinical presentation of isolated dystonia varies dependent on age, early-onset dystonia with limb involvement more often progresses to generalised dystonia and is usually of hereditary origin, while focal dystonia typically presents in adulthood with a limited tendency to spread. Adult-onset focal dystonias are approximately 10 times more frequently encountered than generalised dystonia,[3,81,82] and typically occur in the neck, face or arm. There is evidence of gender bias, with female predominance in cranio-cervical dystonia, and dopa-responsive dystonia, while task-specific dystonia such as musician's dystonia and writer's cramp are more common in males.[8,83,84] Sensory tricks are often seen in focal dystonia to ameliorate the dystonic movement; however, relief is only transient. Although predominantly sporadic, 9% to 30% of cases have an affected relative,[83,85–88] and several genetic loci and genes have been identified. The individual forms of idiopathic, isolated, focal dystonia are discussed below.

Cervical dystonia

This is discussed in detail in Section 1.9.

Blepharospasm

Blepharospasm (BSP) refers to excessive involuntary closure of the eyelids due to spasms of the orbicularis oculi muscles. It is more common in females than males, and is the second most common form of adult-onset dystonia, with estimates ranging from 16 to 133 per million.[89] Onset is typically between the fifth and seventh decade, with initial symptoms such as dryness of the eyes, irritation and photophobia subsequently developing into increased spontaneous blinking and apraxia of eyelid opening.[90] In the majority of cases, the dystonia spreads to neighbouring muscles during the initial five years.[91]

Oromandibular dystonia

This involves the masticatory, lingual, perioral and platysma muscles, with onset typically in the fifth or sixth decade of life, and often as part of cranio-facial segmental or generalised dystonia. Distinct forms of oromandibular dystonia (OMD) can be described as jaw opening, jaw closing, mixed OMD, and jaw deviation, all

impacting speech and swallowing. These visible symptoms frequently impair quality of life and social functioning, and can cause pain.[92]

Laryngeal dystonia

Also known as spasmodic dysphonia, this rare form of dystonia affects the voice and/or breathing caused by intermittent involuntary spasms of the adductor and abductor vocal folds, with average age at onset being 30 – 50 years of age. Adductor symptoms are more common, occurring in around 90% of cases with individuals presenting with roughness, strain and increased expiratory effort during speech caused by involuntary spasms of the thyroarytenoid muscle.[93] Less common is the abductor form, characterised by breathy breaks or aphonia due to increased posterior cricoarytenoid and cricothyroid activity. Dystonic voice tremor frequently manifests in both forms. In addition to these two variants, uncommon forms such as mixed laryngeal dystonia, singer's dystonia and adductor respirator dystonia exist.[94]

Writer's cramp and task specific limb dystonia

Onset is usually in adulthood between the third and sixth decades of life, and unlike other forms of focal dystonia, there is a male preponderance. These dystonias typically affect the arm, facial muscles or larynx, presenting as painless loss of dexterity triggered by performance of a highly specific, over-practiced task. Remissions are rare and almost never sustained. Task-specific dystonias typically progress, affecting other tasks involving fine motor control.[95] Writer's cramp is one of the most recognised forms with clinical presentation beginning with feelings of tension in the fingers and forearm, before progressing to involve excessive flexion of fingers, pronation and ulnar deviation of the hand.[96] Upper limb tremor is also commonly experienced.[97] Other upper limb task-specific dystonias relating to professions include those observed in musicians and sportspeople. Embouchure dystonia (ED), a form of musician's dystonia, affects the muscles of the lower face, jaw, tongue and pharynx, and is typically seen in individuals who play woodwind or brass instruments. Initial symptoms include loss of embouchure control, loss of clarity of articulation and involuntary movements of the lips, jaw or tongue. Once present, symptoms do not usually remit, often spreading to affect other oral tasks such as speaking and eating.[98] Approximately 10% of individuals with ED have co-

occurring writer's cramp, suggesting a potential genetic predisposition to developing focal dystonia.[99]

1.7 Pathophysiology

Many of the classical, presumptive, pathophysiological models of dystonia centre on the direct and indirect pathways of the basal ganglia, with the notion that activation of the former facilities movement, and the latter inhibits movement (Figure 1.3). These models propose that dystonic movement results from disruption to these pathways, in which increased inhibition of thalamo-cortical projections leads to disinhibition of the cortical motor and pre-motor regions. The striatum and basal ganglia structures are connected via several pathways; i) striatal γ-aminobutyric acid (GABA)-ergic projection neurons directly target the internal globus pallidus (GPi) and substantia nigra (SN), ii) the indirect pathway connects the external globus pallidus (GPe) and the subthalamic nucleus (STN). GABAergic projections which form the direct pathway inhibit thalamocortical and brainstem neurons, with glutamatergic neurons from the thalamus projecting back to the striatum. Although the precise mechanisms underlying dystonia remain unknown, disruption to both pathways have been suggested.

In dystonia, reduced outputs from the GPi results in increased thalamic and cortical activity, which in turn results in muscle co-contraction and overflow to adjacent body regions. Activation of GABAergic GPe neurons via the indirect pathway leads to disinhibition of STN glutamatergic neurons, this reduces motor activity through promotion of GPi and SN reticulata (SNr) GABAergic activity via inhibition of thalamic activity. Decreased GABA transmission causes excessive inhibition of the STN, with subsequent deficits in GPi activity. In addition, D1 and D2 dopamine receptors are highly expressed in these pathways, therefore, it has also been proposed that striatal dopamine also plays a role in regulating the direct and indirect pathways and are involved in the preparation and selection of movements.

In more recent years, it has been suggested that dystonia is in fact a network disorder involving the cortico-basal ganglia-thalamo-cortical pathways, with the cerebellum also playing a contributing role. From a neuroanatomical perspective, the cerebellum

has widespread connections to the pre-supplementary motor areas (SMA), SMA, spinal cord, basal ganglia and striatum (Figure 1.4), and is involved in co-ordination of movements, with cerebellar hyperactivity potentially key in driving basal ganglia dysfunction.[100,101]

Improved understanding of dystonia pathophysiology is key in the development of novel therapies, and multiple techniques and approaches have been employed with this in mind. Below we take each of these, discussing the key findings identified in each field.

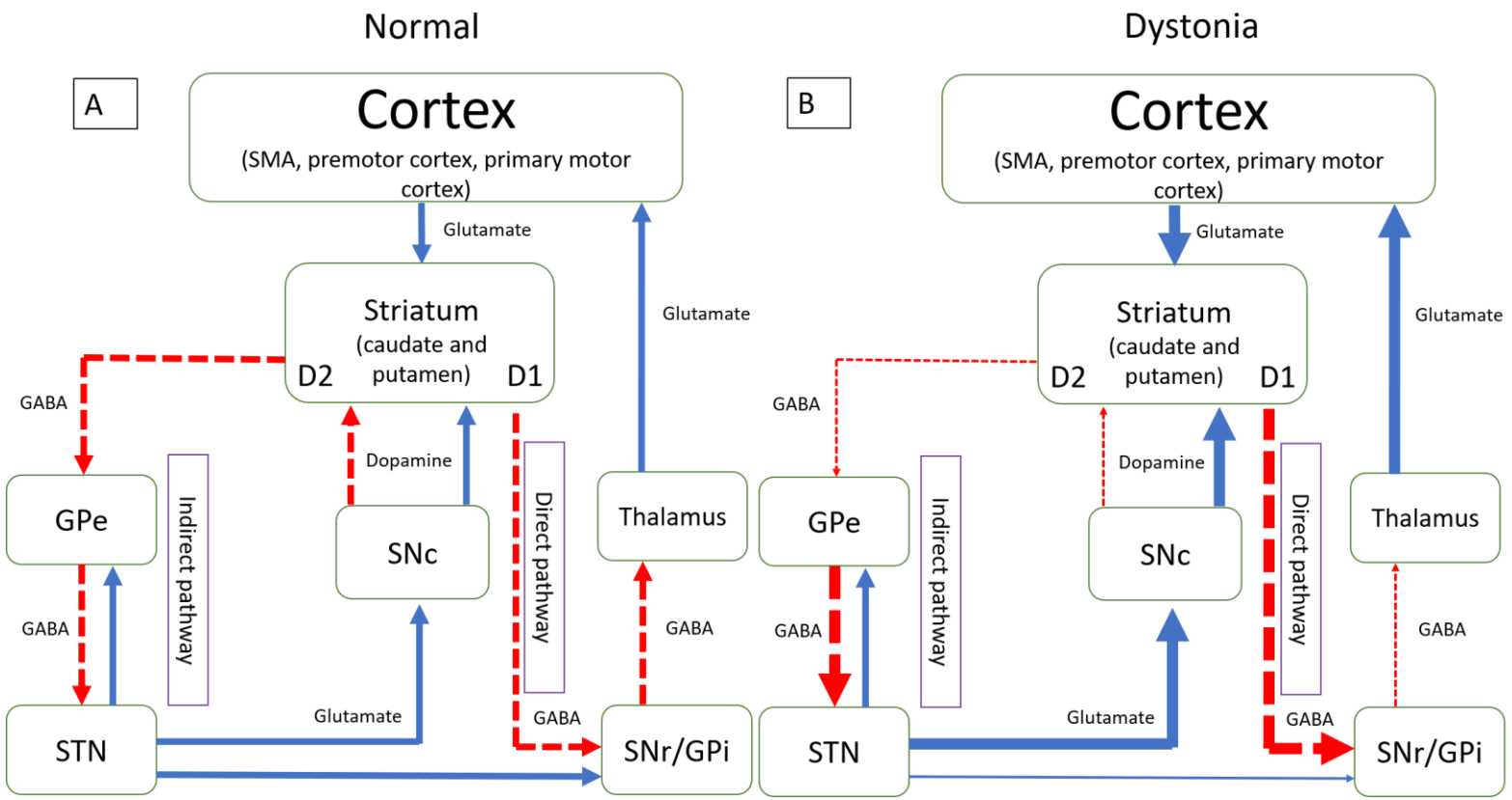

Figure 1.3 Schematic diagram of the motor circuit **(A)** Basal ganglia circuitry in normal pathophysiology **(B)** Motor circuity in dystonia: wide and narrow arrows indicate increased and decreased output, respectively

Key: red dashed lines represent inhibitory projections, blue lines represent excitatory projections

Abbreviations: D1/D2: Dopamine receptors, GPe: Globus Pallidus Externus, GPi: Globus Pallidus Internus, STN: Subthalamic Nucleus, SMA: Supplementary Motor Area, SNr: Substantia Nigra Pars Reticulata, SNc: Substantia Nigra Pars Compact

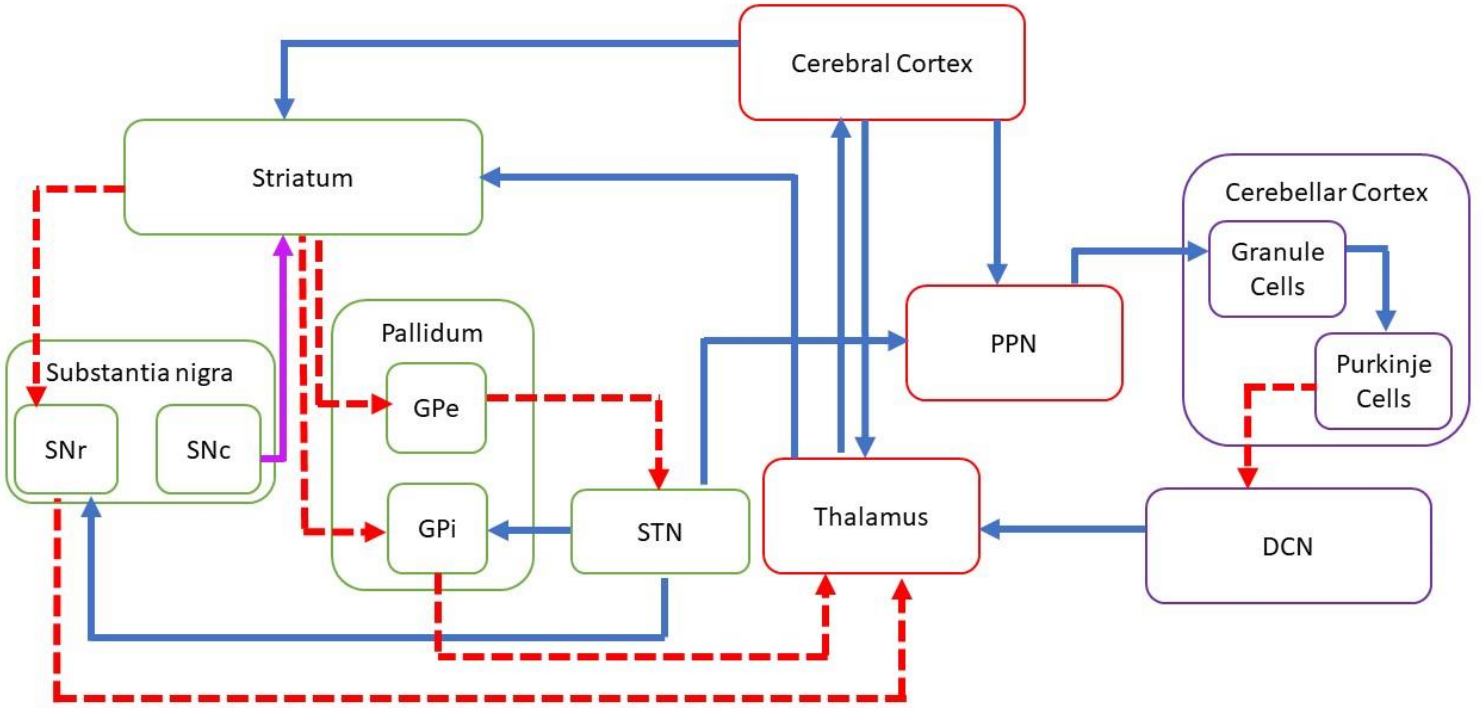

Figure 1.4 Schematic diagram of the basal ganglia and cerebellar connections. Adapted from Nibbeling et al 2017[102]

Key: green boxes represent basal ganglia regions, purple boxes represent the cerebellum, red dashed lines represent inhibitory GABAergic projections, blue lines represent excitatory glutamatergic projections and pink arrows represent dopaminergic projections

Abbreviations: DCN: Deep Cerebellar Nuclei, GPe: Globus Pallidus Externus, GPi: Globus Pallidus Internus, PPN: Pedunculopontine Nucleus, STN: Subthalamic Nucleus, SNr: Substantia Nigra Pars Reticulata, SNc: Substantia Nigra Pars Compact

1.8 Neurophysiology

Physiological studies have identified three underlying mechanisms that are believed to contribute to the excessive muscle activity observed in dystonia: abnormalities in inhibition, synaptic plasticity, and sensory discrimination.

Loss of inhibition

Typically, motor control is maintained by balancing excitatory and inhibitory commands so that desired movement is achieved, and undesired movement prevented. In dystonia, loss of inhibition appears to cause excess co-contraction of antagonist muscles, with this having been demonstrated at multiple levels of the nervous system including the spinal cord, brainstem, and motor cortex. Some of the first evidence of impaired spinal inhibitory mechanisms was confirmed in patients with cervical dystonia and generalised dystonia.[103,104] Altered blink reflex recovery has also been found amongst those with blepharospasm, cervical dystonia, generalised dystonia and manifesting and non-manifesting DYT1 mutation carriers.[105–108]

Transcranial magnetic stimulation (TMS) is a technique used to evoke muscle response contralateral to the stimulated the cortex, which enables measurement of cortical activity. In comparison to controls, reduced short interval intracortical inhibition (SICI) has been reported in several forms of dystonia including focal hand dystonia and cervical dystonia.[109–111] However, evidence is conflicting with several studies having reported no differences in SICI and long interval intracortical inhibition (LICI) between groups.[108,112–114] Long and short afferent-induced inhibition is also reduced amongst patients with focal hand dystonias and CD,[113–115] but again, evidence is inconsistent.[116,117] The silent period is a pause in voluntary muscle activity produced by TMS. A reduction in the duration of the silent period has been shown in the affected muscles of those with spasmodic dysphonia, blepharospasm, cervical dystonia and focal hand dystonia,[108,118–121] as well as extending to non-affected hand musculature in those with cervical dystonia.[122]

Maladaptive neuroplasticity

Neural plasticity is the ability of the nervous system to adapt in response to its environment by reorganising structure, function, or connections. Repetitive motor tasks are believed to play a central role in maladaptive cortical plasticity, leading to reorganisation of the sensorimotor system due to repeated afferent input. Initial evidence supportive of this hypothesis was shown in primates, whereby repetitive input resulted in motor symptoms similar to focal hand dystonia, owing to abnormal remodelling of the primary somatosensory cortex.[123] In keeping with these findings, reorganisation of the sensory homuncular has also been shown in patients with focal hand dystonia.[124] More recent evidence has demonstrated altered plasticity at the cortico-striatal level in DYT1, DYT11 and DYT25 mouse models, abnormalities in long-term depression and deficits in both dopaminergic and cholinergic mediated plasticity has been shown.[125–130]

Abnormal plasticity can also be measured using TMS, whilst simultaneously stimulating a peripheral nerve (paired associated simulation, PAS). This approach can induce plasticity and is believed to represent the mechanisms observed in the synaptic reorganisation, long-term potentiation and depression. When applied to those with focal hand dystonia, associative plasticity was enhanced across the sensorimotor system compared to controls. This pattern is consistent with increased plasticity and reduced spatial specificity,[131–134] in which loss of spatial specificity is thought to be related to loss of inhibition. Altered plasticity has also been observed in the motor cortex and cerebellum of those with cervical dystonia[135–137] and writer's cramp,[113] whereby cerebellar deficits may cause ineffective sensorimotor modulation. These maladaptive changes are not exclusive to dystonia patients but have also been shown in non-manifesting DYT1 mutation carriers,[138] suggesting that this may form a dystonia endophenotype. However, findings are highly variable, with more recent studies showing comparable PAS response between focal dystonias and controls.[113,139–141]

Sensory abnormalities

Various sensory abnormalities have been identified in patients with dystonia, these often precede the onset of motor symptoms[142] and include deficits in temporal and spatial discrimination,[143–145] pain,[146] photosensitivity,[147] and sensory tricks.[148,149]

This, coupled with abnormalities within structures of the sensorimotor network such as the cerebellum, sensory cortex and motor cortex, support the hypothesis that the somatosensory system contributes to mechanisms of dystonia.[150,151] Further, evidence of improved dystonic symptoms following rehabilitation techniques which facilitate processing of proprioceptive information, for example biofeedback training, indicate sensory deficits may have a central role in dystonia pathophysiology.[152,153] Evidence of sensory abnormalities are discussed in more detail in Section 1.8.5.

1.9 Neuroimaging

Advanced neuroimaging techniques have provided a large body of evidence that regions aside from the basal ganglia are involved in dystonia. Although imaging data should be interpreted with care, evidence is presented below from both functional and structural magnetic resonance imaging (MRI) techniques as well as positron emission tomography (PET).

Lesion studies

Lesions spanning the corticospinal tract, basal ganglia, brainstem, thalamus, cerebellum, and parietal cortex have been observed in association with dystonia. The location of these lesions appears to be related to different types of dystonia, for example cervical cord lesions are primarily implicated in cervical dystonia,[154] while loss of Purkinje cells and cerebellar lesions have also been observed in cervical dystonia, blepharospasm and oromandibular dystonia.[155156,157] Interestingly, dystonic clinical manifestation varies depending on thalamic lesion location, with twisting and writhing symptoms associated with disruption to striatopallidal circuitry, and tremulous, jerky dystonia predominantly involving cerebellar circuits.[158]

1.10 Structural Neuroimaging

Volumetric imaging studies

These quantitative tools assess volumetric differences in brain regions between dystonic patients and healthy controls, with volumetric MRI demonstrating a 10% enlargement of the putamen amongst those with focal hand dystonia and blepharospasm.[159] Voxel-based morphometry (VBM), a volumetric method used to

detect differences in brain tissue of predetermined structures has identified changes to the Grey Matter (GM) involving the basal ganglia, thalamus, cerebellum, motor and sensory cortex amongst various forms of dystonia.[160–162] Specifically, abnormal putaminal volume is evident in focal and generalised forms compared to unaffected controls.[163,164]

Diffusion tensor imaging (DTI) and tractography

This imaging technique is based on the principal of water molecule movement and diffusivity along the axon. It measures anisotropy indices such as fractional anisotropy (FA), which reflect white matter integrity and coherence. Several studies have identified reduced axonal integrity along cerebello-thalamo-cortical and cortico-striato-pallido-thalamic tracts amongst cranio-cervical dystonia cohorts compared to controls.[165–167] Two studies of manifesting and non-manifesting DYT1 and DYT6 carriers found abnormalities in the sensorimotor cortex, while a third study showed reduced cerebellar integrity in symptomatic DYT1 and DYT6 carriers.[168–170] A single study assessing structural and functional abnormalities of cortical projections amongst those with embouchure dystonia showed increased axial diffusivity (AD) between the SMA and the superior parietal cortex, and lower AD between the primary somatosensory cortex and putamen.[171] Amongst focal dystonia's mean diffusivity (MD) has been found to be higher in the cerebello-thalamo pathway, with lower white matter FA in connecting pathways.[172] By contrast, FA differences have not been identified in individuals with blepharospasm but have identified increased global and local network efficiency,[173] and increased local diffusion in several regions including the superior longitudinal fasciculus bilaterally and corpus callosum.[174]

1.11 Functional Neuroimaging

Positron emission tomography (PET)

PET studies have shown abnormal metabolic activity in various regions amongst genetic and sporadic dystonia. Knockout *TOR1A* mice demonstrate metabolic changes in the striatum, cerebellum, sensorimotor cortex and subthalamic nucleus (STN).[175] Abnormalities in these structures are also observed in patients with blepharospasm and cervical dystonia, with additional metabolic changes in the basal

ganglia and pre-motor cortex.[176,177] A comparison of cohorts with DYT1 and DYT6 mutations has identified elevated metabolic activity in the striatum, anterior cingulate and cerebellum in the former cohort. By contrast, DYT6 carriers presented with hypometabolism in the putamen, thalamus, cerebellum and upper brainstem and hypermetabolism in the temporal cortex.[178] While both manifesting DYT1 and DYT6 genetic carriers had increased activity in the pre-supplementary motor cortex and parietal association structures.[179] Similarly, cerebral regional blood flow appears to be abnormal in the basal ganglia, thalamus, cerebellum and pre-SMA, and extending to the prefrontal, parietal and temporal regions in those with writer's cramp compared to controls.[180,181]

Single-photon emission computed tomography (SPECT)

The majority of SPECT studies implicate the dopaminergic system in dystonia, particularly CD and writer's cramp. Two studies have shown reduced D2 receptor striatal binding in patients with writer's cramp and CD,[182,183] while a third found elevated asymmetrical striatal binding was contralateral to the direction of head rotation amongst CD cohorts.[184]

Functional magnetic resonance imaging (fMRI)

Functional MRI detects changes associated with blood oxygen levels, with this identifying changes in the basal ganglia, thalamus, cerebellum, and sensorimotor cortex. Further, some studies have found that abnormal sensory processing in the primary somatosensory cortex may contribute to mechanisms of task-specific dystonia,[163] while others have identified an associated between temporal discrimination deficits and alterations in primary somatosensory and frontal cortices.[185] Variation in regional activation are dependent on the type of dystonia and task performance. For example, head rotations in the direction of the dystonic cervical muscle were associated with activation of the anterior cerebellum, whilst rotation in the opposite direction was associated with activation of the sensorimotor areas of the cerebral cortex.[186] More recent studies amongst CD cohorts demonstrate decreased functional connectivity in the right SMA, superior medial prefrontal cortex, right precentral and postcentral gyrus, with negatively relations with symptomatic severity,[187–189] as well as increased connectivity in the left supramarginal gyrus. Some have suggested both hyper- and hypo-connectivity in

bilateral regions of the sensorimotor network may cause dysfunctional sensorimotor integration.[188]

1.12 Neuropathology

Immunostaining studies have found no evidence of neuropathological substrates within the brainstem nuclei or striatum of patients with segmental dystonia.[190] Similarly, several studies have shown the absence of protein aggregates (e.g. torsinA) in those with DYT1 mutations.[191–193] In contrast, small case-series of DYT3 and DYT12 cohorts have reported Purkinje cell loss and astrocytosis in the caudate and putamen in the former, and neuronal loss in the globus pallidus, STN, Purkinje cells of the cerebellum, and red nucleus in the latter.[194,195] Two case-control studies of patients with cervical dystonia have reported pathological changes, one noted ubiquitin-positive inclusions in nigral neurons and significant reductions in Purkinje cell density,[196] while the second study found marked reduction in cholinergic neurons in the pedunculopontine nucleus (PPN).[197]

1.13 Neurosurgery

Limited response to pharmacological treatments has resulted in the development of surgical interventions over the last couple of decades. The majority of these approaches are ablative or stimulation procedures (Section 1.7.4) that target several regions, including the basal ganglia, thalamus and cerebellum. The thalamus was the first region targeted to treat dystonia, although response is limited dependant on type of dystonia being treated. Deep Brain Stimulation (DBS) is effectively used in the management of dystonia, with the GPi considered the best target for multiple forms of dystonia. Often it can take weeks or months to obtain sustained post-operative improvement in dystonic symptoms. These delayed temporal responses imply that DBS may induce reorganisation of cortical and brainstem neuroplasticity in order to restore normal movements.

1.14 Animal models

Evidence from animal models supports that dystonia may arise from dysfunction of the basal ganglia, cerebellum, or thalamus. Several models have been developed, and although useful for understanding anatomical and physiological processes involved

in dystonia, they often fail to recapitulate the clinical phenotypes of dystonia. These models can be further subdivided into genetic and pharmacological models and are discussed below.

The most studied animal model is a transgenic *TOR1A* model. Reduced expression of the torsinA protein in the cerebellum has been shown to result in symptoms similar to dystonia and associated with irregular cerebellar output caused by altered activity in Purkinje cells and cerebellar nuclei.[198,199] DYT11 murine models show impaired motor learning deficits, thought to be caused by nuclear envelope abnormalities in the cerebellar Purkinje cells. Although *tottering* and *leaner* mouse models harbour mutations in the *CACNA1A* gene, coding the highly expressed cerebellar P/Q-type calcium channels, both are phenotypically distinct. Mutations in the former cause paroxysmal dystonia,[200] while the latter have symptoms of generalised dystonia.[201] In spite of this, both models report spontaneous firing of cerebellar cortical neurons correlating to the dystonic attacks,[202–204] and improvement in dystonic movement with the loss of dysfunctional cerebellar Purkinje cells.[201,205] A recent study found that non-manifesting mice harbouring *Gnal* mutations demonstrated changes to cerebello-thalamic plasticity, whereby stimulation of the cerebellar dentate nucleus reduced dystonia severity after cholinergic-induced dystonia via oxotremorine administration.[206] These results suggest that abnormal cerebellar function, rather than cell loss, may cause dystonia.

Other genetically engineered mouse models have implicated the basal ganglia. The *Gunn* rat exhibits movements that are clinically consistent with generalised dystonia with *in vivo* electrophysiological data showing that these abnormalities are related to bursts of activity in the entopeduncular nucleus.[207] A single point mutation affecting tyrosine hydroxylase in mouse models induced a diurnal pattern of abnormal movements similar to those seen in humans with dopa-responsive dystonia.[208] Striatal cholinergic dysfunction has also been demonstrated in *Tor1a, Thap1* and *Gnal* dystonia models, although all models showed altered D2R excitation caused by altered G-protein-coupled receptors, elevated extrastriatal acetylcholine was noted in both DYT1 and DYT6 mice, while no elevation was observed in *Gnal* knock-out mice.[209] More recent approaches have limited torsinA mutations to the medium spiny neurons (MSNs) and demonstrated cell-autonomous effects in nigrostriatal

dopaminergic and cholinergic systems.[210] Further, D2R-expressing-cell-specific DYT1 knock-out mice show significant reduction in striatal torsinA, loss of striatal D2R, reduced striatal cholinergic interneurons, reduced levels of striatal tyrosine hydroxylase, with reduced striatal monoamines related to locomotor deficits.[211]

Animal models that involve lesions and microinjection of pharmacological agents also provide valuable insight. Injections of kainite (glutamate receptor agonist) into the cerebellum of normal mice induced generalised dystonia,[212] whereas dystonia symptoms did not manifest in those lacking Purkinje cells.[213] Other studies have used a pharmacological approach to model rapid-onset dystonia-parkinsonism (DYT12), with partial blockage of striatal and cerebellar sodium pumps via injection of ouabain inducing dystonic symptoms, accompanied by loss of striatal cholinergic and GABAergic interneurons, and striatal dopamine depletion.[214,215]

1.15 Cell models

Induced pluripotent stem cell (iPSC) are derived from cell lines (e.g. blood or skin) of patients diagnosed with specific disorders and are then reprogrammed into an embryonic stem cell-like state. This technology is a valuable tool which enables the modelling of dystonia and has the potential to define disease phenotype and identify novel pathways, contributing to our overall understanding of the disease pathophysiology. IPSCs derived from individuals with X-linked dystonia-parkinsonism (XDP) harbouring mutations in the *TAF1* gene found expression of *TAF1* was reduced in spiny projection neurons due to retrotransposon insertion, and was rescued by excision in patient-derived cells.[216] Further, *in-vitro* models of DYT3 generated from iPSCs have shown more pronounced expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits and lower calcium levels in striatal neurons, often with spontaneous transmission of calcium.[217]

Recent studies have identified the dysregulation of Eukaryotic Initiation Factor 2 α (eIF2α) signalling pathways in several forms of dystonia, including DYT1, DYT6 and DYT16. This translation factor is involved in the ubiquitous cellular response to endoplasmic reticulum (ER) stress, known as the integrated stress response (ISR) and also regulates neuronal events such as synaptic plasticity.[218] DYT1 patient-

derived fibroblasts demonstrated upregulation of Activating Transcription Factor 4 (ATF4) in response to attenuation of the ER stressor thapsigargin, suggesting eIF2α pathway signalling is impaired.[219] Dysregulation of the eIF2α stress response and increased cell susceptibility to ER stress in the lymphoblasts of patients harbouring *PRKRA* mutations (DYT16) further supports the involvement of eIF2α signalling as a disease mechanism.[220] Other studies have used fibroblasts obtained from patients with *TOR1A* mutations (DYT1) to generate iPSCs, and found elevation of Lipin, an enzyme controlled by torsinA. Suppression of Lipin resulted in fewer abnormal movements further confirming its involvement in dystonia.[221]

1.16 Treatment

The management of the motor symptoms of dystonia is complex, with multiple factors needing to be taken into consideration to optimise therapy, for example anatomic distribution, patient's age and the potential for adverse effects. Three main treatments are often used: oral medical therapy, botulinum toxin injections and surgical therapies, in particular deep brain stimulation. Other interventions include physical therapies and psychological approaches to manage both motor and non-motor symptoms.

1.16.1 Physical Therapies

Physical therapies predominantly focus on controlling posture and muscle contractions, using modalities such as biofeedback training, mobilisation techniques and motor learning exercises to help activate 'anti-dystonic' muscles. Although these interventions are rarely used as an alternative therapy for dystonias, there is growing evidence of their potential benefits.[222]

Physiotherapy

Few studies have investigated the efficacy of physiotherapy and active exercise as a self-management approach, with those identified to date predominantly involving cervical dystonia. Programmes have demonstrated limited improvements to motor symptom severity, although quality of life increased in 83% of patients.[223,224] These findings potentially indicate that modification of negative body image and functional disability may have a large impact on improving quality of life. However, evidence

of long-term efficacy is lacking, and their high intensity and frequency make these programs difficult to implement in daily practice.[225]

Occupational therapy

Best studied in focal hand dystonia, constraint-induced therapy attempts to reverse the cortical fusion by immobilising one or several digits with the dystonic finger is required to carry out repetitive exercises in co-ordination with the remaining digits.[226] Several studies have shown mild therapeutic effects,[227,228] with long lasting improvements.[229] Combined with BoNT injections, occupational therapy (OT, specific finger movements in the direction opposite to the dystonic movement) resulted in a significant improvement in functional hand movements (Writer's Cramp Impairment Scale), however, scores on the Writer's cramp Disability Scale (WCDS) and patient-rated subjective scores were not significantly different.[230] Observed benefits have been attributed to cortical reorganisation, but the mechanisms are poorly understood.

1.16.2 Medical Therapies

1.16.2.1 Oral Therapies

Oral medications are predominantly recommended for segmental and generalised dystonia, and to complement botulinum toxin (BoNT) in focal dystonia, although are often limited by their side effects.

Levodopa

Augmentation of dopamine transmission has shown substantial and sustained improvements in a small subset of dystonia, dopa-responsive dystonia (DRD).[231] It is therefore recommended that low therapeutic doses of carbidopa/levodopa (300 mg per day) are trialled in all cases of early-onset dystonia due to phenotypic variability.

Trihexyphenidyl

An anti-cholinergic agent considered as a first-line treatment for the management of generalised dystonia, although placebo-controlled and randomised trials-based evidence is limited. Therapeutic dose varies, but usually begins at 1mg daily. Higher doses can cause drowsiness, confusion, and hallucinations, in addition to more

common adverse effects such as blurred vision and dry mouth. Compared to BoNT therapy, trihexyphenidyl is less effective in the treatment of cervical dystonia.[232]

Benzodiazepines

Muscle relaxants, such as diazepam and clonazepam, are often used in combination with anti-cholinergic agents, however there are no guided recommendations or large randomised controlled data for this indication. Responses vary, although they are especially useful for those with focal dystonia and Myoclonus Dystonia.[233,234] Side effects include sedation, depression, and behavioural disinhibition. Zolpidem, an agent with affinity for a benzodiazepine subtype receptor has shown comparable response rates to trihexyphenidyl amongst generalised dystonia, Meige's syndrome, blepharospasm and focal hand dystonia.[235]

Tetrabenazine

Tetrabenazine functions as a monoamine-depleting agent and has been trialled successfully in cohorts with cranio-cervical dystonia, in particular those with tardive dystonia.[236] Dose-dependent side effects such as depression, sedation, insomnia and parkinsonism have limited its use.

Baclofen

Primarily used to treat spasticity, this muscle relaxant has shown beneficial effects intrathecally and orally, particularly in patients with early-onset *DYT1* mutations[237] and secondary dystonia associated with spasticity or pain.[238–240] Less effective than anti-cholinergic agents, baclofen often causes sedation, dizziness, and impaired concentration.

1.16.2.2 Botulinum Toxin

Botulinum neurotoxin A and B (BoNT) injections into the dystonic muscles, temporarily inhibit acetylcholine release, reducing localised muscle contraction.[241] They are almost exclusively the treatment of choice among focal dystonias including cervical, blepharospasm, oromandibular, laryngeal, limb dystonia and task-specific dystonia.[242] Clinical effects typically appear within 2 – 3 days, with maximal effects reached two weeks after injection, and lasting on average around 12 weeks.[243] While

most patients continue to have long-term benefits after repeated treatment cycles, some become unresponsive, often resulting in discontinuation.[244] Transient adverse effects include excess muscle weakening, which can result in dysphagia in those receiving cervical injections.

1.16.3 Non-invasive brain stimulation (NBIS)

These neuromodulatory techniques induce plastic changes in specific cortical-subcortical networks. Their non-invasive application over selected regions avoids some of the complications associated with brain surgery and adverse effects of oral medication, although they can cause discomfort and may induce seizures.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has shown some promising results as a therapeutic tool for dystonia. Studies of those with DYT1 dystonia, primary segmental dystonia and focal dystonia have shown TMS to result in inhibition of the premotor cortex and anterior cingulate cortex leading to widespread reduction of cortical excitability and improved motor symptoms.[245–250]

Transcranial direct current stimulation (tDCS)

Utilisation of tDCS over the premotor-motor areas of the cerebral cortex among patients with focal hand dystonia transiently improves motor performances and subjective perception of pain.[251,252] Stimulation of the cerebellum has shown conflicting results, one study found improved dystonic symptoms and quality of life,[253] while a second reported no change in clinical symptoms.[254] Only two case reports have sought to determine the therapeutic effects in cervical dystonia, stimulation over both the C4 of the cerebellum and M1 resulted in significant clinical improvements, as well as pain reduction.[255,256]

1.16.4 Surgical interventions

Peripheral Denervation

Peripheral denervation has now been largely surpassed by deep brain stimulation (DBS), but is occasionally used in the treatment of cervical dystonia.[257] Often performed in patients unresponsive to Botulinum toxin, overall improvement is

reported in about two-thirds of cases, with the rate of symptom recurrence ~4.2%.[258,259] Reported post-operative complications include recurrences and/or changes in the pattern of dystonia, likely due to the relatively high rates of re-innervation, accompanied by pain and dysphagia.[259,260]

Lesional surgery

Stereotactic lesioning was initially favoured at the start of the 20th century because of its efficacy in alleviating symptoms in movement disorders. Bilateral stereotactic lesions to the thalamus (thalamotomy) were the most common, although pallidotomy also provided symptomatic relief in generalised dystonia.[261–264] Associated complications include dysarthria, facial weakness, gait imbalance and dysphagia, although these seem to be less prominent than with thalamotomies. The success of pallidotomies to alleviate dystonia in Parkinson's disease (PD), highlighted the internal globus pallidus (GPi) as a potential target for DBS. There has been a resurgence in thalamotomy surgery in recent years with several studies demonstrating long-term remission in focal hand dystonia.[265–267]

Deep Brain Stimulation

DBS is an established treatment for use in Parkinson's disease, essential tremor and dystonia. GPi is considered the optimal target, with beneficial effects shown in patients with *DYT1* mutations, myoclonus dystonia, and segmental and cranio-cervical dystonia.[268–274] Long-term efficacy has been noted in isolated dystonias,[275] with up to ten years sustained benefit in those with *DYT1* mutations.[276] In contrast, the efficacy of GPi-DBS in acquired dystonia is conflicting, suggesting that the location of the brain lesion should be taken into consideration. Those who are younger at the time of surgery (<21 years old), have shorter disease duration (<15 years), lack fixed skeletal deformities or cervical myelopathy are likely to have better post-operative outcomes.[277–279] The most frequent adverse effect of pallidal neurostimulation in those with cervical dystonia is dysarthria. Alternative DBS targets such as the STN are increasingly being suggested due to their lower risk of stimulation-induced parkinsonism.[280]

1.17 Non-motor symptoms

Non-motor symptoms (NMS) are recognised as an important feature in many movement disorders, with many studies now having demonstrated their presence across a range of dystonic disorders.[281–286] However, for the most part they are under reported, under recognised and an unmet need in clinical care. The most common NMS are discussed below, NMS in cervical dystonia will be discussed in more detail in Section 1.9.4. Figures 1.5 and 1.6 show the underlying pathophysiology of dystonia and potential mechanisms of non-motor symptoms.

1.17.1 Psychiatric disorders

Mood disorders

Depression and anxiety are the most recognised non-motor symptoms of dystonia, with prevalence rates varying dependent on the form of dystonia, but it is estimated up to 71% of patients with focal or generalised dystonia experience depression or anxiety in their lifetime.[287] Frequent co-existence of depression and anxiety is well-established in distinct types of primary dystonia, with an excess having been demonstrated in focal dystonia, segmental and generalised dystonia, Myoclonus Dystonia and Paroxysmal Kinesigenic Dyskinesia.[281,282,288–294]

Whether depression and anxiety is due to primary or secondary manifestations of dystonia remains unclear, some studies suggest they are secondary to the combination of motor symptoms and pain as some studies have indicated an improvement to mood when the motor symptoms are successfully treated.[295,296] In contrast, asymptomatic and symptomatic carriers of the *DYT1* mutation have an increased risk of early-onset and recurrent depression in comparison to controls, suggesting that symptoms in this setting are independent of motor symptom severity.[297] Although prone to recall bias, mood disorders are often reported prior to onset of dystonia, corroborating an underlying pathological predisposition.[298–300]

Phobias

High rates of phobias have been noted in primary focal dystonia, in particular social phobia and agoraphobia are four times more likely to affect cervical dystonia cohorts with up to 53% meeting diagnostic criteria,[290,301] although more recent studies have

not found an association between social phobia and cervical dystonia.[286,302] Interestingly, in a large cohort of individuals diagnosed with primary dystonia, all psychiatric symptoms were reported to have begun prior to onset of the motor symptoms, with the exception of social phobia.[303] Development of social phobia may be because of negatively perceived stigma, resulting in avoidance of social situations. In a large multicentre cohort of *SGCE* mutation-positive Myoclonus Dystonia patients, social and specific phobias were one of the most prevalent psychiatric disorders.[293]

Obsessive-compulsive disorder

Frequently reported in patients with Myoclonus Dystonia,[285,304] obsessive-compulsive disorder (OCD) is thought to be a *SGCE* mutation-specific manifestation.[293,305,306] Limited evidence also suggests that OCD may be present at higher rates amongst those with focal dystonias compared to matched controls[288,298,307–309] and the rates observed in the general population,[310] with up to 19.7% meeting diagnostic criteria.[311] In contrast, the frequency of OCD in patients with generalised dystonia was comparable to that of healthy controls.[282]

Alcohol dependence

Given alcohol ingestion can ameliorate dystonic movements, it is not unexpected that alcohol dependence is commonly reported, in particular amongst *SGCE* mutation carriers with Myoclonus Dystonia.[293,305,306,312] Albeit to a lesser extent, substance abuse has also been reported in cohorts of generalised dystonia and cervical dystonia.[299,313,314]

1.17.2 Cognition

Overall, there is conflicting evidence of altered cognitive function in primary dystonia. Several studies have confirmed various cognitive deficits in patients with cranio-cervical dystonia, blepharospasm and generalised dystonia,[315–317] with these including attention-executive deficits[318,319] and cognitive flexibility,[320] while others have found comparable cognitive function to age-matched controls.[321] A recent review concluded cognition remains largely intact with some deficits in executive function in patients with idiopathic and DYT1 dystonia.[322] In DYT11 Myoclonus

Dystonia, mild cognitive abnormalities were found in gene carriers,[323] namely deficits in executive function.[324] In contrast, a single cohort of DYT1 carriers showed no cognitive deficits relative to controls.[325]

1.17.3 Pain

Typically present at the site of the dystonic movement, pain is often reported in those with cervical dystonia, affecting ~2/3rds of cases.[326,327] Patients with other forms of dystonia such as blepharospasm and segmental lower limb dystonia also report pain, although not as extensively.[328,329] Recent evidence suggests that pain is not exclusively driven by excessive muscle contractions with individuals diagnosed with cervical dystonia lacking reduction of perceived pain intensity, as well as related nociceptive evoked potentials in comparison to patients with blepharospasm and controls,[146] suggesting that pain may in part be due to changes to nociceptive processing.

1.17.4 Sleep

Disturbances to sleep have been reported in 40 to 70% of primary dystonia cohorts, associated with restless leg syndrome (RLS), insomnia and depressive symptoms, although daytime sleepiness is comparable to controls.[286,330–333] Often inconclusive when using polysomnography (PSG) to determine sleep architecture, several studies have reported few or no sleep disturbances in those with focal cranio-cervical dystonia. However, three of these studies found a marked decrease in frequency and duration, but not disappearance of dystonic muscle activity,[334–336] while the fourth showed activity over affected cervical muscles significantly decreased to values lower than controls during non-rapid eye movement (NREM) and rapid eye movement (REM) sleep.[337] Other PSG based studies have found sleep fragmentation caused by spontaneous arousal and increased REM sleep latency in those with *GCH1* mutation-positive dopa-responsive dystonia.[338] PSG investigation of primary and secondary torsion dystonia (TD) reported an increased number of sleep spindles in four of the cases compared to control populations.[339]

1.17.5 Sensory abnormalities

Somatosensory temporal and spatial discrimination thresholds are often prolonged in adult-onset primary dystonia and can be altered in both affected and unaffected dystonic regions. Diminished capabilities have been shown in patients with focal hand dystonia,[340,341] blepharospasm,[342] cervical dystonia,[144,343] generalised dystonia[344] and torsion dystonia[345] in comparison to controls. Sensory abnormalities have also been demonstrated amongst *DYT1* manifesting and non-manifesting patients, and unaffected familial relatives of dystonia cohorts in comparison to controls, providing evidence of a genetic susceptibility.[346–348] Injections of BoNT failed to improve temporal discrimination, further supporting primary phenotypic involvement.[349]

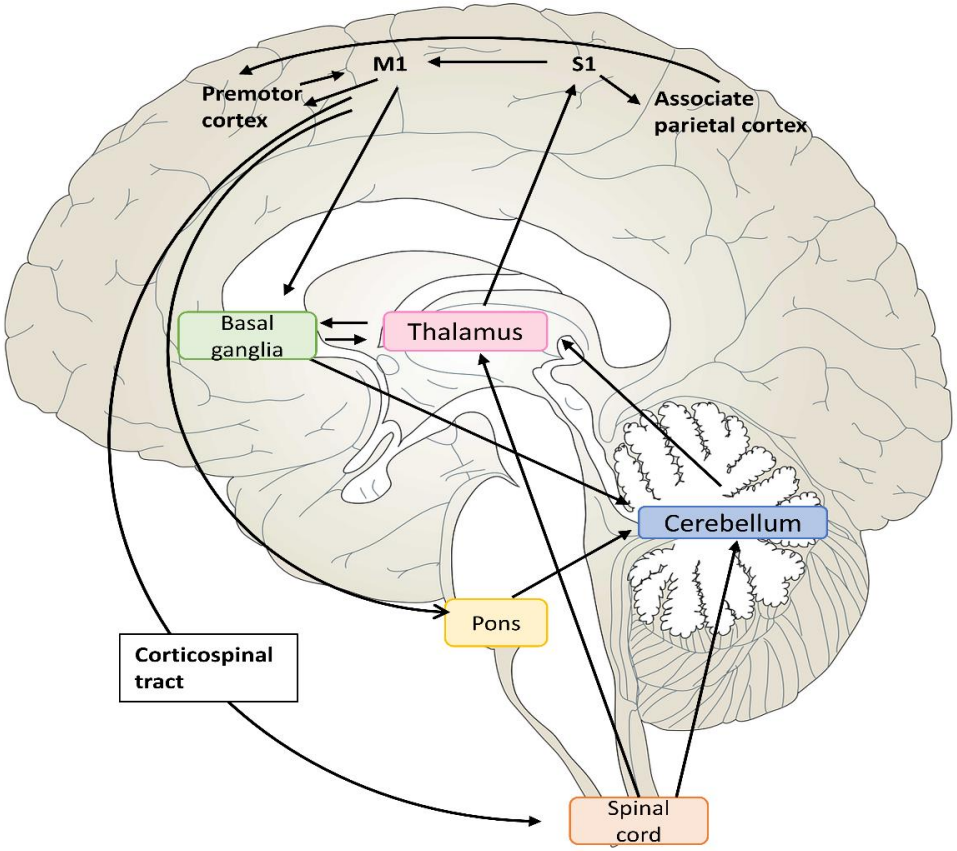

Figure 1.5 Normal pathways between the basal ganglia, thalamus, cortical areas and cerebellum

Dystonia is believed to be caused by abnormalities from any of the above connected network

M1: primary motor cortex, S1, primary somatosensory cortex

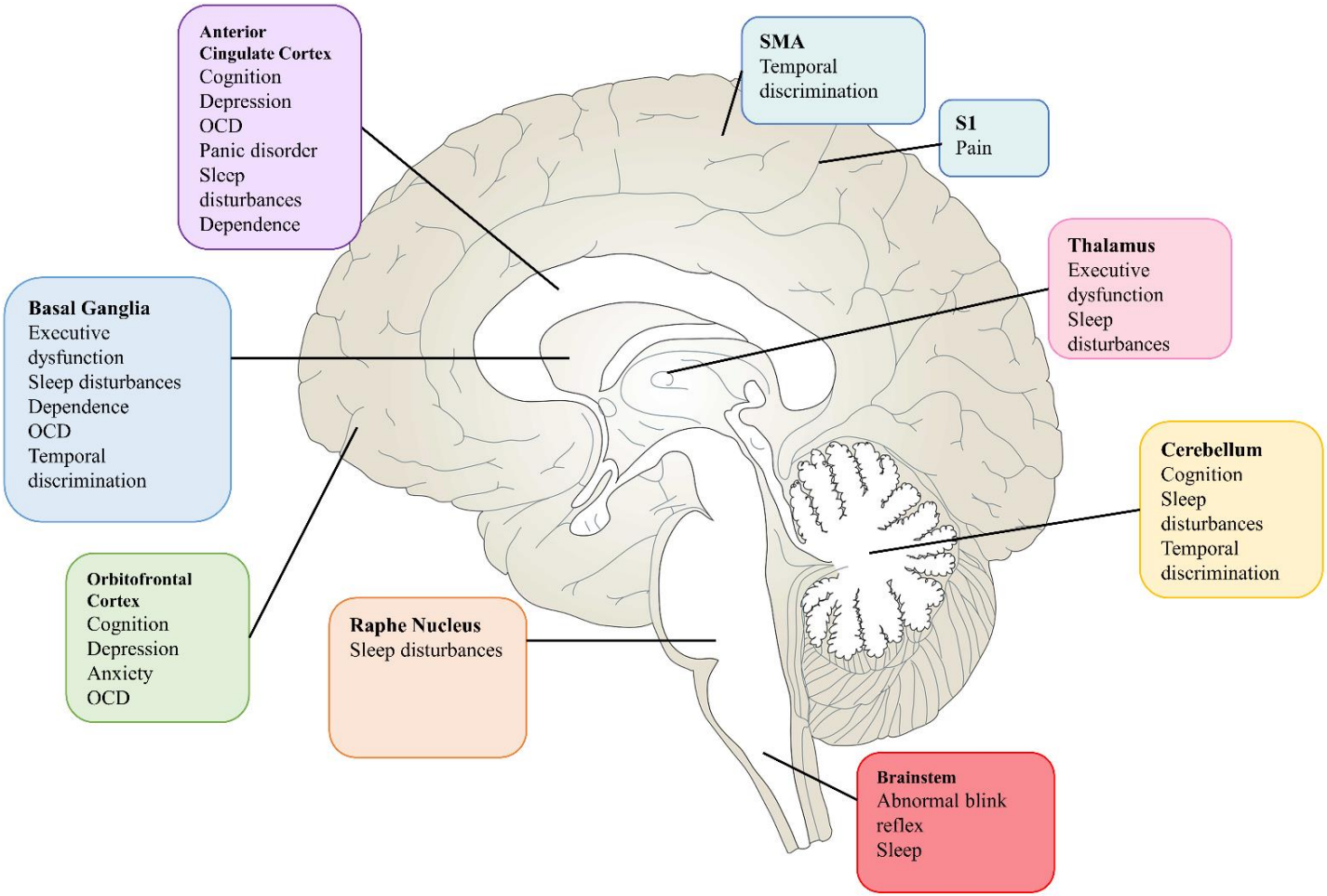

Figure 1.6 Neuroanatomical areas thought to underpin non-motor symptoms in dystonia

Abbreviations: OCD: Obsessive-compulsive disorder, S1: Primary somatosensory cortex, SMA: Supplementary motor area

1.17.6 Relationship between motor and non-motor symptom severity in dystonia

Depression and anxiety, with the exception of one study,[350] does not contribute to the severity of dystonia.[297,351] In keeping with this, depression does not improve following BoNT therapy.[352] Further, a longitudinal study showed that psychiatric abnormalities are relatively stable over the course of five years, in spite of changes in motor scores.[353]

Cognitive deficits are thought to occur due to the distracting effects of motor symptoms, with some supporting evidence showing the severity of Myoclonus Dystonia to correlate with executive function, and BoNT therapy restoring attentional deficits to control values amongst cranial dystonia patients.[316,324] However, there are some inconsistencies, larger case studies have shown that cognitive function is independent of motor symptom severity in patients with blepharospasm, cervical dystonia and generalised dystonia.[317,319] Importantly, those with co-morbid anxiety and depression perform worse on working memory and executive functioning tasks, suggesting that cognitive profile may reflect mood.

A potential hypothesis for observed sleep disturbance is the increased energy demands from muscle activity causing fatigue. Studies relating to PSG and BoNT treatment have been conflicting, two studies found no improvement to reported sleep disturbance in those with cervical dystonia,[332,333] while early polysomnographic studies found impaired sleep efficiency and reduced REM sleep inversely correlated with disease severity.[336] As with cognition, sleep disturbances are highly associated with psychiatric comorbidity, making determination of whether these form primary or reactive components of the disorders difficult to determine.

The relationship between pain and disease severity is more complex, although pain correlated with perceived severity of cervical dystonia, it is unclear as to whether pain is a result of increased severity or if it contributes to perceived severity.[354] Overall, this evidence suggests that non-motor symptoms belong to the clinical spectrum of dystonia, in particular mood related disorders.

Quality of life

Although traditionally defined by motor manifestations, there is growing interest in the impact that non-motor symptoms have on patients' lives, with evidence suggesting a detrimental impact on disability and health-related quality of life (QoL). Previous research has demonstrated reductions in numerous aspects of QoL, particularly physical and social functioning among focal, segmental and generalised dystonia patients in comparison to age-matched controls.[355] Mood disorders, sleep impairment, pain and poor body concept are all established determinants of QoL. Some studies have shown neuropsychiatric disorders to be the most important predictors, while others suggest sleep disorders and impairments are more commonly associated.[283,356]

In a recent study, use of effective sensory tricks in cervical dystonia patients was associated with a higher sleep-related QoL, highlighting its importance.[357] Therapeutic interventions such as BoNT or pallidal DBS have a beneficial effect on QoL, with significant improvements in physical function, social functioning, pain and mental health domains reported.[358,359] The impact of non-motor symptoms on QoL emphasises the importance of their clinical identification and treatment.

Treatment of non-motor symptoms

Pharmacotherapy should be considered cautiously as some anti-depressants can exacerbate and induce acute dystonia, these adverse effects having been observed with mirtazapine (α_2-adrenergic antagonist) and selective serotonin re-uptake inhibitors (SSRI) such as citalopram and sertraline.[360–362] To date, there are limited trials of oral medications used in the management of non-motor symptoms in dystonia, with a recent random control trial (RCT) investigating the use of escitalopram (SSRI) compared to placebo in the management of cervical dystonia motor symptoms, with no improvement demonstrated to either motor or psychiatric symptoms.[363]

Many of the treatments typically used to manage motor symptoms have also shown varying therapeutic effects on non-motor symptoms. BoNT treatment effectively relieves pain associated with cervical dystonia, with up to 90% of patients reporting

improvements.[364] Interestingly, in spite of improved motor symptoms, BoNT did not improve sleep quality in cervical dystonia cohorts.[332] GPi-DBS also provides moderate to marked improvement to pain, between 48% to 75%, showing gradual improvements 12-64 months post-surgery.[271,365–368] However, a single RCT reported no reduction in pain compared to the sham-stimulation group at 3-months follow-up, although after six months of non-blinded GPi stimulation, pain showed significant improvements.[368] Evidence of the therapeutic effects on mood disorders are conflicting, some demonstrate substantial improvements in patients with primary dystonia,[270,279] while others report poor response to stimulation.[275]

An alternative approach is the use of psychological based therapies. Cognitive behavioural therapy (CBT) takes a problem-focused approach to address maladaptive behaviours, thoughts, and emotions. A single pilot study to date has demonstrated the success of CBT in patients with focal dystonia, improving patient depression, anxiety and quality of life.[369] Another form of psychotherapy is mindfulness-based cognitive therapy (MBCT), unlike CBT it encourages participants to observe their thoughts, without challenging or changing them. A programme combining CBT and mindfulness-based principles has demonstrated substantial success, with improvements in mood, pain and dystonia-severity scores at 12-weeks.[370]

1.17.7 Pathological implications

The studies discussed above provide further evidence for the notion that non-motor symptoms may result from a shared neurobiology in primary dystonia. However, co-existence of several non-motor manifestations are often observed, making it difficult to attribute symptoms exclusively to underlying neuropathological changes. Many of these brain networks are interconnected, with the central node likely to be represented by the basal ganglia.

The high prevalence of OCD in focal dystonia and Myoclonus Dystonia potentially reflects a shared dysfunction in basal ganglia-thalamic-cortico-basal neuronal network. Functional imaging studies provide clear support for abnormalities of the orbitofronto-striatal regions in OCD.[371,372] These networks are also implicated in

dystonia, with mouse models expressing decreased *Sgce* showing long-term depression at the corito-striatal synapses.[127] Further, imaging studies performed in idiopathic dystonia and symptomatic *SGCE* positive mutation share similar results, with abnormalities identified in the thalamus, putamen, prefrontal cortex, parietal cortical areas, premotor and somatosensory cortex.[373–375]

The REM phase of sleep appears to be a key period of disruption in dystonia, in particular cervical dystonia. The activated state of REM is promoted by the cholinergic system alone, with the pedunculopontine and laterodorsal tegmental nuclei being key. Cholinergic abnormalities have been noted, with post-mortem analysis of brain tissue from those diagnosed with cervical dystonia and *DYT1* cohorts showing marked reduction of cholinergic neurons in the pedunculopontine nucleus.[197,376]

Several studies have established a strong link between dopaminergic abnormalities and primary dystonia with SPECT imaging identifying marked reduction of striatal dopamine transporter (DAT) and D2/D3 receptor in cervical dystonia cohorts with depression compared to those without depression, and anxiety and depression symptoms inversely correlated with DAT availability in the left putamen.[377,378] Amongst the same cohort, serotonin transporter (SERT) binding in the midbrain positively correlated with dystonic jerks, trending towards reduced binding in patients with co-morbid depression.[379] Ligand-binding studies have also shown that CD patients have higher SERT binding in the dorsal raphe nucleus, with a positive correlation between motor symptoms, pain, and sleep disturbances.

1.18 Adult-onset idiopathic, isolated focal cervical dystonia

1.18.1 Clinical Features

Cervical dystonia, more recently classified as adult-onset idiopathic, isolated focal cervical dystonia (AOIFCD), is characterised by contractions of both agonist and antagonist cervical muscles, resulting in abnormal movements and/or postural changes of the head, neck and shoulders. Deviation of head and neck postures are described as torticollis (neck rotation), anterocollis (head-forward flexion or pulled forward), retrocollis (head-posterior extension or pulled backward), or laterocollis

(head tilt or lateral flexion) and may occur separately or in combination (Figure 1.7).[380]

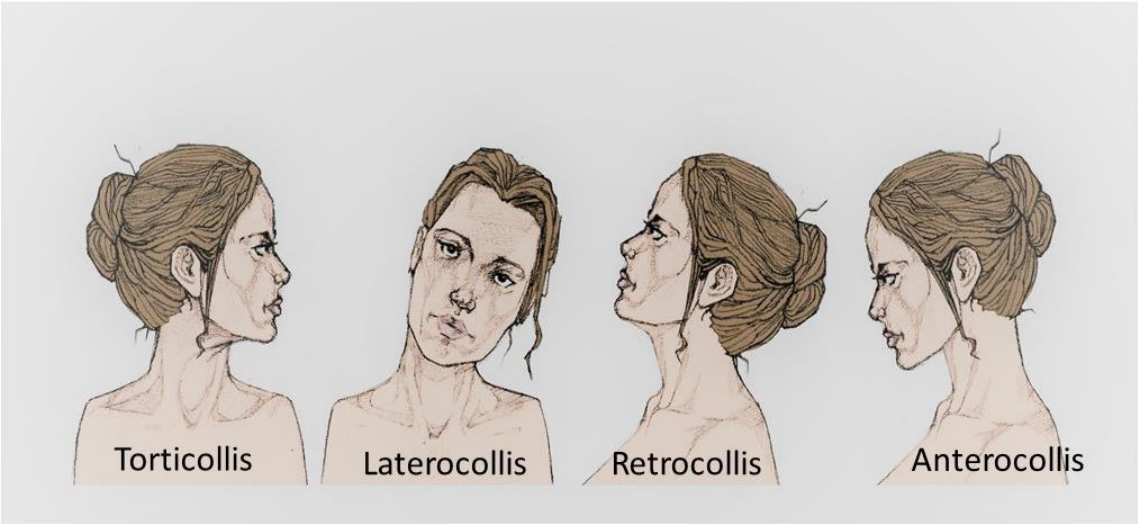

Figure 1.7 Classification of cervical dystonia head positions

(A) Torticollis: horizontal turning of the head (chin-to-shoulder) **(B)** Laterocollis: tilting of the head from side to side (ear-to-shoulder) **(C)** Retrocollis: extension of the neck (head tilting backwards) **(D)** Anterocollis: flexion of the neck (head tilting forwards)

Symptoms manifest gradually, presenting with initial pulling or stiffness in the neck or involuntary twisting or jerking of the head.[380] Intensity tends to worsen over the initial five years but then appears to stabilise,[381] although development of less common symptoms such as jerky head tremors may occur.[382] The distribution of affected body parts may also change over time, most commonly spreading to the upper extremities, head and larynx,[383] with symptom development typically occurring after the age of 50.[384]

Sensory tricks or '*geste antagoniste'*, a hallmark feature of cervical dystonia, are manoeuvres reported by ~80% of patients, and used to alleviate dystonic movements and postures.[385] Gently touching the chin, back or top of the head can diminish symptoms, although benefits are usually transient.[386] The pathophysiology of this phenomenon remains elusive, although recent imaging studies suggest sensory tricks are associated with modulation of functional connectivity within the sensorimotor network which results in improved posture.[387] Interestingly, the presence of a sensory trick is considered a positive predictive factor for responsiveness to

botulinum toxin treatment and contributes to improved quality of life.[357,388] Other mitigating factors include relaxation, lying supine and sleep, while exacerbators consist of stress and self-consciousness (>80% of patients), walking, fatigue and carrying (>70%).[389]

1.18.2 Epidemiology

Prevalence and ethnicity

The prevalence of AOIFCD remains poorly understood with estimates ranging between 28-183 cases per million people,[390] with an epidemiological study across eight European countries suggesting a more moderate rate of 57 per million.[2] It is believed that these values are largely underestimated, as with most dystonic disorders, on account of poor recognition, misdiagnosis and failure to seek medical attention. Prevalence differs among ethnic groups, with incidences significantly greater in Caucasians,[391] particularly those of European descent.[392]

Age and gender

Mean age of onset is 41 years,[393] with cases often manifesting between the fourth and sixth decade of life.[390] Several studies have reported similar age of onset for both sexes,[394] while others, in spite of female preponderance, note earlier dystonia onset in males.[395,396] Females are affected twice as often as males (2:1),[397] potentially owing to higher awareness of symptoms among women, genetic susceptibility and increased exposure to environmental factors.[144]

1.18.3 Aetiology

Environmental influences

Exposure to certain environmental factors can have detrimental effects in patients with a genetic predisposition, however their risk remains largely unknown. Of the few controlled studies available, some have found no evidence to support that prior head trauma is a risk factor,[398] while the majority of literature supports significant associations between surgery, head trauma and CD. Increased pain, depression and frequency of laterocollis have been reported in CD patients with preceding head trauma, compared to those without trauma, in spite of most trauma events being reported several years before AOIFCD onset.[399–401] High frequencies of idiopathic

scoliosis have also been noted in those with CD compared to other outpatient controls, suggesting prior scoliosis may increase the risk of developing CD.[402]

Genetics

AOIFCD is thought to have a significant heritable component, with ~15% of CD cases reporting a positive family history, while co-existent tremor increases this to 50%.[403,404] A recent genome-wide association study (GWAS) found that multiple risk alleles were significantly associated with CD, including *DENND1A*, a nucleotide exchange factor that is expressed in the brain and plays a role in vesicle function, and a second low-frequency variant associated with lower age at onset located within the *GABBR2* gene.[405] This gene encodes a subunit of GABA-B receptors, important for neuronal excitability. Variants in *CIZ1, ANO3, GNAL* and *THAP1* genes have all been identified in those diagnosed with AOIFCD, although genetic testing in the majority remains negative for known Mendelian causes of dystonia to date.

1.18.4 Pathophysiology of motor symptoms

While the mechanisms for cervical dystonia are still debated, abnormalities in the basal ganglia, cerebellum and thalamus are often implicated. Traditionally regarded as a basal ganglia disorder, it is now thought of as a network disorder due to the involvement of the cerebellum and somatosensory cortex. Animal models, imaging and neurophysiological studies provide supporting evidence suggesting alterations of cerebellar activity, connectivity and structure, as well as anatomical defects in the midbrain, brainstem and spinal cord.[101,135,186,406] The proposed mechanisms underlying cervical dystonia are shown in Figure 1.8.

A more recent hypothesis suggests that dysfunction of the basal ganglia and cerebellum arises due to impairments in a midbrain region called head neural integrator (hNI), a circuit that converts pulse activity to steady-state neural firing i.e. signals related to head movement in the former, and signals related to steady head position in the latter.[407] The hNI connects to the substantia nigra, and cerebellum, and receives feedback from the cerebellum, basal ganglia and proprioception which improves the accuracy of the hNI.[408] It is therefore possible that abnormal head

postures may originate due to impaired neural integration from the basal ganglia, cerebellum and proprioception at the hNI. Support for this theory has been demonstrated in the macaque, inactivation of the hNI produced a bi-hemispheric imbalance which resulted in head drifts towards eccentric head orientations similar to dystonic movements.[409] Individuals with CD also present with head-on-trunk orientation dependent drift velocity providing further support a role for this model.[410]

Several studies suggest abnormally enhanced brainstem excitability that presents as an abnormal response to auditory startle reflex,[411] altered blink reflex recovery and masseter muscle reflexes,[412–414] abnormal trigemino-cervical reflex,[415–417] which may contribute to cervical muscle contraction. Other abnormalities in the sensorimotor system are also present in patients with CD, with evidence suggesting that abnormal integration of sensory information is associated with dystonic symptoms. As mentioned in Section 1.195, evidence of this can be seen in the form of increased spatial and temporal somatosensory discrimination.[418]

Deficient inhibition across several levels of the central nervous system including the cortex, basal ganglia, brainstem and spinal cord is thought to reflect dysfunctional GABAergic mechanisms, resulting in excessive movements seen in CD.[143,419] In support of this, reduced GABA availability has been noted within the cerebellum, with an inverse relationship with dystonia severity.[420] Two imaging studies found those with abnormal temporal and visuospatial discrimination threshold values demonstrated altered resting state connectivity in the cerebellar network and decreased cerebellar connectivity with bilateral basal ganglia structures and the dorsolateral prefrontal cortex.[101,421] Cerebellar inhibition has also been found to be absent after repetitive TMS stimulation, suggesting disruption to normal cerebellar plasticity in those with CD.[135]

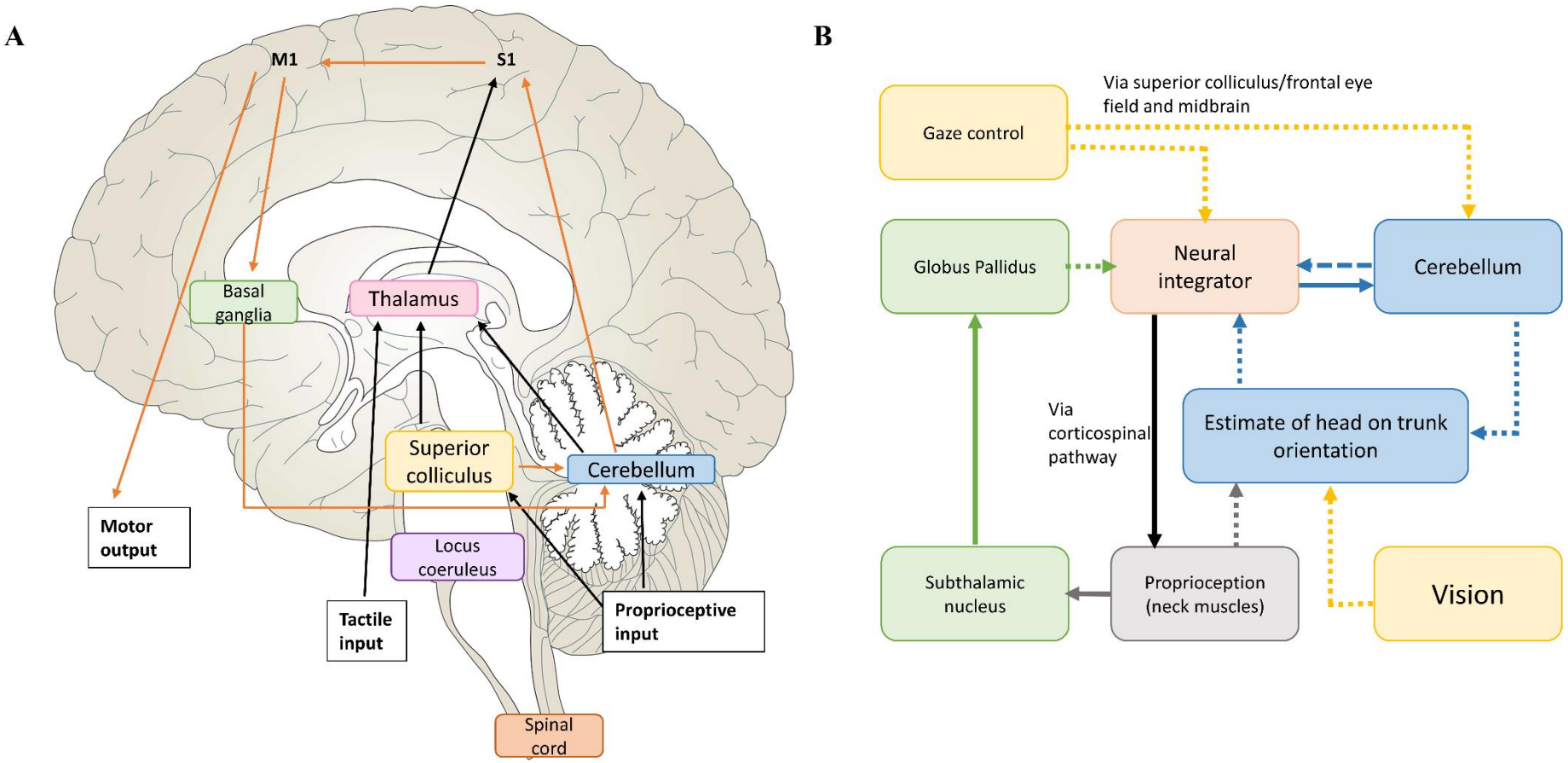

Figure 1.8 Proposed mechanisms of cervical dystonia

A: Orange arrows depict potential impaired pathways in cervical dystonia **B:** Depicts proposed feedback systems, solid arrows show excitatory input, dashed arrows show inhibitory input and dotted arrows depict unconfirmed inputs

1.18.5 Non-motor Symptoms

Elevated rates of non-motor symptoms are consistently reported in those with AOIFCD, with 95% of patients reporting at least one non-motor symptom,[283] and at least 62.5% reporting five.[422] Reported symptoms typically include pain, sleep disturbances (including fatigue) and psychiatric disorders, all negatively impacting quality of life.

Psychiatric disorders

Patients with AOIFCD have an increased risk of psychiatric symptoms, with up to 91% of patients meeting the criteria for a current or lifetime diagnosis of depression, anxiety, social phobia, and to a lesser extent OCD. These disorders often manifest prior to the motor symptoms and do not improve in response to BoNT, suggesting that they may form a primary component of the disorder phenotype. Interestingly, an earlier onset of motor symptoms is often observed in those where mood disorders develop prior motor symptoms.[423] A summary of findings in large case-series and case control studies (Table 1.4) on psychiatric disorders in AOIFCD patients are shown below.

Cognition

Several studies have reported mild cognitive dysfunction including deficits of executive dysfunction, working memory, verbal fluency, cognitive flexibility and theory of mind amongst patients with CD compared to controls.[424,425] In contrast, some have reported comparable executive function, verbal memory and spatial memory functioning between cohorts,[426,427] with confounding factors such as education level, age and medication potentially contributing to these differences, as well as co-morbid mood disorders. Interestingly, by contrast, severe anxiety and depression were associated with improved social perception, likely due to self-adaptation of social skills.[428] Below, Table 1.5 summarises cognitive function amongst CD patients in large case-series and case control studies.

Pain

Pain affects up to 89% of patients with AOIFCD at some point during the disorder.[354] Typically experienced in the head, neck and arm ipsilateral to head

rotation, pain intensity usually varies and can radiate to the upper back and limbs.[429] In general, it is thought that pain reflects altered processing of nociceptive stimuli, rather than originating from muscle activity. CD patients show reduced pain-pressure thresholds and lack physiological reduction in perceived pain intensity, although BoNT treatment is beneficial for pain management.[146,364,430] These findings are described below in large case-series and case-control studies (Table 1.6).

Sleep

There are relatively fewer studies which evaluate sleep disorders in CD, with these predominantly involving use of questionnaires and commonly reporting insomnia, fatigue, poor sleep quality and RLS.[333,431] Three PSG studies have been performed to date, with evidence of increased sleep latency, decreased sleep efficiency, reduced REM sleep, and decreased cervical muscle activity predominantly during NREM sleep compared to controls.[335,337,432] Studies in relation to sleep are shown below in Table 1.7.

Sensory Abnormalities

Temporal discrimination thresholds (TDT) have been proposed as an endophenotype of CD, with abnormalities shown in up to 97% of patients in dystonic and non-dystonic body regions.[433,434] TDT also appears to be heritable with up to 50% penetrance in unaffected first-degree relatives of patients with sporadic cervical dystonia.[144] In spite of improvements in dystonic movements, GPi-DBS does not correct for abnormalities in sensory processing,[435] with a recent study also demonstrating that somatosensory TDT is unrelated to disease severity.[436] Cervical dystonia cohorts also present with deficits in mental rotation and biased spatial attention, although findings here are often contradictory and may reflect cognitive impairment.[424,437–439] Evidence of sensory abnormalities in case-control studies are reported in Table 1.8.

Quality of Life

AOIFCD has a marked impact on QoL, compared to controls several domains of QoL are impaired, including physical, social and emotional functioning.[422] Worsened QoL can be attributed to the non-motor symptoms discussed above, in particular, various studies have reported mood disorders, such as depression and anxiety, and

pain as the main predictors. The studies in Table 1.9 highlight worsened QoL in CD and the need for clinical awareness of non-motor symptoms.

Table 1.4 Studies investigating psychiatric disorders in patients diagnosed with AOIFCD

Author	Year	N	Assessment	Outcome
Large case-series (>5)				
Jahanshani and Marsden	1989	CD (61)	MMPI	Over half of cases (56.6%) had depression
Wenzel et al	1998	CD (44)	SCID-I (DSM-III)	At least one psychiatric disorder was fulfilled in 65.9% of patients. The most frequent were panic disorder (29.5%), depression (25%) and substance abuse (13.6%). OCD was less frequently diagnosed (6.8%). Recall of psychiatric symptoms preceded onset in 43.2% of dystonia symptoms
Müller et al	2002	CD (131)	BDI, SF-36, Tsui scale	47% of patients with CD had depression. Neck pain was positively correlated with BDI total score
Moraru et al	2002	CD (40)	SCID (DSM-III-R), SCL-90, BDI	Anxiety and depression symptoms were present before or during dystonia. Over half of patients (55%) fulfilled lifetime and current diagnoses of at least one psychiatric disorder
Lewis et al	2008	CD (124)	Body Concept Scale, FDQ, Rosenberg's Self-Esteem Scale, BDI, SF-36, EQ-5D	Patients with cervical dystonia reported higher rates of depression than those with spasmodic dysphonia or hemifacial spasm. Self-esteem, body concept and QoL contributed to self-reported depression
Duane and Bakken	2011	CD (108)	MMPI	Half of patients had evidence of depression, 32% anxiety and 32 obsessiveness
Klingelhoefer et al	2014	CD (102)	NMSQuest	30% of patients self-reported feeling sad or depressed
Berardelli et al	2015	CD (23)	SCID-I, TWSTRS	There were no differences in psychiatric disorders on two occasions (five years apart; 65% and 64%), while dystonia severity improved
Tomic et al	2016	CD (19)	BDI, BAI, SF-36, CDQ-24, TWSTRS,	Depression was present in 42.1% of CD patients, and anxiety, mostly moderate, was present in more than half (57.9%). Disability correlated with depression and anxiety, as well as pain
Wagle Shukla et al	2016	CD (39)	FSS, MFI, ESS, PDSS, SF-36, BDI	All CD patients met criteria for diagnosis of depression, 94% had mild depression, the remaining patients had severe depression
Berman et al	2017	CD (255)	BDI, HAM-D, HAM-A, LSAS	Comparison across dystonia cohorts found that cervical dystonia patients were more likely to have greater anxiety than those with limb dystonia, and the highest reported pain. Body pain correlated with worsening severity of psychiatric symptoms
Hentschel et al	2017	CD (85)	BDI	Symptoms of depression were identified in 30% of cases
Mahajan et al	2018	CD (208)	Clinical Interview, HADS, SFHS, CDIP-58, BDI, PHQ9, LSAS, TWSTRS, GDRST	23% (11) CD patients were identified with substance abuse. Those experiencing abuse were more likely to be male, score worse on depression and anxiety scales, and have worse motor severity
Ortiz et al	2019	CD (937)	ICD-10 codes to identify comorbidities	The most prominent comorbidities included depression (14%), anxiety (7%), and back pain (11%)

Supnet et al	2020	CD (149)	BDI, BAI, BFM, Tsui TWSTRS	Of the 50 cases who completed the BAI; 16% had mild anxiety and 16% had moderate anxiety.86% had minimal depression, 6% with mild depression, 6% had moderate depression and 2% had severe depression
Ndukwe et al	2020	CD (193)	BAI, BDI, TWSTRS	41% of females had a history of mood disorders and 26% had onset of mood disorder prior to the development of dystonia, while 32% of males reported history and 17% prior to onset of dystonia. Females with a history of mood disorders had a significantly earlier age at onset of dystonia when compared to females without mood disorders
Han et al	2020	CD (102)	BDI-II, BAI, SAS, DNMSQuest. TWSTRS, CGI-S	Anxiety was present in 65.5% of case. depression in 47.1% and apathy in 30.4%.
Ragee et al	2021	CD (88)	BAI, BDI, DNMSQuest, HADS, TWSTRS	70% of women and 52% of men met the criteria for mood disorders on at least one of the assessment tools
Case-control studies				
van Hoof et al	1987	CD (17) HC unspecified	Psychometric assessment	Two of 17 patients had depression, but there was no difference in personality characteristics (neuroticism) compared to controls
Jahanshahi et al	1988	CD (100) Controls with cervical spondylosis (49)	Torticollis questionnaires (socio-demographic information, course, onset, treatment etc.), EPQ, STAS, LOI-TS, BDI	In cervical dystonia patients, 29.4% were severely depressed, and obsessional trait scale scores were elevated, falling within the range for obsessional patients. There were no differences in anxiety or obsessive symptoms between groups
Jahanshahi et al	1988	CD (85) Controls with cervical spondylosis (49)	BDI, Hopelessness Scale, Torticollis Questionnaire	CD patients had higher BDI scores than the cervical spondylosis group, although there were no differences in prevalence of psychiatric disorders or self-ratings of hopelessness
Bihari et al	1992	CD (22) HC age- and gender-matched (29)	Y-BOCS, SCL-90-R, BDI, MOCI	Patients had higher levels of obsessive-compulsive, depression and anxious symptoms compared to controls
Scheidt et al	1996	CD (266) HC (unspecified)	GSI, SCL-90-R, tsui scale	Depressive symptoms were reported in 23% of patients, and 57% of patients scored higher than the average psychiatric outpatient. More than 50% of patients reported that a stressful life event triggered their illness
Gündel et al	2001	CD (116) HC (483)	SCID-I (DSM-IV), Tsui score	56% of patients met the clinical criteria for current social phobia. Depressive coping behaviour was the only significant predictor of psychiatric comorbidity. Compared to a sample of the general population, social phobia prevalence was increased by a ten-fold
Morau et al	2002	CD (40)	SCID, BDI, SCL-90	In 22 dystonic patients (55%), criteria were reached for at least one psychiatric disorder. Most frequent diagnostic disorders were anxiety (40%) and depression (37.5%).
Gündel et al	2003	CD (48) HC with alopecia, age- and gender-matched	SCID-I (DMS-IV), FKV, SPS, SCL-90-R	A high prevalence of current and lifetime psychiatric comorbidity was found in patients with CD, these include anxiety and depressive disorders. Compared to the matched group, CD patients were at a 3.7 increased risk for comorbidity

Skogseid et al	2007	CD (70) HC (189)	HDS, BDI	Only 13 (19%) patients had a clinically significant depressive symptoms and 7 (10%) had anxiety symptoms
Slawek et al	2007	CD (101) HC age- and sex-matched (84)	MADRS, TWSTRS	Depression was observed in 47.5% of patients
Fabbrini et al	2010	CD (34) HC (62)	Y-BOCS, BDI, HAM-A, GAF	CD patients (26.4%) reached clinical diagnostic criteria for mood disorders compared to controls (6%) and scored higher on the BDI
Paus et al	2011	CD (111) HC age-matched (93)	PSQI, ESS, IRLSSG, BDI, TWSTRS	Depressive symptoms were significantly higher in CD than controls.
Yang et al	2016	CD (60) HC (60)	ESS, PSQI, HAM-A HAM-D, ACE-R, TWSTRS	17 and 12 patients reached diagnostic criteria for anxiety and depression, respectively. Mean scores were significantly higher than controls
Smit et al	2016	CD (50) HC age- and sex-matched (50)	MINI-PLUS, BAI, BDI, Y-BOCS, CGI-S, TWSTRS	Higher prevalence of psychiatric disorders were identified, including depression (54% vs 28%) and anxiety (42% vs 8%). Patients scored significantly higher on Y-BOCS compared to controls, however all scores except one were within the subclinical range
Smit et al	2017	CD (44) HC (43)	FSS, ESS, PSQI, BAI, BDI, RAND-36, TWSTRS, CGI-S	Patients scored significantly worse on the depression and anxiety rating scale
Zoon et al	2018	CD (14) HC age- and sex-matched (14)	BDI, BAI, TWSTRS, CGI-S	Compared to controls, depressive and anxiety symptoms were higher than controls
Novaretti et al	2019	CD (28) HC age-, gender- and education-matched (80)	PSQI, ESS, BDI, BAI, Social Phobia Inventory, Brief Pain Scale, Apathy Scale, WHOQoL-BREF, Tsui Rating Scale	Compared to controls, CD patients showed higher BAI scores and Apathy scale scores.
Ceylan et al	2019	CD (30) HC (30)	SF-36, CDQ-24, CDIP-58, HAS, HDS, BDI, STAI-I, STAI-II, TWSTRS	Eleven patients were diagnosed with depression and high levels of anxiety were found in twelve patients and two had mild anxiety. Compared to controls comorbid psychiatric disorders were elevated. There was a significant improvement in depression and anxiety after botulinum toxin therapy

Timmers et al	2019	CD (51) HC (53)	PSQI, ESS, FSS, Y-BOCS, BAI, BDI, MINI-Plus, RAND-36, CGI-S, TWSTRS	CD patients (65%) had significantly more psychiatric problems compared to controls (35%). Depression (31%) and agoraphobia (24%) were most common
Martino et al	2020	CD (1571)	Population-based study using registers	Individuals with CD had increased risk of depressive disorders. anxiety disorders, suicidal behaviour, schizophrenia and other psychotic disorders, bipolar disorder, substance use disorders and neurodevelopmental disorders compared to the general population
Costanzo et al	2021	CD (57) HC age- sex-matched (53)	SCID-I, SCID-II, HAM-A, HAM-D, IPDS, TWSTRS	39% of the dystonia cohort had the presence of a psychiatric disorder, with 11% having a histrionic personality disorder compared to 2% of controls

Abbreviations: ACE-R: Addenbrooke's Cognitive Examination Revised, BAI: Beck's Anxiety Inventory, BDI: Beck's Depression Inventory, BFM: Burke-Fahn-Marsden, CD: Cervical Dystonia, CDIP-58: CD Impact Profile-58, CDQ-24: Cranio-cervical Dystonia Questionnaire, CGI-S: Clinical Global Impression Scale, DSM: Diagnostic and Statistical Manual of Mental Disorders, EQ-5D: Euro Quality of Life 5 Dimension, EPQ: Eysenck Personality Questionnaire, ESS: Epworth Sleepiness Scale, FDQ: Functional Disability Questionnaire, FKV: Freiburg Questionnaire on Disease Processing, FSS: Fatigue Severity Scale, GAF: Global Assessment of Functioning, GDRST: Global Dystonia Rating Scale-Total, GSI: General Symptom Index, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HAS: Hospital Anxiety Scale, HDS: Hospital Depression Scale, IRLSSG: International Restless Legs Syndrome Study Group, LOI-TS: Leyton Obsessional Inventory-Trait Scale, LSAS: Liebowitz Social Anxiety Scale, MINI-Plus: Mini International Neuropsychiatric Interview-Plus, MFI: Multidimensional Fatigue Inventory, MMPI: Minnesota Multiphasic Personality Inventory, MOCI: Maudsley Obsessive Compulsive Inventory, PDSS: Parkinson's Sleep Scale, PHQ9: Patient Health Questionnaire-9, PSQI: Pittsburgh Quality Index, RAND-36: RAND-36 item Health Survey, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, SAS: Starkstein's Apthy Scale, SCID: Structured Clinical Interview for DSM disorders, SCL-90-R: Symptom Checklist-90-Revised, SF-36: Short Form Survey 36, SFHS: Short Form Health Survey, SPS: Social Phobia Scale, STAI-I/II: State-Trait Anxiety Inventory, STAS: Spielberger Trait Anxiety Scale, WHOQoL-BREF: World Health Organisation Quality of Life, Y-BOCS: Yale-Brown Obsessive Compulsive Scale

Table 1.5 Studies investigating cognition in patients diagnosed with AOIFCD

Author	Year	N	Assessment	Outcome
Large-case series				
Ellement et al	2020	CD (46)	WAIS-IV, WMS-IV, Empathy Quotient, Benton Facial Recognition Task, ToM, SNQ-22, HADS, LSAS TWSTRS	Patients social cognitive function was generally intact, 10 patients had impaired theory of mind, and 5 were impaired on the empathy quotient, worse performance was associated with co-morbid depression
Monaghan et al	2021	CD (46)	TOPF, WASI-II, WAIS-IV, D-KEFS, Purdue Pegboard, RCF, BNT, WMS-IV, RAVLT, FAB, RMET, QCAE, BAI, BDI, HADS, CDIP-58	Cases performed significantly worse than standardised norms on several measures of social cognition, naming they were impaired at recognising emotion. Subtle deficits in processing speed, memory and memory recall were also observed
Case-control studies				
Ploner et al	2005	CD (16) HC (16)	Spatial memory task	There was no evidence of spatial memory deficits
Yang et al	2016	CD (60) HC (60)	ESS, PSQI, HAM-A, HAM-D, ACE-R, TWSTRS	CD patients had significantly lower ACE-R scores (81.93) compared to controls (88.55), 15 patients had cognitive impairment (<75)
Czekóová et al	2017	CD (25) HC age-, gender- and education-matched (26)	Stroop test, TMT, Tower of London, lexical and semantic verbal fluency tasks, WAIS-R, WMS-III, FPRT, QCAE, DERS, MADRS, TWSTRS	Compared to controls, patients with CD performed worse in attention, set-shifting capacity, working memory, processing speed, planning, verbal memory, and verbal fluency. Theory of mind and socio-cognitive functions are also compromised patients
Maggi et al	2019	CD (26) HC; demographically-matched (30)	Modified Card Sorting Test,	On verbal memory and executive function tests patients performed comparable to controls, while CD patients performed worse on prospective memory tests (recognition and time-based tasks)
Conson et al	2020	CD (21) HC (21)	MoCA, letter rotation task, body rotation task	Findings demonstrated difficulty in mental rotation, implicating spatial processing dysfunction
Burke et al	2020	CD (46) HC age-, gender and education-matched (46)	pFSIQ, TOPF-UK, RAVLT, RCFT executive and cognitive composites, HADS, TWSTRS	Patients performed worse on encoding, recall and recognition aspects of memory, as well as social cognition
Feuerstein et al	2020	CD (26) HC age-, gender-, education- and income-matched (16)	MoCA, SNQ22, HADS	Patients with CD had lower social cognition compared to controls
Lagravinese et al	2020	CD with tremor (21) CD without tremor (14) HC age-matched (47)	MMSE, MoCA, clock-drawing task, Trial Making B task, verbal abstraction task, attention, concentration and working memory, ToM, EAT, TWSTRS	Both CD groups were significantly worse at recognising emotional feelings and inferring cognitive mental state. Patients with tremor were more impaired in the advanced test of ToM compared to those without tremor
Costanzo et al	2021	CD (57) HC age- and sex-matched (53)	MoCA, TMT, WMS, n-Back, TWSTRS	Similar performance was found between groups on the MoCA, however, cases scored worse on the TMT and n-Back compared to controls

Bastos et al	2021	CD (50) HC age-, sex- and education-matched (50)	MMSE, UFOV, TMT	No differences were seen between groups on the MMSE score, but patients performed worse on TMA. Patients also performed worse on visual processing speed, divided attention and selective attention
Platho-Elwischger et al	2021	CD (30) HC (33)	Verbal Analogies and nonverbal reasoning subtests of the Intelligence Structure Test 2000-R	There were no differences between groups on nonverbal and verbal reasoning. After botulinum toxin injection nonverbal reasoning scores slightly, with a greater improvement seen in verbal reasoning amongst dystonia patients
Baione et al	2021	CD (22) HC age- and sex-matched (19)	SCWT, MoCA,MMSE, TWSTRS	Individuals with dystonia performed worse than controls during the Stroop test, shown by lower number of correct responses and higher number of errors

Abbreviations: ACE-R: Addenbrooke's Cognitive Examination Revised, BAI: Beck's Anxiety Inventory, BAT: Block Assembly Test, BDI: Beck's Depression Inventory, BNT: Boston Naming Test, BVRT: Benton Visual Retention Test, CD: Cervical Dystonia, CDIP-58: Cervical Dystonia Impact Profile, DERS: Difficulties in Emotion Regulation Scale, D-KEFS: Delis-Kaplan Executive Function System, EAT: Emotion Attribution Task, ESS: Epworth Sleepiness Scale, EQ-5D-5L: EuroQoL Utility Values, FAB: Florida Effect Battery, FPRT: Faux Pas Recognition Test, HADS: Hospital Anxiety and Depression Scale, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HC: Healthy Control, LSAS: Liebowitz Social Anxiety Scale, MADRS: Montgomery–Åsberg Depression Rating Scale, MMSE: Mini-Mental State Examination, MoCa: Montreal Cognition Assessment, NART: National Adult Reading Test, pFSIQ: Predicted Premorbid Full Scale Intelligence, PSQI: Pittsburgh Sleep Quality Index, RCF: Rey Complex Figure, SCWT: Stroop Colour and Word Test, SNQ-22: Social Norms Questionnaire, TEA: Test of Everyday Attention, TMT: Trail Making Test, ToM; Theory of Mind, TOPF-UK: Test of Premorbid Function-UK Edition, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, QCAE: Questionnaire of Cognitive and Affective Empathy, RAVLT: Rey Auditory Verbal Learning Test, RCFT: Rey Complex Figure Test and Recognition, RMT: Recognition Memory Tests, UFOV: Useful Field of View Test, WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WCST: Wisconsin Card Sorting Test, WMS-III: Wechsler Memory Scale-III, WMS-IV: Wechsler Memory Scale-Fourth Edition

Table 1.6 Studies investigating pain in patients diagnosed with AOIFCD

Author	Year	N	Assessment	Outcome
Large-case series				
Chan et al	1991	CD (266)	Clinical information from the Dystonia Inventory Database	Pain occurred in 75% of patients and contributed to disability. It was strongly associated with constant head turning, presence of spasm and severity of head turning
Tarsy et al	1999	CD (35)	Pain questionnaire designed for retrospective assessment	32 (91%) of patients experienced pain, located most frequently in the neck (100%), shoulder (73.5%) and lower back (29.4%). Neck pain was ipsilateral (71.8%). The most common quality of pain was aching (43.8%), followed by pulling (34.3%). The majority of patients had pain more than 75% of the time pre-treatment
Hilker et al	2001	CD (25)	SF-36, EQ-5D, Tsui scale	Pain (SF-36) was significantly higher in CD patients indicating a higher disability. BoNT substantially relieved pain
Carmargo et al	2008	CD (45)	TWSTRS	Patients with CD complain of pain more often than other forms of dystonia. BoNT was beneficial for controlling pain, and was shown to significantly improve complaints of pain and intensity
Klingelhoefer et al	2014	CD (102)	NMSQuest	Nearly half of patients reported pain (43.1%)
Charles et al	2014	CD (1,037)	PNRS, CDIP-58, TWSTRS	Those with moderate/severe pain had higher dystonia severity and disability compared to those with mild pain. Pain was associated with a higher CDIP-58 score, components impacted include mood, annoyance, sleep, head and neck and upper limb activities, and walking and psychosocial functioning
Williams et al	2017	CD (410)	Medical records and patient history	Rates of pain are most prevalent among CD patients (54.6%), although it was not related to psychiatric comorbidity
Smit et al	2017	CD (40)	RAND-36, TWSTRS, CGI-S	Pain was present in 71.8% of patients
Marciniec et al	2020	CD (60)	TWSTRS	Two thirds of patients suffered from localised pain (66%). Risk of pain was increased by almost a 4-fold in the lateral torticollis phenotype compared to those without
Tinazzi et al	2020	CD; focal or segmental/multifocal (603)	Data retrieved from the Italian Dystonia Registry	Sensory tricks and lower education level were significant predictors of pain
Case-control studies				
Lobbezoo et al	1996	CD (9) HC age- and gender-matched (9)	Two nights of PSG, visual analogue scale of pain	Pain was reduced by ~50% during overnight sleep
Lobbezoo et al	1996	CD (9) HC age- and gender-matched (5)	Pain-pressure threshold assessed by spring-loaded, hand-held algometer	Average pain-pressure threshold was two times lower than controls, and at maximal voluntary contraction was two times higher than while at rest
Kutvonen et al	1997	CD (39) HC (18)	Pressure algometry and manual palpation	Two-thirds of patients reported continuous or intermittent pain. Pain was asymmetric and widespread over the neck and shoulders. There was no difference between groups w
Paus et al	2011	CD (111) HC age-matched (93)	PSQI, ESS, IRLSSG, BDI, TWSTRS	Pain was significantly more frequent in CD (87%) than controls. All patients attributed pain to dystonia. BoNT therapy relieved pain in 3/4 of CD patients
Tinazzi et al	2012	CD (20) HC (21)	Laser-evoked potentials	No difference in laser pain rating was found between groups

Smit et al	2016	CD (50) HC age- and sex-matched (50)	CGI-S, TWSTRS	Pain was associated with age, psychiatric co-morbidity, disability and dystonia motor severity
Morgante et al	2018	CD (10) HC age- and gender-matched (16)	Psychophysical testing of tactile and pain thresholds and pain tolerance using electrical pulses, HAM-A, HAM-D, BFMDRS, TWSTRS	Pain threshold and tolerance among CD cohort were reduced
Tinazzi et al	2019	CD (15) HC (15)	Conditioned pain modulation (painful condition stimulus and painful test stimulus)	Patients with CD lacked physiological reduction of perceived intensity of a painful test stimulus and related evoked potential, suggesting pain reflects dysfunction of the descending pain pathway

Abbreviations: BDI: Beck's Depression Inventory, BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale, BoNT: Botulinum Neurotoxin, CD: Cervical Dystonia, CDIP-58: Cervical Dystonia Impact Profile, CGI-S: Clinical Global Impression Scale jerks-tremor, ESS: Epworth Sleepiness Scale, EQ-5D: Euro Quality of Life 5 Dimension, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HC: Healthy Control, IRLSSG: International Restless Legs Syndrome Study Group, NMSQuest: Non-Motor Symptom Questionnaire, PNRS: Pain Numeric Rating Scale, PSG: Polysomnography, RAND-36: RAND-36 item Health Survey, SF-36: Short Form 36 Survey, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale,

Table 1.7 Studies investigating sleep in patients diagnosed with AOIFCD

Author	Year	N	Assessment	Outcome
Large-case series				
Klingelhoefer et al	2014	CD (102)	NMSQuest	60% of patients presented with insomnia of sleep onset and maintenance, 51% self-reported fatigue and 40% reported not feeling refreshed after an overnight sleep
Wagle Shukla et al	2016	CD (39)	FSS, MFI, ESS, PDSS, SF-36, BDI	Based on FSS scores, half of patients experienced moderate to severe fatigue. When using the MFI, patients scored worse on mental fatigue
Han et al	2020	CD (102)	PSQI, ESS, MFI, TWSTRS, CGI-S	Excessive daytime sleepiness was observed in 20.2% of cases and impaired sleep quality (PSQI) was shown in 67.3%. General fatigue was reported in 57.5% of patients
Case-control studies				
Trotti et al	2009	CD (43) Other focal dystonia, including hemifacial spasm, cranial dystonia, writer's cramp and facial tics (19) HC age- and gender-matched (49)	ESS, pain scores, TWSTRS	21% of cervical dystonia patients had an abnormal ESS scores compared to none of the control groups. Anticholinergic medication accounted for some increased excessive daytime sleepiness. No significant difference in mean ESS scores was found between CD and control groups
Avanzino et al	2010	CD (46) HC age- and gender-matched (56)	PSQI, ESS, BDI	Cervical dystonia patients had increased PSQI scores compared to controls, 72% were poor sleepers. Impaired sleep was not associated with disease duration when controlling for depression. Patients were not affected by daytime sleepiness
Paus et al	2011	CD (111) HC age-matched (93)	PSQI, ESS, IRLSSG, BDI, TWSTRS	Sleep quality was impaired in 45% of patients, 22% assumed these were due motor symptoms. 39% of patients had amelioration of sleep problems following BoNT. 20 patients reached the criteria for RLS, often occurring after dystonia onset. Sleep bruxism was common (28%)
Eichenseer et al	2014	CD (54) HC (55)	PSQI, ESS, TWSTRS, CDIP-58, BDI, HAM-A	PSQI scores were significantly higher in CD compared to controls. ESS had no significant difference between groups. BoNT did not improve sleep quality, in spite of dystonia severity improvement
Yang et al	2016	CD (60) HC (60)	ESS, PSQI, HAM-A, HAM-D, ACE-R, TWSTRS	Sleep quality was higher than controls, with 71.7% having poor sleep. When adjusted for depression and anxiety, the PSQI was no longer significantly different to controls. 12 CD patients had excessive daytime sleepiness but did not reach statistical significance.
Smit et al	2017	CD (44) HC (43)	FSS, ESS, PSQI, BAI, BDI, RAND-36, TWSTRS, CGI-S	Fatigue was significantly influence by anxiety, depression and pain. Excessive daytime sleepiness was also influenced by depression. Sleep quality (PSQI) was influenced by TWSTRS pain score
Zoon et al	2018	CD (14) HC age- and sex-matched (14)	PSQI, FSS, TWSTRS, CGI-S	Dystonia patients had significantly higher fatigue compared to controls. No significant difference was observed using the PSQI
Novaretti et al	2019	CD (28) HC age-, gender- and education-matched (80)	PSQI, ESS, BDI, BAI, Social Phobia Inventory, Brief Pain Scale, Apathy Scale, WHOQoL-BREF, Tsui Rating Scale	CD patients presented with higher PSQI scores compared to controls
Timmers et al	2019	CD (51) HC (53)	PSQI, ESS, FSS, Y-BOCS, BAI, BDI, MINI-Plus, RAND-36, CGI-S, TWSTRS	Sleep problems were significantly more common in CD, 61% vs 36% in controls. PSQI, FSS and ESS scores were all significantly higher in dystonia compared to controls

Lobbezoo et al	1996	CD (9) HC age- and gender-matched (9)	Two nights of PSG, visual analogue scale of pain	No PSG-derived sleep values significantly differed from controls, although there were significant differences in sleep latency among CD group. Cervical muscle activity was decreased when lying down and was gradually abolished during transitions from wakefulness to light NREM
Antelmi et al	2017	CD (20) HC age- and gender-matched (22)	Full night of vPSG, visual analogue scales of pain, PLMS, ESS, PSQI, BDI, TWSTRS	Patients showed higher self-reported complaints of impaired sleep (PSQI), these did not correlate with depression scores. vPSG showed decreased sleep efficiency and increased sleep latency compared to controls. Activity in cervical muscles disappeared during all sleep stages, reaching significance compared to controls
Costanzo et al	2021	CD (57) HC age- sex-matched (53)	PSQI, ESS, TWSTRS	Sleep disturbance was found in 47% of cases and 28% of controls, and excessive sleepiness was present in 21% of the former and 4% of the latter
Ray et al	2021	CD (50) HC (13)	v-PSG, MSQ, IRLSSG, ESS, PSQI, HAM-A, HAM-D, TWSTRS	Of the 13 patients who underwent PSG, REM sleep duration was significantly reduced in dystonia patients compared to controls. Cases also had decreased propensity for spindle generation and maintenance. Excessive daytime sleepiness was present in 20% of patients and poor sleep quality in 26%. 10% of patients also had RBD and 8% had RLS. Sleep impairment was related to depression, anxiety and poor self-esteem

Abbreviations: ACE-R: Addenbrooke's Cognitive Examination Revised, BoNT: Botulinum Neurotoxin, CD: Cervical Dystonia, CDIP-58: Cervical Dystonia Impact Profile, CGI-S: Clinical Global Impression Scale jerks-tremor, BAI: Beck's Anxiety Inventory, BDI: Beck's Depression Inventory, ESS: Epworth Sleepiness Scale, FSS: Fatigue Severity Scale, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HC: Healthy Control, IRLSSG: International Restless Legs Syndrome Study Group, MINI-Plus: Mini International Neuropsychiatric Interview-Plus, MFI: Multidimensional Fatigue Inventory, MSQ: Mayo sleep questionnaire, NMSQ: Non-Motor Symptoms Questionnaire, NREM: Non-Rapid Eye Movement Sleep, PDSS: Parkinson's Disease Sleep Scale, PLMS: Periodic Leg Movements during Sleep, PSG: Polysomnography, PSQI: Pittsburgh Sleep Quality Index, RAND-36: RAND-36 item Health Survey, RLS: Restless Leg Syndrome, SF-36: Short Form 36 Survey, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, vPSG: Video Polysomnography, WHOQoL-BREF: World Health Organisation Quality of Life, Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

Table 1.8 Case-control studies investigating sensory abnormalities in AOIFCD cohorts

Author	Year	N	Assessment	Outcome
Temporal Discrimination				
Molloy et al	2003	CD (10) HC age-matched (11)	SDT using the Grating Orientation Task	Spatial discrimination thresholds were increased in cervical dystonia compared to controls
Tinazzi et al	2004	CD (10) Cervical pain but no dystonia (5) HC (10)	TDT paradigm: tactile, visual, and visuo-tactile stimuli	Patients performed worse than controls in the tactile and combined tasks, visual tasks did not differ between groups
Walsh et al	2007	CD (20) HC (18)	SDT paradigm, TWSTRS	Baseline SDT scores were greater in CD patients than controls. Following BoNT, there was an improvement in SDT at one month
Bradley et al	2009	CD (20) Unaffected first-degree relatives (42) Unaffected second-degree relatives (32) HC (43)	TDT, VBM, fMRI	Nearly all CD patients (95%) had abnormal TDTs. Deficits in TDT was shown in unaffected relatives to patients with cervical dystonia in comparison to healthy controls. This was associated with increased putaminal volume
Scontrini et al	2011	CD (24) HC age-matched (16)	STDT paradigm (neck, hand and eye), TWSTRS	Temporal discrimination values were higher in all three bodies in CD patients compared to controls, BoNT treatment did not restore thresholds
Bradley et al	2012	CD (37) HC (51)	TDT paradigm: visual, tactile and mixed stimuli	Among CD patients, abnormal TDTs were found in 36 patients (97%) Compared to controls, mean TDT were slower in several subtypes of primary dystonia
Kägi et al	2013	CD (32) HC (unspecified)	TDT paradigm: visual, tactile and combined stimuli, TWSTRS	Patients with a sensory trick performed better in the crossmodal TDT task compared to patients with an absent effect of a sensory trick
Kimmich et al	2014	CD (84) Unaffected first-degree relatives (158) HC (192)	TDT paradigm during fMRI	Unaffected relatives of CD patients with abnormal TDTs had hypoactivation in the putamen
Antelmi et al	2017	CD (19) HC age- and gender-matched (19)	STDT using the ascending staircase method, SSEP, TWSTRS	Higher STDT values and reduced suppression of cortical and sub-cortical paired-pulse somatosensory evoked potentials were shown in patients compared to controls.
Sadnicka et al	2017	CD (22) HC age-matched (22)	TDT: temporal resolution paradigm, interval discrimination	Performance was delayed and more variable in the temporal resolution task in patients, while response times were comparable on discrimination thresholds

Kägi et al	2017	CD (45) Unaffected first-degree relative (14) HC (23)	TDT paradigm: visual, tactile and visuo-tactile stimuli, TMS, mental rotation	Five out of 14 non-affected relatives had abnormal TDT, however no difference between patients and controls were observed
Ganos et al	2017	CD (17) HC age-matched (19)	Somatosensory inhibition: grating orientation test, interdigital feedforward subliminal inhibition, somatosensory temporal inhibition: temporal discrimination threshold, feedforward subliminal inhibition, motor spatial inhibition: surround inhibition, motor temporal inhibition: short interval intracortical inhibition	A deficit in somatosensory spatial inhibition was observed in patients, who demonstrated increased threshold values
Chillemi et al	2017	CD (21) HC age-matched (22)	Recognition tasks (visuo-spatial, audio-spatial, visuo-temporal and audio-temporal)	Spatial processing alterations were associated impaired in laterocollis subgroups compared to controls, while temporal processing impairments were shown in torticollis subgroups
Conte et al	2017	CD (10) HC age-matched (30)	STDT: tactile stimuli	High STDT values remained unchanged over an eight-year follow-up, in spite of worsened severity
Erro et al	2018	CD (12) HC age-matched (12)	STDT paradigm	STDT was higher in all CD patients in comparison in controls, and impaired inhibition of the sensory and motor systems
Chen et al	2018	CD (18) HC age- and gender-matched (18)	STDT using a mismatch negativity paradigm: tactile stimuli	Dystonic patients showed deficits in pre-attentive somatosensory error detection compared to controls. Somatosensory MMN amplitude was smaller and correlated to sensory TDT
Junker et al	2019	CD (29) HC age- and gender-matched (29)	Blink reflex R2 recovery cycle and TDT paradigm (tactile, visual and visual-tactile stimuli)	Elevated tactile and visual-tactile TDTs were found in CD patients compared to controls, but no abnormalities of the blink recovery were demonstrated
Spatial Tasks				
Müller et al	2005	CD (28) HC age-matched (28)	"What's Straight Ahead?" task in the light and dark, BORB, VOSP, Tsui scale	Marked impairment in perception of egocentric space was observed in patients compared to controls
Filip et al	2017	CD (25) HC age- and gender-matched (25)	Visuospatial task requiring predictive motor timing, fMRI, TWSTRS	Patients performed worse on time estimation tasks (i.e. less successful at hitting the target) compared to controls. No difference between the groups were found on the visuomotor control task
Chillemi et al	2017	CD (23) HC age-, gender-, and education-matched (12)	Visuospatial task: line bisection task	Torticollois cohorts showed a significantly greater leftward deviation compared to controls

Bradnam et al	2019	CD (21) HC age- and gender-matched ()	Spatial neglect battery test: Line Bisection, Bells Cancellation, Landmark Task, Temporal Order Judgement, walking-based visual search task using eye tracking, CDQ	Spatial bias in CD patients was not found, although increased eye movements during the walking task compensate tor head rotations
Mental Rotation				
Leplow et al	1994	CD (18) HC (18)	Visuospatial tasks: perception of the subjective vertical, orientation and discrimination of left and right, Route Walking test, Body Placing Test, Ratcliff Figures, Benton's Line Orientation Task, Dot Localisation, Draw-A-Bicycle	CD patients performed poorly on orientation and showed errors on the subjective vertical task. Deficits were attributed to attention deficits
Hinse et al	1996	CD (15) HC age- and gender-matched (15)	Visuospatial testing: judgement of the visual vertical, Benton's line-orientation test, Route Walking test, personal-orientation test, Ratcliffe's mental re-orientation test, standardised road-map of direction sense, Hebb's recurring-digits test, Corsi's block tapping test, IQ	Performance on several visuospatial tasks, in particular those that require mental manipulation, were impaired in comparison to controls
Fiorio et al	2007	CD (12) HC age-matched (12)	Laterality judgements of body parts and objects	Reaction times were significantly slower when determining laterality of body parts in CD patients compared to controls, whereas accuracy and reaction times were similar to controls for laterality of objects
Conson et al	2020	CD (21) HC age-matched (21)	Letter rotation (spatial) and front-facing and back-facing human images (egocentric)	Selective impairment on letter rotation was reported in CD patients, while performance on laterality judgement of facing bodies was comparable to controls

Abbreviations: BoNT: Botulinum Neurotoxin, BORB; Birmingham Object Recognition Battery, CD; Cervical dystonia, CDQ: Cranio-cervical Dystonia Questionnaire, IQ: Intelligence quotient, fMRI: Functional Magnetic Resonance, HC; Healthy Control, MMN: Mismatch Negativity Paradigm, SDT: Spatial Discrimination Thresholds, SSEP: Somatosensory Evoked Potentials, STDT: Somatosensory Temporal Discrimination Threshold, TDT: Temporal Discrimination Task, TDMT: Temporal Discrimination Movement Threshold, TMS: Transcranial Magnetic Stimulation, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, VBM: Voxel-Based Morphometry, VOSP: Visual Object and Space Perception Batter

Table 1.9 Studies investigating quality of life in AOIFCD

Author	Year	N	Assessment	Outcome
Large-case series				
Hilker et al	2001	CD (25)	SF-36, EQ-5D, Tsui scale	In all eight domains of the SF-36 QoL, patients sored below the mean of an age-matched population. CD patients had significant levels of depression and negative body image
Ben-Shlomo et al	2002	CD (289)	SF-36	Physical and mental quality of life were predicted by several factors including self-esteem and self-deprecation, disease severity, stigma, anxiety, and depression
Camfield et al	2002	CD (289)	SF-36	Patients with cervical dystonia scored worse in all eight domains compared to published normative values. Scores for mental health and emotional role limitation were worse. Increasing age was associated with a decrease in physical QoL
Müller et al	2002	CD (131)	BDI, SF-36, Tsui scale	CD patients scored significantly worse in all eight domains of the SF-36 compared the general population. Neck pain was associated with lower scores in all SF-36 domains, Tsui score was negatively correlated with only one of the domains (role limitation: emotional)
Pekmezovic et al	2009	CD (91)	SF-36, HAM-A, HAM-D	Pain, anxiety, and depression were the most significant contributors to impaired QoL
Queiroz et al	2011	CD (77)	SF-36, TWSTRS	Severity of CD was related to worse QoL
Werle et al	2014	CD (70)	SF-36, CDQ-24, TWSTRS	Worse QoL was associated with greater disability, greater severity of CD, and increased pain. Important predictors of QoL were stigma, depression, pain and difficulties with activities of daily living
Wagle Shukla et al	2016	CD (39)	SF-36, FSS, MFI, ESS, PDSS, BDI	The mean score for patients was 60.9%, 54.6% were impaired on a physical component, while 43.6% had worse mental components of the scale
van den Dool et al	2016	CD (96)	SF-36, CDQ-24, FDQ, BAI, BDI, HAM-D, TWSTRS, Tsui scale	Psychiatric features had the strongest contribution to disability, followed by pain
Tomic et al	2016	CD (19)	BDI, BAI, SF-36, CDQ-24, TWSTRS,	Mild cervical dystonia had a negative impact on QoL. Physical, social and emotional aspects were most detrimentally affected. Stigma also influenced social and professional life. Depression was the main predictor of poor QoL
Smit et al	2017	CD (40)	RAND-36, TWSTRS, CGI-S	Loss of confidence was positively related to jerks-tremor
Benadof et al	2019	CD (188)	CDIP-58, TWSTRS	Patients who had a more effective sensory trick was associated with higher sleep-related quality of life

Supnet et al	2020	CD (149)	SF-36, BFM, Tsui TWSTRS	Physical functioning was the only SF-36 subscale associated with CD severity
Han et al	2020	CD (102)	SF-36, TWSTRS, CGI-S	Non-motor symptoms were linked to poor health related QoL, with excessive daytime sleepiness being the most common, followed by sleep, depression and fatigue
Case-control studies				
Skogseid et al	2007	CD (70) HC (189)	SF-36, GHQ-30, GSCL, HDS, BDI	The mean scores of SF-36 was lower in all domains in CD patients compared to the general population. Well-being and social function scales (GHQ-30) and the fatigue and musculoskeletal scales (GSCL) were also significantly worse. 13 patients with high depression scores scored lower on all domains of QoL (SF-36). Reduced QoL was associated with depressive symptoms and more severe disease
Slawek et al	2007	CD (101) HC age- and sex-matched (84)	SF-36, TWSTRS	In comparison to controls, CD patients had reduced functioning on all SF-36 domains, with women showing growing impairments. Following botulinum toxin injections, energy and vitality and pain subscores of the SF-36 improved
Smit et al	2016	CD (50) HC age- and sex-matched (50)	RAND-36, CGI-S, TWSTRS	All eight domains of the HR-QoL were significantly lower compared to controls. Psychiatric co-morbidities were the most important predictor of decreased HR-QoL
Smit et al	2017	CD (44) HC (43)	RAND-36, FSS, ESS, PSQI, BAI, BDI, TWSTRS, CGI-S	Patients had significantly worse QoL on 8 domains (except expected health change) compared to controls. Fatigue had a detrimental impact on physical functioning, mental health and pain. Excessive daytime sleepiness had a negative influence on mental health and vitality
Timmers et al	2019	CD (51) HC (53)	RAND-36, PSQI, ESS, FSS, Y-BOCS, BAI, BDI, MINI-Plus, CGI-S, TWSTRS	Fatigue was associated with a worse physical QoL, and depression and anxiety symptoms were associated with a lower mental QoL
Ceylan et al	2019	CD (30) HC (30)	SF-36, CDQ-24, CDIP-58, HAS, HDS, BDI, STAI-I, STAI-II, TWSTRS	The results in vitality, mental health and perception of general health were below normal values. Following botulinum toxin therapy, all scales and subscales used to assess the quality of life were significantly improved

Abbrevations: BAI: Beck's Anxiety Inventory, BDI: Beck's Depression Inventory, BoNT: Botulinum Neurotoxin, CD: Cervical Dystonia, CDIP-58: Cervical Dystonia Impact Profile, CDQ-24: Cranio-cervical dystonia questionnaire, CGI-S: Clinical Global Impression Scale jerks-tremor, DNMSQuest: Dystonia Non-Motor Symptoms Questionnaire, ESS: Epworth Sleepiness Scale, EQ-5D: Euro Quality of Life 5 Dimension, EQoLVAS: EQoL visual analogue score, FDQ: Functional Disability Questionnaire, FSS: Fatigue Severity Scale, GHQ-30: General Health Questionnaire-30, GSCL: Giessen Somatic Symptom Check List, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HAS: Hospital Anxiety Scale, HC: Healthy Control, HDS: Hospital Depression Scale, MINI-Plus: Mini International Neuropsychiatric Interview-Plus, MFI: Multidimensional Fatigue Inventory, NMSQ: Non-Motor Symptoms Questionnaire, PDSS: Parkinson's Disease Sleep Scale, PNRS: Pain Numeric Rating Scale, PSQI: Pittsburgh Sleep Quality Index, QoL: Quality of Life, RAND-36: RAND-36 item Health Survey, SAS: Starkstein's Apathy Scale, SF-36: Short Form 36 Survey, STAI-I/II: State-Trait Anxiety Inventory, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale, Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

1.18.6 Pathophysiology of non-motor symptoms

As discussed above, it has been suggested that cervical dystonia is a network disorder, involving the basal-ganglia-cerebello-thalamo-cortical circuit, with some small case-series identifying structural alterations in several regions including the caudate, putamen, corpus callosum, thalamus, basal ganglia, cerebellum and sensorimotor cortex amongst patients with AOIFCD.[165,440,441] Similarly, several neurotransmitters have been implicated in AOIFCD, these include GABA, acetylcholine (ACh) and the monoamines; dopamine (DA) and serotonin (5-HT). Alterations in their transmission and pathways are discussed below in the context of non-motor symptoms (Figure 1.9 and 1.10). Figure 1.10 only includes studies which investigate neurotransmitters in AOIFCD patients/models in direct relation to NMS.

Psychiatric disorders

Structural and functional abnormalities have been found within the subcortical limbic system, mainly the amygdala, hippocampus and dorsomedial thalamus in depression and anxiety. These regions can become hyperactive in depression, which implies a loss of inhibition may account for pathophysiological changes. Similarly, a loss of inhibitory function has been demonstrated in several cortical regions amongst cervical dystonia cohorts.[442]

Several lines of evidence suggest monoaminergic abnormalities, in particular disruption to striatal dopaminergic and serotonergic pathways may contribute to psychiatric symptoms in AOIFCD. Genomic analysis using polymerase chain reaction showed an association between AOIFCD and a polymorphism in the D5 receptor gene, which belong to a class of D1-like striatal receptors.[443] Protein analysis of striatal DAT, and D2 and D3 receptors showed reduced binding in the striatum of AOIFCD patients with depression compared to those without.[378] Finally, SPECT imaging of AOIFCD patients demonstrated reductions of dopaminergic striatal binding and SERT binding in the midbrain, with psychiatric symptoms trending towards being significantly different compared to those without.[182,379] Furthermore, serotonin modulates neuronal plasticity, which is known to be involved in dystonia pathophysiology.[444]

GABA is the major inhibitory neurotransmitter in the central nervous system which has been implicated in alcohol dependence and anxiety. $GABA_A$ receptors are important modulators of anxiety and stress, with widespread hippocampal receptor deficits reported in patients with anxiety disorder.[445] Several studies have also implicated an increased risk of alcohol dependence in polymorphic $GABA_A$ receptor subunit genes.[446] Amongst AOIFCD cohorts, PET tracers have identified a significant increase in $GABA_A$ receptor binding in the precentral gyrus and the parahippocampal gyrus compared to controls. In addition, $GABA_A$ availability within the cerebellum was inversely related to dystonia severity, while availability in the thalamus was inversely correlated with disease duration.[420] These findings indicate that hippocampal and cerebellar loss of inhibition due to GABAergic alterations could be causal in psychiatric disorders.

Cognition

Functional imaging has confirmed reduced connectivity within a network involving the prefrontal cortex, premotor cortex, superior parietal lobule and middle temporal gyrus, while increased connectivity was shown within the anterior cingulate cortex and parietal cortex in those with AOIFCD. These findings are consistent with cortical regions associated with cognitive function, and have the potential to explain impaired spatial cognition and deficits in motor planning within AOIFCD.[424,438] Interestingly, BoNT partially restored abnormal connectivity and increased activity within the sensorimotor and primary visual network towards comparable levels in controls.[447,448] Further, transient improvements in spatial acuity post-BoNT suggests deficits are secondary to disorganised neural networks.[449] However, these findings could also suggest that patients exert additional effort to suppress dystonic movements during cognitive performance and as a result, this may slow attentional demands.

Dopaminergic receptors are involved in several processes including cognition and learning, with receptors D1 and D2 having a prominent role. A single study assessing neurophysiological activity noted a decrease in striatal D2 long-term potentiation and long-term depression which was able to explain performance on reward-learning tasks, indicating that poor task performance was due to excessive striatal D2 receptor function.[450] Elevated striatal cholinergic dysfunction, essential in

motor learning, and D2 receptor excitation has been shown in *THAP1* dystonic mice models, although the relation between acetylcholine and learning has not been explicitly studied in humans.[209]

Robust evidence has shown that serotonin is associated with cognitive function, especially memory, learning and attentional processes. The majority of 5-HT_{1A} receptors are located in the limbic structures, in particular the hippocampus. Amongst AOIFCD cohorts, the use of imaging techniques such as VBM and ligand-binding imaging have noted hippocampal volumetric alterations and reduced SERT binding compared to controls, however cognitive function has yet to be investigated.[451,452] Collectively, this evidence suggests that altered output from the striatum to the prefrontal cortices and the hippocampus in those with cervical dystonia, may at least in part, contribute to cognitive deficits.

In contrast, others have suggested that normal performance on some cognitive tasks but worse performance on spatial manipulation tasks may relate to abnormal head postures rather than being of a cognitive nature.[322] In line with this, some AOIFCD patients show neglect-like patterns, and make more eye movements to compensate for their head position during spatial neglect tasks.[453]

Pain

Although still a matter of debate, pain was initially thought to originate from prolonged muscle contraction. More recent evidence suggests that abnormalities in transmission and processing of nociceptive stimuli are involved in pain development. A recent study found a novel association between sensory tricks and neck pain in AOIFCD patients, with evidence to suggest a common pathophysiological pathway, specifically the cerebellum.[387,454] Altered sensory input from the neck such as pain, is likely to cause neuroplastic changes in the cerebellum which may influence the expression of motor outputs.[455] Glutamate, a widespread excitatory neurotransmitter, is an important pain mediator, with receptors located within the cerebellum, hippocampus and the cerebral cortex. Although its specific role in relation to pain remains unclear, there is robust evidence which implicates cerebellar involvement during pain processing. Those treated with riluzole, an anti-glutamatergic agent

which also inhibits GABA reuptake, showed significant improvements in dystonia severity.[456]

The insular cortex has functional connectivity to the somatosensory cortex, and also plays a central role in pain perception.[457] Given that the insula is an integrator of sensory inputs, it is not unexpected that fMRI studies have shown impaired activity during sensorimotor activation amongst AOIFCD cohorts.[458] Although its exact role in cervical dystonia is not clear, increased activation of the insula following BoNT may reflect induced reorganisation which in turn, reduces pain.[448] In contrast, other studies have found laser evoked potentials originating in the insula are normal amongst this cohort, which suggests there is no overactivity of ascending nociceptive pathways.[459] Rather, a recent study demonstrated impairments in the descending inhibitory pain modulatory system in those with and without pain with evidence implicating that patients may be predisposed to pain.[146] This pathway involves processing of nociceptive information through brainstem structures such as the subnucleus reticularis dorsalis, ventromedial medulla and the periaqueductal gray matter, and projects to the pre-frontal and cingulate cortex, whereby nociceptive neurons are augmented by GABAergic neurons. Others have postulated that GABAergic output of the GPi may be reduced, resulting in pronounced inhibition of the thalamus, a central structure in the processing and relay of pain.[460] The role of GPi in pain has been highlighted through DBS, which has been shown to significantly improve pain and motor function.[275] Loss of inhibition in the basal ganglia and brainstem structures is likely to enhance pain-driven motor responses.

Sleep

A potential hypothesis for the sleep disturbance observed is ongoing increased muscle activity in those with AOIFCD. However, polysomnographic evidence has identified reduced abnormal muscle activity whilst lying down,[335] with a recent study finding decreased activity compared to controls.[337] Other non-motor symptoms such as pain and mood disorders are also thought to exacerbate sleep disturbances, although pain intensity and unpleasantness (visual analogue scales collected before and after sleep) decreased by 50% overnight[335] and poor sleep quality persists when controlling for anxiety and depression.[332] It is important to note that medications

frequently used to manage dystonia affect sleep architecture and can cause rebound insomnia, with these including benzodiazepines and anti-cholinergic drugs.

Consistency of disrupted sleep is likely caused by the underlying disease pathology of cervical dystonia. There is considerable overlap across the cortical structures and neurotransmitters involved in dystonia and sleep, with evidence for involvement of both the brainstem and basal ganglia in the promotion of sleep and the pathogenesis of cervical dystonia. In addition, a number of neurotransmitters are involved in the co-ordination of smooth movements and maintaining the sleep/wake cycle, including GABA, glutamate, acetylcholine and the monoamine neurotransmitters; DA and 5-HT. Newer models of the sleep/wake circuit recognise that fast-acting neurotransmitters glutamate and GABA are responsible for maintaining the sleep/wake circuit, while excitatory neurotransmitters have a modulatory role.[461]

Although its exact role within sleep is not clear, several lines of evidence implicate dysfunctional basal ganglia involvement: firstly, high innervation of the striatum from sleep-related regions such as the brainstem, thalamus and cerebral cortex; secondly, recordings of the striatal medium spiny neurons in mice and the STN in patients with PD exhibit increased activity during wake and REM sleep;[462,463] and thirdly, striatal and GPe lesions in mice produced substantial changes in sleep architecture, including pronounced insomnia and fragmented sleep and wakefulness.[464] Imaging studies have demonstrated increased GM in the GP and decreased fractional anisotropy in the pallidum, putamen and caudate amongst patients with cervical dystonia.[406,441] Further, the co-morbidity of RLS and AOIFCD has led to speculations of dopamine abnormalities in the basal ganglia as a central underlying pathophysiology,[333] whereby higher genetic risk because of dopaminergic abnormalities in the basal ganglia is a plausible explanation.

Abnormalities in serotonin have also been implicated in cervical dystonia, functional PET imaging has also shown a relationship between sleep disturbances and fatigue, and the medial raphe nucleus, caudate nucleus and hippocampus.[452] Immunocytochemical staining in AOIFCD patients has highlighted the loss of cholinergic neurons in the PPN, a structure involved in the generation of REM sleep.[197] PET tracers have been employed to characterise dysfunction to GABAergic

inhibition in AOIFCD patients and have shown a significant increase in $GABA_A$ levels in the thalamus and cerebellum, however, it remains unclear whether increased availability is to compensate for reduced GABAergic inputs or as a result of elevated glutamatergic innervations.[420]

Sensory Abnormalities

The basal ganglia, in particular, the putamen and caudate, as well as the superior colliculus and substantia nigra appear to be implicated in temporal processing. The superior colliculus (SC) is a midbrain structure involved in the integration of sensory information in order to localise attention and co-ordinate orienting movements, with projections to the dopaminergic cells of the SN pars compacta and thalamic neurons. These midbrain dopaminergic neurons are believed to initiate responses to salient events and modulate the SC. Animal models of cervical dystonia have identified modified activity of the superior colliculus,[465] similarly, an fMRI study in humans has shown reduced superior collicular activation in those with abnormal temporal discrimination.[466] Dysfunction of the putamen is also coherent with TDT abnormalities, with imaging studies showing reduced putaminal D2 receptors and putaminal activity during discrimination tasks amongst those with AOIFCD.[144,182,345]

Deficits in temporal discrimination and cervical dystonia may also reflect alterations in GABA transmission. GABAergic neurons project from the basal ganglia, to the caudate nucleus and the substantia nigra reticulata (SNr), which subsequently provide inhibitory innervation to the intermediate layers of the SC and thalamic nuclei. GABAergic mechanisms play an important role in sensory discrimination, while MRI studies have shown that discrimination thresholds are inversely related with sensorimotor GABA levels.[467] Previous studies have shown that injection of muscimol ($GABA_A$ agonist) into the SNr in non-human primate models evoked dystonic head tilts similar to cervical dystonia, with these movements attenuated with SC disinhibition.[465] Although there is no direct evidence, increased deficits in temporal discrimination amongst older females with AOIFCD reflects similar patterns of age-related decline in cerebral GABA levels of healthy participants.[419]

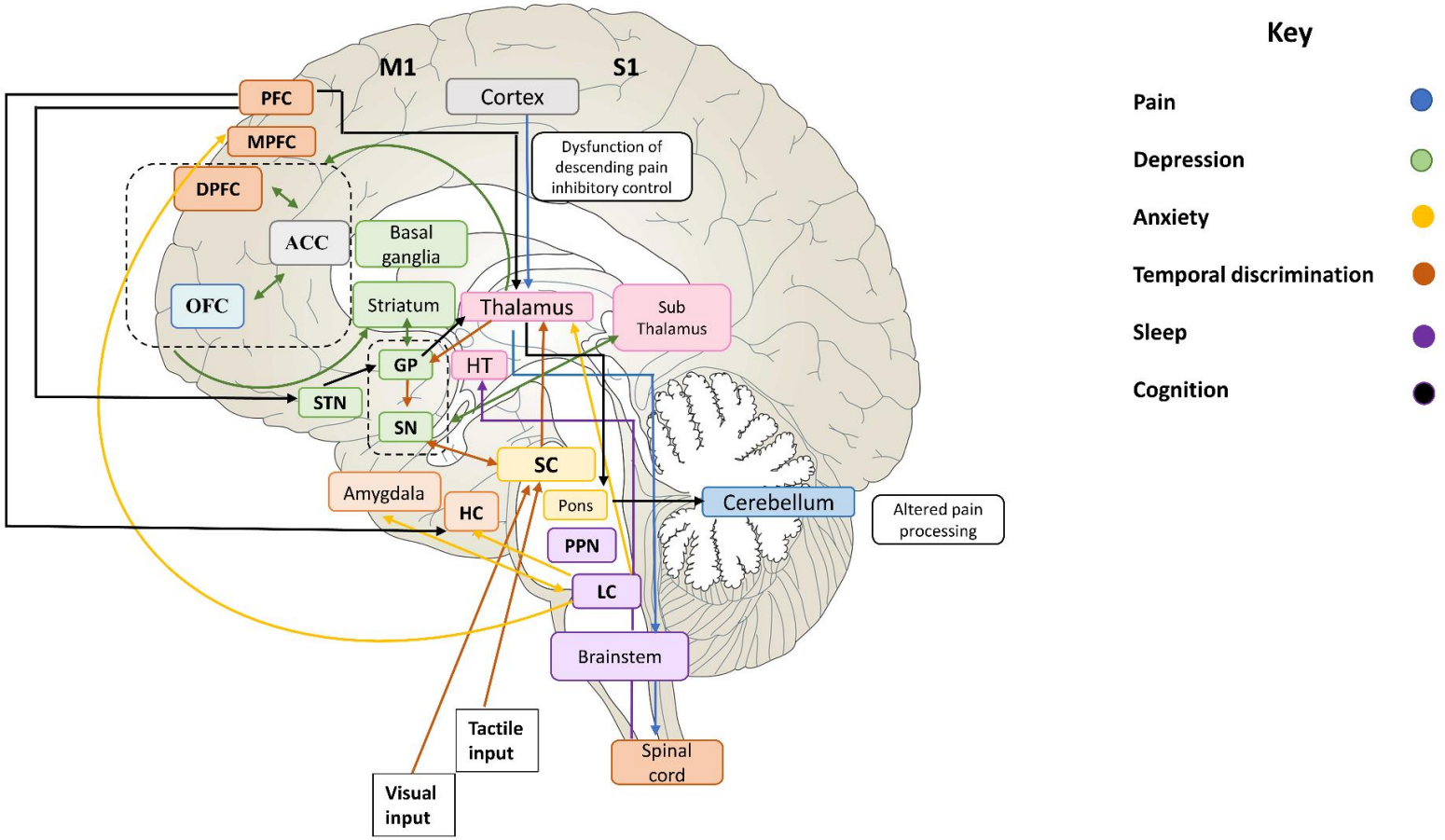

Figure 1.9 Mechanisms underpinning non-motor symptoms in cervical dystonia

Abbreviations: ACC: Anterior Cingulate Cortex, DPFC: Dorsolateral Prefrontal Cortex, GP: Globus Pallidus, HC: Hippocampus, LC: Locus Coeruleus, MPFC: Medial Prefrontal Cortex, OFC: Orbitofrontal Cortex, PPN: Pedunculopontine Nucleus, SC: Superior Colliculus, STN: Subthalamic Nucleus

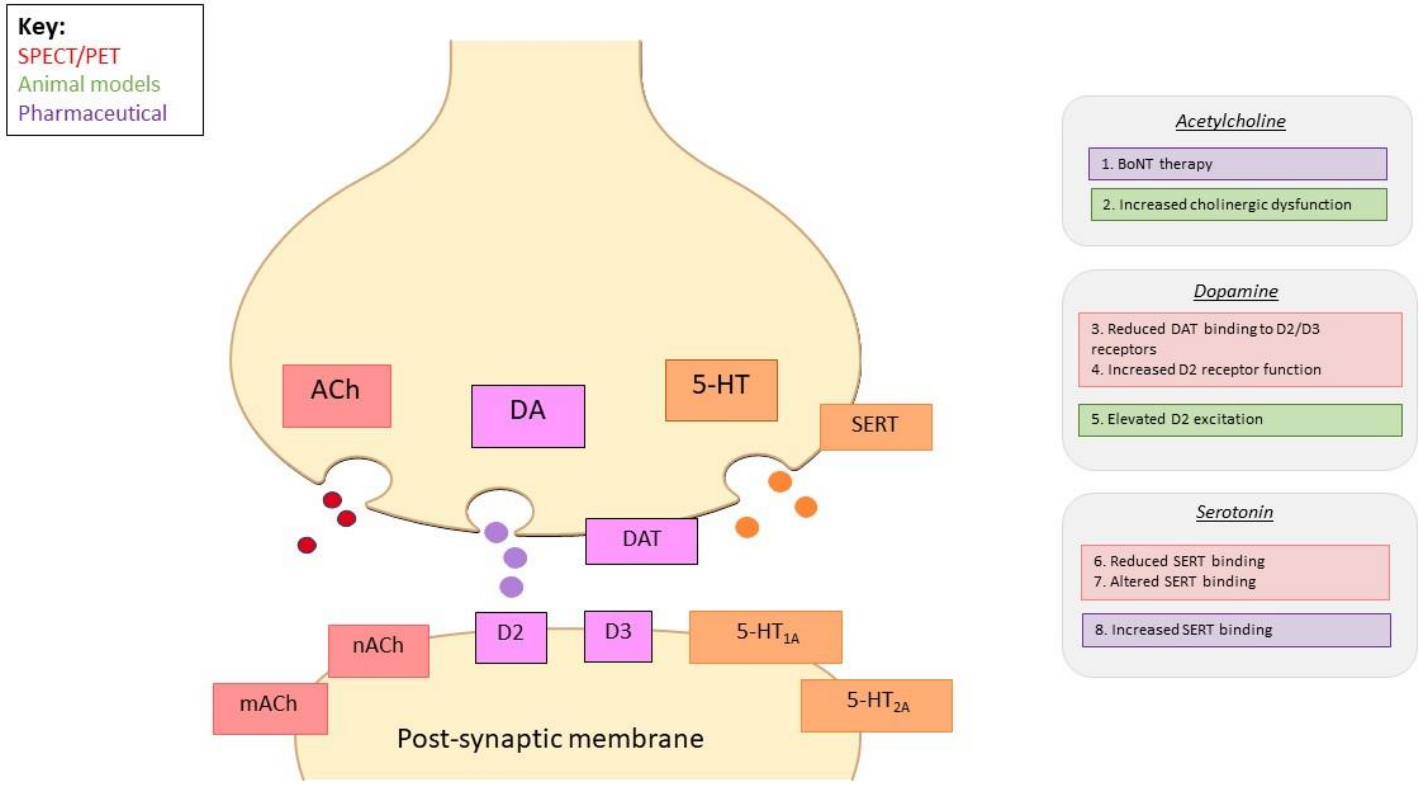

Figure 1.10: Neurotransmitters implicated in non-motor symptoms and cervical dystonia

1. BoNT improves pain, depression, anxiety and restores attentional deficits 2. Impaired motor learning in *THAP1* mouse models with cholinergic dysfunction 3. Reduced DAT binding in the striatum of depressed CD patients 4. Decreased striatal D2 LTP and LTD during reward-learning task 5. Elevated D2 excitation in *THAP1* mouse models in those with impaired motor learning 6. Reduced SERT binding in the midbrain of CD patients with psychiatric disorders 7. SERT binding in the medial raphe nucleus was inversely related to fatigue and positively related to binding in the caudate nucleus and sleep disorders 8. Increased extrastriatal SERT binding after escitalopram treatment improves dystonic severity and psychiatric symptoms

1.19 Thesis Objectives

The principal aims of this thesis are:

- To establish robust epidemiological characteristics for dystonic disorders using population-wide, anonymised, routinely collected data (Chapter 3)
- To investigate links between social economic status and diagnosis of dystonia (Chapter 3)
- Use of this electronic health record cohort to determine the rates of diagnosed co-morbid, psychiatric disorders and therapeutic intervention (Chapter 4)
- Focusing on one of the least well characterised and poorly described non-motor symptoms – sleep disturbance – and evaluating the evidence for sleep disruption across the wider spectrum of movement disorders (Chapter 5)
- Investigate sleep disturbances in multiple forms of dystonia using subjective and objective data collected as part of the UK Biobank (Chapter 6)
- Development and validate an algorithm that allows for use of 'real-life' wrist actigraphy data to examine sleep architecture (Chapter 7)
- To use the above algorithm to examine sleep in those diagnosed with AOIFCD compared to unaffected control participants over a one-week period, and comparison of these objective measures against more subjective questionnaire-based assessment (Chapter 7).

2 Methods and Materials

2.1 Introduction

The following chapter describes the methods and materials used for extraction of health data from the Secure Anonymised Information Linkage (SAIL) databank and the UK Biobank, as well as participant recruitment, assessment and data collection.

2.2 Secure Anonymised Information Linkage (SAIL) Databank

Background

The Secure Anonymised Information Linkage (SAIL) system is a databank containing electronically stored, anonymised person-based information (www.saildatabank.com). SAIL is operated by the Health Information Research Unit (HIRU) at Swansea University and was established in 2007, with the aim to enhance patient care by amassing a wide range of data accessible for research purposes. SAIL contains data about the population of Wales, a country with a population of 3.15 million in 2019.[468] Due to the longitudinal nature of the data, SAIL encompasses over 5 million people who have been recipients of medical services in Wales. The databank contains records from 100% of Welsh hospitals, and approximately 80% of Welsh GP practices.

2.2.1 Data anonymisation

SAIL overcomes potential breaches to confidentiality by using a split-file approach, whereby datasets from various data-providing organisations (e.g. NHS Wales Informatics Service, Office of National Statistics) are separated into demographic data (name, address, date of birth, gender and National Health Service (NHS) Number) and clinical data (includes diagnostic tests, therapeutic procedures and interventions). Clinical data is transferred directly to the Health Information Research Unit (HIRU) where it is anonymised and encrypted. Demographic data is sent to a trusted third party, NHS Wales Informatics Service (NWIS), where it is matched against records in the Welsh Demographic Service (WDS) database and anonymised using an Anonymous Linking Field (ALF). Each individual is assigned a unique ALF, which is a 10-digit number based on a person's National Health Service (NHS) number. The ALF, together with a minimal demographics dataset

(week of birth, gender and Lower Super Output Area (LSOA) of residence) is sent to HIRU where it can later be re-joined with clinical data. Further encryption of the ALF (ALP-E) prevents re-identification of individuals, with encryption then applied before data is allocated to a project (ALF-PE).[469] These processes are illustrated in Figure 2.1.

2.2.2 Data linkage

As briefly described above, assignment of a unique ALF allows for linkage of SAIL datasets. This method of linking data enables information from multiple sources to be combined, providing opportunity for research or a far wider spectrum of variables. Reliable linkage relies on the use of a consistent identifier for each individual, whereby an exact match can be created (deterministic record linkage, DRL), or a probabilistic record linkage (PRL) can be used if similar but not all unique identifiers are available. Linkage Matching Algorithm for Consistent Results in Anonymised Linkage (MACRAL), a Structured Query Language (SQL) based algorithm applies DRL and PRL matching techniques which use identifiable information obtained from the NHS Administrative Register (NHSAR) including name, address, postcode, gender, date of birth, general practice details and NHS number. Probabilities are then assigned to indicate the confidence with which the ALF belongs to the individual. Within GP datasets, ALF generation has an accuracy of more than 99.99%.[470] Figure 2.2 shows the matching process.

2.2.3 Data access

As part of the application process, researchers must complete an Information Governance Review Panel (IGRP) form detailing the scope of the project, including detailing datasets required, information required from each dataset, outline analysis plans, costs and anticipated timescales. Requests are reviewed by HIRU and an independent review panel to assess compliance with information governance, standard operating procedures and data management policies, as well as consider the disclosure risk. The IGRP includes representatives from Informing Healthcare, the NHS National Public Health Service for Wales, the British Medical Association and Involving People.[471] Once approved, a data view is created by HIRU staff and made available. Data users are required to sign an access agreement for responsible data

utilisation in accordance with the policies in place and provide proof of Safe Researcher Training. SAIL data can be accessed through use of the remote desktop portal, in the UK Secure Research Platform (SeRP), also referred to as the SAIL Gateway. Approved data users can access their provisioned data remotely via a Virtual Private Network (VPN) and a YubiKey authentication token, which when inserted into the Universal Serial Bus slot conveys a one-time password. Data must be analysed within the Gateway and can only be exported from the Gateway following SAIL approval.[469]

2.2.4 Ethics and approval

SAIL uses anonymised data and therefore does not require an additional ethical application to the Research Ethics Committee for individual projects. SAIL uses a two-stage application process which requires approval from the IGRP (Reference: 0768, see Appendix 1 for application), which consists of a panel of independent specialists in informatics governance and lay people which oversees research taking place within SAIL. Approved projects must be deemed feasible and present no risk to patient identification. Individual data is not allowed to be taken out of SAIL, to protect patient identity, groups with less than 5 persons are not allowed to be reported. Data must be requested out, where it is reviewed by the SAIL Analyst Team to ensure these rules are adhered to.

2.2.5 Technology

Data in the SAIL databank was queried using structured query language (SQL) via DB2 (Database 2) platform (Data Warehouse Edition on Advanced Interactive eXecutive (AIX)) running on an International Business Machines ‘P’ series computer: DeepBlue-C, a database management system.[472]

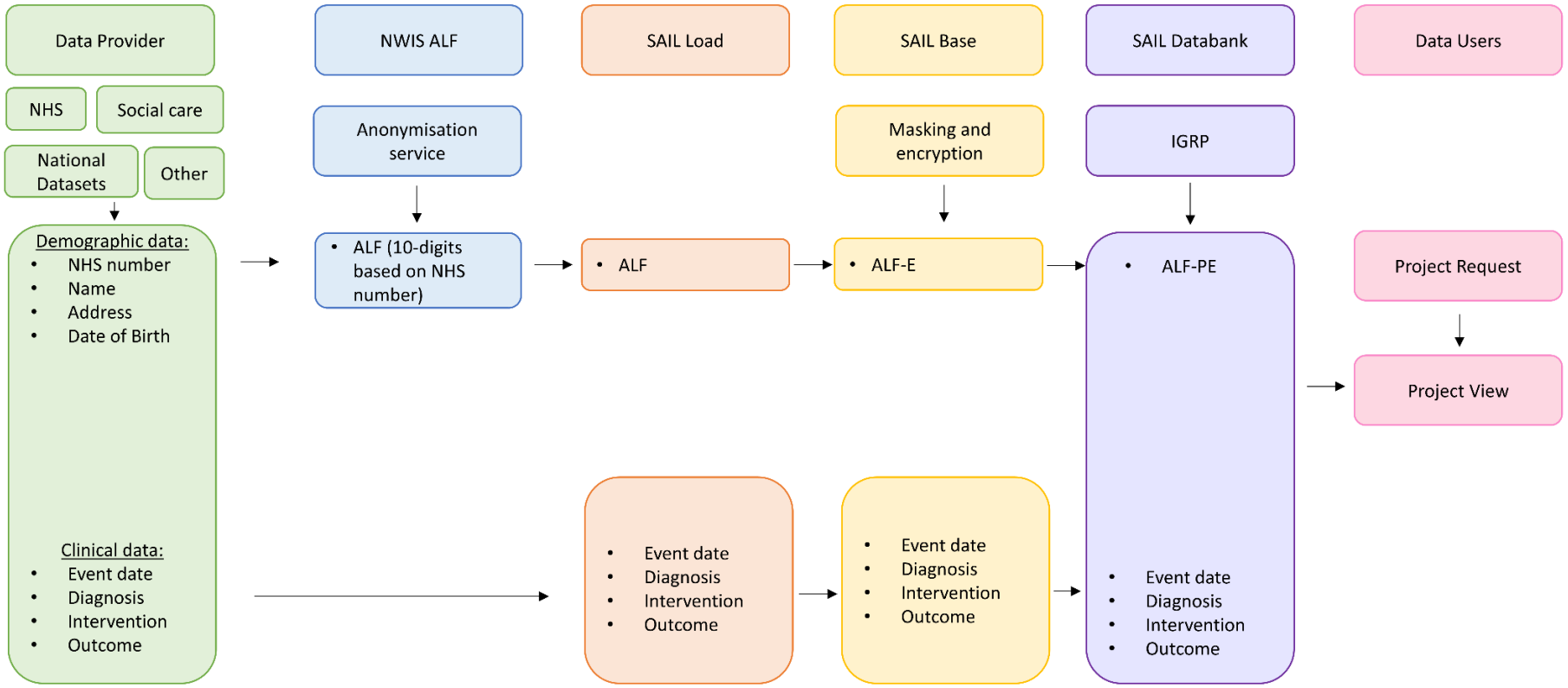

Figure 2.1 Data extraction and processes from data providers to the SAIL databank

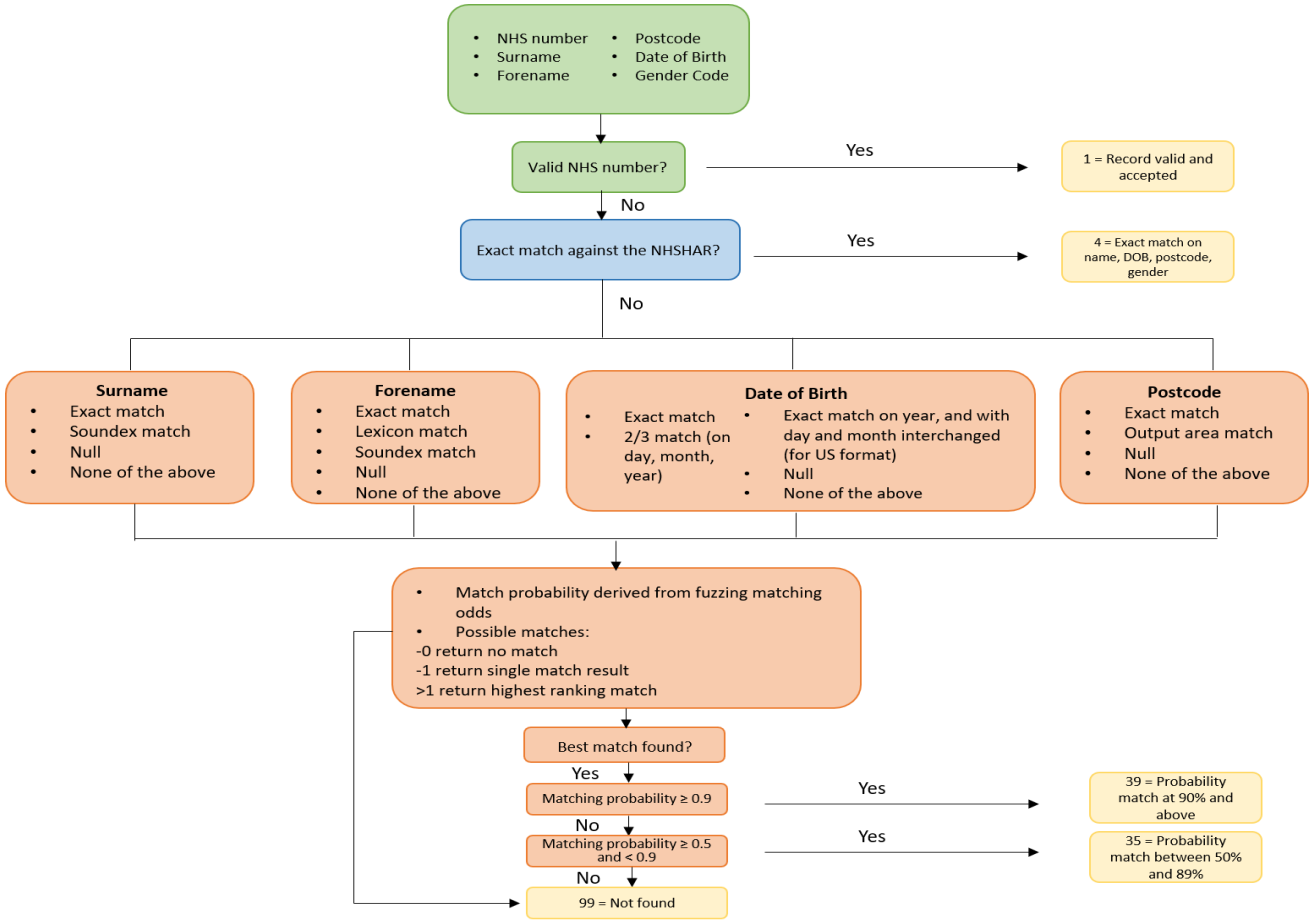

Figure 2.2 Matching process via the Matching Algorithm for Consistent Results (MACRAL) in Anonymised Linkage algorithm

Records which have a valid NHS number are accepted. The algorithm begins by checking for an exact match is checked against name, address/postcode, date of birth and gender code (DRL). PRL is then performed on the remaining unmatched records to a lower threshold of 50%. Adapted diagrammatic representation from Lyons *et al*[470]

Key: green boxes: demographic data from HIRU**, blue boxes:** Deterministic Record Linkage**, yellow boxes:** indicates how an ALF was allocated**, orange boxes:** Fuzzy Matching Process

2.2.6 Data sets

The following core datasets in SAIL were used for analysis during this thesis.

2.2.6.1 Welsh Longitudinal General Practice dataset (WLGP)

Approximately 80% of Welsh GP practices provide electronic health records to the SAIL databank, using the Read Code version 2 system. There are over 300,000 Read codes which can be used to attain information on diagnoses, prescriptions, signs, symptoms, and administrative procedures. This dataset also contains demographic data including week of birth, sex, dates of the beginning/end of registration with a GP practice. Time coverage varies considerably between practices and individuals. The average GP practice has 5000 registered patients, although this value can range from 1000 to 30,000, with patients able to opt out of their data being provided to SAIL by informing their GP. Overall, the estimated opt out rate is <0.025%.

2.2.6.2 Patient Episode Database for Wales (PEDW)

This hospital admissions dataset comprises both attendance and clinical information. The clinical information component includes diagnoses and operations performed at all NHS Wales Hospitals from 1997. Information is collected from the central Patient Administrative System such as speciality of care, admission and discharge dates. Patient notes are transcribed into coding terminology, typically using the International Classification of Diseases version 10 (ICD-10) system.

2.2.6.3 Outpatient Dataset (OPD)

Information for all NHS Wales hospitals outpatient appointments, such as speciality of care, appointment date and attendance status are detailed in this dataset. Diagnoses within OPD are coded using ICD-10 and operations or procedures using the OPER4 system. The OPD dataset commenced in 2004 and is ongoing.

2.2.6.4 Welsh Demographic Service (WDS)

Introduced in 2009, this dataset contains administrative information about individuals in Wales that use NHS services, these include practice registration history, and anonymised demographics such as week of birth, gender, address, and Welsh Index of Multiple Deprivation (WIMD) score linked by the address postcode.

Welsh Index of Multiple Deprivation

The Welsh Index of Multiple Deprivation (WIMD) is the Welsh Government's official measure of deprivation, which identifies and ranks all small areas in Wales from 1 (most deprived) to 1909 (least deprived). Following the 2011 Census, 1909 of these small areas called LSOA, were defined in Wales, each with a population of ~1600 people. LSOA are grouped into decile or quintile groups according to WIMD score, with 1 being the most deprived and 10 (or 5) being the least deprived.[473] The WIMD index is updated every four or five years, with small changes to the relative weights applied to the eight domains of deprivation. Captured domains include income, employment, health, education, access to services, housing, community safety and physical environment (see Appendix 2).[473]

2.2.6.5 Annual District Death Extract (ADDE)

This consists of data collected from death registrations throughout Wales and England derived from the death certification and registration system, detailing information such as the date, location of death (LSOA), place of death (hospital, home etc.) and causes of all deaths as well as contributory comorbidities relating to residents in Wales. Underlying causes of death are coded using the ICD-10 classification system.

2.2.7 Dystonia cohort

Primary and secondary healthcare records were used to derive the dystonia cohort using Read codes (version 2) and International Classification of Diseases version-10 (ICD-10), respectively. Codes used to identify individuals with dystonia are shown in Table 2.1, the development and validation of these codes are detailed in Chapter 3. Exclusion codes detailed in Table 2.2 – 2.4.

Table 2.1 Read Codes and ICD-10 codes used to identify cases of dystonia

Dystonia subtype	ICD-10 Code	Read Code	Read Code Description
Genetic torsion dystonia	G24.1		
Idiopathic torsion dystonia		F136.	Idiopathic torsion dystonia
		F137.	Symptomatic torsion dystonia
		F137y	Symptomatic torsion dystonia OS
		F137z	Symptomatic torsion dystonia NOS
		F138.	Fragment of torsion dystonia
		F138z	Torsion dystonia fragment NOS
Idiopathic nonfamilial dystonia	G24.2		
Idiopathic familial dystonia		F1360	Idiopathic familial dystonia
Cervical dystonia	G24.3	F1382	Spasmodic torticollis
		16A3.	Torticollis - symptom
		N135.	Torticollis unspecified
		N1350	Intermittent torticollis
		N135z	Torticollis NOS
Idiopathic Orofacial dystonia	G24.4		
Blepharospasm	G24.5	F1380	Blepharospasm
Writer's cramp		F1383	Organic Writer's cramp
Myoclonic dystonia		F13B.	Myoclonic dystonia
Segawa syndrome		F13C.	Segawa syndrome
Other	G24.8	Fyu24	[X]Other dystonia
Unspecified	G24.9	Fyu2A	[X]Dystonia, unspecified
		F13X.	Dystonia, unspecified
Tremor		1B22.	Has a tremor

Table 2.2 Read Codes and ICD-10 codes used to exclude any potential secondary causes of dystonia

Clinical Terminology	Read code	ICD-10 code
Dystonia		
Paroxysmal dystonia	F13A.	
Drug induced dystonia	F1312	G240
Parkinson's Disease and secondary parkinsonism		
Parkinson's Disease	F12..	G20
Parkinson's disease NOS	F12z.	
O/E Parkinson gait	2994.	
O/E - Parkinson posture	2987.	
O/E - Parkinsonian tremor	297A.	
Dementia in Parkinson's disease	Eu023	
FH: Parkinsonism	129Z.	
Secondary parkinsonism due to other external agents	F12W.	
Parkinsonism secondary to drugs	F121.	
Malignant neuroleptic syndrome	F122.	
Postencephalitic parkinsonism	F123.	
Vascular parkinsonism	F124.	
Syphilitic parkinsonism	A94y1	
Secondary parkinsonism, unspecified	F12X.	
Secondary parkinsonism		G21
History of Parkinson's disease	147F.	
Cerebral degeneration in Parkinson's disease	F11x9	
Huntington's Disease		G10
Huntington's chorea	F134.	
Dementia in Huntington's disease	Eu022	
FH: Huntington's chorea	1291.	
Chorea		
Other choreas	F135.	
Hemiballismus	F1350	

Paroxysmal chorea-athetosis	F1351	
Drug-induced chorea	F1352	
Other choreas NOS	F135z	
Ataxia		
Cerebral ataxia	F11y1	
Cerebellar ataxia NOS	F143.	
Cerebellar ataxia in diseases EC	F144.	
Cerebellar ataxia due to alcoholism	F1440	
Cerebellar ataxia due to myxoedema	F1441	
Cerebellar ataxia due to neoplasia	F1442	
Cerebellar ataxia in disease NOS	F144z	
Congenital nonprogressive ataxia	F145.	
Early onset cerebellar ataxia with hypogonadism	F146.	
Friedreich's ataxia	F140.	
Spinocerebellar disease	F14..	
Spinocerebellar disease NOS	F14z.	
Other spinocerebellar diseases	F14y.	
Hereditary ataxia		G11
Degenerative diseases of the basal ganglia		G23
Other basal ganglia degenerative diseases	F130.	
Dejerine-Thomas syndrome	F1300	
Hallervorden-Spatz disease	F1301	
Striatonigral degeneration	F1302	
Parkinsonism with orthostatic hypotension	F1303	
Progressive supranuclear ophthalmoplegia	F1304	
Shy-Drager syndrome	F1305	
Aicardi Goutieres syndrome	F1306	
Other basal ganliga degenerative diseases NOS	F130z	
Steele-Richardson-Olszewski syndrome	F24y2	
Myoclonus		
Myoclonus	F132.	
Familial essential myoclonus	F1320	
Progressive myoclonic epilepsy	F1321	

Myoclonic encephalopathy	F1322	
Myoclonic jerks	F1323	
Other specified myoclonus	F132y	
Myoclonus NOS	F132z	
O/E myoclonus	2979.	
Benign neonatal sleep myoclonus	F13z5	
Extrapyramidal diseases and movement disorders		
Other extrapyramidal diseases of basal ganglia		G25
Extrapyramidal and movement disorders in diseases classified elsewhere		G26
Other extrapyramidal disease and abnormal movement disorders	F13..	
Other/unspecified extrapyramidal/abnormal movement disorders	F13z.	
Unspecified extrapyramidal disease	F13z0	
Stiff-man syndrome	F13z1	
Restless leg syndrome	F13z2	
Akinetic rigid syndrome	F13z3	
Hyperekplexia	F13z4	
Neuroferritinopathy	F13z6	
Extrapyramidal disease and abnormal movement disorder NOS	F13zz	
Other/unspecified extrapyramidal/abnormal movement disorders	F139.	
Paroxysmal non-kinesigenic dyskinesia	F1390	
Paroxysmal kinesigenic dyskinesia	F1391	
Essential and other specified forms of tremor	F131.	
Benign essential tremor	F1310	
Familial tremor	F1311	
Drug-induced tremor	F1312	
Essential and other specified forms of tremor NOS	F131z	
Degenerative diseases of the nervous system		
Other degenerative diseases of nervous system, not elsewhere classified		G31
Cerebral degenerations usually manifest in childhood	F10..	

Leucodystrophy	F100.
Krabbe's disease	F1000
Schulz's disease	F1001
Pelizaeus-Merzbacher disease	F1002
Leucodystrophy NOS	F100z
Cerebral lipidoses	F101.
Jansky-Bielschowsky disease	F1010
Kuf's disease	F1011
Spielmeyer-Vogt (Batten) disease	F1012
Tay-Sach’s disease	F1013
Gangliosidosis	F1014
Retinal dystrophy in cerebroretinal lipidosis	F1015
Sandhoff disease	F1016
Cerebral lipidoses NOS	F101z
Cerebral degeneration in lipidoses EC	F102.
Cerebral degeneration in Gaucher's disease	F1020
Cerebral degeneration in Niemann-Pick disease	F1021
Cerebral degeneration in lipidosis NOS	F102z
Cerebral degeneration in diseases EC	F103.
Cerebral degeneration in Hunter's disease	F1030
Cerebral degeneration in mucopolysaccharidoses	F1031
Cerebral degeneration in disease NOS	F103z
Other cerebral degenerations in childhood	F10y.
Alper's disease	F10y0
Leigh's disease	F10y1
PEHO syndrome	F10y2
Other cerebral degenerations in childhood NOS	F10yz
Childhood cerebral degenerations NOS	F10z.
Other cerebral degenerations	F11..
Alzheimer's disease	F110.
Alzheimer's disease with early onset	F1100
Alzheimer's disease with late onset	F1101
Pick’s disease	F111.

Senile degeneration of brain	F112.
Acquired communicating hydrocephalus	F113.
Normal pressure hydrocephalus	F1130
Communicating hydrocephalus - acquired NOS	F113z
Acquired obstructive hydrocephalus	F114.
Hydrocephalus	F115.
Lewy body disease	F116.
Infantile posthaemorrhagic hydrocephalus	F117.
Frontotemporal degeneration	F118.
Post-traumatic hydrocephalus, unspecified	F11X.
Cerebral degeneration in other disease EC	F11x.
Cerebral degeneration due to alcoholism	F11x0
Cerebral degeneration due to beriberi	F11x1
Cerebral degeneration due to cerebrovascular disease	F11x2
Cerebral degeneration due to congenital hydrocephalus	F11x3
Cerebral degeneration due to neoplastic disease	F11x4
Cerebral degeneration due to myxoedema	F11x5
Cerebral degeneration due to vitamin B12 deficiency	F11x6
Cerebral degeneration due to Jakob - Creutzfeldt disease	F11x7
Cerebral degeneration due to progressive multifocal leukoencephalopathy	F11x8
Cerebral degeneration other disease NOS	F11xz
Other cerebral degeneration	F11y.
Reye's syndrome	F11y0
Corticobasal degeneration	F11y2
Other cerebral degeneration NOS	F11yz
Cerebral degeneration NOS	F11z.
Hereditary spastic paraplegia	F141.
Primary cerebellar degeneration	F142.
Marie's cerebellar ataxia	F1420
Sanger-Brown cerebellar ataxia	F1421
Dyssynergia cerebellaris myoclonica	F1422
Primary cerebellar degeneration NOS	F142z

Other spinocerebellar diseases	F14y.
Ataxia-telangiectasia	F14y0
Corticostriatal-spinal degeneration	F14y1
Other spinocerebellar disease NOS	F14yz
Anterior horn cell disease	F15..
Werdnig - Hoffmann disease	F150.
Spinal muscular atrophy	F151.
Unspecified spinal muscular atrophy	F1510
Kugelberg - Welander disease	F1511
Adult spinal muscular atrophy	F1512
X-linked bulbo-spinal atrophy	F1513
Spinal muscular atrophy NOS	F151z
Other anterior horn cell disease	F15y.
Anterior horn cell disease NOS	F15z.
Motor neurone disease	F152.
Amyotrophic lateral sclerosis	F1520
Progressive muscular atrophy	F1521
Progressive bulbar palsy	F1522
Pseudobulbar palsy	F1523
Primary lateral sclerosis	F1524
Motor neurone disease NOS	F152z
Other diseases of spinal cord	F16..
Syringomyelia and syringobulbia	F160.
Syringomyelia	F1600
Syringobulbia	F1601
Syringomyelia or syringobulbia NOS	F160z
Vascular myelopathies	F161.
Myelopathy due to acute infarction of spinal cord	F1610
Myelopathy due to arterial thrombosis of spinal cord	F1611
Myelopathy due to oedema of spinal cord	F1612
Myelopathy due to haematomyelia	F1613
Subacute necrotic myelopathy	F1614
Anterior spinal artery thrombosis	F1615

Vascular myelopathy NOS	F161z	
Subacute combined degeneration of spinal cord	F162.	
Myelopathy due to disease EC	F163.	
Myelopathy due to intervertebral disc disease	F1630	
Myelopathy due to neoplastic disease	F1631	
Myelopathy due to spondylosis	F1632	
Myelopathy due to disease NOS	F163z	
Brown-Sequard syndrome	F164.	
Other myelopathy	F16y.	
Drug induced myelopathy	F16y0	
Radiation induced myelopathy	F16y1	
Other myelopathy NOS	F16yz	
Myelopathy NOS	F16z.	
Hereditary and degenerative diseases of the CNS OS	F1y..	
Fragile X associated tremor ataxia syndrome	F1y0.	
Hereditary and degenerative diseases of the central nervous system NOS	F1z..	
Demyelinating diseases of the central nervous system		
Other central nervous system demyelinating diseases	F21..	
Neuromyelitis optica	F210.	
Schilder's disease	F211.	
Acute and subacute haemorrhagic leukoencephalitis [Hurst]	F212.	
Clinically isolated syndrome	F213.	
Acute disseminated demyelination, unspecified	F21X.	
Other acute disseminated demyelination		G36
Other specified central nervous system demyelinating disease	F21y.	G37
Central nervous system demyelination NOS	F21z.	
Marchiafava-Bignami disease	F21y0	
Central pontine myelinosis	F21y1	
Binswanger's disease	F21y2	
Central demyelination of corpus callosum	F21y3	
Subacute necrotizing myelitis	F21y4	
Concentric sclerosis	F21y5	

Vanishing white matter disease	F21y6	
Other specified central nervous system demyelination NOS	F21yz	
Transverse myelitis	F037.	
Varicella transverse myelitis	F0370	
Multiple sclerosis	F20..	G35
FH: Multiple sclerosis	1292.	
Multiple sclerosis NOS	F20z.	
Multiple sclerosis of the brain stem	F200.	
Multiple sclerosis of the spinal cord	F201.	
Generalised multiple sclerosis	F202.	
Exacerbation of multiple sclerosis	F203.	
Benign multiple sclerosis	F204.	
Malignant multiple sclerosis	F205.	
Primary progressive multiple sclerosis	F206.	
Relapsing and remitting multiple sclerosis	F207.	
Secondary progressive multiple sclerosis	F208.	
Niemann-Pick disease	C3272	
Progressive supranuclear palsy	F24y0	
Wilson's disease	C3510	
Multiple system atrophy	F174.	
Multiple system atrophy, cerebellar variant	F1740	
Multiple system atrophy, Parkinson variant	F1741	
[X] Lewy body dementia	Eu025	
Cerebral palsy		G80
Athetoid cerebral palsy	F1370	
Congenital cerebral palsy	F23..	
Congenital diplegia	F230.	
Congenital paraplegia	F2300	
Cerebral palsy with spastic diplegia	F2301	
Congenital diplegia NOS	F230z	
Congenital hemiplegia	F231.	
Congenital quadriplegia	F232.	
Congenital monoplegia	F233.	

Infantile hemiplegia NOS	F234.	
Other congenital cerebral palsy	F23y.	
Ataxic infantile cerebral palsy	F23y0	
Flaccid infantile cerebral palsy	F23y1	
Spastic cerebral palsy	F23y2	
Dyskinetic cerebral palsy	F23y3	
Ataxic diplegic cerebral palsy	F23y4	
Choreoathetoid cerebral palsy	F23y6	
Other infantile cerebral palsy NOS	F23yz	
Congenital cerebral palsy NOS	F23z.	
FH: Infantile cerebral palsy	1295.	
Cerebral palsy, not congenital or infantile, acute	G669.	
Tics/tic disorders		F95
Gilles de la Tourette's disorder	E2723	
[X]Combined vocal and multiple motor tic disorder [de la Tourette]	Eu952	
Tic - symptom	1B24.	
O/E - spasm/tic	2974.	
Tic disorder unspecified	E2720	
Transiet childhood tic	E2721	
Chronic motor tic disorder	E2722	
Tic NOS	E272z	
[X]Tic disorders	Eu95.	
[X]Transient tic disorder	Eu950	
[X]Chronic motor or vocal tic disorder	Eu951	
[X]Involuntary excessive blinking	Eu953	
[X]Other tic disorders	Eu95y	
[X]Tic disorder, unspecified	Eu95z	
Tics	E272.	
Tics of organic origin	F133.	
Brain tumour		
Neuroblastoma	B546.	
[M]Neuroblastoma NOS	BBc1.	

[M]Olfactory neuroblastoma	BBcC.	
Benign neoplasm of brain and other parts of central nervous system		D33
Benign neoplasm of brain	B7F0.	
Benign neoplasm of brain, supratentorial	B7F00	
Malignant neoplasm of brain	B51..	C71
Malignant neoplasm of cerebrum (excluding lobes and ventricles)	B510.	
Malignant neoplasm of basal ganglia	B5100	
Malignant neoplasm of cerebral cortex	B5101	
Malignant neoplasm of corpus striatum	B5102	
Malignant neoplasm of globus pallidus	B5103	
Malignant neoplasm of hypothalamus	B5104	
Malignant neoplasm of thalamus	B5105	
Malignant neoplasm of cerebrum NOS	B510z	
Malignant neoplasm of frontal lobe	B511.	
Malignant neoplasm of temporal lobe	B512.	
Malignant neoplasm of hippocampus	B5120	
Malignant neoplasm of uncus	B5121	
Malignant neoplasm of temporal lobe NOS	B512z	
Malignant neoplasm of parietal lobe	B513.	
Malignant neoplasm of occipital lobe	B514.	
Malignant neoplasm of cerebral ventricles	B515.	
Malignant neoplasm of floor of cerebral ventricle	B5151	
Malignant neoplasm of cerebral ventricle NOS	B515z	
Malignant neoplasm of cerebellum	B516.	
Malignant neoplasm of brain stem	B517.	
Malignant neoplasm of cerebral peduncle	B5170	
Malignant neoplasm of medulla oblongata	B5171	
Malignant neoplasm of midbrain	B5172	
Malignant neoplasm of pons	B5173	
Malignant neoplasm of brain stem NOS	B517z	
Malignant neoplasm of other parts of brain	B51y.	

Malignant neoplasm of corpus callosum	B51y0
Malignant neoplasm of tapetum	B51y1
Malignant neoplasm, overlapping lesion of brain	B51y2
Malignant neoplasm of other part of brain NOS	B51yz
Malignant neoplasm of brain NOS	B51z.
Secondary malignant neoplasm of brain	B5830
Neoplasm of unspecified nature of brain	BA06.
Neoplasm of uncertain behaviour of brain	B9250
Neoplasm of uncertain or unknown behaviour of brain, infratentorial	B9253
Malignant neoplasm, overlapping lesion of brain and other part of central nervous system	B52W.
Neoplasm of uncertain or unknown behaviour of brain, supratentorial	B9252
[M]Astrocytoma NOS	BBbB.
[M]Pilocytic astrocytoma	BBbG.
[M]Fibrillary astrocytoma	BBbF.
[M]Gemistocytic astrocytoma	BBbE.
[M]Protoplasmic astrocytoma	BBbD.
[M]Astrocytoma, anaplastic type	BBbC.
[M]Subependymal astrocytoma NOS	BBb3.
[M]Subependymal giant cell astrocytoma	BBb4.
[M]Subependymoma	BBb3.
[M]Glioma NOS	BBb0.
[M]Gliomas	BBb..
[M]Glioma, malignant	BBb0.
[M]Gliomatosis cerebri	BBb1.
[M]Mixed glioma	BBb2.
[M]Subependymal glioma	BBb3.
[M]Choroid plexus papilloma NOS	BBb5.
[M]Choroid plexus papilloma, malignant	BBb6.
[M]Ependymoma NOS	BBb7.
[M]Ependymoblastoma	BBb8.

[M]Ependymoma, anaplastic type	BBb8.
[M]Papillary ependymoma	BBb9.
[M]Myxopapillary ependymoma	BBbA.
[M]Spongioblastoma NOS	BBbH.
[M]Spongioblastoma polare	BBbJ.
[M]Glioblastoma NOS	BBbL.
[M]Giant cell glioblastoma	BBbM.
[M]Glioblastoma with sarcomatous component	BBbN.
[M]Primitive polar spongioblastoma	BBbP.
[M]Oligodendroglioma NOS	BBbQ.
[M]Oligodendroglioma, anaplastic type	BBbR.
[M]Oligodendroblastoma	BBbS.
[M]Medulloblastoma NOS	BBbT.
[M]Desmoplastic medulloblastoma	BBbU.
[M]Medullomyoblastoma	BBbV.
[M]Cerebellar sarcoma NOS	BBbW.
[M]Monstrocellular sarcoma	BBbX.
[M]Pleomorphic xanthoastrocytoma	BBbZ.
[M]Primitive neuroectodermal tumour	BBba.
[M]Peripheral neuroectodermal tumour	BBba0
[M]Glioma NOS	BBbz.
Cerebral meningioma	B7F20
Benign neoplasm of pineal gland	B7H3.
Malignant neoplasm of pineal gland	B543.
Neoplasm of uncertain behaviour of pineal gland	B921.
[M]Pinealoma	BBa1.
Malignant neoplasm of olfactory bulb	B5200
[M]Olfactory neuroepithelioma	BBcD.
[M]Olfactory neurogenic tumour	BBcA.
Pituitary adenoma	B7H2.
Benign neoplasm of pituitary gland	B7H20
Benign neoplasm of Rathke's pouch	B7H21
Benign neoplasm of sella turcica	B7H22

Benign neoplasm of craniopharyngeal duct	B7H23
Benign neoplasm of pituitary gland and craniopharyngeal duct NOS	B7H2z
Malignant neoplasm of pituitary gland	B5420
[M]Pituitary adenomas and carcinomas	BB5V.
[M]Prolactinoma	BB5y4
[M]Pituitary adenoma or carcinoma NOS	BB5Vz
Cerebral metastasis	B5832
Secondary malignant neoplasm of brain or spinal cord NOS	B583z
[M]Craniopharyngioma	BBa0.
Benign neoplasm of craniopharyngeal duct	B7H23
Malignant neoplasm of craniopharyngeal duct	B5421
Neoplasm of uncertain behaviour of craniopharyngeal duct	B9201
[M]Chordoma	BBa5.
[M]Schwannoma NOS	BBe5.
[M]Schwannoma, malignant	BBe7.
Acoustic neuroma	B7F10
[M]Primitive neuroectodermal tumour	BBba.
[M]Haemangioblastic meningioma	BBd7.
[M]Meningiomas	BBd..
[M]Meningioma NOS	BBd0.
[M]Meningiomatosis NOS	BBd1.
[M]Meningioma, malignant	BBd2.
[M]Meningotheliomatous meningioma	BBd3.
[M]Fibrous meningioma	BBd4.
[M]Psammomatous meningioma	BBd5.
[M]Angiomatous meningioma	BBd6.
[M]Haemangiopericytic meningioma	BBd8.
[M]Transitional meningioma	BBd9.
[M]Papillary meningioma	BBdA.
[M]Meningeal sarcomatosis	BBdB.
[M]Meningioma NOS	BBdz.

Spinal meningioma	B7F40	
Metabolic disorders		
Disorders of aromatic amino-acid metabolism		E70
Other disturbances of aromatic amino-acid metabolism	C302.	
Alkaptonuria	C3020	
Hydroxykynureninuria	C3021	
Indicanuria	C3022	
Tyrosinosis	C3023	
Tyrosinuria	C3024	
Lowe disease	C3025	
Hypertyrosinaemia	C3026	
Albinism	C3027	
Ocular albinism	P3y0.	
Chediak-Higashi syndrome	C3028	
Hermansky-Pudlak syndrome	C3029	
Partial albinism	C302A	
Other specified disturbance of aromatic amino-acid metabolism	C302y	
Disturbance of aromatic amino-acid metabolism NOS	C302z	
Phenylketonuria	C301.	
Disturbance of histidine metabolism	C305.	
Histidinaemia	C3050	
Imidazole aminoaciduria	C3051	
Histidinuria	C3052	
Other specified disturbance of histidine metabolism	C305y	
Disturbance of histidine metabolism NOS	C305z	
Disorders of fatty-acid metabolism	C308.	
Medium chain acyl-CoA dehydrogenase deficiency	C3080	
Multiple acyl-CoA dehydrogenase deficiencies	C3081	
X-linked adrenoleucodystrophy	C3082	
Glutaryl CoA dehydrogenase deficiency	C309.	
Tryptophan malabsorption syndrome	C30A.	
Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism		E71

Disturbances of branched-chain amino-acid metabolism	C303.
Leucinosis	C3030
Isoleucinosis	C3031
Hypervalinaemia	C3032
Maple syrup urine disease	C3033
Hypervalinaemia	C3034
Other specified disturbance of branched chain amino-acid metabolism	C303y
Disturbance of branched-chain amino-acid metabolism NOS	C303z
Disorders of amino-acid transport	C300.
Cystinosis	C3000
Cystinuria	C3001
Fanconi-de-Toni syndrome	C3003
Hartnup disease	C3004
Succinic semialdehyde dehydrogenase deficiency	C3005
Acquired Fanconi syndrome	C3006
Adult Fanconi syndrome	C3007
Juvenile nephropathic cystinosis	C3008
Adult cystinosis	C3009
Congenital Fanconi syndrome	C300A
Dibasic aminoaciduria - type I	C300B
Lysinuric protein intolerance	C300C
Infantile nephropathic cystinosis	C300D
Dibasic aminoaciduria	C300E
Other specified amino-acid transport disorder	C300y
Amino-acid transport disorder NOS	C300z
Glutaric aciduria Type 1	C30y8
Homocystinuria	C3043
Disturbance of urea cycle metabolism	C306.
Hyperornithinaemia	C3060
Citrullinaemia	C3061
Argininosuccinic aciduria	C3062
Hyperargininaemia	C3063

Hyperammonaemia	C3064
Other specified disturbance of urea cycle metabolism	C306y
Disturbance of urea cycle metabolism NOS	C306z
Disturbance of sulphur-bearing amino-acid metabolism	C304.
Cystathioninaemia	C3040
Cystathioninuria	C3041
Methioninaemia	C3042
Homocystinuria	C3043
Sulphite oxidase deficiency	C3044
Hyperhomocysteinaemia	C3045
Other specified disturbance of sulphur-bearing amino-acid metabolism	C304y
Disturbance of sulphur-bearing amino-acid metabolism NOS	C304z
Disturbance of other straight-chain amino-acid metabolism	C307.
Hyperglycinaemia	C3070
Disturbance of threonine metabolism	C3071
Disturbance of serine metabolism	C3072
Disturbance of glutamine metabolism	C3073
Hyperlysinaemia	C3074
Pipecolic acidaemia	C3075
Saccharopinuria	C3076
Glucoglycinuria	C3077
Other specified disturbance of other straight-chain amino-acid metabolism	C307y
Disturbance of other straight-chain amino-acid metabolism NOS	C307z
Disturbance of other specified amino-acid metabolism	C30y.
Alaninaemia	C30y0
Ethanolaminuria	C30y1
Glycoprolinuria	C30y2
Hydroxyprolinaemia	C30y3
Hyperprolinaemia	C30y4
Prolinuria	C30y5
Iminoacidopathy	C30y6

Sarcosinaemia	C30y7	
Other specified disturbance of amino-acid metabolism	C30yy	
Disturbance of other specified amino-acid metabolism NOS	C30yz	
Other disorders of amino-acid metabolism		E72
Disturbance of amino-acid transport or metabolism NOS	C30z.	
Disorders of carbohydrate transport and metabolism	C31..	
Other disorders of carbohydrate metabolism		E74
Glycogenosis - glycogen storage disease	C310.	
McArdle's disease	C3100	
Generalised glycogenosis	C3101	
Hepatorenal glycogenosis	C3102	
Glycogenosis of liver and muscle	C3103	
Glycogenosis with hepatic cirrhosis	C3104	
Other specified glycogenosis	C310y	
Glycogenosis NOS	C310z	
Galactosaemia	C311.	
Galactose-1-phosphate uridyl transferase deficiency	C3110	
Galactokinase deficiency	C3111	
Other specified galactosaemia	C311y	
Galactosaemia NOS	C311z	
Hereditary fructose intolerance	C312.	
Lactase deficiency	C3137	
Lactose intolerance	C3131	E73
Primary lactose intolerance	C3133	
Secondary lactose intolerance	C3134	
Acquired fructose intolerance	C316.	
Disorders of pyruvate metabolism and gluconeogenesis	C315.	
Pyruvate dehydrogenase deficiency	C3150	
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes	C3151	
Kearns-Sayre syndrome	C3152	
Other disorders of carbohydrate transport and metabolism	C31y.	
Essential benign pentosuria	C31y0	

Fucosidosis	C31y1
Oxalosis	C31y2
Mannosidosis	C31y3
Xylosuria	C31y4
Primary oxaluria	C31y5
Oxaluria NEC	C31y6
Aspartylglucosaminuria	C31y7
Glycerol kinase deficiency	C31y8
Disorder of glycoprotein metabolism, unspecified	C31yX
Other disorders of carbohydrate transport and metabolism NOS	C31yz
Disorder of carbohydrate transport or metabolism NOS	C31z.
Disorders of lipoid metabolism	C32..
Pure hypercholesterolaemia	C320.
Familial hypercholesterolaemia	C3200
Hyperbetalipoproteinaemia	C3201
Hyperlipidaemia, group A	C3202
Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia	C3203
Fredrickson's hyperlipoproteinaemia, type IIa	C3204
Familial defective apolipoprotein B-100	C3205
Polygenic hypercholesterolaemia	C3206
Other specified pure hypercholesterolaemia	C320y
Pure hypercholesterolaemia NOS	C320z
Pure hyperglyceridaemia	C321.
Hypertriglyceridaemia	C3210
Mixed hyperlipidaemia	C322.
Familial combined hyperlipidaemia	C3220
Hyperchylomicronaemia	C323.
Hyperlipidaemia NOS	C324.
Lipoprotein deficiencies	C325.
High density lipoid deficiency	C3250
Hypo-alpha-lipoproteinaemia	C3251
Hypo-beta-lipoproteinaemia	C3252
A-beta-lipoproteinaemia	C3253

Lipoprotein deficiency NOS	C325z	
Lipodystrophy	C326.	
Progressive lipodystrophy	C3260	
Lipodystrophy NOS	C326z	
Lipidoses	C327.	
Chemically induced lipidosis	C3270	
Krabbe's disease	F1000	
Gaucher's disease	C3271	
Niemann-Pick disease	C3272	
Wolman disease	C3273	
Alpha-galactosidase A deficiency	C3274	
Lipidoses NOS	C327z	
Dyslipidaemia	C328.	
Hypercholesterolaemia	C329.	
Other disorders of lipoid metabolism	C32y.	
Liposynovitis prepatellaris	C32y0	
Launois-Bensaude's lipomatosis	C32y1	
Lipoid dermatoarthritis	C32y2	
Pelvic lipomatosis	C32y3	
Lipase deficiency	C32y4	
Steatosis	C32y5	
Lipomatosis NEC	C32y6	
Other disorder of lipoid metabolism NOS	C32yz	
Disorders of lipoprotein metabolism and other lipidemias		E78
Disorders of sphingolipid metabolism and other lipid storage disorders		E75
Disorders of mineral metabolism	C35..	E83
Disorders of iron metabolism	C350.	
Haemochromatosis	C3500	
Haemosiderosis, primary	C3501	
Haemosiderosis, acquired	C3502	
Idiopathic pulmonary haemosiderosis	C3503	
Haemosiderosis NOS	C3504	

Other specified disorder of iron metabolism	C350y
Disorder of iron metabolism NOS	C350z
Disorders of copper metabolism	C351.
Hepatolenticular degeneration (Wilson's disease)	C3510
Hypercupraemia	C3511
Disorder of copper metabolism NOS	C351z
Disorders of magnesium metabolism	C352.
Hypermagnesaemia	C3520
Hypomagnesaemia	C3521
Hypomagnesaemic tetany	C3522
Disorder of magnesium metabolism NOS	C352z
Disorders of phosphorus metabolism	C353.
Hypophosphatasia	C3530
Hypophosphatasia rickets	C3531
Vitamin-D-resistant rickets	C3532
Hypophosphataemia	C3533
Hyperphosphataemia	C3534
Acquired hypophosphataemia	C3535
Renal failure-associated hyperphosphataemia	C3536
X-linked hypophosphataemic rickets	C3537
Autosomal dominant hypophosphataemic rickets	C3538
Autosomal recessive hypophosphataemic rickets	C3539
Disorder of phosphorus metabolism NOS	C353z
Disorders of calcium metabolism	C354.
Hypocalcaemia NEC	C3540
Hypercalcaemia NEC	C3541
Idiopathic hypercalcaemia	C3542
Pseudohypoparathyroidism	C3543
Hypercalcinuria	C3544
Familial benign hypercalcaemia	C3545
Hypocalcaemic tetany	C3546
Nephrocalcinosis	C3547
Other calcinosis	C3548

Calcium deficiency	C3549	
Metastatic calcification	C354A	
Calciphylaxis	C354B	
Cortical nephrocalcinosis	C354C	
Familial hypocalciuric hypercalcaemia	C354D	
Other specified disorder of calcium metabolism	C354y	
Disorder of calcium metabolism NOS	C354z	
Disorders of zinc metabolism	C355.	
Acrodermatitis enteropathica	C3550	
Disorders of phosphatases	C356.	
Disorder of other specified mineral metabolism	C35y.	
Disorder of mineral metabolism NOS	C35z.	
Disorders of bilirubin excretion	C374.	
Crigler - Najjar syndrome	C3740	
Dubin - Johnson syndrome	C3741	
Gilbert's syndrome	C3742	
Rotor syndrome	C3743	
Other specified congenital hyperbilirubinaemia	C374y	
Congenital hyperbilirubinaemia NOS	C374z	
Mucopolysaccharidosis	C375.	
Mannosidosis	C3750	
Mucopolysaccharidosis, type 1	C3751	
Mucopolysaccharidosis, type II	C3752	
Mucopolysaccharidosis, type III	C3753	
Mucopolysaccharidosis, type IV	C3754	
Pyknodysostosis	C3755	
Mucopolysaccharidosis, type VI	C3756	
Mucopolysaccharidosis, type VII	C3757	
Multiple sulphatase deficiency	C3758	
Disorders of glycosaminoglycan metabolism		E76
Disorder of glucosaminoglycan metabolism, unspecified	C375X	
Other specified mucopolysaccharidosis	C375y	
Mucopolysaccharidosis NOS	C375z	

Disorders of glycoprotein metabolism	C377.	E77
Defects in post-translational modification of lysosomal enzymes	C3770	
Mucolipidosis type III	C3771	
Other disorders of purine and pyrimidine metabolism	C372.	
Disorders of purine and pyrimidine metabolism		E79
Hypoxanthine-guanine-phosphoribosyltransferase deficiency	C3720	
Xanthinuria	C3721	
Hyperuricaemia without signs of inflammatory arthritis and tophaceous disease	C3722	
Lesch-Nyhan syndrome	C3723	
Urate nephropathy	C3724	
Acute urate nephropathy	C3725	
Other disorder of purine or pyrimidine metabolism NOS	C372z	
Hyperuricaemia without signs of inflammatory arthritis and tophaceous disease	C3722	
Gangliosidosis	F1014	
Lipofuscinosis NEC	F427K	
Lipofuscinosis NOS	F427K	
Cerebral degeneration in mucopolysaccharidoses	F1031	
Disorders of porphyrin metabolism	C371.	
Disorders of porphyrin and bilirubin metabolism		E80
Congenital porphyria	C3710	
Erythropoietic protoporphyria	C3711	
Acute intermittent porphyria	C3712	
Protocoproporphyria	C3713	
Porphyria cutanea tarda	C3714	
Coproporphyria	C3715	
Pseudoporphyria	C3716	
Porphyria NOS	C371z	
Other deficiencies of circulating enzymes	C376.	
Alpha-1-antitrypsin deficiency	C3762	
Other specified circulating enzyme deficiency	C376y	
Alpha-1-antitrypsin hepatitis	C3761	

Deficiency of circulating enzyme NOS	C376z	
Plasma protein metabolism disorders	C33..	
Polyclonal hypergammaglobulinaemia	C330.	
Waldenstrom's hypergammaglobulinaemic purpura	C3300	
Benign primary hypergammaglobulinaemic purpura	C3301	
Polyclonal hypergammaglobulinaemia NOS	C330z	
Monoclonal paraproteinaemia	C331.	
Other paraproteinaemias	C332.	
Cryoglobulinaemic purpura	C3320	
Cryoglobulinaemic vasculitis	C3321	
Benign paraproteinaemia	C3322	
Paraproteinaemia NOS	C332z	
Macroglobulinaemia	C333.	
Waldenstrom's macroglobulinaemia	C3330	
Alpha heavy chain disease	C3331	
Gamma heavy chain disease	C3332	
Heavy chain disease	C3333	
Macroglobulinaemia NOS	C333z	
Amyloidosis		E85
Other disorder of plasma protein metabolism	C33y.	
Hypoproteinaemia	C33y0	
Other specified other disorders of plasma protein metabolism	C33yy	
Other disorders of plasma protein metabolism NOS	C33yz	
Disorder of plasma protein metabolism NOS	C33z.	
Tumour lysis syndrome	C37yD	
Metabolic syndrome	C1A0.	
Smith - Lemli - Opitz syndrome	PKy63	
Lipoid dermatoarthritis	C32y2	
Acute rheumatic fever		
Acute rheumatic fever	G0...	
Rheumatic fever without heart involvement	G00..	
Rheumatic fever with heart involvement	G01..	
Acute rheumatic pericarditis	G010.	

Acute rheumatic endocarditis	G011.	
Acute rheumatic myocarditis	G012.	
Other acute rheumatic heart disease	G01y.	
Acute rheumatic pancarditis	G01y0	
Other acute rheumatic heart disease NOS	G01yz	
Rheumatic chorea	G02..	I02
Rheumatic chorea with heart involvement	G020.	I01
Rheumatic chorea without mention of heart involvement	G021.	I00
Rheumatic chorea NOS	G02z.	
Other specified acute rheumatic fever	G0y..	
Acute rheumatic fever NOS	G0z..	
Congenital malformations of the central nervous system		
Anencephaly and similar malformations	Q00	
Anencephalus	P00..	
Acrania	P000.	
Amyelencephalus	P001.	
Hemicephaly	P002.	
Other specified anencephalus	P00y.	
Anencephalus NOS	P00z.	
Craniorachischisis	P01..	
Iniencephaly	P02..	
Iniencephaly - closed	P020.	
Open iniencephaly	P021.	
Iniencephaly NOS	P02z.	
Encephalocele	P20..	
Meningoencephalocele	P204.	
Nasofrontal encephalocele	P206.	
Frontal encephalocele	P205.	
Meningocele - cerebral	P203.	
Encephalocystocele	P200.	
Encephalomyelocele	P201.	
Hydromeningocele - cranial	P202.	
Occipital encephalocele	P20z0	

Encephalocele of other specified site	P20z1	
Encephalocele NOS	P20z.	
Encephalocele		Q01
Microcephalus	P21..	
Microcephaly		Q02
Hydromicrocephaly	P210.	
Micrencephaly	P211.	
Microcephalus NOS	P21z.	
Congenital hydrocephalus	P23..	Q03
Aqueduct of Sylvius anomaly	P230.	
Aqueduct of Sylvius obstruction	P2300	
Aqueduct of Sylvius stenosis	P2301	
Atresia of aqueduct of Sylvius NEC	P2302	
Aqueduct of Sylvius anomaly NOS	P230z	
Foramen of Magendie atresia	P231.	
Foramen of Luschka atresia	P232.	
Atresia of foramina of Magendie and Luschka	P233.	
Hydranencephaly	P234.	
X-linked hydrocephalus	P235.	
Other specified congenital hydrocephalus	P23y.	
Congenital hydrocephalus NOS	P23z.	
Congenital absence of corpus callosum	P2280	
Aicardi syndrome	P2283	
Anomaly of corpus callosum NOS	P228z	
Aplasia of corpus callosum	P2282	
Hypoplasia of corpus callosum	P2281	
Anomalies of corpus callosum	P228.	
Arhinencephaly	P224.	
Septo-optic dysplasia	P246.	
Megalencephaly	P249.	
Congenital cerebral cyst	P240.	
Single congenital cerebral cyst	P2400	
Multiple congenital cerebral cysts	P2401	

Schizencephaly	P2402	
Congenital cerebral cyst NOS	P240z	
Other nervous system congenital anomalies	P2...	
Macroencephaly	P241.	
Macrogyria	P242.	
Porencephaly	P243.	
Ulegyria	P244.	
Congenital adhesions of cerebral meninges	P245.	
Dysplasia of cerebral cortex	P247.	
Congenital dilated lateral ventricles of brain	P248.	
Hemimegalencephaly	P24A.	
Multiple brain anomalies	P24x.	
Other specified brain anomalies NOS	P24z.	
Spina bifida	P1...	Q05
Spina bifida with hydrocephalus	P10..	
Unspecified spina bifida with hydrocephalus	P100.	
Spina bifida with hydrocephalus, unspecified	P1000	
Cervical spina bifida with hydrocephalus	P1001	
Thoracic spina bifida with hydrocephalus	P1002	
Lumbar spina bifida with hydrocephalus	P1003	
Spina bifida with hydrocephalus NOS	P100z	
Arnold - Chiari syndrome	P101.	
Chiari malformation type I	P1010	
Chiari malformation type II	P1011	
Chiari malformation type III	P1012	
Chiari malformation type IV	P1013	
Spina bifida with hydrocephalus of late onset	P104.	
Spina bifida with stenosis of aqueduct of Sylvius	P105.	
Spina bifida with hydrocephalus - open	P102.	
Unspecified spina bifida with hydrocephalus - open	P1020	
Cervical spina bifida with hydrocephalus - open	P1021	
Thoracic spina bifida with hydrocephalus - open	P1022	
Lumbar spina bifida with hydrocephalus - open	P1023	

Sacral spina bifida with hydrocephalus - open	P1024
Spina bifida with hydrocephalus - open NOS	P102z
Spina bifida with hydrocephalus - closed	P103.
Unspecified spina bifida with hydrocephalus - closed	P1030
Cervical spina bifida with hydrocephalus - closed	P1031
Thoracic spina bifida with hydrocephalus - closed	P1032
Lumbar spina bifida with hydrocephalus - closed	P1033
Sacral spina bifida with hydrocephalus - closed	P1034
Spina bifida with hydrocephalus - closed NOS	P103z
Other specified spina bifida with hydrocephalus	P10y.
Dandy - Walker syndrome with spina bifida	P10y0
Other spina bifida with hydrocephalus NOS	P10yz
Spina bifida with hydrocephalus NOS	P10z.
Spina bifida without mention of hydrocephalus	P11..
Spina bifida without mention of hydrocephalus, unspecified	P110.
Spina bifida without mention of hydrocephalus, site unspecified	P1100
Cervical spina bifida without mention of hydrocephalus	P1101
Thoracic spina bifida without mention of hydrocephalus	P1102
Lumbar spina bifida without mention of hydrocephalus	P1103
Unspecified spina bifida without mention of hydrocephalus NOS	P110z
Spina bifida NOS	P1z..
Amyelia	P25y0
Other specified spinal cord anomalies	P25..
Diastematomyelia	P250.
Hydromyelia	P251.
Congenital tethering of spinal cord	P252.
Spinal cord anomalies NOS	P25z.
Atelomyelia	P25y1
Congenital anomaly of spinal meninges	P25y2
Defective development of the cauda equina	P25y3
Spinal cord hypoplasia	P25y4
Other specified spinal cord anomalies NOS	P25yz

Reduction deformities of brain	P22..	
Hypoplasia of brain, part unspecified	P222.	
Agyria	P223.	
Microgyria	P226.	
Congenital bilateral perisylvian syndrome	P2260	
Holoprosencephaly	P225.	
Anomalies of cerebrum	P227.	
Congenital hypoplasia of cerebrum	P2271	
Anomaly of cerebrum NOS	P227z	
Anomalies of hypothalamus	P229.	
Anomalies of cerebellum	P22A.	
Congenital absence of cerebellum	P22A0	
Hypoplasia of cerebellum	P22A1	
Aplasia of cerebellum	P22A2	
Anomaly of cerebellum NOS	P22Az	
Other specified reduction deformities of brain	P22y.	
Cebocephaly	P22y0	
Familial aplasia of the vermis	P22y1	
Gillespie syndrome	P22y2	
Partial absence of septum pellucidum	P22y3	
Other reduction deformity of brain NOS	P22yz	
Reduction deformities of brain NOS	P22z.	
Marcus - Gunn syndrome	P2x4.	
Agenesis of nerve, unspecified	P2x0.	
Gillespie syndrome	P22y2	
Structural central nervous system abnormality	P2x8.	
Other specified nervous system anomalies NOS	P2xz.	
Unspecified nervous system anomaly of brain, cord and nervous system	P2y..	
Congenital brain anomaly	P2y0.	
Congenital spinal cord anomaly	P2y1.	
Unspecified nervous system anomaly NOS	P2yz.	
Other congenital malformations of brain		Q04

Other congenital malformations of spinal cord	Q06
Other congenital malformations of nervous system	Q07

Table 2.3 Parkinson's medication Read Codes used to exclude those with co-morbid dystonia diagnoses

Parkinson's medication	Read code
AMANTADINE HYDROCHLORIDE 50mg/5mL syrup	dq44.
AMANTADINE HYDROCHLORIDE 100mg capsules	dq4z.
SYMMETREL [PARK] 100mg capsules	dq41.
SYMMETREL [PARK] 50mg/5mL syrup	dq42.
*MANTADINE 100mg capsules	dq43.
*PARLODEL [PARK] 1mg tablets	dq51.
*PARLODEL [PARK] 2.5mg tablets	dq52.
PARLODEL [PARK] 5mg capsules	dq53.
PARLODEL [PARK] 10mg capsules	dq54.
*PARLODEL STARTER	dq55.
BROMOCRIPTINE [PARK] 1mg tablets	dq56.
BROMOCRIPTINE [PARK] 5mg capsules	dq57.
BROMOCRIPTINE 2.5mg tablets	dq5y.
BROMOCRIPTINE 10mg capsules	dq5z.
ELDEPRYL 5mg tablets	dq61.
ELDEPRYL 10mg tablets	dq62.
*ELDEPRYL 10mg/5mL syrup	dq63.
*VIVAPRYL 5mg tablets	dq64.
*VIVAPRYL 10mg tablets	dq65.
*STILLINE 5mg tablets	dq66.
*STILLINE 10mg tablets	dq67.
*CENTRAPRYL 5 tablets	dq68.
*CENTRAPRYL 10 tablets	dq69.
*CENTRAPRYL 10 tablets	dq69.
ZELAPAR 1.25mg tablets	dq6A.
SELEGILINE HYDROCHLORIDE 1.25mg tablets	dq6w.
SELEGILINE HYDROCHLORIDE 10mg/5mL syrup	dq6x.
SELEGILINE HYDROCHLORIDE 10mg tablets	dq6y.
SELEGILINE HYDROCHLORIDE 5mg tablets	dq6z.
LISURIDE 200micrograms tablets	dq71.

*REVANIL 200micrograms tablets	dq72.
PERGOLIDE 50micrograms tablets	dq81.
PERGOLIDE 250micrograms tablets	dq82.
PERGOLIDE 1mg tablets	dq83.
PERGOLIDE 50micrograms+250micrograms tablets starter pack	dq89.
PERGOLIDE 50micrograms tablets starter pack	dq88.
*CELANCE 50micrograms tablets	dq84.
*CELANCE 250micrograms tablets	dq85.
*CELANCE 1mg tablets	dq86.
CELANCE 50micrograms tablets starter pack	dq87.
CELANCE 50micrograms+250micrograms tablets starter pack	dq8A.
*BRITAJECT 20mg/2mL injection	dq91.
APOMORPHINE HYDROCHLORIDE 20mg/2mL injection	dq92.
*BRITAJECT 50mg/5mL injection	dq93.
APOMORPHINE HYDROCHLORIDE 50mg/5mL injection	dq94.
APOMORPHINE HYDROCHLORIDE 30mg/3mL prefilled pen	dq95.
BRITAJECT 30mg/3mL prefilled pen	dq96.
APO-GO 20mg/2mL injection	dq97.
APO-GO 50mg/5mL injection	dq98.
APO-GO 30mg/3mL prefilled pen	dq99.
APO-GO PFS 50mg/10mL injection solution prefilled syringe	dq9A.
APOMORPHINE HYDROCHLORIDE 50mg/10mL prefilled syringe	dq9z.
ROPINIROLE 0.25mg tablets	dqA1.
ROPINIROLE 1mg tablets	dqA2.
ROPINIROLE 2mg tablets	dqA3.
ROPINIROLE 5mg tablets	dqA4.
*REQUIP 0.25mg tablets	dqA5.
REQUIP 1mg tablets	dqA6.
REQUIP 2mg tablets	dqA7.
REQUIP 5mg tablets	dqA8.
ROPINIROLE 250micrograms+500micrograms+1000micrograms tablets starter pack	dqA9.
EPPINIX XL 3mg m/r tablets	dqAA.

EPPINIX XL 4mg m/r tablets	dqAB.
EPPINIX XL 6mg m/r tablets	dqAC.
EPPINIX XL 8mg m/r tablets	dqAD.
ROPINIROLE 500micrograms+1mg+2mg tablets follow on pack	dqAa.
REQUIP tablets starter pack	dqAb.
REQUIP tablets follow-on pack	dqAc.
ADARTREL 2mg tablets	dqAd.
ROPINIROLE 500micrograms tablets	dqAe.
ADARTREL 500micrograms tablets	dqAf.
REQUIP XL 2mg m/r tablets	dqAg.
REQUIP XL 4mg m/r tablets	dqAh.
REQUIP XL 8mg m/r tablets	dqAi.
ROPINIROLE 2mg m/r tablets	dqAj.
ROPINIROLE 4mg m/r tablets	dqAk.
ROPINIROLE 8mg m/r tablets	dqAl.
REPINEX XL 2mg m/r tablets	dqAm.
REPINEX XL 4mg m/r tablets	dqAn.
REPINEX XL 8mg m/r tablets	dqAo.
RAPONER XL 2mg m/r tablets	dqAp.
RAPONER XL 3mg m/r tablets	dqAq.
ROPINIROLE 3mg m/r tablets	dqAr.
RAPONER XL 4mg m/r tablets	dqAs.
RAPONER XL 6mg m/r tablets	dqAt.
ROPINIROLE 6mg m/r tablets	dqAu.
RAPONER XL 8mg m/r tablets	dqAv.
AIMPART XL 2mg m/r tablets	dqAw.
AIMPART XL 4mg m/r tablets	dqAx.
AIMPART XL 8mg m/r tablets	dqAy.
EPPINIX XL 2mg m/r tablets	dqAz.
CABERGOLINE 1mg tablets	dqB1.
CABERGOLINE 2mg tablets	dqB2.
CABERGOLINE 4mg tablets	dqB3.
CABASER 1mg tablets	dqB4.

CABASER 2mg tablets	dqB5.
*CABASER 4mg tablets	dqB6.
TOLCAPONE 100mg tablets	dqC1.
*TOLCAPONE 200mg tablets	dqC2.
TASMAR 100mg tablets	dqC3.
*TASMAR 200mg tablets	dqC4.
ENTACAPONE 200mg tablets	dqD1.
COMTESS 200mg tablets	dqD2.
AZILECT 1mg tablets	dqF1.
RASAGILINE 1mg tablets	dqFz.
NEUPRO 2mg/24hours transdermal patches	dqG1.
NEUPRO 4mg/24hours transdermal patches	dqG2.
NEUPRO 6mg/24hours transdermal patches	dqG3.
NEUPRO 8mg/24hours transdermal patches	dqG4.
NEUPRO transdermal patches starter pack	dqG5.
NEUPRO 1mg/24hours transdermal patches	dqG6.
NEUPRO 3mg/24hours transdermal patches	dqG7.
ROTIGOTINE 3mg/24hours transdermal patches	dqGt.
ROTIGOTINE 1mg/24hours transdermal patches	dqGu.
ROTIGOTINE 2mg+4mg+6mg+8mg/24hours transdermal patches starter pack	dqGv.
ROTIGOTINE 8mg/24hours transdermal patches	dqGw.
ROTIGOTINE 6mg/24hours transdermal patches	dqGx.
ROTIGOTINE 4mg/24hours transdermal patches	dqGy.
ROTIGOTINE 2mg/24hours transdermal patches	dqGz.
MIRAPEXIN 88micrograms tablets	dqE1.
MIRAPEXIN 180micrograms tablets	dqE2.
MIRAPEXIN 700micrograms tablets	dqE3.
MIRAPEXIN 350micrograms tablets	dqE4.
MIRAPEXIN 260micrograms m/r tablets	dqE5.
MIRAPEXIN 520micrograms m/r tablets	dqE6.
MIRAPEXIN 1.05mg m/r tablets	dqE7.
MIRAPEXIN 2.1mg m/r tablets	dqE8.
MIRAPEXIN 3.15mg m/r tablets	dqE9.

MIRAPEXIN 1.57mg m/r tablets	dqEA.
MIRAPEXIN 2.62mg m/r tablets	dqEB.
PRAMIPEXOLE 1.1mg tablets	dqEo.
PRAMIPEXOLE 2.62mg m/r tablets	dqEp.
PRAMIPEXOLE 1.57mg m/r tablets	dqEq.
PRAMIPEXOLE 3.15mg m/r tablets	dqEr.
PRAMIPEXOLE 2.1mg m/r tablets	dqEs.
PRAMIPEXOLE 1.05mg m/r tablets	dqEt.
PRAMIPEXOLE 520micrograms m/r tablets	dqEu.
PRAMIPEXOLE 260micrograms m/r tablets	dqEv.
PRAMIPEXOLE 350micrograms tablets	dqEw.
PRAMIPEXOLE 88micrograms tablets	dqEx.
PRAMIPEXOLE 180micrograms tablets	dqEy.
PRAMIPEXOLE 700micrograms tablets	dqEz.

Table 2.4 Levodopa medications used to exclude dystonia patients with co-morbid diagnosis of tremor (Read Code: 1B22.)

Levodopa medication	Read code
*LEVODOPA 125mg capsules	dq11.
*LEVODOPA 250mg capsules	dq12.
*LEVODOPA 500mg capsules	dq13.
*LEVODOPA 500mg tablets	dq14.
*BROCADOPA 125mg capsules	dq15.
*BROCADOPA 250mg capsules	dq16.
*BROCADOPA 500mg capsules	dq17.
*LARODOPA 500mg tablets	dq18.
MADOPAR-62.5 capsules	dq21.
MADOPAR-125 capsules	dq22.
MADOPAR-250 capsules	dq23.
MADOPAR-62.5 dispersible tablets	dq24.
MADOPAR-125 dispersible tablets	dq25.
MADOPAR CR-125 m/r capsules	dq26.
CO-BENELDOPA 12.5/50 capsules	dq27.
CO-BENELDOPA 25/100 capsules	dq28.
CO-BENELDOPA 50/200 capsules	dq29.
CO-BENELDOPA 12.5/50 dispersible tablets	dq2a.
CO-BENELDOPA 25/100 m/r capsules	dq2b.
CO-BENELDOPA 25/100 dispersible tablets	dq2c.
SINEMET-110 TAVLETS	dq31.
SINEMET-275 tablets	dq32.
SINEMET-PLUS tablets	dq33.
SINEMET LS tablets	dq34.
CO-CARELDOPA 12.5/50 tablets	dq35.
CO-CARELDOPA 10/100 tablets	dq36.
CO-CARELDOPA 25/100 tablets	dq37.
CO-CARELDOPA 25/250 tablets	dq38.
SINEMET CR m/r tablets	dq39.
HALF-SINEMET CR m/r tablets	dq3A.

STALEVO 50mg / 12.5mg / 200mg tablets	dq3B.
STALEVO 100mg / 25mg / 200mg tablets	dq3C.
STALEVO 150mg /37.5mg / 200mg tablets	dq3D.
TILOLEC 100mg/25mg m/r tablets	dq3E.
TILOLEC 200mg/50mg m/r tablets	dq3F.
DUODOPA 5mg/20mg/mL intestinal gel cassette 100mL	dq3G.
CARAMET CR 25mg/100mg m/r tablets	dq3H.
CARAMET CR 50mg/200mg m/r tablets	dq3I.
STALEVO 200mg/50mg/200mg tablets	dq3J.
STALEVO 125mg/31.25mg/200mg tablets	dq3K.
STALEVO 75mg/18.75mg/200mg tablets	dq3L.
STALEVO 175mg/43.75mg/200mg tablets	dq3M.
SASTRAVI 50mg/12.5mg/200mg tablets	dq3N.
SASTRAVI 75mg/18.75mg/200mg tablets	dq3O.
SASTRAVI 100mg/25mg/200mg tablets	dq3P.
SASTRAVI 125mg/31.25mg/200mg tablets	dq3Q.
SASTRAVI 150mg/37.5mg/200mg tablets	dq3R.
SASTRAVI 175mg/43.75mg/200mg tablets	dq3S.
SASTRAVI 200mg/50mg/200mg tablets	dq3T.
STANEK 50mg/12.5mg/200mg tablets	dq3U.
STANEK 75mg/18.75mg/200mg tablets	dq3V.
STANEK 100mg/25mg/200mg tablets	dq3X.
STANEK 125mg/31.25mg/200mg tablets	dq3Y.
STANEK 150mg/37.5mg/200mg tablets	dq3Z.
CO-CARELDOPA 50/200 m/r tablets	dq3a.
CO-CARELDOPA 25mg/100mg m/r tablets	dq3b.
STANEK 175mg/43.75mg/200mg tablets	dq3c.
STANEK 200mg/50mg/200mg tablets	dq3d.
LEVODOPA 175mg/CARBIDOPA 43.75mg/ENTACAPONE 200mg tablets	dq3s.
LEVODOPA 75mg/CARBIDOPA 18.75mg/ENTACAPONE 200mg tablets	dq3t.
LEVODOPA 125mg/CARBIDOPA 31.25mg/ENTACAPONE 200mg tablets	dq3u.
LEVODOPA 200mg/CARBIDOPA 50mg/ENTACAPONE 200mg tablets	dq3v.
CO-CARELDOPA 5mg/20mg/mL intestinal gel casette 100mL	dq3w.

LEVODOPA 150mg / CARBIDOPA 37.5mg / ENTACAPONE 200mg tablets	dq3x.
LEVODOPA 100mg / CARBIDOPA 25mg / ENTACAPONE 200mg tablets	dq3y.
LEVODOPA 50mg / CARBIDOPA 12.5mg / ENTACAPONE 200mg tablets	dq3z.

2.2.8 Quality checking of data

Although routinely collected health data is of great use for research, it is important to note that it is collected for costing purposes or aid decision making processes. The majority of data is entered by trained professionals, however there is the potential for human error. For example, diagnoses/prescription can be entered retrospectively, or entered by two different individuals where it appears on two separate occasions. As a result, several diagnostic codes can appear before electronic records were integrated into healthcare systems, suggesting historical information of diagnosis. Other common errors include incorrect date of death (diagnostic codes entered after death), incorrect gender code assigned (males pregnant) and incorrect date of birth. These factors should be taken into account when using SAIL databank and use of other datasets may allow for cross checking.

2.2.9 Structured Query Language (SQL)

SQL queries were used to join multiple datasets together and combine individual records for statistical analysis. Unique identifiers called ALFs (Section 2.1.2) are present in all datasets and can be used to join different tables. These aggregated tables can then be filtered down to create a final dataset for analysis.

2.2.10 Statistical Analysis

The SAIL gateway has several software packages for data analysis. In this thesis, the open-source R statistical software (version 4.0.4) was used to undertake statistical analysis and produce figures.

2.3 UK Biobank

Background

The UK Biobank (UKBB) (http://www.ukbiobank.ac.uk) is a population-based cohort of approximately half a million individuals aged 40 to 69 who were registered with the National Health Service (NHS). Individuals were recruited between 2006 and 2010, with initial baseline assessments taking place in one of the 22 centres in England, Scotland and Wales, these involved physical and cognitive measures, extensive lifestyle and health-related data collection through interviews and

touchscreen questionnaires, and collection of samples including blood, saliva and urine to perform genotyping, and haematological and biochemistry assays.[474] Additional data collection incorporated into the UKBB includes: imaging, eye measures, tests of hearing and arterial stiffness, cardiorespiratory fitness, activity (acceleration) data over 7-days and completion of regular online questionnaires related to diet, occupational history, pain, cognitive function, digestive health and mental health. Protocols for individual tests are available online (https://biobank.ctsu.ox.ac.uk/crystal/docs.cgi). Individuals' health can also be followed through linkage data obtained through electronic health-related records from the UK National Health Service including death, cancer, hospital admissions available for the entire cohort. Primary care records are also available for ~45% of the participants, which captures diagnosis, symptoms, prescriptions, test results and referrals.[474] Data availability differs between suppliers, whereby data from Wales is obtained via the SAIL Databank (see Section 2.2), Albasoft provides data from GP practices in Scotland and, in England practice management systems (TPP: https://www.tpp-uk.com and Vision: (https://www.visionhealth.co.uk) supply data. The majority of the missing cohort are mainly participants registered with EMIS (https://www.emishealth.com) practices across England which UKBB are in the process of securing access. Individual data is anonymised, allowing researchers access to the data, with the aim of improving public health.[475]

2.3.1 Ethics

The UKBB has approval from the North West Multi-centre Research Ethics Committee (MREC) (reference 21/NW/0157). All participants gave written informed consent. The data used in this thesis was released to Cardiff University following project application to UKBB (Project Code: 13310).

2.3.2 Data sets

Primary care data

Data from general practice (GP) records is available for approximately 45% of UKBB participants. Data includes coded clinical events such as diagnoses, symptoms, test results, procedures and prescriptions, as well as most secondary care interactions being reported back to GPs. Clinical events are coded using Read codes

(version 2) and those used to identify individuals with dystonia are shown in Table 2.1.

Secondary care data

Primary diagnosis codes were obtained from individuals' hospital inpatient records (data-field 41262 and 42040). Diagnoses were coded according to the International Classification of Diseases version-10 (ICD-10) and are detailed in Table 2.1. Individuals with secondary forms of dystonia, including drug-induced dystonia (G240) and any other movement disorder or related condition (G0—G998, F95) were excluded (Table 2.2).

Sleep characteristics

Baseline data related to sleep behaviours were analysed and are shown in Table 2.3. These questions were completed using a touchscreen device during initial face-to-face assessments (2006-2010). If participants were unsure, they were instructed to make their best estimate or select 'Do not know' and were instructed to answer the question in the last four weeks if their response varied substantially.

Accelerometer data

There are an increasing number of tools being used to assess sleep in the community, one of these is wrist-worn accelerometer devices. 103,712 participants from the UKBB wore Axivity AX3 wrist-worn devices over 7-days between June 2013 and December 2015.[476] Participants were asked to wear the accelerometer continuously on their dominant wrist from the point of receiving the wrist-worn device. Information was extracted from 100Hz (hertz) raw triaxial acceleration data with a dynamic range of +-8g obtained. Devices were configured to begin and stop data collection at pre-specified dates. Participants were then asked to return the devices in a pre-paid envelope after the monitoring period (https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=141141). The descriptions and methods are available online (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/PhysicalActivityMonitor.pdf). Devices were calibrated to local gravity, resampling and epoch generation using procedures described elsewhere.[477] Physical activity was generated by averaging all worn and imputed values. . Data was derived by processing raw accelerometer data

(5-second epoch time series) from Continuous Wave Accelerometer (CWA) files, a binary format developed by Axivity. CWA files were processed and analysed using R package GGIR (version 2.3-0; http://cran.r-project.org).[478] This package allows for the estimation of the sleep period window from accelerometer data by detecting periods of non-movement using the Distribution of Change in Z-Angle (HDCZA) algorithm. Processing of data including calibration, resampling and epoch generation has been described elsewhere (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/PhysicalActivityMonitor.pdf).[476] In brief, acceleration signals were calibrated to local gravity using stationary periods in ten second windows where all three axials had a standard deviation of <13 milli-gravity (mg). Stationary periods were then used to optimise the gain and offset for each axis to fit a unit gravity sphere using ordinary least squares linear regression. Although the accelerometer was setup to record at 100Hz, sample rates can fluctuate between 94-104Hz. Therefore, valid data was resampled to 100Hz using linear interpolation, except for interruptions lasting longer than 1 second which were set to missing. The sample level Euclidean norm minus one (ENMO) of the acceleration in the three raw signals were calculated to quantify the acceleration related to the movement registered (expressed as mg).[479] A fourth order Butterworth low pass filter with a cut-off frequency of 20Hz was used to remove machine noise. Five second epochs were generated by combining the sample level data, allowing for description of the overall level and distribution of physical activity intensity. An empirical cumulative distribution function from all available five second epochs were generated to represent the distribution of time spent in different levels of physical activity intensity.[480] Non-wear time was removed, this was defined as consecutive episodes lasting for at least 60 minutes. The same standard deviation thresholds to identify stationary episodes were applied, as described above in the calibration process.

Individuals with <72 hours of data or who did not have data in each one-hour period of the 24-hour cycle were excluded from onward analysis (n = 29,765). Eighty percent (80.6%) of participants wore the device for at least 150 hours of the scheduled 168 hours.[476] A .csv time series file was generated for each participant, which included i) raw acceleration data ii) average acceleration by day and by hour iii) acceleration intensity distribution iv) wear time/non-wear time and duration by

day and by hour v) accelerometer calibration and quality metrics. These files were then imported into R for further analysis to determine specific sleep parameters.

Table 2.5 ICD-10 codes used to identify dystonia cohort

Dystonia subtype	ICD-10 Code	Read Code	Read Code Description
Genetic torsion dystonia	G24.1		
Idiopathic torsion dystonia		F136.	Idiopathic torsion dystonia
		F137.	Symptomatic torsion dystonia
		F137y	Symptomatic torsion dystonia OS
		F137z	Symptomatic torsion dystonia NOS
		F138.	Fragment of torsion dystonia
		F138z	Torsion dystonia fragment NOS
Idiopathic nonfamilial dystonia	G24.2		
Idiopathic familial dystonia		F1360	Idiopathic familial dystonia
Cervical dystonia	G24.3	F1382	Spasmodic torticollis
		16A3.	Torticollis - symptom
		N135.	Torticollis unspecified
		N1350	Intermittent torticollis
		N135z	Torticollis NOS
Idiopathic Orofacial dystonia	G24.4		
Blepharospasm	G24.5	F1380	Blepharospasm
Writer's cramp		F1383	Organic Writer's cramp
Myoclonic dystonia		F13B.	Myoclonic dystonia
Segawa syndrome		F13C.	Segawa syndrome
Other	G24.8	Fyu24	[X]Other dystonia
Unspecified	G24.9	Fyu2A	[X]Dystonia, unspecified
		F13X.	Dystonia, unspecified
Tremor		1B22.	Has a tremor

Table 2.6 Exclusion codes for UK Biobank cohorts

Clinical Terminology	Read code	ICD-10 code
Dystonia		
Drug induced dystonia	F1312	G24.0
Parkinson's Disease and secondary parkinsonism		
Parkinson's Disease	F12..	G20
Parkinson's disease NOS	F12z.	
O/E Parkinson gait	2994.	
O/E - Parkinson posture	2987.	
O/E - Parkinsonian tremor	297A.	
Dementia in Parkinson's disease	Eu023	
FH: Parkinsonism	129Z.	
Secondary parkinsonism due to other external agents	F12W.	G21.2
Parkinsonism secondary to drugs	F121.	G21.1
Malignant neuroleptic syndrome	F122.	G21.0
Postencephalitic parkinsonism	F123.	G21.3
Vascular parkinsonism	F124.	G21.4
Syphilitic parkinsonism	A94y1	
Secondary parkinsonism, unspecified	F12X.	G21.9
Secondary parkinsonism		G21
Other secondary parkinsonism		G21.8
Parkinsonism in diseases EC		G22
History of Parkinson's disease	147F.	
Cerebral degeneration in Parkinson's disease	F11x9	
Huntington's Disease		G10
Huntington's chorea	F134.	
Dementia in Huntington's disease	Eu022	
FH: Huntington's chorea	1291.	
Chorea		
Other choreas	F135.	G255
Hemiballismus	F1350	
Paroxysmal chorea-athetosis	F1351	
Drug-induced chorea	F1352	G254
Other choreas NOS	F135z	
Myoclonus		
Myoclonus	F132.	G253
Ataxia		
Cerebral ataxia	F11y1	
Cerebellar ataxia NOS	F143.	

Cerebellar ataxia in diseases EC	F144.	
Cerebellar ataxia due to alcoholism	F1440	
Cerebellar ataxia due to myxoedema	F1441	
Cerebellar ataxia due to neoplasia	F1442	
Cerebellar ataxia in disease NOS	F144z	
Congenital nonprogressive ataxia	F145.	
Early onset cerebellar ataxia with hypogonadism	F146.	
Friedreich's ataxia	F140.	
Spinocerebellar disease	F14..	
Spinocerebellar disease NOS	F14z.	
Other spinocerebellar diseases	F14y.	
Hereditary ataxia		G11
Degenerative diseases of the basal ganglia		G23
Other basal ganglia degenerative diseases	F130.	
Dejerine-Thomas syndrome	F1300	
Hallervorden-Spatz disease	F1301	G23.0
Striatonigral degeneration	F1302	G23.2
Parkinsonism with orthostatic hypotension	F1303	
Progressive supranuclear ophthalmoplegia	F1304	G23.1
Shy-Drager syndrome	F1305	
Aicardi Goutieres syndrome	F1306	
Other basal ganliga degenerative diseases NOS	F130z	
Steele-Richardson-Olszewski syndrome	F24y2	
Other specified degenerative diseases of basal ganglia		G23.8
Degenerative disease of basal ganglia, unspecified		G23.9
Extrapyramidal diseases and movement disorders		
Stiff-man syndrome	F13z1	
Restless leg syndrome	F13z2	
Akinetic rigid syndrome	F13z3	
Hyperekplexia	F13z4	
Neuroferritinopathy	F13z6	
Extrapyramidal disease and abnormal movement disorder NOS	F13zz	
Other/unspecified extrapyramidal/abnormal movement disorders	F139.	
Paroxysmal non-kinesigenic dyskinesia	F1390	
Paroxysmal kinesigenic dyskinesia	F1391	
Essential and other specified forms of tremor		
Drug-induced tremor	F1312	G25.1
Benign essential tremor	F1310	
Other cerebral degenerations		
Alzheimer's disease	F110.	
Alzheimer's disease with early onset	F1100	

Alzheimer's disease with late onset	F1101	
Pick’s disease	F111.	
Senile degeneration of brain	F112.	
Lewy body disease	F116.	
Frontotemporal degeneration	F118.	
Corticobasal degeneration	F11y2	
Hereditary and degenerative diseases of the CNS OS		
Fragile X associated tremor ataxia syndrome	F1y0.	
Hereditary and degenerative diseases of the central nervous system NOS	F1z..	
Demyelinating diseases of the central nervous system		
Niemann-Pick disease	C3272	
Progressive supranuclear palsy	F24y0	
Wilson's disease	C3510	
Multiple system atrophy	F174.	
Multiple system atrophy, cerebellar variant	F1740	G23.3
Multiple system atrophy, Parkinson variant	F1741	
Tics/tic disorders		F95
Gilles de la Tourette's disorder	E2723	
[X]Combined vocal and multiple motor tic disorder [de la Tourette]	Eu952	
Tic - symptom	1B24.	
O/E - spasm/tic	2974.	
Tic disorder unspecified	E2720	
Transiet childhood tic	E2721	
Chronic motor tic disorder	E2722	
Tic NOS	E272z	
[X]Tic disorders	Eu95.	
[X]Transient tic disorder	Eu950	
[X]Chronic motor or vocal tic disorder	Eu951	
[X]Involuntary excessive blinking	Eu953	
[X]Other tic disorders	Eu95y	
[X]Tic disorder, unspecified	Eu95z	
Tics	E272.	
Tics of organic origin	F133.	
Other degenerative diseases of nervous system, NEC		G31
Multiple Sclerosis		G35
Other acute disseminated demyelination		G36
Neuromyelitis optica [Devic]		G36.0
Other specified acute disseminated demyelination		G36.8
Acute disseminated demyelination, unspecified		G36.9

Other demyelinating diseases of central nervous system	G37
Infantile cerebral palsy	G80
Spastic cerebral palsy	G80.0
Spastic diplegia	G80.1
Infantile hemiplegia	G80.2
Dyskinetic cerebral palsy	G80.3
Other infantile cerebral palsy	G80.8
Infantile cerebral palsy, unspecified	G80.9

Key: EC; Elsewhere Classified, FH; Family History, NEC; Not Elsewhere Classified, NOS; Not Otherwise Specified, O/E; On Examination

Table 2.7 Baseline sleep data

Description	Data field	Question	Data coding
Chronotype (morning/evening person)	1180	"Do you consider yourself to be?"	1 Definitely a 'morning' person 2 More a 'morning' than 'evening' person 3 More an 'evening' than a 'morning' person 4 Definitely an 'evening' person -1 Do not know -3 Prefer not to answer
Sleep duration	1160	"About how many hours sleep do you get in every 24 hours? (please include naps)"	-1 Do not know -3 Prefer not to answer
Daytime dozing	1220	"How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)"	0 Never/rarely 1 Sometimes 2 Often 3 All of the time -1 Do not know -3 Prefer not to answer
Insomnia	1200	"Do you have trouble falling asleep at night or do you wake up in the middle of the night?"	0 Never/rarely 1 Sometimes 2 Often 3 Usually -3 Prefer not to answer
Snoring	1210	"Does your partner or a close relative or friend complain about your snoring?"	1 Yes 2 No -1 Do not know -3 Prefer not to answer

2.3.3 Statistical analysis

Statistical analyses were performed using R 4.0.1. Raw acceleration data files were processed and analysed using R package GGIR (version 2.3-0; http://cran.r-project.org) (see section 2.3.2).[478] The new generation of accelerometers, worn both day and night, allows the measurement of both physical activity and sleep. Through use of GGIR, an algorithm developed to process and analyse data collected with wearable raw acceleration sensors, analysis of both types of data using a single tool is possible without the need for pre-required programming expertise. The GGIR algorithm has been utilised across a wide variety of study designs and populations,

demonstrating the advantages of using accelerometer instead of questionnaire data.[481–484]

Categorical data was compared between groups using chi-square test. The normality of data was examined and was found to deviate from the normal distribution. Mann-Whitney U tests were used to assess any difference in cases and controls, with Bonferroni corrections applied for multiple comparisons. Associations between physical activity, psychiatric and pain diagnoses and accelerometery outcomes were assessed using linear regression analysis. Concordance between self-reported sleep properties and accelerometery-derived sleep measures were also examined for using linear regression. All of the analyses outlined above were adjusted for age at recruitment and sex.

2.4 Move Wales: Welsh Movement Disorder Research Network (WMDRN)

2.4.1 Case ascertainment

Patient recruitment took place throughout the United Kingdom (UK) via movement disorder specialists at several NHS partner organisations, as shown in Figure 2.3. We also developed a website (www.movementdisorders.wales) to facilitate participant sign up for individuals with dystonia, as well as healthy volunteers. A diagrammatic description of the recruitment and assessment process can be seen in Figure 2.4.

Figure 2.3 Recruitment sites throughout the UK

2.4.2 Patient information and informed consent

All participants provided informed for participation in the study. We explained the nature of the study, its purpose and associated procedures, the potential risks and benefits of participation to each patient. For those interested, a patient information sheet was provided, and individuals were given an opportunity to ask questions either via email or telephone (Appendix 3.1 - 3.3). Participants were made aware that participation was entirely voluntary and that they may withdraw from the study at any time without his or her treatment being affected and without the need to provide

a reason for this decision. Informed consent was sought from all participations following a minimum of 24 hours via paper copy or for those unable to travel to the research appointment, using a remote web-based electronic consent form (Appendix 4.1- 4.3). This was generated via the Bristol Online Survey website, and a link was sent to the participant's email address for completion. A pre-paid envelope was provided by the research team to return the consent form if completing a paper copy. Completed consent forms were filed and stored in a secure cabinet, and electronic copies were stored on an encrypted external hard drive within the research department.

2.4.3 Data Collection

2.4.3.1 Self-completed questionnaires

Following consent, a pack of standardised questionnaires were sent in the post for self-completion. Participants were also given several means of contacting the research team (telephone, email and postal address) if they should encounter any problems or require further assistance. An online version (via Bristol Online Surveys) was also available to those who requested an electronic copy. This was administered by Cardiff University and ensured data security, back-up and long-term storage of the data. Following consent, each participant was allocated a unique identifier which are unrelated to any properties of the participant and were allocated consecutively as participants were recruited (e.g. MW/2021/001 or MD/0595). Identifiers were added to the front of the paper questionnaire of given electronically to participants to enter. No key identifiers were included, and this allowed to anonymisation during analysis.

Collected data included basic demographic information (e.g. date of birth, ethnicity, education, employment), family medical history and past medical history (Table 2.4). Data related to non-motor symptoms was also collected and is shown in Table 2.5 (Appendix 5).

Table 2.8 Reported demographic variables

Demographic variable	Question
Date of birth, Age	What is your date of birth? How old are you?
Age of onset of dystonia symptoms	What was your age of onset of Myoclonus Dystonia/Dystonia symptoms?
Gender	What is your gender?
GP details	Please write here your General Practitioner (GP) contact details (Name and Address):
Ethnicity	Please state the ethnic origin of yourself, your mother and your father by ticking below:
Educational attainment	What was the highest level of education that you completed?
Employment status	What is your current state of employment?
Marital status	What is your marital status?
Family history	Please state your Family History (i.e. known key conditions experienced by your immediate family – mother, father, siblings, aunts, uncles)
General health	Do you have any other problems with your general health? IF YES, please select the condition(s) from the list below:
Smoking	How much do you smoke per day?
Alcohol	How much alcohol do you drink per week (units/week)? Please refer to the image below for the drink measurements equivalent to 1 unit:
Botulinum toxin (Botox) treatment	Are you receiving Botox treatments for your dystonia symptoms? IF YES: How effective has this Botox treatment been for you? How frequently are you having the Botox treatment?
Deep brain stimulation treatment	Have you previously had Deep Brain Stimulation (DBS), or been referred for DBS? IF YES: How effective has this DBS been for you?
Medication	Are you currently taking any medications for your dystonia symptoms? IF YES: What medication(s) are you currently taking (including doses)?

Table 2.9 Questionnaires used to assess non-motor symptoms

Non-motor symptom	Questionnaires
Psychiatric disorders	MINI International Neuropsychiatric Interview [M.I.N.I] Screen (MMS)
Anxiety	Health Anxiety Inventory (HAI)
Depression	Beck's Depression Inventory (BDI)
Personality disorder	Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD)
Obsessive-compulsive disorder	Yale-Brown Obsessive-Compulsive Scale (YBOCS)
Sleep	Pittsburgh Sleep Quality Index (PSQI), Sleep Disorders Questionnaire (SDQ), Epworth Sleepiness Scale (ESS)
Pain	Chronic Pain Acceptance Questionnaire, pain time course images, Pain Catastrophising Scale PCS)
Quality of Life	Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36)

For participants affected with a movement disorder, further information pertaining to movement disorder symptomatology at onset and examination, current medication, response to medication and motor disability (Burke-Fahn-Marsden dystonia scale) were collected. Patients were provided with a pre-paid envelope to return the completed questionnaire. Participants were contacted every 12 months to complete the same questionnaire pack, providing longitudinal data for longer term analysis.

2.4.3.2 Clinic assessments

For those that lived locally, an appointment for a clinical assessment was made at a time convenient for the patient. The following assessments were performed face-to-face.

2.4.3.2.1 Mini-International Neuropsychiatric Interview (M.I.N.I)

The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a brief structured diagnostic interview for psychiatric disorders according to ICD-10 (Appendix 6).[485] It screens for 19 psychiatric disorders including major depressive disorder, anxiety disorders, substance dependence and abuse, eating disorders, psychotic disorders and anti-social personality disorder. It only requires "yes" or "no" answers and probably diagnoses are given based on responses in each category.

2.4.3.2.2 Intelligence Quotient (IQ) test

To estimate IQ, we used the National Adult Reading Test (NART) (Appendix 7). The test comprises of 50 written words in British English which all have irregular spelling. If participants were unsure on how to pronounce a word, they were encouraged to guess. The following equation was used to predict IQ: 127.7 – 0.826 x Errors on NART. No time limit was imposed.

2.4.3.2.3 Cognitive assessment

The Cambridge Neuropsychological Test Automated Battery (CANTAB: www.cantab.com) was used to assess cognition in those attending clinic. Cambridge Cognition Limited set up and managed the application as part of this research study. The privacy policy, made available to participants, explains what happens to the information gathered by this application (Appendix 8). CANTAB offer a wide range of cognitive tests, but a battery was selected based on previous research findings in dystonia. We focused on six cognitive tests to assess working memory,[315,425] executive function,[324] visual memory and attention,[316–318] and social and emotion recognition,[486,487] information relating to these are detailed below. Web-based testing was also available, and a link was provided to participants who expressed contact electronically. The web-based assessment included the Spatial Working Memory and One Touch Stockings of Cambridge tests. CANTAB tests show moderate correlation to standard neuropsychological test measures (e.g. Wechsler Adult Intelligence Scale).[488]

Emotional Recognition Task (ERT)

Assesses the participant's ability to identify six basic emotions (sadness, happiness, fear, anger, disgust or surprise). Each face is displayed for 200ms, the participant must then select which emotion the face displayed from 6 options.

Multitasking Test (MTT)

This test assesses the participant's ability to manage conflicting information and ignore task-irrelevant information. Participants must select the left or right button

according to the ‘side on which the arrow appeared’ or the ‘direction in which the arrow was pointing’.

One Touch Stockings of Cambridge (OTS)

A test of executive function based on the Tower of Hanoi test. It assesses spatial planning and working memory subdomains. Participants are shown three colour balls held in stockings and they must copy the pattern displayed working out in their head how many moves the solution requires before selecting the appropriate response.

Spatial Span (SSP)

Participants are shown boxes which change colour in a variable sequency. The participant is then instructed to select the boxes which changed colour in the same order, with sequences gradually increasing from two to nine. This task assesses visuospatial working memory capacity.

Spatial Working Memory (SWM)

This task requires retention and manipulation of visuospatial information. A number of coloured boxes are shown on the screen, with the aim of the participant finding a yellow ‘token’ in each of a number of boxes via process of elimination. The number of boxes gradually increase to a maximum of 12 boxes.

Paired Associates Learning (PAL)

A test of visual memory and new learning, this task involves boxes which “open” in a randomised order, with one or more containing a pattern. Participants are then shown the pattern in the middle of the screen, one at a time and must select the box which it was originally located in. If an error is made, the sequences are shown again to remind them of the location.

2.4.4 Data management

All participants were given a unique study identifier number, used to code their biological sample. Clinical data is stored on a clinical database on an NHS network computer. Anonymised genetic data is stored on a University Research Database, as

is information related to annual questionnaire completion including results and total scores of standardised questionnaires. Data was analysed anonymously.

2.4.5 Study compliance and confidentiality

Project protocols and documentation were reviewed and approved by the West Midlands - Edgbaston Research Ethics Committee for Wales (REC reference: 18/WM/0031) Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study, and Wales Research Ethics Committee 3 (REC reference: 14/WA/0017) for Move Wales. NHS (Research and Development) permission was also obtained (Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study: IRAS (Integrated Research Application System) project ID: 236219 and Move Wales: IRAS project ID: 146495). To ensure confidentiality was maintained at all times, members of the team received adequate training in maintaining patient confidentiality and were aware of the laws that safeguard privacy at every stage of the research study. Personal information was kept in accordance with the Data Protection Act 1998 or General Data Protection Regulation, as applicable.

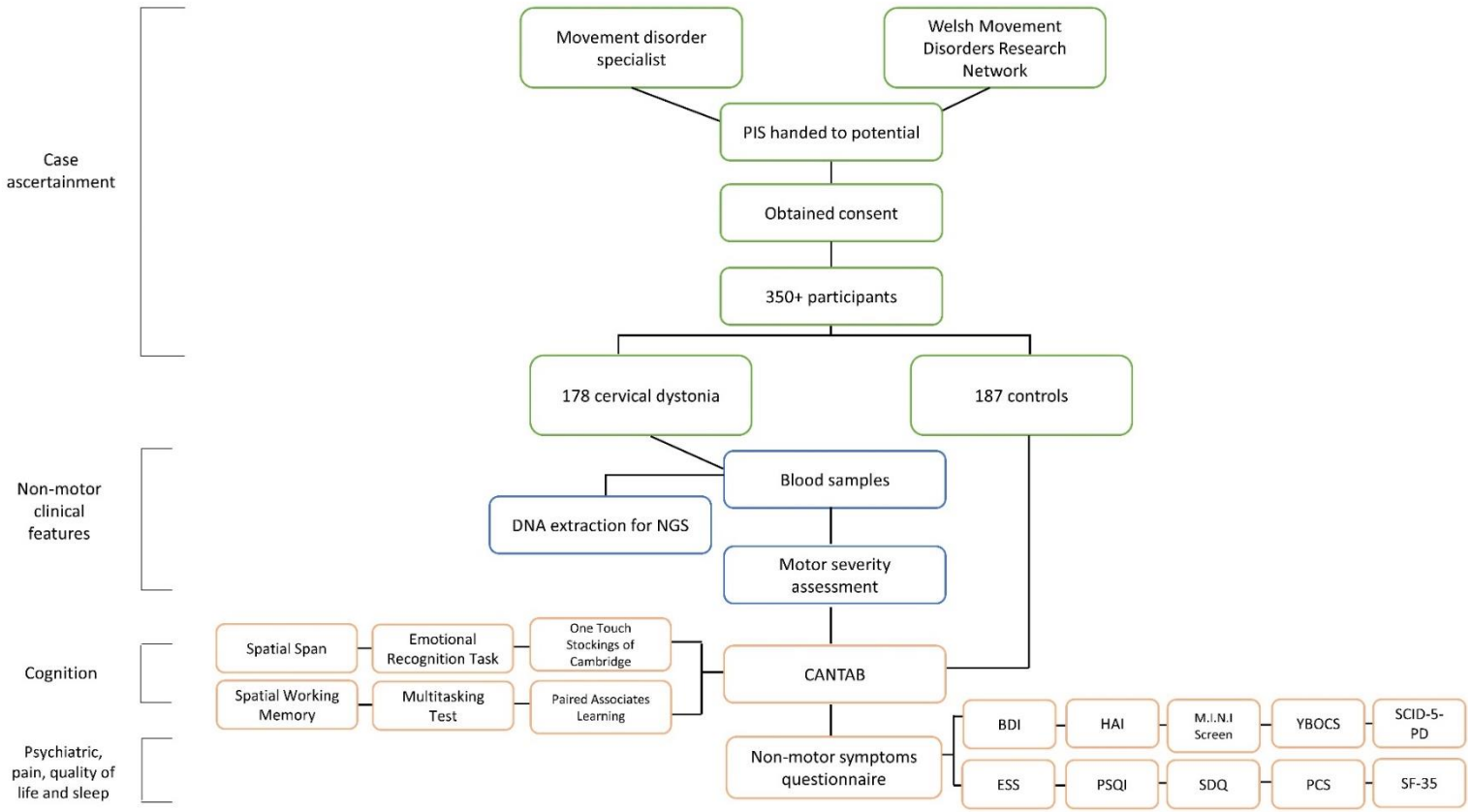

Figure 2.4 Diagrammatic representation of recruitment

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; NSG, Next Generation Sequencing; PIS, Patient Information Sheet; BDI, Becks Depression Inventory; ESS, Epworth Sleepiness Scale; HAI, Health Anxiety Inventory; M.I.N.I, MINI International Neuropsychiatric Interview; PCS, Pain Catastrophising Scale; PSQI, Pittsburgh Sleep Quality Index; SCID-5-PD, SDQ, Sleep Disorders Questionnaire; SF-36, Short Form 36 Health Survey; Structured Clinical Interview for DSM-5 Personality Disorders, YBOCS, Yale-Brown Obsessive-Compulsive Scale

2.5 Sleep derived accelerometer data collection

2.5.1 Participants

Participants diagnosed with cervical dystonia and those with no known neurological deficits (control cohort) were recruited via the Welsh Movement Disorders Research Network (see section 2.4). Participants were invited to participate in research investigating sleep variables derived from accelerometer-based measures. Standardised questionnaires were used to collect baseline clinical information, including sex, date of birth, current medication and receipt of any ongoing treatment with botulinum toxin injections (BoNT) (Appendix 5 Q1-14). Participants were required to own an Apple iPhone due to poor data quality in Android devices. Participants were reimbursed for their time with a one-off payment of £10 in the form of an Amazon voucher.

2.5.2 Ethics

Ethical approval was obtained from the School of Medicine Research Ethics Committee (SOMREC) (Reference: 19/87). Informed written consent was obtained from participants. Personal information was kept in accordance with the Data Protection Act 1998 or General Data Protection Regulation, as applicable. This was achieved by assigning a unique study code to data when registering for the study.

2.5.3 Study design

Patient reported outcomes (PROs) were captured via a mobile application (app, Oxygen by Aparito) specifically designed and developed for the purpose of the study. Participants received a notification when PROs for each 24-hour period became available. The wearable device (Vivosmart 4, Garmin) was also paired to the app, allowing accelerometer data to sync to the mobile via Bluetooth. To encourage the syncing of the data, PROs were strategically placed throughout the day with participants also instructed to sync data manually. The frequency of the PROs are shown below in Figure 2.5.

Timeline (days):	0	1	2	3	4	5	6	7
Questionnaires								
PSQI	●							
ESS	●							
DNMSQuest	●							
Sleep diary		●	●	●	●	●	●	●
Sleep scale		●	●	●	●	●	●	●
Pain scale		●	●	●	●	●	●	●
Anxiety scale		●	●	●	●	●	●	●
Quality of Life scale		●	●	●	●	●	●	●

Figure 2.5 Frequency of questionnaires

Abbreviations: DNMSQuest; Dystonia Non-motor Symptoms Questionnaire, ESS; Epworth Sleepiness Scale, PSQI; Pittsburgh Sleep Quality Index

2.5.3.1 Subjective questionnaires

Self-reported questionnaires used throughout the study are described below.

Pittsburgh Sleep Quality Index (PSQI)

A standardised sleep questionnaire assessing sleep quality and disturbances relating to sleeping habits during the past month (Appendix 9).[489,490] It contains seven components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. Scores are calculated for each component ranging from 0 (no difficulty) to 3 (severe difficulty) and are summed to produce a global score (0 to 21). Higher scores indicate worse sleep quality, a global score >5 indicates poor sleep quality.

Epworth Sleepiness Scale (ESS)

This self-administered questionnaire contains eight questions used to routinely assess daytime sleepiness on a four-point scale (0-3) relating to the participants chances of dozing/falling asleep during eight different activities (Appendix 10).[491] Scores can range from 0-24, with higher scores indicating that the person has a higher sleep propensity in daily life. In general scores can be interpreted as: lower normal (0-5),

higher normal (6-10), mild excessive (11-12), moderate excessive (13-15) or severe excessive daytime sleepiness (16-24).

Dystonia non-motor symptoms questionnaire (DNMSQuest)

The DNMSQuest is a 14-item self-completed questionnaire examining the presence of a range of NMS in individuals with cranio-cervical dystonia during the past month.[492] Responses are binary (yes/no), whereby summing of the "yes" answers gives the total number of NMS experienced. Seven domains are assessed including, sleep, autonomic symptoms, fatigue, emotional well-being, stigma, activities of daily living and sensory symptoms. Four question directly relating to dystonia were removed for the control cohort (Q7 "Do you suffer from loss of self-confidence due to stigma of visible dystonia?", Q10 "Do you experience unpleasant sensations such as numbness, tingling or pins and needles in the body area or nearby the body area of your dystonia?", Q12 "Does your dystonia affect your vision?", Q13 "Do you suffer from pain of the body area or near to the body area of your dystonia?"). For these four questions, controls were scored "no", therefore their total remained out of 14.

Sleep diary

Often regarded as the 'gold-standard' for subjective sleep assessments, sleep diaries are a useful tool in identifying sleep habits. Questions included: time of going to bed, time of trying to go to sleep, approximately how long it took them to fall asleep, how many times they woke in the night and the duration of the wakeful period, the time they woke in the morning and the time they rose in the morning (Appendix 11).

Visual Analogue Scales (VAS)

Proceeding the initial standardised baseline assessments, participants were asked to rate their daily experience of sleep, pain, anxiety, quality of life for the day before using a scale (1 – 10). Daily questions included: Last night, how well did you sleep (1 being poor, 10 being good)? Yesterday, how much pain did you experience (1 being no pain, 10 being the worst pain possible)? Yesterday, how anxious were you (1 being no anxiety, 10 being extremely anxious)? Yesterday, to what extent did your physical health or emotional problems interfere with your normal social activities? (1 being no interference, 10 extreme interference)?

2.5.4 Wrist-worn device

Participants wore a consumer-grade wearable (Vivosmart 4, Garmin) on their non-dominant wrist for seven days, coinciding with the sleep diary and non-motor symptoms recording. Devices were worn continuously, with the exception of daily charging which resulted in removal for a proportion of the day. A minimum of fourteen hours of recorded data was required for each 24-hour period (12.00PM - 11.59 AM). The Garmin Vivosmart 4 is a microelectromechanical systems (MEMS) triaxial accelerometer. Data was sampled at a rate of 1Hz. In addition to triaxial acceleration (x, y, z), heart rate (HR), step count and pulse oximetry were recorded.

2.5.5 Sleep/wake algorithm

We used a published algorithm validated against PSG to derive sleep/wake and/or to determine sleep stages in our own data, detailed below.

Walch's et al. algorithm

We modified Walch et al. (2019) validated algorithm to derive sleep/wake and sleep stages from raw triaxial acceleration and HR data.[493] Using these two features, logistic regression, *k*-nearest neighbours, a random forest classifier and a neural net were used as models for our comparison. Code used to perform analysis and generate figures is available at https://github.com/ojwalch/sleep_classifiers. Models were trained using the datasets described below.

2.5.6 Datasets

Initial training of the model was done with either the Multi-ethnic Study of Atherosclerosis (MESA) or the Apple Watch (data collected by Walch et al. (2019)). HR data was only available from PSG recordings for the former dataset, therefore we tested both to compare whether this impacted sleep/wake and sleep stage detection. These datasets are detailed below.

Multi-ethnic Study of Atherosclerosis (MESA)

The National Sleep Research Resource (NSRR: https://sleepdata.org/) provides access to the MESA dataset, a longitudinal investigation of factors associated with the development of subclinical cardiovascular disease and progression to clinical

cardiovascular disease.[494,495] Data consists of seven days of motion data from wrist-worn actigraphy-derived activity counts and a full night of PSG collected (2010 – 2012). Actigraphy recorded activity counts in 1/30Hz and electrocardiography (ECG) is recorded at 256Hz. A total of 6,814 individuals from diverse ethnicities (black, white, Hispanic and Chinese-American) aged 45-84 were recruited, of these 2,237 underwent polysomnography. For the purpose of the study, we used 1,835 subjects with recorded actigraphy and PSG data.

Apple Watch

This sample (n =31) included a digital sleep diary, 7-14 days of raw acceleration and HR data (Apple Watch Series 2 and 3, Apple Inc) and a night of concurrent PSG (https://github.com/ojwalch/sleep_accel).[493]

2.5.7 Predictive models

Four commonly used machine learning algorithms were utilised using Python's sklearn (version 0.20.3) to compare different classification algorithms.

1. Logistic regression: used to directly estimate the probability of a binary response
2. *k*-nearest neighbours is a non-parametric learning algorithm that calculates the distance of a new data point to all other training points. It then selects the *k*-nearest data points and assigns the data point to the class to which the majority of the *k* data points belong.
3. Random forest is an ensemble of decision tree classifiers. The members of the ensemble are obtained by applying bootstrap aggregation to decision learners. A training set repeatedly selects B random samples (without replacement) of the same size, each tree uses the randomly selected data as the training set and fits a decision tree to the training sample resulting in a decision tree (forest). Test samples are then classified by taking a majority vote over the class labels produced by the tree of forests.
4. Neural net makes predictions by comparing the prediction to the desired output and adjusting its internal state to predict correctly next time.

The hyperparameters searched for each classifier are provided in the Table below (2.6).

Table 2.10 Hyper-parameter search table

Classifier	Hyperparameter	Weights
Logistic regression	C	[0.001, 0.01, 0.1, 1, 10, 100]
	penalty	[L1, L2]
k-nearest neighbours	n_neighbours	[500, 1000]
Random forest	max_depth	[10, 50, 100]
Neural net	alpha	[0.1, 0.01, 0.001, 0.0001, 0.00001]

2.5.8 Algorithm training/validation

Models were trained and tested using Monte Carlo cross-validation, the dataset was randomly split 50 times into a training set (approximately 70% of the subjects) and testing set (~30%). The classification ability of each algorithm was summarised using receiver operating characteristics (ROC) curves and precision-recall curves. ROC curves are created by varying a threshold parameter and plotting the true positive and false-positive rates at a threshold against each other.[496] Higher area under the ROC curve suggests that the model is better able to distinguish classes. Precision-recall curves were also plotted due to class imbalance between sleep and wake, the recall (*x*-axis) is the fraction of wake epochs scored correctly, and the precision (*y*-axis) shows the fraction of all epochs labelled wake that were true.[497] Better classification is indicated by curves tending towards the top right. Higher area under the ROC curve (AUC) suggest that the model is better able to distinguish classes.

Each ROC and precision-recall curve for sleep/wake and wake/NREM/REM classification represents the average performance across all 50 training and testing sets. Bland-Altman plots visualise the differences between classifier and PSG values (*y*-axis) versus PSG values (*x*-axis). This plot was generated using fixed thresholds for wake ($^{\theta}W = 0.3$) and REM sleep ($^{\theta}REM = 0.35$). The fraction of true sleep epochs scored correctly (sensitivity), the fraction of true wake epochs scored correctly (specificity), accuracy was determined and averaged across trials.

2.5.9 Performance measures

Agreement between the predicted classes and PSG sleep stages were assessed using accuracy and Cohen's kappa coefficient of agreement (κ). Agreement was computed for two classes (sleep/wake) and three classes (wake, NREM and REM) over the

average data splits of the kappa value using thresholds that generate the highest accuracy. We calculated sensitivity and positive predictive value (PPV) in respect to the detection of the positive class.

2.5.10 Data processing and analysis

Triaxial data was pre-processed, filtered and calibrated by Garmin. Outcomes were averaged across valid days. We derived sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), sleep efficiency (SE), REM sleep minutes and NREM sleep minutes from our raw triaxial acceleration and heart rate data using Walch's algorithm.

2.5.11 Statistical analysis

Walch's algorithm was written and run using Python (Python Software Foundation, http://www.python.org). The overall score of baseline standardised questionnaires (PSQI, ESS and DNMSQuest) were compared using Student *t*-test or Mann-Whitney U methods. Mean scores of sleep measures from the wrist-worn device and sleep diary were calculated per participant and compared between groups using a Mann-Whitney U test.[498–502] Agreement between sleep measures derived from the wrist-worn device and sleep diary were assessed using Bland-Altman plots and intraclass correlation coefficient (ICC) and compared using a paired *t*-test. We evaluated the relations between the wrist-worn sleep parameters and the sleep PROs using a repeated measures correlation.

3 Adult-onset idiopathic dystonia: a national data-linkage study to determine epidemiological, social deprivation and mortality characteristics

3.1 Introduction

As discussed in Chapter 1, the true prevalence of dystonia remains largely unknown and varies widely across distinct studies. Accurate epidemiological information is vital, not only for improved understanding of the disorder but also to ensure better provisioning of clinical services, providing context for diagnostic decision-making, as well as insights into the life expectancy and co-morbidities.

To date, several methodological approaches have been used for cohort ascertainment including service-based, linkage record-based and population-based studies, with some also involving confirmatory clinical diagnosis. Although it is difficult to determine, these differences in study design may go some way to explain the varied prevalence rates observed to date. Table 3.1 summarises the main prevalence studies of dystonia.

Predominant types of prevalence studies amongst dystonia cases include service-based and population-based. Service-based studies are more common, with twenty studies ascertaining patients from referrals to inpatient clinics. Prevalence estimates amongst this study design are often in the lower end of the range, varying between 6.1 and 70.1 per 100,000,[503,504] while a meta-analysis of twelve service-based studies estimate an overall global prevalence of 16.43 per 100,000.[8] Of the four record linkage studies, estimates are similar to service-based studies (~30 per 100,000), likely due to assessment of medical records.[3,397,505] Eight studies have used a population-based approach, identifying cases from the general community using door-to-door surveys or electronic questionnaires. In comparison to health record-based approaches prevalence rates appear higher owing to poor response rate and lack of diagnostic screening tools.[382,506] Amongst these studies two notable outliers estimate a prevalence of 732 and 410 per 100,000.[7,382]

However, use of traditional service-based methods to determine the prevalence of dystonia has several limitations. Firstly, identification through medication records reflects only those seeking treatment, missing those that cannot access routine clinical care. Secondly, given the degree of clinical heterogeneity, dystonia frequently goes undiagnosed or is misdiagnosed, further limiting the data derived

from this approach. Although the number of patients identified in service-based studies is larger than population-based studies, these factors are likely to contribute to the under-ascertainment of cases. To counter this, population-based studies can be used to identify a broader group of cases, although this approach has its own limitations, such as cost, practicality, response bias and assurance of an accurate diagnosis.

Work to date also suggests that geographical location may also affect prevalence. Northern European and American countries tend to have a higher prevalence than those observed in Asia and Southern Europe.[83,382,504,506,507] However, the higher rates of AOIFCD in the Caucasian population compared to other races may explain geographical variations.[392] Interestingly, a higher prevalence of dystonia (60.2 per 100,000)[508] and an unusual form of thumb flexion dystonia (75/227)[509] has been noted in the Faroe Islands, potentially due to the genetic nature of dystonia and founder effects.

Another way to undertake epidemiological studies is through the use of linked healthcare data records, overcoming many of the limitations outlined above. Due to the elevated rates of chronic diseases, co-ordination across different care settings is required to meet the rise in healthcare demands. Often patient outcomes remain separated and fragmented, however, bringing information together allows a more comprehensive understanding of patient healthcare. As individuals interact with health and other services, data is collected as part of an interaction and stored electronically. Data from separate sources relating to the same individual can be combined, allowing for the identification of relationships between factors which may not be evident in a single source.

Increasingly, linkage of data has become a central tool in health research because of its many advantages. Firstly, diseases may not manifest until several years after the initial incidence or other historic factors may contribute to disease onset, in these cases retrospective analysis may provide valuable information. Secondly, longitudinal data is accessible allowing for health events to be followed-up, while also reducing the number of participants lost to follow-up. Thirdly, concurrent diseases may occur or be associated with social economic factors, although often not

reported together data linkage allows for co-morbidity to be investigated. Finally, it can be difficult to generate sufficient information on rare diseases, however, linkage from multiple sources over several years and across diverse geographic areas may increase case numbers.

Table 3.1 Summary of studies investigating the prevalence of dystonia

Author	Year	Country	Study design	Type of Dystonia	Age of study population	Population size	Female:Male ratio	Mean age at onset (SD)	Prevalence per 100,000
Population-based studies†									
Li et al[510]	1985	China	Population-based	Focal/Generalised dystonia	All ages	63,195	-	-	Generalised:5 Focal: 3 Overall: 7.91
Kandil et al[511]	1994	Egypt	Population-based	Focal dystonia	All ages	42,000	Focal: 0.33:1 Drug-induced: 1:1 Encephalitic: all males (0:3) Overall: 0.4:1	Focal: 34.6 ± 4.9 Drug-induced: 28 ± 12.4 Encephalitic: 31.3 ± 6.4	Focal: 10 Drug-induced: 10 Encephalitic: 7 Overall: 26
Müller et al[512]	2002	Italy	Population-based	Focal/Segmental dystonia	≥50	707	1:1	50.5 (median)	732
Jankovic et al[382]	2007	USA	Population-based	Focal/Segmental dystonia	≥18	60,062	-	-	390
Das et al[506]	2007	India	Population-based	Primary dystonia	All ages	52,377	-	-	Primary: 43.91 Early onset: 5.72 Late onset: 38.18
El Tallawy et al[513]	2010	Eygpt	Population-based	Dystonia – not specified	All ages	62,583	-	-	30.36

El Tallawy et al[507]	2013	Eygpt	Population-based	Dystonia – not specified	All ages	33,285	-	-	39.11
Badry et al[514]	2019	Egypt	Population-based	Primary dystonia	All ages	33,285	2:1	-	9.01
Service-based studies‡									
Nakashima et al[503]	1995	Japan	Service-based	Focal dystonia	All ages	244,935	1.14:1	-	Focal:6.12
ESDE Collaborative Group[515]	2000	France, Austria, England, Spain, Finland, Germany, Portugal, Italy	Service-based	Focal/Segmental dystonia	> 20	5,792,937	Focal: 1.5:1 Segmental: 1.9:1	-	Focal: 11.7 Segmental: 3.2 Focal and segmental: 14.8
Defazio et al[516]	2001	Italy	Service-based	Focal/Segmental dystonia	All ages	67,606	8:1	Female: 60 Male: 40 Overall: 57.4	Focal and segmental: 13.3 Focal BSP: 7.4 Segmental BSP: 5.9
Castelon Konkiewitz et al[517]	2002	Germany	Service-based	Focal/Segmental/Generalised dystonia	All ages	1,322,883	Segmental: 2.3:1 Generalised: 1.0:1	Generalised: 9.8 ± 2.9 Segmental: 55.0 ± 12.8	Focal: 10.1 Segmental: 3.0 Generalised: 0.3 Overall: 17.4

Matsumoto et al[5]	2003	Japan	Service-based	Focal/Segmental/Generalised dystonia	All ages	1,459,130	1.1:1	Primary: 48.8 ± 16.5	Generalised: 0.07 Focal: 10.1
Pekmezović et al[396]	2003	Serbia	Service-based	Focal/Segmental dystonia	≥20	1,602,226	Focal: 1.5:1 Segmental: 1.1:1 Overall: 1.4:1	Female: 48.8 ± 13.0 Male: 41.8 ± 16.5 Both: 46.0 ± 14.9	Focal:11.2 Segmental: 2.2 Overall: 13.6
Le et al[518]	2003	Norway	Service-based	Focal/Segmental dystonia	All ages	508,726	2.1:1	46.3	25.4
Asgeirsson et al[519]	2006	Iceland	Service-based	Focal/Segmental/Generalised dystonia	All ages	288,801	1.9:1	42.7	Generalised: 0.3 Focal: 31.2 Segmental: 3.1 Overall: 37
Sugawara et al[4]	2006	Japan	Service-based	Focal/Generalised dystonia	All ages	1,166,967	-	-	Generalised: 0.68 Focal: 14.4 Overall: 15.1
Cossu et al[520]	2006	Italy	Service-based	Focal dystonia	All ages	1,652,332	2.5:1	58.5 ± 13	3.22

Fukuda et al[521]	2006	Japan	Service-based	Focal dystonia	All ages	247,973	0.9:1	Female: 54.3 ± 13.2 Male: 43.5 ± 13.0 Both: 48.6 ± 14.0	13.7
Papantonio et al[522]	2009	Italy	Service-based	Focal/Segmental dystonia	>17	541,653	1.46:1	-	Focal and segmental: 12.74 (adjusted: 13.8)
Bhidayasiri et al[523]	2011	Thailand	Service-based	Focal/Segmental/Generalised dystonia	All ages	1,039,595	1.18:1	Males: 42.0 ± 18.1 Females: 47.3 ± 18.4	Primary dystonia: 13.6 Focal dystonia: 14.3 Overall: 19.9
Joensen[508]	2016	Faroe Islands	Service-based	Focal dystonia	All ages	48,100	1.9:1		60.2
Atehortúa et al[504]	2016	Colombia	Service-based	Focal/Segmental/Generalised dystonia	All ages	6,221,742	1.6:1	44	Focal: 7.6 Segmental: 1.1 Generalised: 0.7 Overall: 71.2
Wang et al[6]	2016	China	Service-based	Late-onset dystonia	>26	54,938,000	2:1	48.54 ± 13.08	2.7

Williams et al[83]	2017	Republic of Ireland	Service-based	Focal dystonia	≥20	4,588,252	-	-	17.8
Ortiz et al[81]	2018	Finland	Linkage-record base and service-based	Focal/Segmental/Generalised dystonia	≥20	2,043,819	Generalised: 2.5:1 Segmental: 3.7:1 Overall: 2.7:1	Generalised 49 ± 12 Segmental: 58 ± 12 Overall: 54 ± 12	Generalised: 0.2 Segmental: 3.3 Overall: 40.5
Louis et al[509]	2019	Faroe Islands	Service-based	Focal/Segmental dystonia	≥40	24,154	-		8.28
Record-linkage studies§									
Nutt et al[3]	1988	USA	Record-linkage	Focal/Generalised dystonia	All ages	56,433	Generalised: all males (0:3) Focal: 1.46:1	Generalised: 20 Focal: -	Generalised: 3.4 Focal: 29.5 Overall: 33.67
Duffey et al[524]	1998	England	Record-linkage	Focal/Generalised	All ages	2,605,100	Generalized: 1.3:1 Overall: 2.1:1	Generalized: 16.7	Generalized: 1.4 Focal: 12.9 Overall: 14.3
Butler et al[397]	2004	England	Record-linkage	Focal/Segmental/Generalised	All ages	2,605,100	Generalized: 1.6:1	Generalized: 1.6:1	Generalized: 1.6:1

Hellberg et al[505]	2019	Sweden	Linkage record-based	Primary dystonia	All ages	9,640,000	-	-	35.1

†Population-based approaches identify cases from the general community to represent the population e.g. door-to-door surveys or electronic questionnaires. ‡Ascertain cases from inpatient clinics e.g. service users. §Combines data from health and other services e.g. medical records, death records and socioeconomic status

A number of linkage centres exist world-wide, each using different linkage approaches depending on the country. The Scandinavian countries link data between nationwide registers by using unique individual identification numbers given at birth, database include MigMed2 (Sweden) and Statistics Norway. Databanks in Australia (Centre for Data Linkage, CDL), New Zealand (Integrate Data Infrastructure, IDI) and the UK (Secure Anonymous Linkage, SAIL and Clinical Data Linkage Service, CDLS) use unique anonymous identifiers to link datasets (see Chapter 2 for more detail), while the Clinical Evaluative Sciences (ICES, Canada) uses a similar method, data is identifiable in order to perform linkage but later de-identified for research purposes. Notable health data linkage projects in the USA include the nationwide Million Veteran Program (MVP) which focuses on the healthcare of veterans, while the Rochester Epidemiology Project (EDP, Minnesota) collaborates with health care providers such as the Mayo Clinic. The International Health Data Linkage Network (IHDLN, 2008) was established to facilitate collaboration and record research outputs, to date, it has ~1,100 participating data linkage centres in 55 countries.

Three studies have estimated the incidence of dystonia, all within the USA, three studies estimate incidences of cervical dystonia between 0.8 and 1.18 per 100,000 person-years[3,391,392] while incidence rates of other types of dystonia varied between 0.2 and 0.4 per 100,000 person-years.[3] It is likely that these are minimum estimates, given the underdiagnosis of dystonia.

In the UK, the dystonia prevalence has been studied only three times in England, with one of these forming part of a larger European study. Of these three studies, none of which are within the last decade, the number of cases ascertained were relatively small and limited to catchment areas making these studies vulnerable to local clusters. There is currently no literature available concerning dystonia in the Welsh population, and a record linkage-based approach has yet to be employed, in spite of two available UK healthcare linkage databases, the CDLS and SAIL (see Section 2.2 for more information on the SAIL databank).

In this chapter we aimed to derive an algorithm to identify individuals diagnosed with dystonia, and to establish key epidemiological characteristics, including links to deprivation and causes of mortality.

3.2 Methods

3.2.1 Study design and data sources

Using a retrospective population-based cohort study design, we identified patients diagnosed with dystonia within the SAIL Databank (Swansea University, UK: www.saildatabank.com). SAIL is a databank containing anonymised, electronic, person-based health, social and education data about the population of Wales. Clinical and demographic data from multiple data-providing organisations, including Welsh General Practices, Public Health Wales NHS Trust, Digital Health and Care Wales, HDR Wales, Welsh Government, Office for National Statistics, Welsh Ambulance Service NHS Trust, Intensive Care National Audit & Research Centre, are anonymised and encrypted by a trusted third party, the NHS Wales Informatics Service (NWIS), and transferred directly to SAIL. Individuals are reliably matched against records and anonymised using a unique Anonymous Linking Field. This matching algorithm has demonstrated high specificity (>99%) and sensitivity (>95%) and enables linkage across different datasets at a person-based level (Section 2.2.2).[469,470]

Our study population was formed from primary care (Welsh Longitudinal General Practice dataset, WLGP) and secondary care (Patient Episode Database for Wales, PEDW and Outpatient Dataset, OPD) between January 1994 (utilization of the reference population and the first monogenic form of dystonia identified in 1994 (DYT5a))[48] December 2017. At the time of analysis, primary care and secondary care data were available for ~80% and 100% of the Welsh population respectively. Time coverage varies between GP practices, and there are dates with higher periods of data capture within SAIL, for example 2004–2007. Inpatient (PEDW) and outpatient (OPD) datasets commenced in 1997 and 2004 respectively. We recorded demographic characteristics including age, sex, GP registration history and deprivation. We measured deprivation using the Welsh Index of Multiple Deprivation (WIMD) obtained from the Welsh Demographic Service Dataset

(WDSD) which contains administrative data on all persons registered with a primary care practice in Wales.[473] Date and cause of death (if applicable) were obtained from the Annual District Death Extract (ADDE) (Section 2.3). Data was analysed from September 2020 to May 2021.

3.2.2 Reference population and diagnostic validation

Anonymised records from 90 patients, with a confirmed diagnosis of adult-onset idiopathic, isolated focal cervical dystonia (AOIFCD) were linked to records held in SAIL. Each participant was recruited via the Welsh Movement Disorders Research Network Study (REC reference: 14/WA/0017, IRAS ID: 146495), were clinically assessed and had their National Health Service (NHS) records reviewed by a neurologist with expertise in movement disorders (K.J.P). These patients formed the reference population for our derived cohort of individuals diagnosed with dystonia.

3.2.3 Sensitivity algorithm

A list of Read Codes (version 2) and ICD (International Classification of Diseases) version 10 codes were selected and used to identify individuals with a primary and/or secondary dystonia diagnosis. All codes relevant to dystonia including diagnosis, symptoms and therapy were reviewed by a clinical neurologist with movement disorder expertise. Code lists were created to maximise the positive predictive value, while maintaining a reasonable sensitivity. In a step-wise manner, Read Codes that did not contribute to the identification of the reference cohort were removed. All ICD-10 codes, excluding drug-induced dystonia, were used. Sensitivity analyses of Read Codes are available in Appendix 12. A full list of the final Read and ICD-10 Codes are summarised in Table 3.2.

Table 3.2 ICD-10 Codes and Read Codes used to identify dystonia patients in hospital and GP electronic records, respectively

Dystonia subtype	ICD-10 Code	Read Code	Read Code Description
Genetic torsion dystonia	G24.1		
Idiopathic torsion dystonia		F136.	Idiopathic torsion dystonia
		F137.	Symptomatic torsion dystonia
		F137y	Symptomatic torsion dystonia OS
		F137z	Symptomatic torsion dystonia NOS
		F138.	Fragment of torsion dystonia
		F138z	Torsion dystonia fragment NOS
Idiopathic nonfamilial dystonia	G24.2		
Idiopathic familial dystonia		F1360	Idiopathic familial dystonia
Cervical dystonia	G24.3	F1382	Spasmodic torticollis
		16A3.	Torticollis – symptom
		N135.	Torticollis unspecified
		N1350	Intermittent torticollis
		N135z	Torticollis NOS
Idiopathic Orofacial dystonia	G24.4		
Blepharospasm	G24.5	F1380	Blepharospasm
Writer's cramp		F1383	Organic Writer's cramp
Myoclonic dystonia		F13B.	Myoclonic dystonia
Segawa syndrome		F13C.	Segawa syndrome
Other	G24.8	Fyu24	[X]Other dystonia
Unspecified	G24.9	Fyu2A	[X]Dystonia, unspecified
		F13X.	Dystonia, unspecified
Tremor		1B22.	Has a tremor

Abbreviations: NOS; Not Otherwise Specified, OS; Other Specified, [X] = External causes of morbidity and mortality

3.2.4 Dystonia diagnosis

An individual was defined as having a diagnosis of dystonia if their GP or hospital record contained a Read Code version 2 or ICD-10 code from the list of codes (Table 3.2). Dystonia subtypes were not mutually exclusive, an individual could have more than one dystonia subtype. Results from primary and secondary care extracts were combined to create a joined dystonia cohort. Individuals diagnosed with a potential secondary cause of dystonia were excluded (Table 2.2-2.4).[505,525] Our stringent exclusion criteria removed diagnostic codes linked with tremor (apart from dystonic tremor) and diagnoses that may include tremor as part of the phenotype. Medicine codes for all forms of dopaminergic therapy were also included in this exclusion algorithm, providing an additional mechanism to exclude degenerative forms of tremor. Inclusion of the tremor code was shown to increase the sensitivity of our patient identification algorithm by 6% (73% to 79%) in our validation cohort, allowing for recognition of dystonic tremor as a form of primary dystonia, while limiting the possibility of including other forms of tremor.

Additionally, individuals were required to be resident in Wales at the time of diagnosis and have an age, sex and GP registration date recorded. Individuals born before 1st January 1900 and over the age of 100 were excluded. Entry date into the cohort was the first date of a new dystonia diagnosis and the last date of follow-up was the earliest GP de-registration (from a contributing practice), date of death or the end of the study period, whichever was first. Figure 3.1 summarises how the dystonia cohort was derived.

We identified all dystonia cases in primary and secondary care datasets, however further analysis including epidemiological, deprivation and mortality characterisation focuses on individuals with adult-onset idiopathic dystonia (≥ 20 years of age).

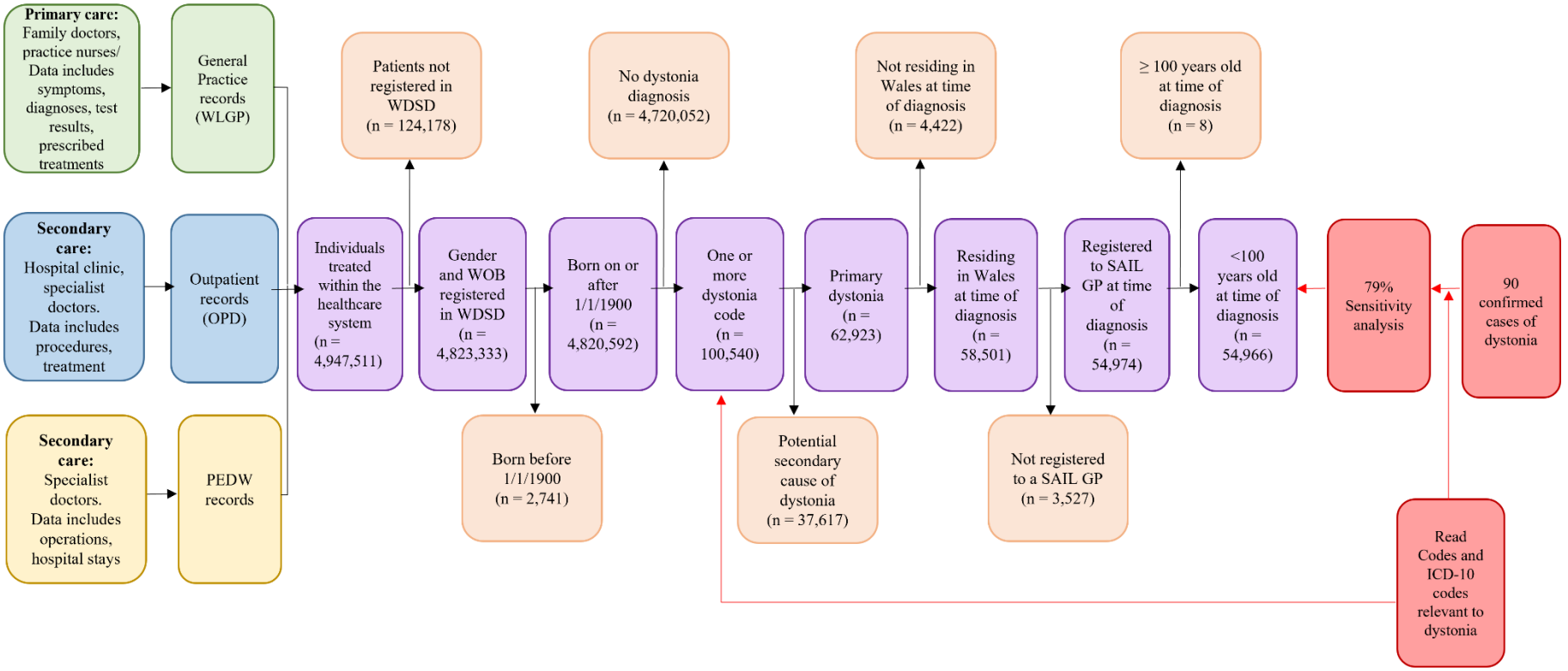

Figure 3.1 Flow diagram of cohort development

3.2.5 Incidence and prevalence

Estimates for prevalence and incidence were calculated annually for the study period (January 1994–December 2017). Prevalence was calculated by dividing the number of people diagnosed with dystonia mid-year (30th June) by the mid-year population estimate. Incidence was calculated by dividing the number of newly diagnosed cases (no previous diagnosis) for that year by the mid-year population estimate. The mid-year population was estimated by the total number of Welsh residents with a recorded sex and age, registered to a GP practice on 30th June of that year.

3.2.6 Deprivation score

Deprivation scores were derived using WIMD 2014 quintiles according to Lower Super Output Area (LSOA) of residence (2011) (Section 2.3.5.4). WIMD identifies and ranks all LSOAs in Wales from 1 (most deprived) to 1909 (least deprived), each LSOA is then grouped into quintiles with 1 being the most deprived and 5 being the least deprived.[473] The WIMD quintile was assessed at three dates: study entry, time of dystonia diagnosis, and exit date from the study (study end December 2017, de-registration from GP, moving out of Wales, or death).

3.2.7 Mortality

Date and underlying causes of death during the study period were determined from the ADDE (Section 2.3.5.5). Underlying causes of deaths coded using ICD-9 were converted to ICD-10.

3.2.8 Statistical analysis

Data was analysed using R software (version 4.0.4). Where applicable, a t-test or Mann-Whitney U was used to determine any significant difference in the median age at diagnosis and subtype of dystonia, and Wilcoxon signed-rank test used to determine changes to WIMD quintile following diagnosis.

3.3 Results

3.3.1 Validating the dystonia diagnosis

The optimised case-ascertainment algorithm (Figure 3.1), had a diagnostic sensitivity of 79%, identifying 70/89 of the clinically confirmed reference population (one patient could not be identified within SAIL).

3.3.2 Dystonia cohort

A total of 54,966 patients were identified as having been diagnosed with dystonia between 1st January 1994 and 31st December 2017. Of these, 54,488 were identified from primary care (GP records) and 478 from secondary care (hospital records). Of these, 41,660 were determined to have adult-onset symptoms (aged ≥ 20 years) and 13,306 young-onset forms of dystonia (aged < 20 years) (Table 3.3). In adult-onset forms, the female:male ratio was 1.7:1. Fourteen cases had more than one dystonia diagnosis. The most common combination of diagnoses was cervical dystonia and unspecified (n = 8). No cases of idiopathic familial dystonia or Segawa syndrome were identified, irrespective of levodopa medication exclusion.

3.3.3 Prevalence and Incidence rates

There were 32,662 patients diagnosed with adult-onset idiopathic dystonia at the mid-point of 2017 providing a crude prevalence of 1.2% amongst the Welsh population (Figure 3.2). During the study period, 41,660 new cases of adult-onset idiopathic dystonia were reported, giving a mean incidence of 87.6/100,000/year, varying between 49.9/100,000/year in 1994 and 96.2/100,000/year 2017. The maximum incidence was 112.7/100,000/year in 2006 (Figure 3.3 and Table 3.4). Dystonia incidence increased in males and females, 23.5/100,000 to 62.6/100,000 (1994 and 2017), and 45.5/100,000 to 95.1/100,000 (1994 and 2017), respectively.

Table 3.3 Summary of clinical characteristics for adult-onset idiopathic cases (≥ 20 years)

	Overall dystonia	**Genetic torsion dystonia**	**Idiopathic torsion dystonia**	**Idiopathic non-familial dystonia**	**Cervical dystonia**	**Idiopathic orofacial dystonia**	**Blepharospasm**	**Writer's cramp**	**Mycolonus dystonia**	**Other/ Unspecified**	**Tremor associated with dystonia**
Total participants	41,660	5	39	<6	26,563	24	1,181	41	8	604	13,207
Sex											
Female (%)	26,311 (63)	<>	26 (67)	<>	17,185 (65)	16 (66.7)	773 (65)	25 (61)	<>	375 (62)	7,905 (60)
Male (%)	15,349 (37)	<>	13 (33)	<>	9,378 (35)	8 (33.3)	408 (35)	16 (39)	<>	229 (38)	5,302 (40)
Median age of diagnosis (IQR)	42 (28)	49 (9)	49 (22)	38.5 (13.5)	38 (20)	72.5 (27.25)	48 (29)	40 (21)	44.5 (13.75)	48 (29)	55 (34)
Female median age of diagnosis	41*	55	47.5	38.5	37*	73	51*	36	44	48*	55
Male median age of diagnosis	43	45	50	-	39	72.5	45	43.5	68	45	55

*Significant difference in age at onset between sexes ($p<0.05$) †Wilcoxon signed-rank test. <>Masked to prevent identification of small numbers (<5) -No data available

No cases of Segawa syndrome or Idiopathic Familial dystonia were identified.

Table 3.4 Annual incidence and mid-year point prevalence rates for adult-onset idiopathic dystonia cases

Year	Number of new dystonia cases	Number of new male dystonia cases	Number of new female dystonia cases	General population	Incidence per 100,000	Mid-year prevalence	Male mid-year prevalence	Female mid-year prevalence	Mid-year general population	Mid-year point prevalence per 100,000 (%)
1994	829	274	555	2,387,092	49.85	392	133	259	2,387,951	16.42 (0.02)
1995	875	302	573	2,411,453	51.13	1,263	420	843	2,413,550	52.33 (0.05)
1996	874	296	578	2,426,292	52.47	2,056	689	1,367	2,429,537	84.63 (0.08)
1997	996	349	647	2,446,118	59.20	2,950	1,010	1,940	2,450,694	120.37 (0.12)
1998	1,031	387	644	2,456,320	59.68	3,867	1,334	2,533	2,471,221	156.48 (0.16)
1999	1,140	421	719	2,481,424	63.35	4,844	1,697	3,147	2,488,703	194.64 (0.19)
2000	1,182	419	763	2,497,982	67.01	5,796	2,033	3,763	2,506,613	231.23 (0.23)
2001	1,279	435	844	2,515,706	71.75	6,848	2,376	4,472	2,525,873	271.11 (0.27)
2002	1,579	553	1,026	2,531,727	84.92	8,055	2,795	5,260	2,543,627	316.67 (0.32)
2003	1,821	635	1,186	2,556,581	97.28	9,544	3,316	6,228	2,570,531	371.29 (0.37)
2004	2,029	721	1,308	2,589,075	104.09	11,219	3,908	7,311	2,605,341	430.62 (0.43)
2005	2,141	780	1,361	2,616,458	110.42	13,007	4,540	8,467	2,635,190	493.59 (0.49)
2006	2,253	843	1,410	2,636,218	112.66	14,900	5,213	9,687	2,657,535	560.67 (0.56)
2007	2,212	844	1,368	2,650,409	109.53	16,685	5,872	10,813	2,674,089	623.95 (0.62)
2008	2,278	802	1,476	2,663,164	111.37	18,490	6,522	11,968	2,689,309	687.54 (0.69)
2009	2,137	792	1,345	2,666,675	102.00	20,265	7,127	13,138	2,695,097	751.92 (0.75)
2010	2,112	804	1,304	2,667,017	100.37	21,942	7,718	14,224	2,697,599	813.39 (0.81)
2011	2,188	826	1,362	2,663,147	104.39	23,523	8,251	15,272	2,695,725	872.60 (0.87)
2012	2,219	845	1,374	2,669,648	103.83	25,254	8,893	16,361	2,704,405	933.81 (0.93)
2013	2,048	769	1,279	2,670,845	98.55	26,808	9,464	17,344	2,707,537	990.12 (0.99)
2014	2,112	805	1,307	2,674,547	99.68	28,303	10,050	18,253	2,713,203	1043.16 (1.04)
2015	2,035	780	1,255	2,674,043	93.45	29,802	10,577	19,225	2,714,556	1097.86 (1.10)
2016	2,213	844	1,369	2,655,271	100.37	31,286	11,150	20,136	2,697,528	1159.80 (1.16)
2017	2,077	823	1,254	2,633,845	96.21	32,662	11,701	20,961	2,677,690	1219.78 (1.22)
Total	41,660	15,349	26,311							

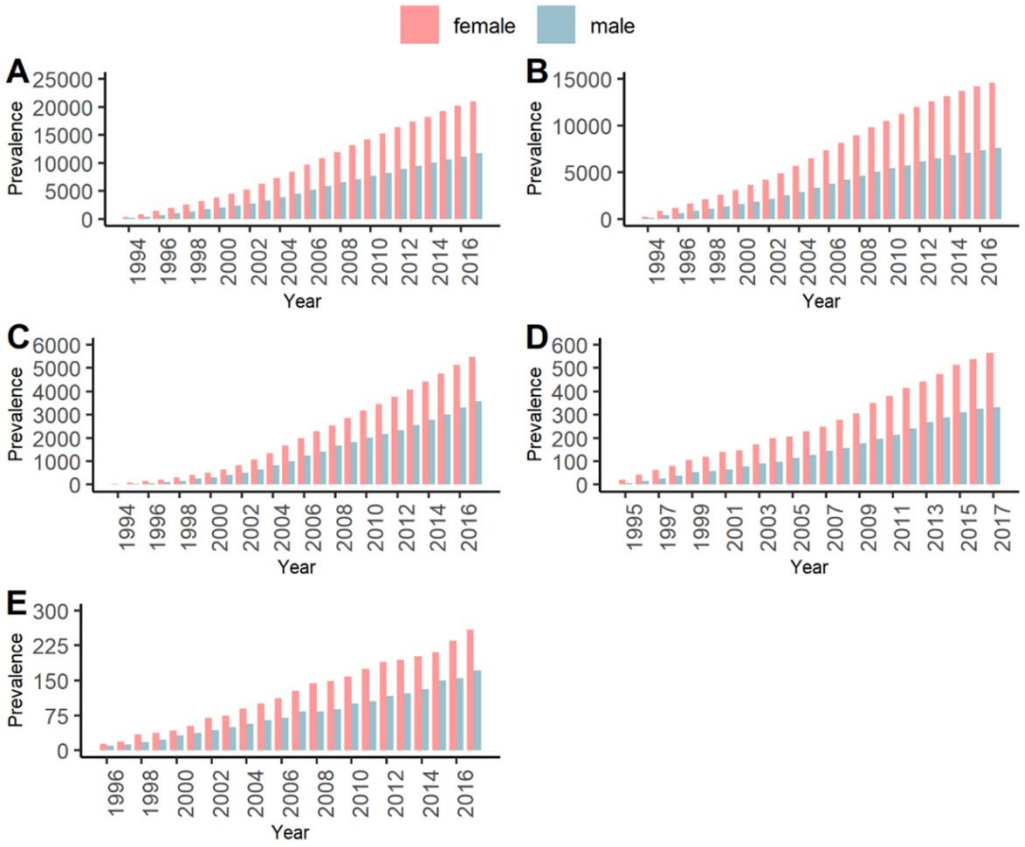

Figure 3.2 Trends in prevalence for adult-onset idiopathic dystonia by sex and dystonia subtype

A: Overall dystonia **B:** Cervical dystonia **C:** Tremor associated with dystonia **D:** Blepharospasm (masked in 1994) **E:** Other/unspecified (prevalence masking in 1994 and 1995)

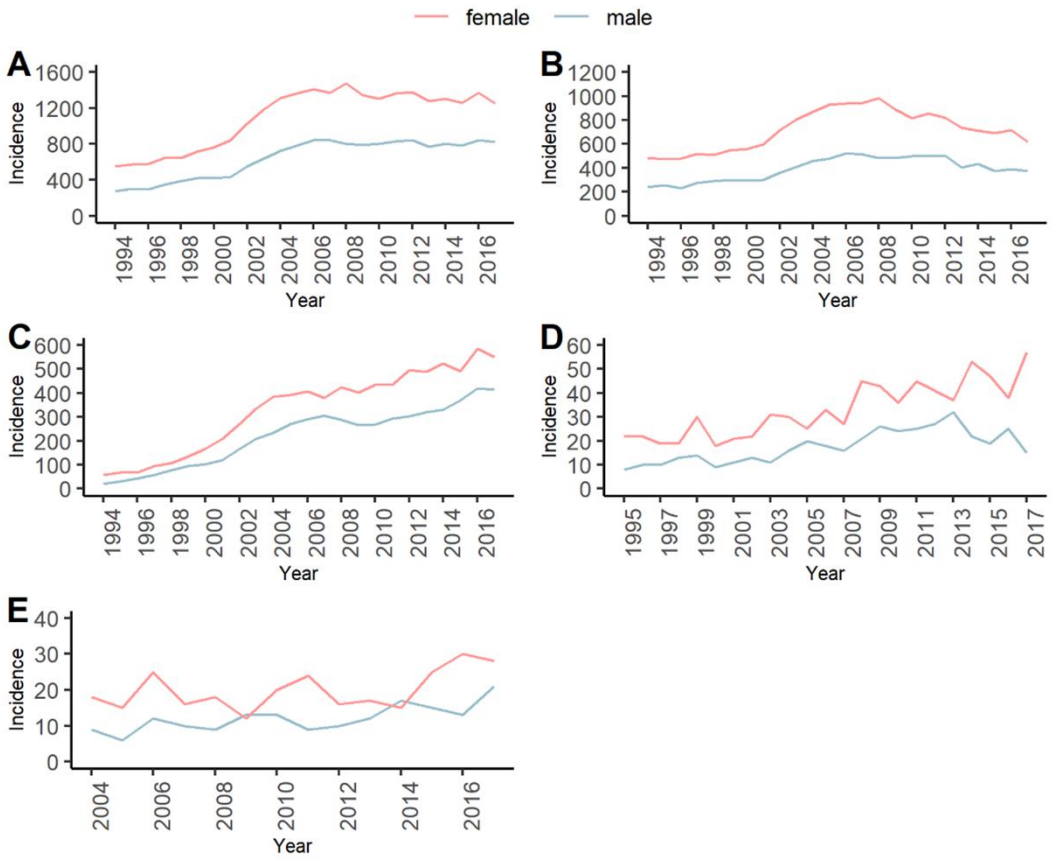

Figure 3.3 Trends in incidence for adult-onset idiopathic dystonia by sex and dystonia subtype

A: Overall dystonia **B:** Cervical dystonia **C:** Tremor associated with dystonia **D:** Blepharospasm (masked in 1994) **E:** Other/unspecified (incidence masked <2004)

3.3.4 Deprivation

At the time of diagnosis, adult-onset cases were equally distributed across deprivation quintiles (Table 3.5 and Figure 3.4A and 3.5A). There were no significant changes in deprivation quintile throughout the study between: entry into the dataset (during the study period) and diagnosis (median 0, $p < 0.01$; Figure 3.6A); diagnosis and follow-up (median 0, $p < 0.01$; Figure 3.6B) and entry into the study and follow-up (median 0, $p < 0.01$).

3.3.5 Mortality

There were 4315 deaths (10%) in the adult-onset dystonia cohort (Table 3.6). Distribution of mortality data by dystonia syndromes, including the 10 most common causes of death, is shown in Figure 3.7.

Table 3.5 Deprivation quintile at dystonia diagnosis for adult-onset idiopathic cases (≥ 20 years)

	Overall dystonia	**Genetic torsion dystonia**	**Idiopathic torsion dystonia**	**Idiopathic non-familial dystonia**	**Cervical dystonia**	**Idiopathic orofacial dystonia**	**Blepharospasm**	**Writer's cramp**	**Mycolonus dystonia**	**Other/ Unspecified**	**Tremor associated with dystonia**
1 (%) most deprived	7,986 (19.17)	<>	<>	<>	4,927 (18.55)	<>	139 (11.77)	6 (14.63)	<>	134 (22.19)	2,768 (20.96)
2 (%)	8,389 (20.14)	<>	8 (20.51)	<>	5,294 (19.93)	<>	218 (18.46)	7 (17.07)	<>	127 (21.03)	2,735 (20.71)
3 (%)	8,952 (21.49)	<>	<>	<>	5,817 (21.90)	<>	267 (22.61)	10 (24.39)	<>	119 (19.70)	2,731 (20.68)
4 (%)	8,012 (19.23)	<>	9 (23.08)	<>	5,169 (19.46)	<>	258 (21.85)	6 (14.63)	<>	106 (17.55)	2,458 (18.61)
5 (%) least deprived	8,321 (19.97)	<>	13 (33.33)	<>	5,356 (20.16)	<>	299 (25.32)	12 (29.27)	<>	118 (19.54)	2,515 (19.04)
Median follow-up in years (IQR)	23.50 (7.65)	9.52 (10.51)	23.98 (8.06)	17.42 (6.60)	23.97 (6.44)	12.46 (8.82)	23.11 (8.40)	21.37 (12.69)	16.76 (7.93)	21.64 (10.54)	22.12 (9.58)
Median change in WIMD quintile at follow-up (p-value)	0 (<0.001)†	0	0 (0.41)†	0	0 (<0.001)†	0 (0.67)†	0 (0.02)†	0 (0.34)†	0 (1)†	0 (0.38)†	0 (0.03)†
Median change in WIMD quintile from entry into dataset to diagnosis (p-value)	0 (<0.001)†	0	0 (0.29)†	0	0 (<0.001) †	0 (0.37) †	0 (< 0.01) †	0 (0.14) †	0 (0.59) †	0 (0.57) †	0 (<0.001) †

*Significant difference in age at onset between sexes (p<0.05) †Wilcoxon signed-rank test. <>Masked to prevent identification of small numbers (<5) -No data available

No cases of Segawa syndrome or Idiopathic Familial dystonia were identified.

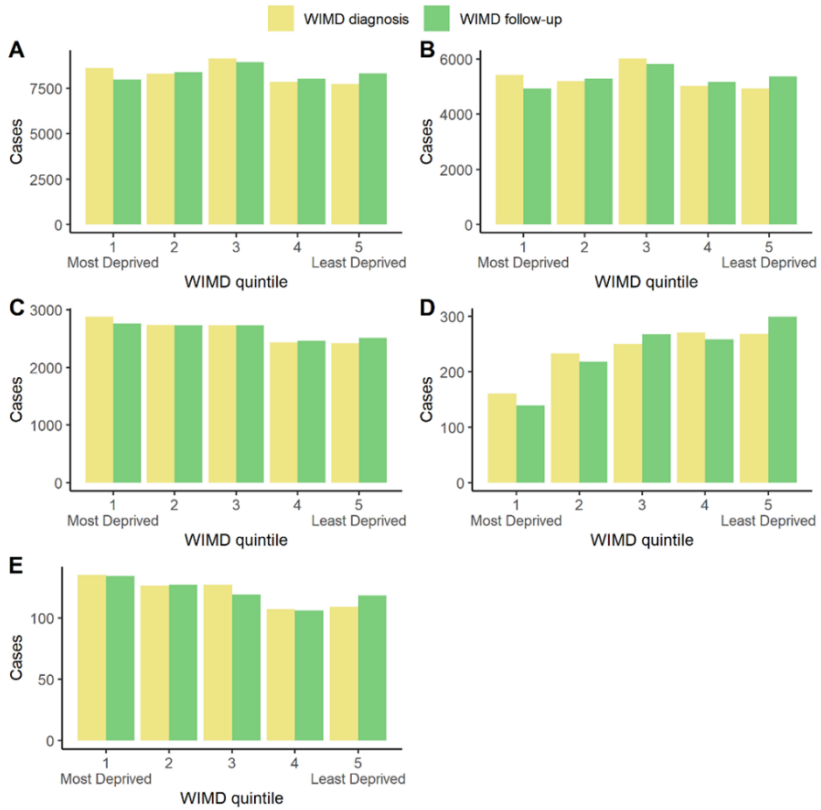

Figure 3.4 Number of cases per WIMD quintile at entry into dataset (during study period) and diagnosis by dystonia subtype in adult-onset forms

WIMD quintile 1 is most deprived and 5 is least deprived

A: Overall dystonia **B:** Cervical dystonia **C:** Tremor associated with dystonia **D:** Blepharospasm **E:** Other/unspecified

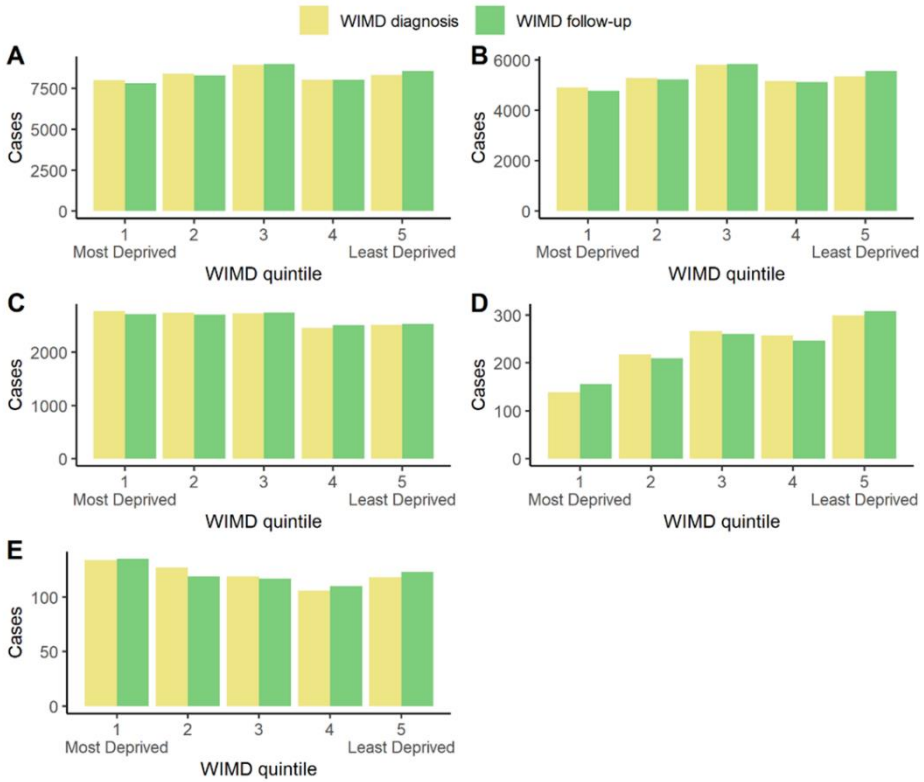

Figure 3.5 Number of cases per WIMD quintile at diagnosis and follow-up by dystonia subtype in adult-onset forms

WIMD quintile 1 is most deprived and 5 is least deprived

A: Overall dystonia **B:** Cervical dystonia **C:** Tremor associated with dystonia **D:** Blepharospasm **E:** Other/unspecified

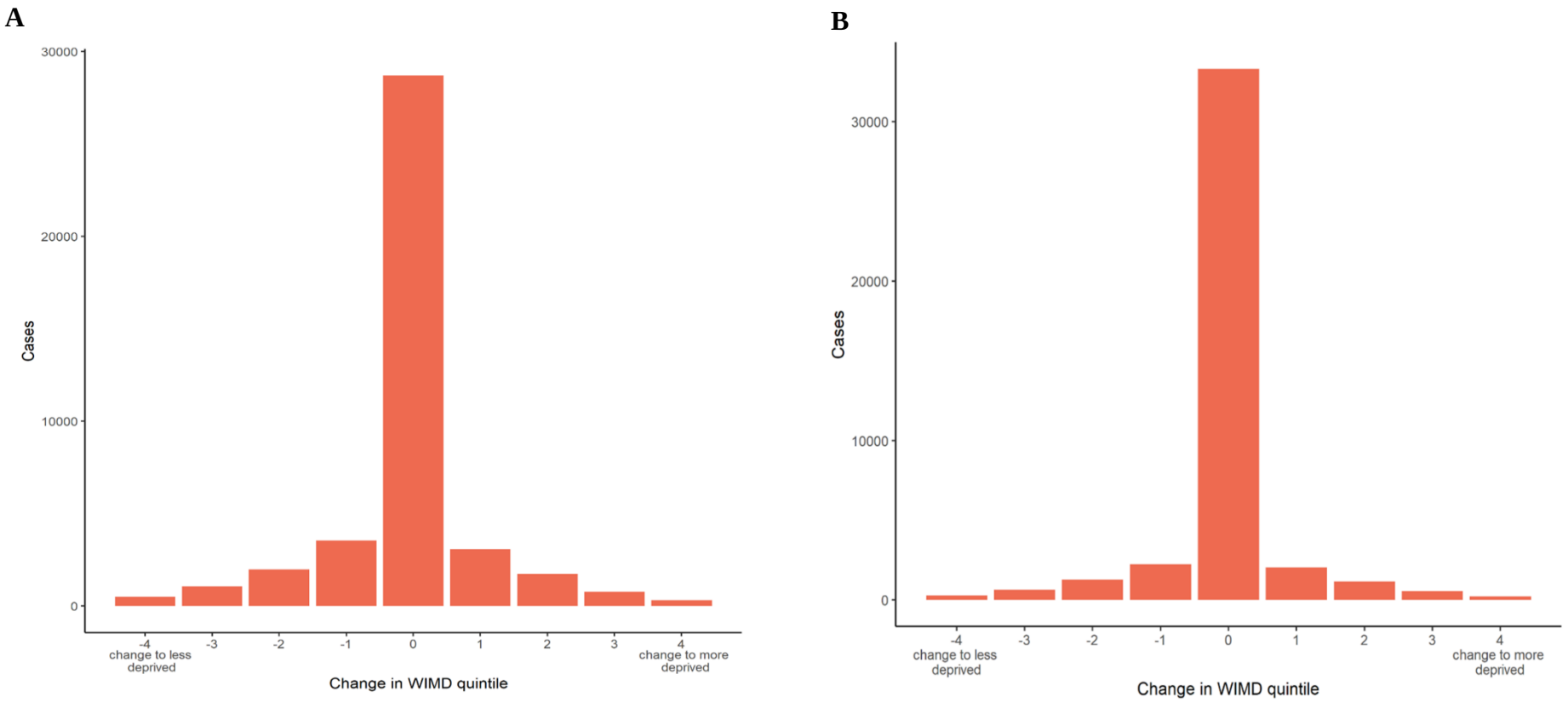

Figure 3.6 Change in WIMD quintile

A) at entry into dataset (during study period) and diagnosis by dystonia subtype in adult-onset forms and **B)** at diagnosis and follow-up by dystonia subtype in adult-onset forms. Change in WIMD quintile = (WIMD quintile at time of diagnosis) – (WIMD quintile at end of follow up)

Table 3.6 Mortality characteristics for adult-onset idiopathic cases (≥ 20 years)

	Overall dystonia	**Genetic torsion dystonia**	**Idiopathic torsion dystonia**	**Idiopathic non-familial dystonia**	**Cervical dystonia**	**Idiopathic orofacial dystonia**	**Blepharospasm**	**Writer's cramp**	**Myoclonus dystonia**	**Other/ Unspecified**	**Tremor associated with dystonia**
Deceased	4,315	<6	5	-	1,475	13	155	<6	<6	93	2,567
Age at death (years)											
<45	149	<>	<>		71	-	<>	<>	<>	6	69
45-64	577	<>	<>		253	-	<>	<>	<>	12	299
65-84	2,048	<>	<>		701	<>	74	<>	<>	44	1,214
≥85	1,541	<>	<>		450	<>	69	<>	<>	31	985
Female deceased (%)	2,417 (56)	<>	<>		755 (51)	8 (62)	110 (71)	<>	<>	64 (69)	1,475 (57)
Male deceased (%)	1,898 (44)	<>	<>		720 (49)	5 (38)	45 (29)	<>	<>	29 (31)	1,092 (43)
Median age at death (IQR)	80 (17)	65 (10)	70 (7)		79 (19)	76 (12)	83 (13)	70.5 (12.5)	69 (26)	78 (19)	81 (16)
Female median age at death	82	65	72.5		80	82.5	85	<>	<>	79	83
Male median age at death	78	-	70		78	75	79	74	<>	72	78

*Significant difference in age at onset between sexes ($p<0.05$) †Wilcoxon signed-rank test. <>Masked to prevent identification of small numbers (<5) -No data available

No cases of Segawa syndrome or Idiopathic Familial dystonia were identified.

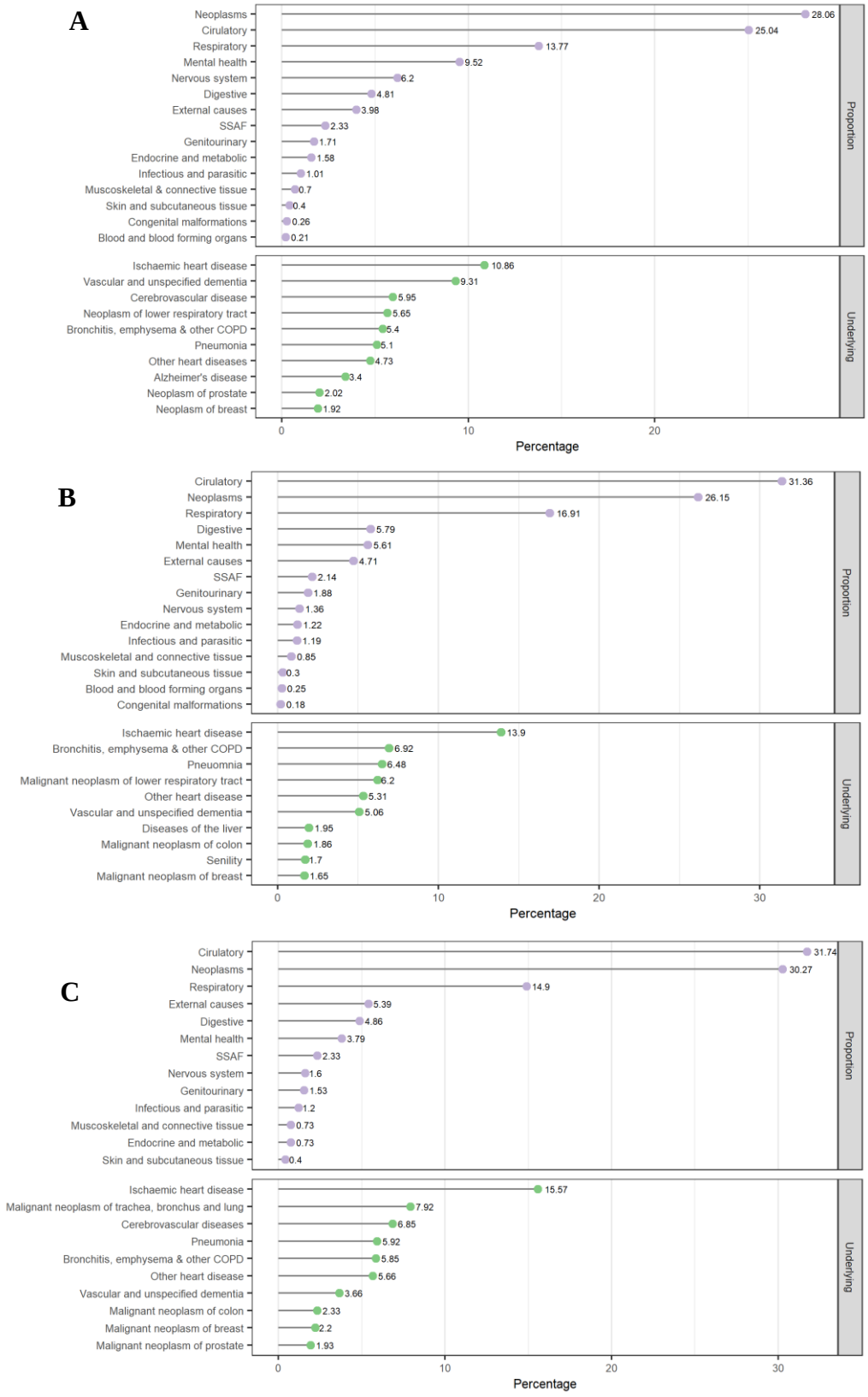

Figure 3.7 Mortality data of cases including leading underlying causes of death and proportions of death categorised by causes in adult-onset idiopathic dystonia

A: General population in Wales (2017) **B:** Overall dystonia **C:** Cervical dystonia

Abbreviations: SSAF; Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

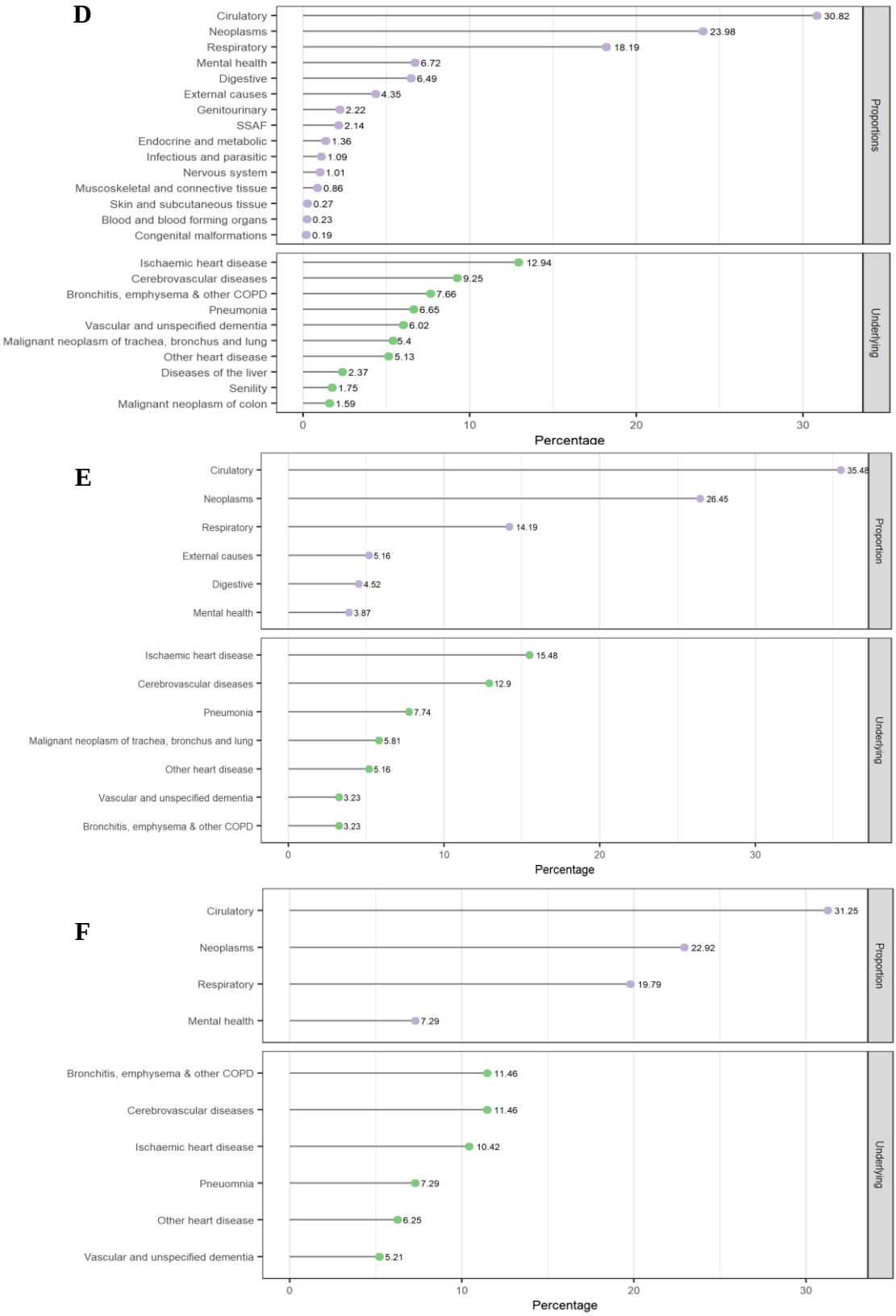

Figure 3.8 ***continued*** Mortality data of cases including leading underlying causes of death and proportions of death categorised by causes in adult-onset idiopathic dystonia

D: Dystonia tremor **E:** Blepharospasm **F:** Other/unspecified

Abbreviations: SSAF; Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

3.4 Discussion

Our longitudinal, nationwide population-based cohort study has combined anonymised electronic data derived from General Practice (family doctor/community healthcare) and hospital records for over 3.6 million Welsh individuals to estimate the prevalence and incidence rates for dystonia and its multiple subtypes. We maintained terminology of Read Codes and ICD-10 Codes for a true reflection of their use within primary and secondary care. Our case ascertainment algorithm demonstrated an overall sensitivity of 79%, identifying 70/89 of the clinically confirmed cases. The mid-year point prevalence of adult-onset idiopathic dystonia in Wales increased from 16.4/100,000 (0.02%) in 1994 to 1219.8/100,000 (1.2%) in 2017, with an increase in annual incidence from 49.9/100,000 (1994) to 96.2/100,000 (2017). Individuals diagnosed with adult-onset idiopathic dystonia were found to be equally distributed across measures of socioeconomic deprivation at time of diagnosis, with no evidence of change in deprivation over time. There were 4315 deaths in those diagnosed with adult-onset idiopathic dystonia, with ischaemic heart disease, cerebrovascular diseases, pneumonia and bronchitis, emphysema and other chronic obstructive pulmonary diseases being the most common causes of death.

Previous estimates of dystonia prevalence, from service or population based studies, have varied between 6.1 and 70.1 per 100,000 in the former,[503,504] to between 7.91 and 732 per 100,000 in the latter.[7,510] However, these approaches are likely to introduce bias, identifying only those seeking out or receiving clinical care, as well as under-ascertaining cases, suggesting that rates of dystonia within the population are higher than previously suggested.[526] In support of this, our results suggest an overall prevalence of dystonia syndromes of 1219.8/100,000 (1.2%), which given the unbiased nature of the case identification, suggest a more accurate population-based value. The median age at diagnosis (42 years) and proportion of male to females (1:1.7) determined in this study is consistent with previous studies, suggesting that the cohort identification criteria were appropriately applied.

Amongst population based studies, two of the highest notable outliers estimated a prevalence of 732/100,000 (0.73%) and 390/100,000 (0.39%).[7,382] Previous UK-based studies have reported prevalence rates of 38 per 100,000 in those diagnosed

with focal dystonia, higher than other European studies reported over the same period.[82,397,516,518,519]. The UK study also used a linkage-based approach, ascertaining cases by reviewing hospital records, as well as recruiting individuals registered as members to The Dystonia Society, and via a postal survey.[524] Our study has expanded upon this using detailed linked data available across the whole of Wales. More recent epidemiological studies of dystonia show a trend towards elevated estimates compared to the literature prior to 2012,[526] which may be in part due to an ageing population, increased clinical recognition of dystonia and identification of an ever expanding number of causative genes.[527]

Three US-based studies have estimated the incidence of cervical dystonia between 0.8 and 1.18 per 100,000 person-years[3,391,392], while incidence rates of other types of dystonia varied between 0.2 and 0.4/100,000 person-years.[3] As with the multiple factors influencing prevalence rates, it is likely that these estimates are lower than true population values. In comparison, we found an average annual incidence of 87.65/100,000, increasing from 49.85/100,000 cases (1994) to 96.21/100,000 (2017). New cases were highest between 2004 and 2008, ranging from 104.09 and 112.66 per 100,000. These dates coincide with a known period of higher data capture within SAIL,[528] while electronic records prior to 2000 in the SAIL databank are sparse, providing a likely explanation for the more marked increase in numbers after this time. However, rates have slowly decreased since 2011, plateauing at ~100/100,000. Elevated rates of incidence are consistent with increased recognition, awareness, and improved availability of neurological services.

Our study demonstrated that deprivation scores did not change following a diagnosis of dystonia, arguably an unexpected finding given the potential for dystonia to impact employment and social interaction. To our knowledge there has been no research which directly investigates changes in deprivation, with previous studies that have included measures of this nature identifying conflicting findings. A population-based survey in India found no significant differences in dystonia prevalence estimates when comparing slum and non-slum dwellers, in spite of their socioeconomic differences.[506] Other studies have also noted that dystonia affects employment, with pain and severity of symptoms impacting work status in up to 40% of cases.[529] However, given that many of the treatments typically used to

manage motor symptoms, notably botulinum neurotoxin (BoNT) and deep brain stimulation (DBS), have been shown to improve quality of life, reduce pain and motor severity, it is plausible that this may contribute to maintained working status.[530,531] Interestingly, increased rates of DBS surgery have been observed in the USA between 2002 (n = 2372) and 2014 (n = 5260), with a similar trend likely in the UK.[532]

To our knowledge, ours is the first study to assess mortality in patients with dystonia. Of the cohort, 10% died during the study period with a median age at death of 80 years. There was no evidence of higher levels of premature death (<75 years of age) amongst the dystonia cohort (35.9%) which was comparable to rates in the general population in Wales (31.7%, 2017). Amongst our cohort, males and females had a comparable median age of death (78 and 82 years respectively) to the life expectancy in Wales (78.5 years and 82.3 years, 2017-2019).[533] Males diagnosed with other/unspecified forms of dystonia and Writer's cramp were younger than the expected median age (72 and 74 years, respectively), while both males and females (70 and 72.5 years) with idiopathic torsion dystonia were younger at death. The most common causes of death included respiratory disorders, circulatory disorders, cancers or dementia, in keeping with the leading causes of deaths registered in England and Wales (2017).[534] Comparable causes of death were also noted amongst dystonia subtypes (Figure 3.5).

As with all record-linkage based studies there are several limitations. Firstly, those who have not sought medical attention, either in the community or hospital-based specialist care, will not be captured by this analysis. Dystonia is primarily diagnosed in secondary care by a specialist, and subsequently coded in primary care by General Practitioners. Our algorithm was 79% sensitive with 74% of the reference population being identified from primary records alone. Although there is little incentive for GPs to subtype dystonia, in general, there is evidence to suggest that primary care coding is relatively accurate in the UK.[535] Several previous studies, using the SAIL database, have validated the accuracy of using these diagnosis codes for case ascertainment of other neurological conditions.[536–538] However coding practices may vary between GPs as well as having the potential to change with time. Further, there is always the potential for diagnostic misclassification through coding. For example,

we did not identify any cases of idiopathic familial dystonia. This likely reflects the focus on achieving the most accurate clinical diagnosis for the individual patient, with information relating to other affected family members not always being known to the patient and/or the treating clinician. It is also important to highlight that hospital inpatient and outpatient data provided only a small increase in case ascertainment sensitivity (0.9%). Our validation cohort consisted of individuals seen in one specialist service and it may be that these individuals were more likely to get a primary care dystonia code when compared to individuals seen in other services. Alternatively, it may be because hospital coding is primarily related to recording the admission or attendance, with the reasons for being admitted and comorbidities being less frequently documented.[537] We were also unable to obtain a measure of specificity for our case ascertainment algorithm for the dystonia cohort as we were unable to upload a relevant negative control group e.g. unrelated disorder such as hemifacial spasm, and a related dystonic disorders such as drug-induced dystonia. It therefore remains possible that we included a proportion of cases without dystonia. However, we sought to account for this by applying stringent exclusion criteria that would account for most known causes of acquired dystonia or misdiagnosis of dystonia. Lastly, deprivation is difficult to measure, and although the WIMD is one of the more comprehensive deprivation scores available, it does not cover every aspect of deprivation. It is also an area-based not an individual-based measure of deprivation. It is therefore possible that an increase in deprivation for an individual would not change their WIMD score if they did not move address. We may therefore lack recognition of social change in deprivation.

Our results indicate that prevalence and incidence rates of dystonia are higher than previously estimated, 1220/100,000/year (1.2%) and 96/100,000/year respectively, potentially indicating more accurate population estimates given the unbiased nature of patient identification. We have shown that a diagnosis of dystonia does not appear to have a detrimental impact on socioeconomic status, with no changes in deprivation observed at follow-up. In addition, there was no evidence of decreased life expectancy and causes of underlying death mirroring that of the Welsh leading causes of death. The findings from this work have important implications for patients, carers, healthcare providers, third sector organisations and healthcare

policy, with our case-ascertainment algorithm providing a platform for application in future population-based dystonia studies.

4 Longitudinal analysis of the relationship between motor and psychiatric symptoms in dystonia

4.1 Introduction

Historically, dystonia was considered a psychiatric disorder, or labelled psychogenic, owing to the nature of the symptoms, which are often exacerbated by stress. Dystonia, as a diagnosis in itself, was initially proposed at the First International Dystonia Symposium (1975) with reference made to its non-progressive nature and association with lesions of the nervous system.[539]

Prominent psychiatric symptoms have been recognised across the spectrum of dystonic disorders,[285,286] extending from broad diagnostic groups, [288,290,303,540] to specific genetically inherited forms.[306] Single case reports have identified ADHD,[56,541] anorexia nervosa,[542] and schizoaffective disorder[543] and ~10-30% prevalence rates of behaviour disorder[544] amongst those with *SGCE* mutations. ASD and ADHD have also been reported in genetic variants including *KCNMA1*,[545] *KMT2B*,[546] *CHD8*,[547] and GCH1 deficiency,[548,549] and NR4A2.[550] Cases of bipolar disorder have been observed amongst those with rapid-onset dystonia-Parkinsonism (RDP) and DYT1 mutation carriers,[551,552] although in the latter carriers did not have an increased risk compared to non-carriers.[297]

A broad spectrum of psychiatric disturbances have been described in those with idiopathic dystonia, identifying elevated rates of depression and anxiety,[300,353] affecting up to 71% of patients with dystonia in their lifetime.[287] High rates of phobias have also been noted, in particular social phobia and agoraphobia.[290,301] Small numbers of bulimia nervosa,[303] eating disorders,[525,553] substance use disorders,[303,310,525,554,555] bipolar disorder,[290,525,555,556] schizophrenia,[525] autism spectrum disorder (ASD),[525] and attention deficit hyperactive disorder (ADHD)[525,555] have been reported amongst idiopathic dystonia cohorts.

Debate continues as to whether these psychiatric symptoms represent a primary phenotypic component of dystonia or are a secondary response to a chronic disabling disorder. Studies focused on genetically defined populations have provided some support for these being a component of the dystonia phenotype with asymptomatic and symptomatic carriers of the DYT1 (*TOR1A* gene, encoding TorsinA) mutation shown to have an increased risk of early-onset and recurrent depression in

comparison to controls.[297] Whilst others have suggested a greater likelihood of psychiatric symptoms being secondary to motor symptoms and pain, with evidence of improved mood with treatment of the motor symptoms.[296] In addition, a longitudinal follow-up study (5 years) showed stable psychiatric symptoms in the context of varying motor severity scores.[353] Onset of mood disorders have also been reported prior to dystonia, suggesting, that at least in a proportion of cases, psychiatric features are part of the dystonia phenotype.[300,303]

Studies have yet to examine both the rate and temporal relationship of psychiatric disorders at scale in idiopathic dystonia, with many cross-sectional studies limited by recall bias, and further complicated by the frequently observed diagnostic delay in dystonia.[391] Use of detailed population-based data overcomes both recall and referral bias, while a longitudinal linkage approach has the potential to examine the association and subsequent risk of co-morbid psychiatric disorders in pre- and post-dystonia diagnostic periods. Using the Secure Anonymised Information Linkage (SAIL) Databank, this study represents the first to undertake case-control comparison of linked clinical data, examining the rate and temporal pattern of psychiatric diagnoses and prescribed psychiatric medication in idiopathic dystonia, providing opportunity to further examine the relationship between dystonia and psychiatric symptomatology, at scale.

4.2 Methods

4.2.1 Study design and data sources

Using a cohort and case-control design, we investigated the rate of psychiatric diagnoses and medication in individuals diagnosed with dystonia, and its associated risk of psychiatric diagnoses within the SAIL Databank (Swansea University, UK: www.saildatabank.com). SAIL is a data repository containing anonymised, routinely collected health, education and social care data covering the population of Wales. Clinical and demographic data is provided from several sources including primary and secondary care records. Records can be linked between datasets for research purposes, the linkage procedures, approaches, structures and management of the SAIL databank are discussed in Section 2.3.

Derivation and diagnostic validation of the dystonia cohort has been described in Section 3.2.4. In brief, we developed a case-ascertainment algorithm to identify individuals with idiopathic dystonia within primary and secondary care datasets. A reference population of 90 patients with a clinically confirmed diagnosis of adult-onset idiopathic focal cervical dystonia (AOIFCD) were anonymously linked to records in SAIL. Codes relevant to dystonia were reviewed and the final code list was created to maintain reasonable sensitivity (79% sensitivity). A person was defined as having a diagnosis of dystonia if their primary or secondary care records contained a Read code or International Classification of Diseases version 10 (ICD-10) code for dystonia (Table 2.1). Using this previously validated method, 54,966 individuals with an idiopathic dystonia diagnosis were identified between January 1994 and December 2017. Our focus was on investigation of those with a diagnosis of idiopathic dystonia according to the most recent dystonia classification system,[9] and therefore potential causes or diagnoses leading to a secondary dystonia were excluded from this cohort (Table 2.2-2.4). Dystonia is primarily diagnosed in secondary care by a specialist, and subsequently coded in primary care by general practitioners. Genetic data is not available within SAIL databank, except for potential inference from diagnoses of Dopa Responsive Dystonia and Myoclonus Dystonia.

We obtained data on psychiatric diagnoses and prescribing information using primary care (Welsh Longitudinal General Practice dataset, WLGP) and secondary care datasets (Patient Episode Database for Wales, PEDW and Outpatient Dataset, OPD) between January 1994 and December 2017. Read codes can be used to attain information on diagnoses, prescriptions, symptoms and administrative procedures, with previous work demonstrating the accuracy of primary care coding in the UK.[535] Primary care and secondary care data were available for ~80% and 100% of the Welsh population, respectively. We recorded demographic characteristics including age, sex, GP registration history and deprivation index using the Welsh Index of Multiple Deprivation (WIMD) using the Welsh Demographic Data Service (WDSD) which contains data on all persons registered with a primary care practice in Wales.[473]

4.2.2 Study cohort

The dystonia cohort consisted of 54,166 individuals diagnosed with idiopathic dystonia between January 1994 and December 2017 (see Section 3.3.2). This cohort was subdivided into those <20 years and >20 years of age at dystonia diagnosis to better reflect the current dystonia classification system.[9] Dystonia cases were matched to a control population (n=216,574) on: year of birth, sex, year of study entry, year of follow-up and deprivation index quintile. Those with a primary and potential secondary cause of dystonia were excluded (Table 2.2-2.4). The majority of the dystonia cohort (n = 54,121, 99.9%) were randomly matched on a 1:4 (case:control) basis however, this was not possible for the remaining 45 cases, each of whom were match on a ratio of 1:1–3. Individuals prescribed an antipsychotic prior to a diagnosis of dystonia were excluded so as not to include potential cases of drug-induced dystonia (n=1577). Included individuals were required to be resident in Wales at the time of index date and have an age, sex and GP registration date recorded. We defined the index date as the date of first dystonia diagnosis for dystonia cases and their respective matched controls. Due to the small sample size those with 'other' and 'unspecified' dystonia were combined.

4.2.3 Ascertainment of psychiatric diagnosis and prescriptions

An individual was defined as having a psychiatric disorder if their General Practice (GP, primary care) or hospital record (secondary care) contained a previously validated Read version 2 or ICD-10 code (International Classification of Diseases version 10) (Appendix 13).[557] We included codes for depression, anxiety, severe mental illness (SMI; schizophrenia, schizotypal and delusional disorders, bipolar disorder, other mood-related disorders and other severe mental illness), substance use disorder (SUD), eating disorders, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and conduct disorder. Use of hypnotics, antidepressants, anxiolytics and antipsychotics were obtained from primary GP records (Appendix 14).[558,559] We examined prescriptions without inference to their diagnosis. Individuals with dystonia who were prescribed a benzodiazepine (Table 4.1) and had no recorded psychiatric diagnoses were considered to have no recorded psychiatric medication due to benzodiazepines, at times, being used to manage the motor symptoms of dystonia. The majority of medications are electronically

prescribed by GPs, whereby a Read code is entered for each prescription e.g. monthly. Diagnoses and prescription records were obtained throughout the study period (January 1994 – December 2017) and those recorded 12 years before to 12 years after the index date were analysed. In an attempt not to bias findings, we limited our analysis to this period due to differences in data availability dependent upon when an individual received a dystonia diagnosis. Psychiatric outcomes were examined individually and combined as all psychiatric diagnoses/prescriptions when investigating first-time psychiatric events.

Table 4.1 Benzodiazepine codes used to remove individuals with no recorded psychiatric diagnoses

Hypnotics		
	d14..	Flumtrazepam - discontinued
	d15..	Flurazepam
	d16..	Loprazolam
	d17..	Lormetazepam
	d18..	Nitrazepam
	d1a..	Temazepam (hynotic)
	d1b..	Triazolam - discontinued
Anxiolytics		
	d21..	Diazepam
	d22..	Alprazolam
	d23..	Bromazepam
	d26..	Clobazam
	d29..	Ketazolam - discontinued
	d2a..	Lorazepam (anxiolytic)
	d2b..	Medazepam - discontinued
	d2d..	Oxazepam

4.2.4 Deprivation score

Deprivation scores were derived using WIMD 2014 quintiles according to Lower Super Output Area (LSOA) of residence (2011). WIMD identifies and ranks all LSOAs in Wales from 1 (most deprived) to 1909 (least deprived), each LSOA is then grouped into quintiles with 1 being the most deprived and 5 being the least deprived (see Section 2.3.5.4).[473] The WIMD quintile was assessed at three dates, entry into the study dataset, index date and at the end of the study (December 2017), de-registration from GP, moving out of Wales, or at the time of death.

4.2.5 Statistical analyses

Data was analysed using R software (version 4.0.1). Dystonia and control groups were compared using Chi-square and Wilcoxon signed-rank test to determine changes to WIMD quintile. In the case-control study, we calculated the annual incidence rate (IR) for each psychiatric diagnosis during the study period (12 years before or after index date). The number of cases/controls with a new diagnostic code was divided by the sum of cases/controls person-time at risk in each time-period. Person-time was calculated within each time-period as the time to incident comorbidity, end of follow-up within the time-period, the end of the time-period, the end of the study or death. Psychiatric diagnoses and prescriptions occurring on the same day as the index date were included in the year before the index date time-period. Poisson regression was used to calculate the incidence rate ratio (IRR). Logistic regression was used to calculate the association of psychiatric disorders or prescribed psychiatric drugs and the risk of idiopathic dystonia, expressed as odds ratios (ORs), both with 95% confidence intervals (CIs) and Bonferroni correction ($p = 0.002$ and $p = 0.005$ respectively). Regression analyses were adjusted for time in study. Wilcoxon signed-rank tests were used to determine changes in WIMD quintile.

4.2.6 Ethics

This study design uses anonymized, routinely collected data and therefore does not require ethical approval and written informed consent. The SAIL independent Information Governance Review Panel (IGRP), experts in information governance

and members of the public, approved this study (Reference: 0768) (see Section 2.3.9).

4.3 Results

A total of 28,666 idiopathic dystonia cases (54.5%) and 96,705 controls (44.7%) were identified as having a psychiatric diagnosis or prescription. Of these, 22,682 cases (43.1%) and 67,458 (31.1%) controls had a new psychiatric diagnosis, and 23,793 cases (45.2%) and 82,096 (37.9%) controls were prescribed a new psychiatric medication, both demonstrating significantly higher levels in the dystonia cohort compared to controls ($p<0.001$) (Table 4.2).

Table 4.2 Demographics for cases and controls with a first-time psychiatric diagnosis or medication during the study period

	Overall (%) (52,589)	**Cervical dystonia (%)** (36,341)	**Blepharospasm (%)** (1,262)	**Tremor (%)** (14,308)	**Other (%)** (578)	**Controls (%)** (216,574)
Overall number of first-time psychiatric diagnosis	**21,354 (40.6)**	**13,943 (38.4)**	**460 (36.5)**	**6,667 (46.6)**	**251 (43.4)**	64,084 (29.6)
Pre dystonia	**12,095 (56.6)**	7,194 (51.6)	**280 (60.9)**	**4,427 (66.4)**	**177 (70.5)**	33,551 (52.4)
Post dystonia	**9,259 (43.4)**	6,749 (48.4)	**180 (39.1)**	**2,240 (33.6)**	**74 (29.5)**	30, 533 (47.6)
Sex						
Male	6,693 (31.3)	**4,075 (29.2)**	141 (30.7)	**2,376 (35.6)**	94 (37.5)	19,823 (30.9)
Female	14,661 (68.7)	**9,868 (70.8)**	319 (69.3)	**4,291 (64.4)**	157 (62.5)	44,261 (69.1)
Aged ≥20 years	17,542 (82.1)	**11,077 (79.4)**	**435 (94.6)**	**5,793 (86.9)**	211 (84)	52,366 (81.7)
Aged <20 years	3,812 (17.9)	**2,866 (20.6)**	**25 (5.4)**	**874 (13.1)**	40 (15.9)	11,718 (18.3)
Aged ≥20 years						
Pre dystonia	**11,207 (63.9)**	6,628 (59.8)	<>	**4,135 (71.4)**	**153 (72.5)**	31,201 (59.6)
Post dystonia	**6,335 (36.1)**	4,449 (40.2)	<>	**1,658 (28.6)**	**58 (27.5)**	21,165 (40.4)
Aged <20 years						
Pre dystonia	**888 (23.3)**	566 (19.7)	<>	**292 (33.4)**	**24 (60)**	2,350 (20.05)
Post dystonia	**2,924 (76.7)**	2,300 (80.3)	<>	**582 (66.6)**	**16 (40)**	9,368 (79.95)
Overall first-time psychiatric prescription	**21,996 (41.8)**	**14,384 (39.6)**	**519 (41.1)**	**6,760 (47.2)**	**295 (51)**	77,757 (35.9)
Pre dystonia	**13,565 (61.7)**	**8,296 (57.7)**	**341 (65.7)**	**4,698 (69.5)**	**211 (71.5)**	39,993 (51.4)
Post dystonia	**8,431 (38.3)**	**6,088 (42.3)**	**178 (34.3)**	**2,062 (30.5)**	**84 (28.5)**	37,764 (48.6)
Sex						
Male	6,705 (30.5)	**4,002 (27.8)**	156 (30.1)	**2,424 (35.9)**	**112 (38)**	23,117 (57.8)
Female	**15,291 (69.5)**	**10,382 (72.2)**	363 (69.9)	**4,336 (64.1)**	**183 (62)**	54,640 (42.2)
Aged ≥20 years	**19,224 (87.4)**	**12,287 (85.4)**	**500 (96.3)**	**6,142 (90.9)**	262 (88.8)	68,918 (88.6)
Aged <20 years	**2,772 (12.6)**	**2,097 (14.6)**	**19 (3.7)**	**618 (9.1)**	33 (11.2)	8,839 (11.4)
Aged ≥20 years						
Pre dystonia	**13,105 (68.2)**	**7,975 (64.9)**	<>	**4,575 (74.5)**	<>	39,171 (56.8)
Post dystonia	**6,119 (31.8)**	**4,312 (35.1)**	<>	**1,567 (25.5)**	<>	29,747 (43.2)
Aged <20 years						
Pre dystonia	**460 (16.6)**	**321 (15.3)**	<>	**123 (19.9)**	<>	822 (9.3)
Post dystonia	**2,312 (83.4)**	**1,776 (84.7)**	<>	**495 (80.1)**	<>	8,017 (90.7)
Number of psychiatric prescriptions during study period	1,246,558	613,347	29,675	576,244	25,049	3,845,023

Number of psychiatric prescriptions per person (mean (SD))	50.4 (98.7)	39.1 (76.5)	49.1 (85.7)	71.4 (128.4)	73.7 (129.1)	45.06 (108.6)
Number of different medications prescribed (mean(SD))	3.2 (2.5)	3.1 (2.4)	3 (2.4)	3.5 (2.7)	3.4 (2.4)	2.62 (2.2)

P-values are all vs controls. Bold p-values represent significant values post Bonferroni correction for multiple comparisons

4.3.1 Psychiatric diagnoses

Individuals with idiopathic dystonia and all subtypes were significantly more likely to be diagnosed with multiple (two or more) psychiatric diagnoses when compared to controls ($p < 0.001$) (Figure 4.1). In those with dystonia, cervical dystonia and tremor, a higher frequency of multiple diagnoses were also observed in both age categories but was greater in those ≥ 20 years at diagnosis ($p < 0.001$) (Figure 4.1(B)). The proportions of diagnoses by age, pre and post diagnosis, are shown in Figure 4.2. First recorded diagnoses of anxiety ($p = 0.002$), conduct disorder ($p < 0.001$), depression ($p < 0.001$) and SUD ($p < 0.001$) predated dystonia diagnosis, while a higher rate of ASD and SMI ($p < 0.001$) diagnoses post-dated overall dystonia. A comparable incidence of ADHD ($p = 0.7$) and eating disorder ($p = 0.06$) was observed before and after dystonia diagnosis (Table 4.3). Similar patterns were observed amongst those with dystonic tremor, whilst depression, anxiety and SUD pre-dated blepharospasm and other dystonia ($p < 0.001$). Interestingly, incidence of depression was comparable ($p=0.7$) and higher rates of anxiety was observed after cervical dystonia diagnosis ($p<0.001$).

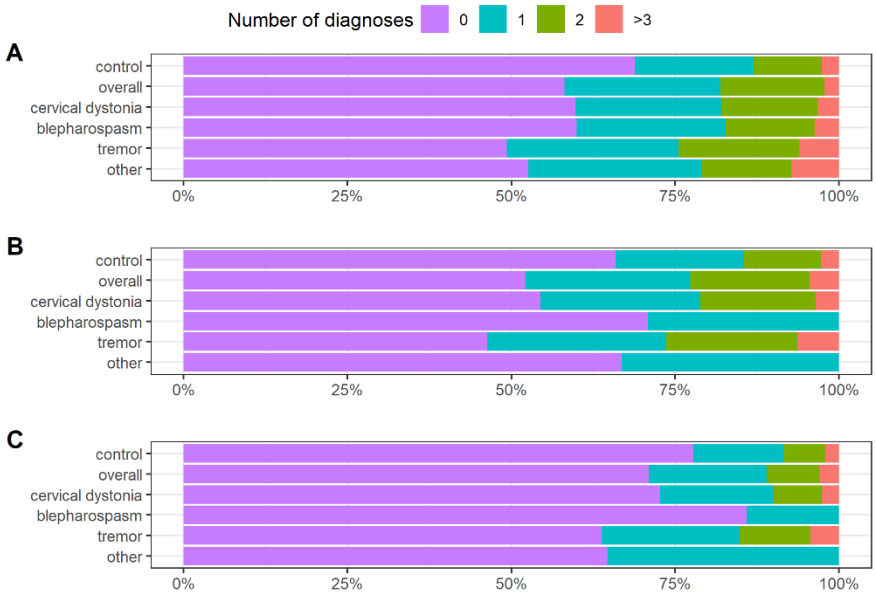

Figure 4.1 Number of different diagnoses in **A)** overall **B)** ≥20 years at index date **C)**< 20 years at index date

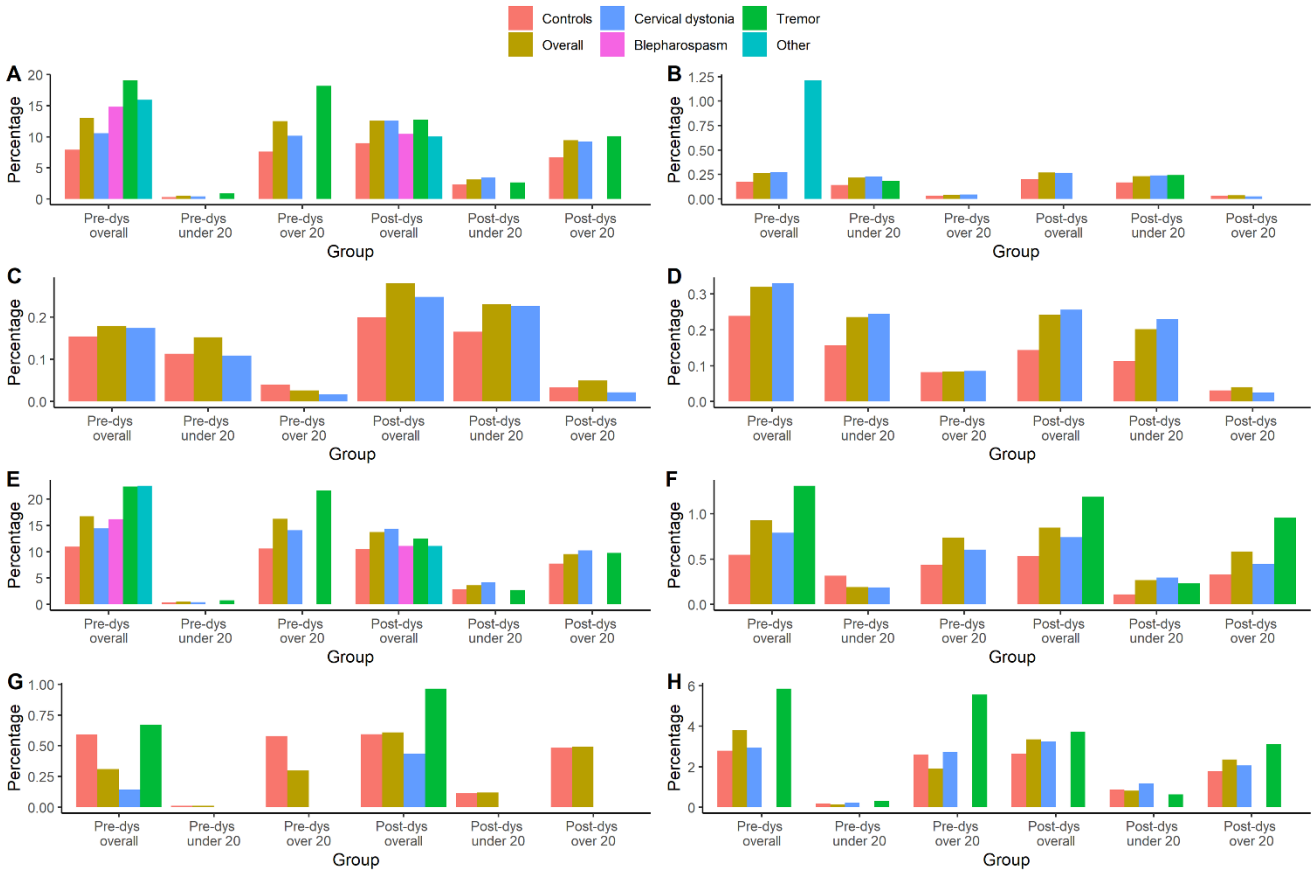

Figure 4.2 Proportions of diagnoses by age and time for cases and controls

A: Anxiety **B:** Attention Deficit Hyperactive Disorder **C:** Autism Spectrum Disorder **D:** Conduct disorder **E:** Depression **F**: Eating Disorder **G**: Severe mental illness **H**: Substance use disorder

Table 4.3 Subtypes of psychiatric diagnoses in cases and controls by time and age

	Overall (%)	Cervical dystonia (%)	Blepharospasm (%)	Tremor (%)	Other (%)	Controls (%)
Overall Psychiatric Diagnoses						
Depression	**16,030 (30.5)**	**10,482 (28.8)**	**344 (27.3)**	**4,985 (34.8)**	**194 (33.6)**	46,567 (21.5)
Anxiety	**13,468 (25.6)**	**8,425 (23.2)**	**319 (25.3)**	**4,554 (31.8)**	**150 (26)**	36,466 (16.8)
Substance use disorder	**3,764 (7.2)**	**2,247 (6.2)**	78 (6.1)	**1,374 (9.6)**	**59 (10.2)**	11,776 (5.4)
Eating disorder	**933 (1.8)**	**556 (1.5)**	<>	**357 (2.5)**	<>	2,345 (1.1)
Severe mental illness	**483 (0.9)**	**210 (0.6)**	<>	**234 (1.6)**	**24 (4.2)**	2,565 (1.2)
Conduct disorder	**295 (0.6)**	**213 (0.6)**	<>	72 (0.5)	<>	830 (0.4)
ADHD	**279 (0.5)**	**196 (0.5)**	<>	73 (0.5)	<>	824 (0.3)
ASD	**241 (0.5)**	153 (0.4)	<>	79 (0.5)	<>	763 (0.4)
Pre-dystonia						
Depression	**8,802 (16.7)**	**5,255 (14.5)**	**204 (16.2)**	**3,201 (22.4)**	**130 (22.5)**	23,695 (10.9)
Anxiety	**6,861 (13)**	**3,845 (10.6)**	**187 (14.8)**	**2,728 (19.1)**	**92 (15.9)**	17,080 (7.9)
Substance use disorder	**1,999 (3.8)**	1,070 (2.9)	<>	**839 (5.9)**	**39 (6.7)**	6,042 (2.8)
Eating disorder	**487 (0.9)**	**287 (0.8)**	<>	**187 (1.3)**	<>	1,185 (0.5)
Conduct disorder	**168 (0.3)**	**120 (0.3)**	<>	<>	<>	518 (0.2)
Severe mental illness	**163 (0.3)**	**52 (0.1)**	<>	96 (0.7)	<>	1,277 (0.6)
ADHD	**137 (0.3)**	**99 (0.3)**	<>	<>	**7 (1.2)**	385 (0.2)
ASD	94 (0.2)	63 (0.2)	<>	<>	<>	332 (0.2)
Post-dystonia						
Depression	**7,228 (13.7)**	**5,227 (14.4)**	140 (11.1)	**1,784 (12.5)**	64 (11.1)	22,872 (10.6)
Anxiety	**6,607 (12.6)**	**4,580 (12.6)**	132 (10.5)	**1,826 (12.8)**	58 (10)	19,386 (9)
Substance use disorder	**1,765 (3.4)**	**1,177 (3.2)**	<>	**535 (3.7)**	20 (3.5)	5,734 (2.6)
Eating disorder	**446 (0.8)**	**269 (0.7)**	<>	**170 (1.2)**	<>	1,160 (0.5)
Severe mental illness	320 (0.6)	**158 (0.4)**	<>	**138 (1)**	<>	1,288 (0.6)
ASD	**147 (0.3)**	90 (0.2)	<>	<>	<>	431 (0.2)
ADHD	142 (0.3)	97 (0.3)	<>	<>	<>	439 (0.2)
Conduct disorder	**127 (0.2)**	**93 (0.3)**	<>	<>	<>	312 (0.1)
Over 20s						
Overall						
Depression	**13,844 (26.3)**	**8,828 (24.3)**	<>	**4,488 (31.4)**	**174 (30.1)**	39,683 (18.3)
Anxiety	**11,526 (21.9)**	**7,029 (19.3)**	**305 (24.2)**	**4,048 (28.3)**	**129 (22.3)**	30,871 (14.3)
Substance use disorder	**3,109 (5.9)**	**1,742 (4.8)**	<>	**1,241 (8.7)**	<>	9,520 (4.4)

Eating disorder	**693 (1.3)**	**381 (1)**	<>	<>	<>	1,659 (0.8)
Severe mental illness	**415 (0.8)**	**169 (0.5)**	<>	**214 (1.5)**	<>	2,301 (1.1)
Conduct disorder	65 (0.1)	40 (0.1)	<>	<>	<>	245 (0.1)
ADHD	42 (0.08)	26 (0.07)	<>	<>	<>	147 (0.07)
ASD	40 (0.08)	14 (0.04)	<>	<>	<>	160 (0.07)
Pre-dystonia						
Depression	**8,539 (16.2)**	**5,113 (14.1)**	<>	**3,092 (21.6)**	<>	22,987 (10.6)
Anxiety	**6,570 (12.5)**	**3,690 (10.2)**	<>	**2,605 (18.2)**	<>	16,445 (7.6)
Substance use disorder	**1,875 (3.6)**	995 (2.7)	<>	**796 (5.6)**	<>	5,671 (2.6)
Eating disorder	**387 (0.7)**	**219 (0.6)**	<>	<>	<>	948 (0.4)
Severe mental illness	**157 (0.3)**	**49 (0.1)**	<>	<>	<>	1,254 (0.6)
Conduct disorder	44 (0.08)	31 (0.09)	<>	<>	<>	178 (0.08)
ADHD	22 (0.04)	16 (0.04)	<>	<>	<>	76 (0.04)
ASD	14 (0.03)	6 (0.02)	<>	<>	<>	87 (0.04)
Post-dystonia						
Depression	**5,305 (10.1)**	**3,715 (10.2)**	<>	**1,396 (9.8)**	<>	16,696 (7.7)
Anxiety	**4,956 (9.4)**	**3,339 (9.2)**	**<>**	**1,443 (10.1)**	<>	14,426 (6.7)
Substance use disorder	**1,234 (2.3)**	**747 (2.1)**	<>	**445 (3.1)**	<>	3,849 (1.8)
Eating disorder	**306 (0.6)**	**162 (0.4)**	<>	<>	<>	711 (0.3)
Severe mental illness	258 (0.5)	**<>**	<>	<>	<>	1,047 (0.5)
ASD	26 (0.05)	8 (0.02)	<>	<>	<>	73 (0.03)
Conduct disorder	21 (0.04)	9 (0.02)	-	**12 (0.08)**	-	67 (0.03)
ADHD	20 (0.04)	10 (0.03)	<>	<>	<>	71 (0.03)
Under 20s	13,224					52,895
Overall						
Depression	**2,186 (4.2)**	**1,654 (4,6)**	<>	497 (3.5)	20 (3.5)	6,884 (3.2)
Anxiety	**1,942 (3.7)**	**1,396 (3.8)**	**14 (1.1)**	**506 (3.5)**	21 (3.6)	5,595 (2.6)
Substance use disorder	**655 (1.2)**	**505 (1.4)**	<>	133 (0.9)	<>	2,256 (1)
Eating disorder	**240 (0.5)**	**175 (0.5)**	<>	<>	<>	686 (0.3)
ADHD	**237 (0.5)**	**170 (0.5)**	<>	<>	<>	677 (0.3)
Conduct disorder	**230 (0.4)**	**173 (0.5)**	<>	<>	<>	585 (0.3)
ASD	**201 (0.4)**	**139 (0.4)**	<>	<>	<>	603 (0.3)
Severe mental illness	68 (0.1)	41 (0.1)	<>	20 (0.1)	<>	264 (0.1)
Pre-dystonia						
Anxiety	**291 (0.6)**	**155 (0.4)**	<>	**123 (0.9)**	<>	635 (0.3)
Depression	**263 (0.5)**	142 (0.4)	<>	**109 (0.8)**	<>	708 (0.3)
Conduct disorder	**124 (0.2)**	**89 (0.2)**	<>	<>	<>	340 (0.2)
Substance use disorder	**124 (0.2)**	75 (0.2)	<>	**43 (0.3)**	<>	371 (0.2)

ADHD	**115 (0.2)**	**83 (0.2)**	<>	26 (0.2)	<>	309 (0.1)
Eating disorder	**100 (0.2)**	**68 (0.2)**	<>	<>	<>	237 (0.1)
ASD	80 (0.2)	57 (0.2)	<>	<>	<>	245 (0.1)
Severe mental illness	6 (0.01)	<>	-	<>	<>	23 (0.01)
Post-dystonia						
Depression	**1,923 (3.7)**	**1,512 (4.2)**	<>	388 (2.7)	<>	6,176 (2.9)
Anxiety	**1,651 (3.1)**	**1,241 (3.4)**	<>	383 (2.7)	<>	4,960 (2.3)
Substance use disorder	**531 (1)**	**430 (1.2)**	<>	**90 (0.6)**	<>	1,885 (0.9)
Eating disorder	140 (0.3)	**107 (0.3)**	<>	33 (0.2)	<>	449 (0.2)
ADHD	122 (0.2)	**87 (0.2)**	-	35 (0.2)	-	368 (0.2)
ASD	**121 (0.2)**	82 (0.2)	<>	<>	<>	358 (0.2)
Conduct disorder	**106 (0.2)**	**84 (0.2)**	<>	<>	<>	245 (0.1)
Severe mental illness	62 (0.1)	<>	<>	<>	<>	241 (0.1)
Anxiety disorders						
Panic	**1,367 (2.6)**	**862 (2.4)**	28 (2.2)	**454 (3.2)**	<>	3,214 (1.5)
Specific isolated phobia	**454 (0.9)**	**316 (0.9)**	**<>**	**116 (0.8)**	<>	205 (0.1)
Generalised	**326 (0.6)**	**204 (0.6)**	<>	**112 (0.8)**	<>	876 (0.4)
Other/unspecified anxiety	**285 (0.5)**	**178 (0.5)**	8 (0.6)	**94 (0.7)**	5 (0.9)	717 (0.3)
Mixed anxiety	**222 (0.4)**	135 (0.4)	<>	**78 (0.5)**	<>	710 (0.3)
OCD	170 (0.3)	113 (0.3)	<>	47 (0.3)	<>	597 (0.3)
Agoraphobia	83 (0.2)	49 (0.1)	<>	<>	<>	277 (0.1)
Other/unspecified phobia	71 (0.1)	48 (0.1)	<>	<>	-	205 (0.1)
Social	17 (0.03)	9 (0.02)	-	8 (0.06)	<>	50 (0.02)
Childhood anxiety	7 (0.01)	7 (0.02)	-	-	-	14 (0.01)

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, OCD: Obsessive-Compulsive Disorder

Note: percentages can be >100% where participants had more than one prescription

P-values are all vs controls. Bold p-values represent significant values post Bonferroni correction for multiple comparisons

<> represents masked values

- represents null values

4.3.2 Prescriptions

Two or more psychiatric medications were prescribed at a higher rate amongst the dystonia cohort compared to controls (p <0.001) (Figure 4.3(A)), with an increased frequency of multiple prescription in both age groups (Figure 4.3(B and C)), observed to a greater extent in those ≥ 20 years at diagnosis (p <0.001). Significantly higher rates of prescription were also observed pre-index diagnosis within the dystonia cohort, compared to post-dystonia diagnosis across antidepressants and anxiolytics (Table 4.4, Figure 4.4). By contrast, antipsychotics post-dated dystonia diagnosis (p < 0.001) and hypnotics were equally distributed pre- and post-dystonia diagnosis (p=0.03). Antidepressants pre-dated all subtypes of dystonia except for cervical dystonia where higher frequencies were observed post diagnosis (p=0.1).

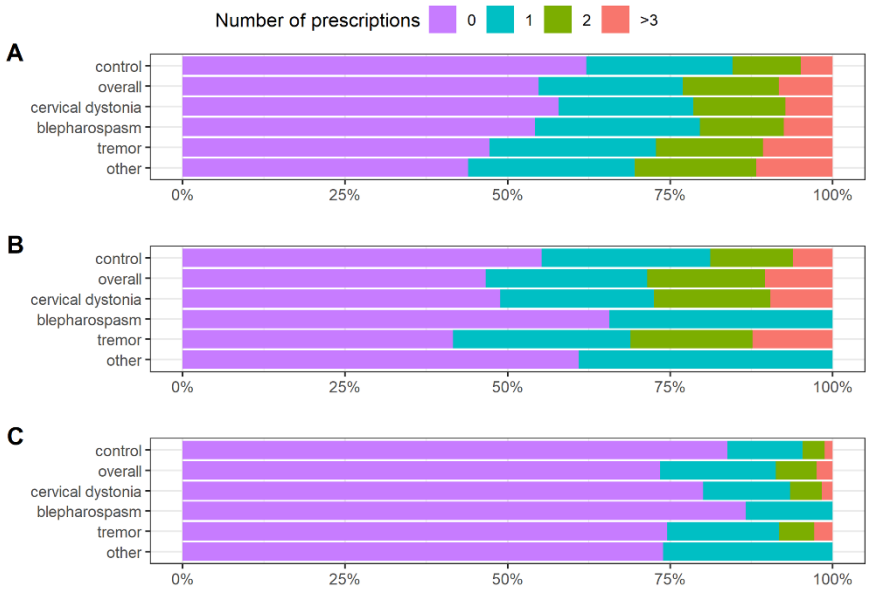

Figure 4.3 Number of different prescriptions in **A)** overall **B)** ≥20 years at index date **C)** <20 years at index date

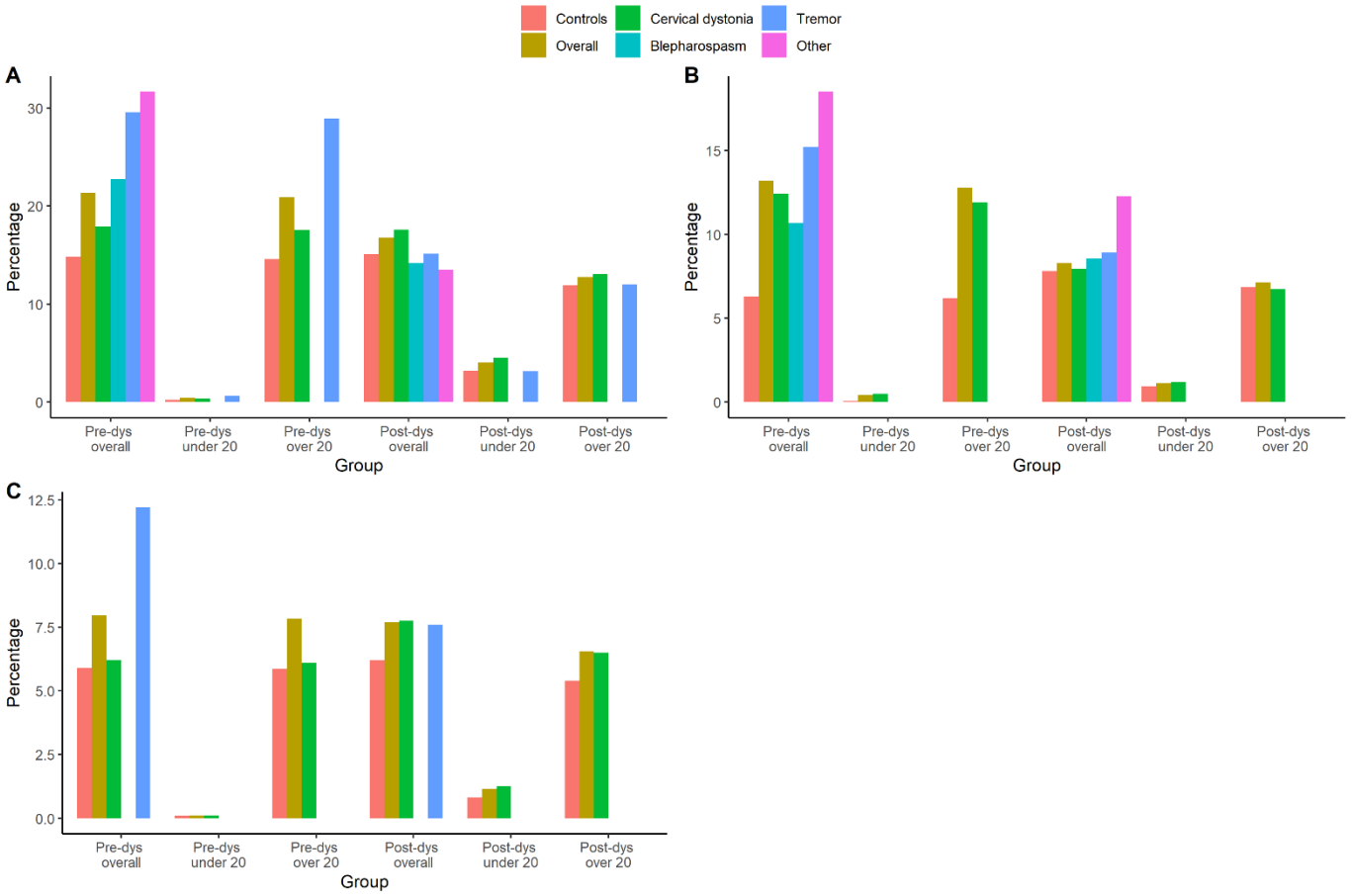

Figure 4.4 Proportions of prescriptions by age and time for cases and controls

A: Antidepressants **B:** Anxiolytics **C:** Hypnotics

Table 4.4 Subtypes of psychiatric prescriptions in cases and controls

	Cases (%)	Cervical dystonia	Blepharospasm	Tremor	Other	Controls (%)
Overall psychiatric prescription						
Antidepressants	**20,049 (38.1)**	**12,901 (35.5)**	**466 (36.9)**	**6,390 (44.7)**	**261 (45.2)**	64,830 (29.9)
Anxiolytics	**11,297 (21.5)**	**7,401 (20.4)**	**243 (19.3)**	**3,453 (24.1)**	**178 (30.8)**	30,519 (14.1)
Hypnotics	**8,233 (15.7)**	**5,075 (14)**	**200 (15.8)**	**2,830 (19.8)**	**117 (20.2)**	26,354 (12.2)
Antipsychotics	**1,164 (2.2)**	**575 (1.6)**	<>	**520 (3.6)**	<>	6,086 (2.8)
Pre-dystonia						
Antidepressants	**11,221 (21.3)**	**6,509 (17.9)**	**287 (22.7)**	**4,227 (29.5)**	**183 (31.7)**	32,135 (14.8)
Anxiolytics	**6,944 (13.2)**	**4,513 (12.4)**	**135 (10.7)**	**2,177 (15.2)**	**107 (18.5)**	13,615 (6.3)
Hypnotics	**4,188 (8)**	2,259 (6.2)	**<>**	**1,745 (12.2)**	<>	12,875 (5.9)
Antipsychotics	**<>**	<>	<>	**<>**	<>	2,521 (1.2)
Post-dystonia						
Antidepressants	**8,828 (16.8)**	**6,392 (17.6)**	179 (14.2)	2,163 (15.1)	78 (11.8)	32,695 (15.1)
Anxiolytics	**4,353 (8.3)**	2,888 (7.9)	108 (8.6)	**1,276 (8.9)**	**71 (10.8)**	16,904 (7.8)
Hypnotics	**4,045 (7.7)**	**2,816 (7.7)**	<>	**1,085 (7.6)**	**<>**	13,479 (6.2)
Antipsychotics	**<>**	<>	**<>**	**<>**	<>	3,565 (1.6)
Over 20s						
Antidepressant	**17,695 (33.6)**	**11,126 (30.6)**	**452 (33.7)**	**5,847 (40.9)**	**244 (42.2)**	57,390 (26.5)
Anxiolytic	**10,477 (19.9)**	**6,777 (18.6)**	<>	**3,286 (23)**	**<>**	28,291 (13.1)
Hypnotic	**7,571 (14.4)**	**4,577 (12.6)**	<>	**2,682 (18.7)**	<>	24,371 (11.3)
Antipsychotic	**1,020 (1.9)**	**481 (1.3)**	<>	**478 (3.3)**	<>	5,537 (2.6)
Pre-dystonia						
Antidepressants	**10,989 (20.9)**	**6,382 (17.6)**	<>	**4,134 (28.9)**	<>	31,601 (14.6)
Anxiolytics	**6,721 (12.9)**	**4,328 (11.9)**	<>	**<>**	<>	13,437 (6.2)
Hypnotics	**4,127 (7.8)**	2,218 (6.1)	<>	<>	<>	12,679 (5.9)
Antipsychotics	**<>**	<>	<>	**<>**	<>	2,459 (1.1)
Post-dystonia						
Antidepressant	**6,706 (12.8)**	**4,744 (13.1)**	<>	1,713 (11.2)	<>	25,789 (11.9)
Anxiolytic	3,756 (7.1)	2,449 (6.7)	<>	**<>**	<>	14,854 (6.9)
Hypnotic	**3,444 (6.5)**	**2,359 (6.5)**	<>	**<>**	<>	11,692 (5.4)

Antipsychotic	**<>**	<>	<>	**<>**	<>	3,078 (1.4)
Under 20s						
Antidepressant	**2,354 (4.5)**	**1,775 (4.9)**	**14 (1.1)**	543 (3.8)	17 (2.9)	7,440 (3.4)
Anxiolytic	**820 (1.6)**	**624 (1.7)**	<>	167 (1.2)	**<>**	2,228 (1)
Hypnotic	**662 (1.3)**	**498 (1.4)**	<>	148 (1)	<>	1,983 (0.9)
Antipsychotic	144 (0.3)	94 (0.3)	<>	42 (0.3)	<>	549 (0.3)
Pre-dystonia						
Antidepressants	**232 (0.4)**	**127 (0.3)**	<>	**93 (0.6)**	<>	534 (0.2)
Anxiolytics	**223 (0.4)**	**185 (0.5)**	<>	**<>**	<>	178 (0.08)
Hypnotics	61 (0.1)	41 (0.1)	<>	<>	<>	196 (0.09)
Antipsychotics	<>	<>	<>	<>	<>	62 (0.0.03)
Post-dystonia						
Antidepressant	**2,122 (4)**	**1,648 (4.5)**	<>	450 (3.1)	<>	6,906 (3.2)
Hypnotic	**601 (1.1)**	**457 (1.3)**	<>	<>	<>	1,787 (0.8)
Anxiolytic	**597 (1.1)**	**439 (1.2)**	<>	<>	<>	2,050 (0.9)
Antipsychotic	<>	<>	<>	<>	<>	487 (0.2)
Most commonly prescribed anxiolytics during the study period						
1	**Diazepam: 10,341 (91.5)**	**Diazepam: 6,887 (93.1)**	Diazepam: 220 (90.5)	Diazepam: 3,060 (88.6)	Diazepam: 156 (87.6)	Diazepam: 26,806 (87.8)
2	Hydroxyzine: 860 (7.6)	**Hydroxyzine: 514 (6.9)**	Hydroxyzine: <>	Hydroxyzine: 302 (8.7)	Hydroxyzine: <>	Hydroxyzine: 2,454 (8)
3	**Buspirone: 470 (4.2)**	Buspirone: 253 (3.4)	Lorazepam: <>	**Chlordiazepoxide: 231 (6.7)**	Lorazepam: <>	Lorazepam: 1,785 (5.8)
4	**Lorazepam: 458 (4.1)**	**Lorazepam: 199 (2.7)**	Buspirone: 11 (4.5)	Lorazepam: 230 (6.7)	Buspirone: <>	Buspirone: 999 (3.3)
5	**Chlordiazepoxide: 422 (3.7)**	Chlordiazepoxide: 180 (2.4)	Oxazepam: 5 (2.1)	**Buspirone: 195 (5.6)**	Chlordiazepoxide: 5 (2.8)	Chlordiazepoxide: 882 (2.9)
Most commonly prescribed antidepressants during the study period						
1	**Citalopram: 10,638 (53.1)**	**Citalopram: 6,821 (52.9)**	Citalopram: 213 (45.7)	**Citalopram: 3,467 (54.3)**	Amitriptyline: 118 (45.2)	Citalopram: 31,290 (48.3)
2	**Amitriptyline: 7,818 (39)**	**Amitriptyline: 4,869 (37.7)**	**Amitriptyline: 209 (44.8)**	**Amitriptyline: 2,612 (40.9)**	**Citalopram 116 (44.4)**	Amitriptyline: 21,646 (33.4)
3	**Fluoxetine: 6,767 (33.8)**	**Fluoxetine: 4,469 (34.6)**	Fluoxetine: 148 (31.8)	**Fluoxetine: 2,060 (32.2)**	Fluoxetine:<>	Fluoxetine: 19,005 (29.3)

4	**Sertraline:4,736 (23.6)**	**Sertraline: 2,916 (22.6)**	Sertraline: 94 (20.2)	**Sertraline: 1,668 (26.1)**	Sertraline: <>	Sertraline: 13,572 (20.9)
5	**Mirtazapine: 3,564 (17.8)**	Mirtazapine: 2,116 (16.4)	Mirtazapine: 58 (12.4)	**Mirtazapine: 1,338 (20.9)**	Mirtazapine: <>	Mirtazapine: 10,290 (15.9)
Number of different types of prescribed anxiolytics						
1	**9,963 (88.2)**	6,730 (90.9)	**205 (84.4)**	**2,852 (82.6)**	155 (87.1)	27,773 (91)
2	**1,198 (10.6)**	599 (8.1)	<>	<>	<>	2,456 (8)
≥3	136 (1.2)	72 (1)	<>	<>	<>	290 (1)
Number of different types of prescribed antidepressants						
1	**8,636 (43.1)**	**5,727 (44.4)**	220 (47.2)	**2,571 (40.2)**	**104 (39.8)**	34,060 (52.5)
2	**4,859 (24.2)**	3,112 (24.1)	120 (27.8)	1,548 (24.2)	71 (27.2)	15,083 (23.3)
≥3	**6,546 (32.7)**	**4,058 (31.5)**	126 (27)	**2,267 (35.5)**	**86 (33)**	15,662 (24.2)

Note: percentages can be >100% where participants had more than one prescription

P-values are all vs controls. Bold p-values represent significant values post Bonferroni correction for multiple comparisons <> represents masked values

4.3.3 Time between diagnoses

The time (years) between first psychiatric diagnosis/prescription (Figure 4.5 and 4.6) and index date was significantly shorter in dystonia overall, cervical dystonia and tremor compared to controls, with a significantly shorter time interval to psychiatric diagnosis/prescription seen post-index date, and shortest for those ≥ 20 years at dystonia diagnosis (Table 4.5).

4.3.4 Deprivation

There were no changes in deprivation quintile between entry into the dataset and follow-up for cases with and without psychiatric diagnoses (Figure 4.7) or prescriptions (median 0, p = 0.2, median 0, p = 0.05) (Figure 4.8), with this pattern replicated in the cervical dystonia (median 0, p = 0.03, median 0, p = 0.09), blepharospasm (median 0, p = 0.6, median 0, p = 0.8), tremor (median 0, p =0.7, median 0, p = 0.4), other dystonia (median 0, p = 0.2, median 0, p = 0.8) and control cohorts (median 0, p < 0.01, median 0, p = 0.08) (Figure 4.9 and 4.10).

4.3.5 Association between dystonia and psychiatric diagnosis

Individuals with dystonia had an increased risk for aggregated psychiatric diagnoses and all specific psychiatric disorders except for reduced risk for SMI (Table 4.6). Those with dystonia had a higher risk of anxiety, eating disorders and depression (aOR [95% CI]: 1.64 [1.61–1.68], 1.62 [1.5–1.75], 1.55 [1.51–1.58], respectively). Those ≥20 years had an increased risk of psychiatric diagnoses when compared to those <20 years (aOR [95% CI]: 1.72 [1.68–1.76] vs aOR: 1.4 [1.34–1.47]). Increased risk of anxiety and depression were also higher risk amongst those with cervical dystonia (aOR [95% CI]: 1.41 [1.37–1.45]; 1.41 [1.37–1.44]) (Table 4.7), blepharospasm (aOR [95% CI]: 1.64 [1.44–1.86]; 1.34 [1.18–1.52]) (Table 4.8), and nearly twice as high in dystonic tremor (aOR [95% CI]: 2.35 [2.26–2.44]; 1.98 [1.91–2.06]) (Table 4.9) and in other forms of dystonia (aOR [95% CI]: 1.82 [1.5–2.19]; 1.95 [1.63–2.32]) (Table 4.10). Interestingly, those with other/unspecified dystonia were at highest risk for SMI (aOR [95% CI]: 3.67 [2.37–5.4]) and ADHD (aOR [95% CI]: 3.66 [1.66–6.89]). ASD was not associated with subtypes of dystonia, except for dystonic tremor (aOR [95% CI]: 1.58 [1.24–1.98]).

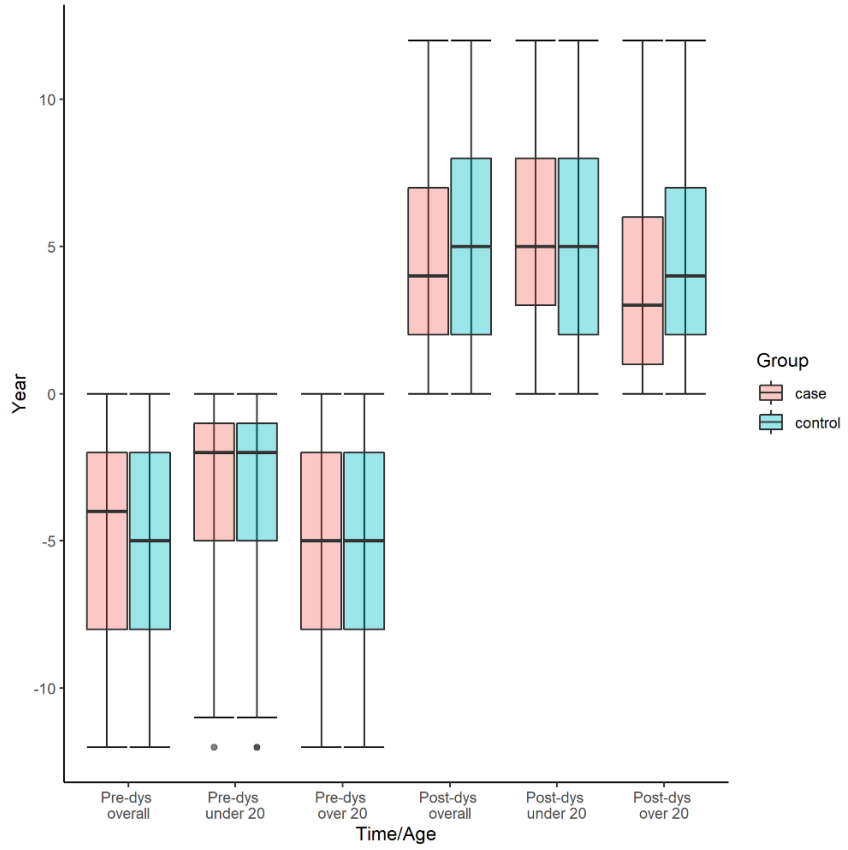

Figure 4.5 Median time (years) from first psychiatric diagnoses to index date

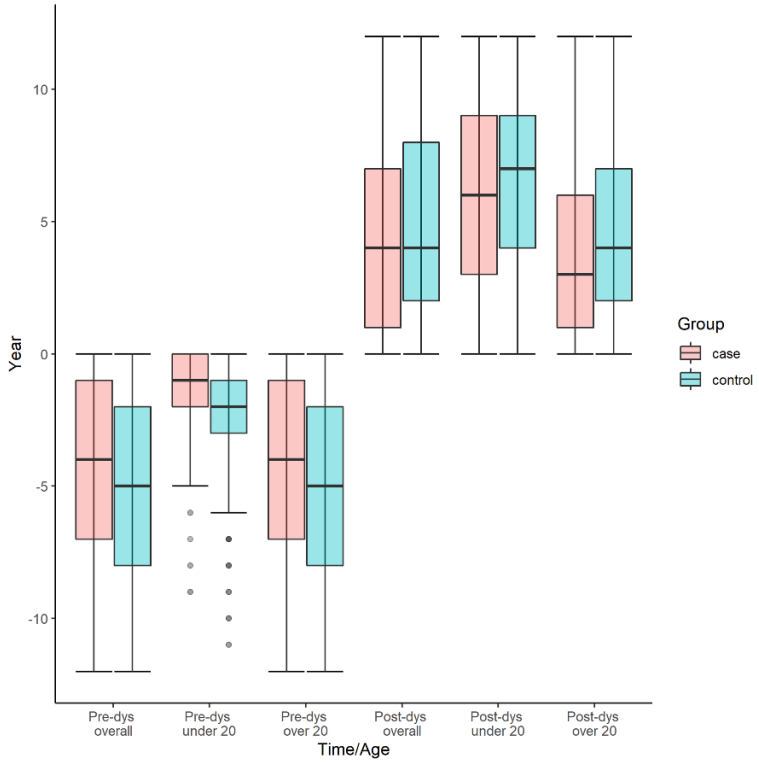

Figure 4.6 Median time (years) from first psychiatric prescriptions to index date

Table 4.5 Number of pre and post psychiatric diagnoses and median time (years) from/to first psychiatric diagnosis/medication from/to index date

	Overall	Cervical dystonia	Blepharospasm	Tremor	Other	Controls
Diagnosis						
Overall						
Pre dystonia						
Median time between mental disorder and dystonia (IQR)	**4.45 (5.8)**	**4.58 (5.62)**	5.05 (6.15)	**4.13 (6.12)**	4.62 (5.8)	4.88 (5.75)
Post dystonia						
Median time between diagnoses (IQR)	**3.86 (5.44)**	**4.33 (5.49)**	**3.72 (4.78)**	**2.42 (4.72)**	3.03 (5.59)	4.63 (5.55)
Over 20						
Pre dystonia						
Median time between mental disorder and dystonia (IQR)	**4.68 (5.81)**	**4.8 (5.62)**	5.22 (6.09)	**4.4 (6.15)**	4.96 (5.31)	5.07 (5.73)
Post dystonia (n,%)						
Median time between diagnoses (IQR)	**3.19 (4.93)**	**3.6 (4.99)**	3.43 (4.56)	**1.97 (4.45)**	2.78 (5.03)	4.07 (5.23)
Under 20						
Pre dystonia						
Median time between mental disorder and dystonia (IQR)	**2.08 (3.79)**	**2.38 (3.69)**	0.99 (0.23)	1.62 (3.7)	**1.37 (5.9)**	2.48 (4.03)
Post dystonia						
Median time between diagnoses (SD) (overall)	**5.4 (5.64)**	5.79 (5.35)	5.23 (4.91)	**3.6 (5.27)**	4.92 (4.9)	5.98 (5.63)
Medication						
Overall						
Pre dystonia (n,%)						
Median time between mental disorder and dystonia (IQR)	**3.96 (6.02)**	**3.69 (5.83)**	5.37 (5.82)	**4.4 (6.21)**	**3.35 (5.45)**	4.52 (5.07)
Post dystonia (n,%)						
Median time between diagnoses (IQR)	**3.83 (5.69)**	4.31 (5.69)	**3.3 (5.56)**	**2.62 (4.83)**	**2.63 (5.67)**	4.42 (5.63)
Over 20						
Pre dystonia (n,%)						
Median time between mental disorder and dystonia (IQR)	**4.12 (5.98)**	**3.85 (5.82)**	5.38 (5.81)	**4.55 (6.16)**	**3.54 (5.72)**	4.62 (5.71)
Post dystonia (n,%)						

Median time between diagnoses (IQR)	**3.15 (5.07)**	**3.49 (5.19)**	**3.01 (5.22)**	**2.2 (4.32)**	2.63 (5.12)	3.85 (5.29)
Under 20						
Pre dystonia (n,%)						
Median time between mental disorder and dystonia (IQR)	**0.54 (1.84)**	**0.29 (1.71)**	<>	**0.97 (1.84)**	0.76 (1.27)	1.56 (2.42)
Post dystonia (n,%)						
Median time between diagnoses (IQR)	**5.96 (5.62)**	6.38 (5.32)	6.98 (6.5)	**3.87 (5.36)**	**2.57 (6.7)**	6.6 (5.36)

P-values are all vs controls using Mann-Whitney U test. Bold p-values represent significant values post Bonferroni correction for multiple comparisons

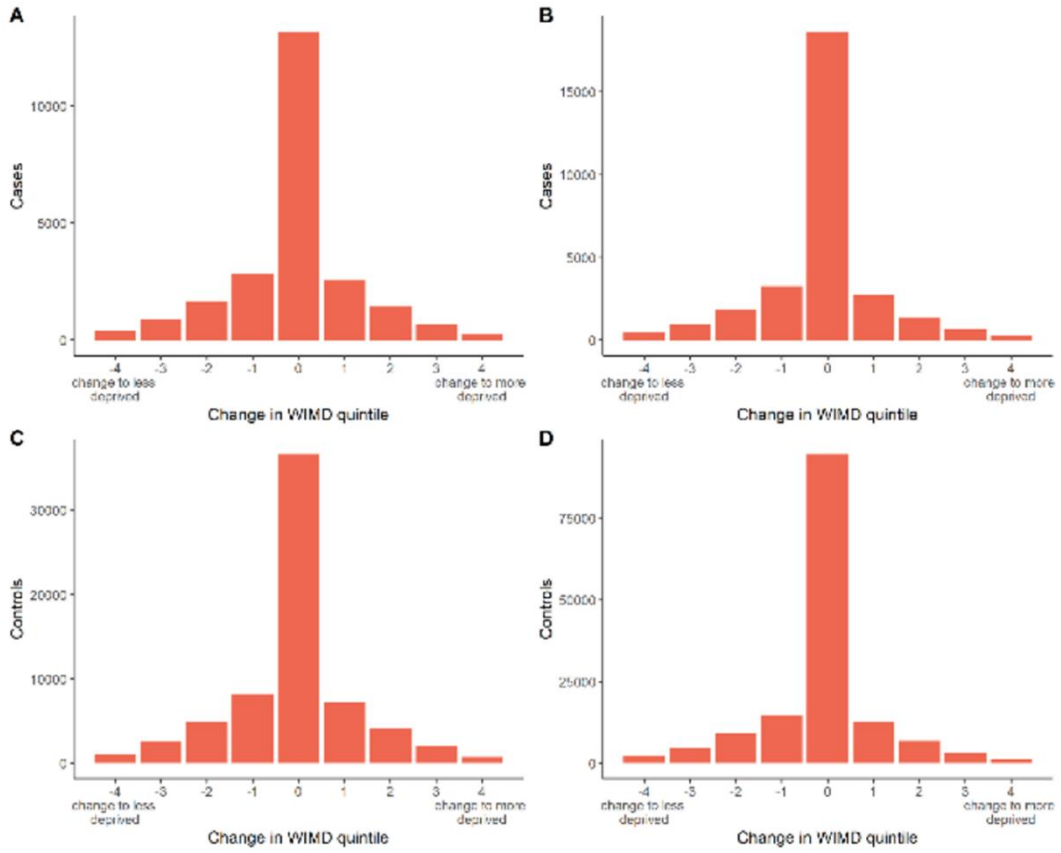

Figure 4.7 Change in WIMD quintile at entry in dataset and follow-up for dystonia cases and controls

A) cases with psychiatric diagnoses **B)** cases without psychiatric diagnoses **C)** controls with psychiatric diagnoses **D)** controls without psychiatric diagnoses

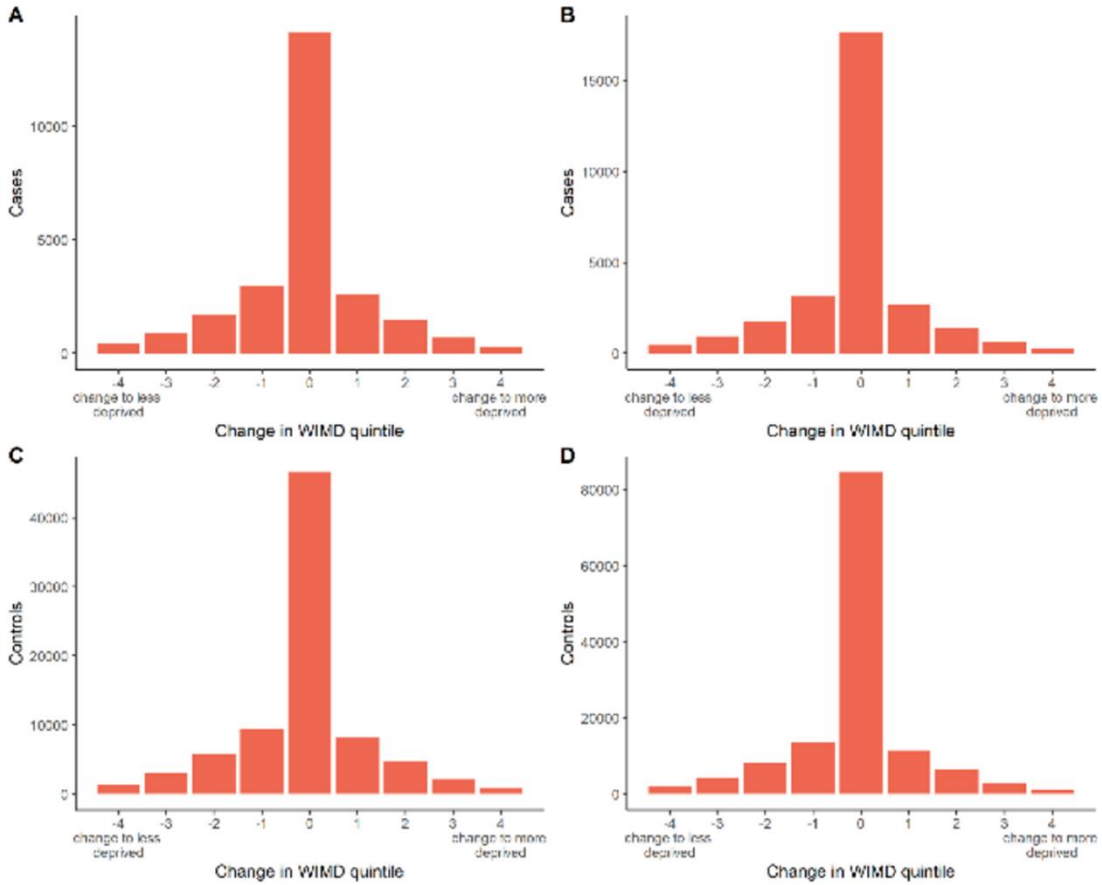

Figure 4.8 Change in WIMD quintile at entry in dataset and follow-up for dystonia cases and controls

A) cases with psychiatric prescriptions **B)** cases without psychiatric prescriptions **C)** controls with psychiatric prescriptions **D)** controls without psychiatric prescriptions

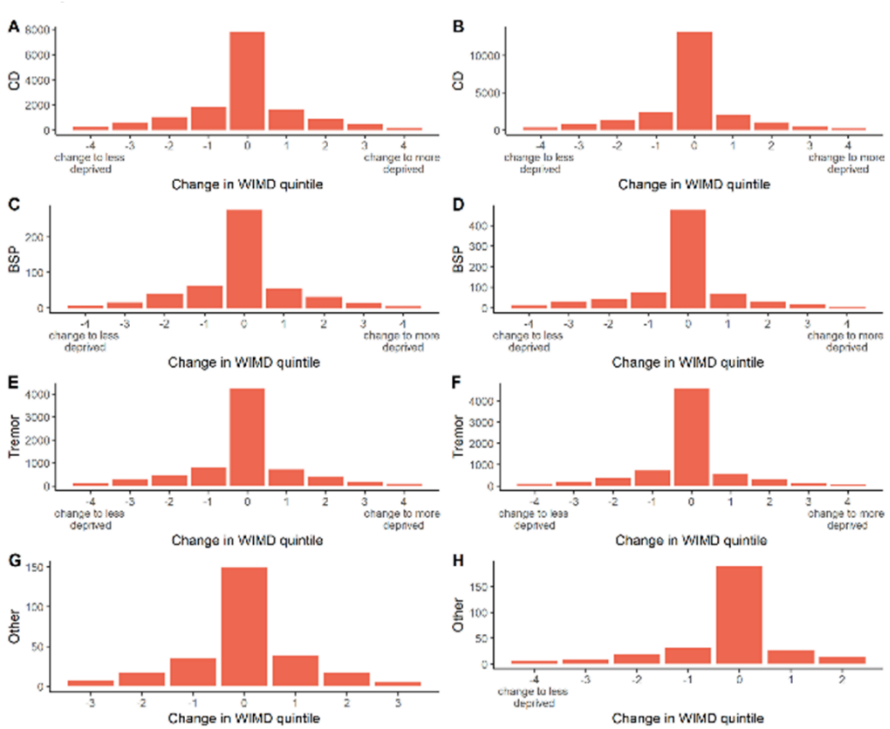

Figure 4.9 Change in WIMD quintile at entry in dataset and follow-up for dystonia cases and controls

Abbreviations: BSP: Blepharospasm, CD: cervical dystonia

A) cervical dystonia with psychiatric diagnoses **B)** cervical dystonia without psychiatric diagnoses **C)** blepharospasm with psychiatric diagnoses **D)** blepharospasm without psychiatric diagnoses **E)** tremor with psychiatric diagnoses **F)** tremor without psychiatric diagnoses **G)** other dystonia with psychiatric diagnoses **H)** other dystonia without psychiatric diagnoses

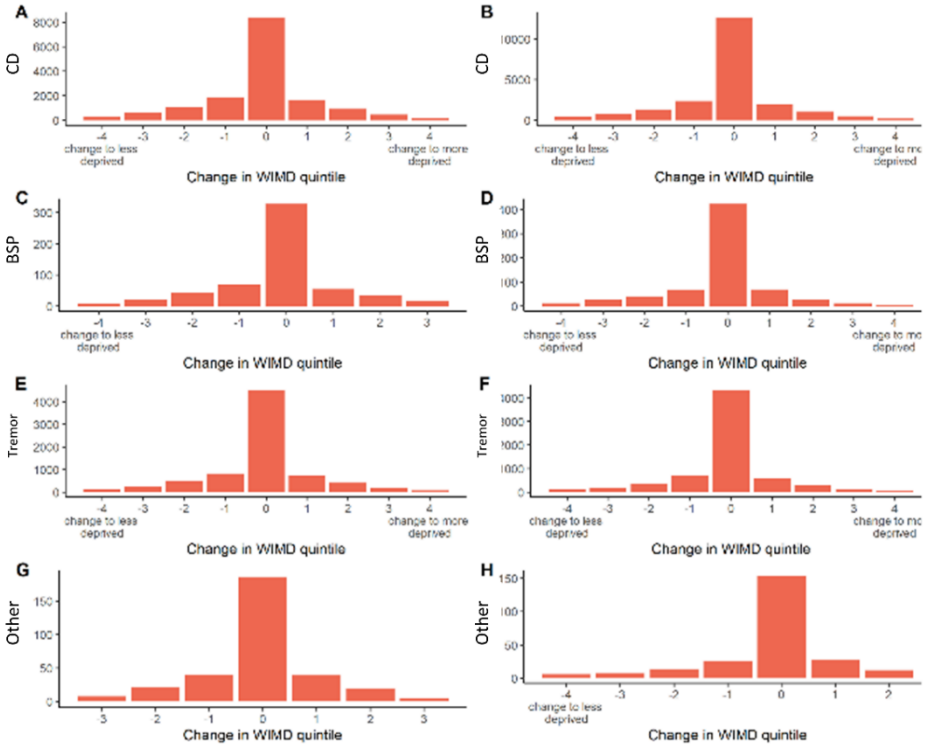

Figure 4.10 Change in WIMD quintile at entry in dataset and follow-up for dystonia cases and controls

Abbreviations: BSP: Blepharospasm, CD: cervical dystonia

A) cervical dystonia with psychiatric prescriptions **B)** cervical dystonia without psychiatric prescriptions **C)** blepharospasm with psychiatric prescriptions **D)** blepharospasm without psychiatric prescriptions **E)** tremor with psychiatric prescriptions **F)** tremor without psychiatric prescriptions **G)** other dystonia with psychiatric prescriptions **H)** other dystonia without psychiatric prescriptions

Table 4.6 Association of psychiatric diagnosis in dystonia in relation to controls

	Diagnosis overall		**ADHD**		**Anxiety disorder**		**ASD**		**Conduct disorder**		**Depression**		**Eating disorder**		**SMI**		**SUD**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI [α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Dystonia	**1.68:1.64-1.71**	**1.62:1.59-1.66**	**1.4:1.22-1.6**	**1.41:1.22-1.61**	**1.7:1.66-1.74**	**1.64:1.61-1.68**	**1.3:1.12-1.5**	**1.33:.1.15-1.54**	**1.47:1.28-1.67**	**1.42:1.25-1.63**	**1.6:1.57-1.64**	**1.55:1.51-1.58**	**1.65:1.53-1.78**	**1.62:1.5-1.75**	**0.77:0.7-0.85**	**0.76:0.69-0.84**	**1.34:1.29-1.39**	**1.3:1.25-1.35**
Sex																		
Female	**1.75:1.7-1.79**	**1.69:1.64-1.73**	**1.48:1.12-1.95**	**1.49:1.12-1.96**	**1.73:1.68-1.79**	**1.67:1.63-1.72**	1.25:0.93-1.66	1.28:0.95-1.7	**1.47:1.92-1.8**	**1.42:1.15-1.74**	**1.63:1.59-1.68**	**1.58:1.54-1.62**	**1.66:1.52-1.81**	**1.63:1.49-1.77**	**0.77:0.68-0.87**	**0.75:0.66-0.85**	**1.32:1.25-1.39**	**1.28:1.21-1.35**
Male	**1.61:1.56-1.66**	**1.56:1.51-1.61**	**1.37:1.17-1.6**	**1.37:1.17-1.6**	**1.69:1.62-1.77**	**1.64:1.58-1.71**	**1.32:1.11-1.56**	**1.34:1.13-1.58**	**1.46:1.23-1.74**	**1.43:1.2-1.7**	**1.59:1.53-1.65**	**1.54:1.48-1.6**	**1.64:1.4-1.92**	**1.62:1.38-1.89**	**0.78:0.67-0.92**	**0.77:0.66-0.9**	**1.36:1.29-1.44**	**1.32:1.25-1.39**
Age at index date							*Age at index date*											
< 20 years	**1.43:1.37-1.49**	**1.4:1.34-1.47**	**1.41:1.21-1.64**	**1.4:1.2-1.62**	**1.46:1.38-1.54**	**1.42:1.34-1.51**	**1.34:1.14-1.57**	**1.35:1.15-1.59**	**1.59:1.36-1.85**	**1.55:1.33-1.81**	**1.33:1.26-1.4**	**1.29:1.22-1.36**	**1.41:1.21-1.63**	**1.38:1.19-1.6**	1.03:0.79-1.34	1-0.76:1.3	**1.17:1.07-1.28**	**1.14:1.04-1.24**
≥ 20 years	**1.78:1.74-1.82**	**1.72:1.68-1.76**	**1.19:0.83-1.66**	**1.21:0.85-1.69**	**1.78:1.73-1.82**	**1.72:1.68-1.77**	1.04:0.72-1.45	1.01:0.98-1.04	1.1:0.83-1.44	1.06:0.8-1.38	**1.69:1.65-1.73**	**1.64:1.6-1.68**	**1.75:1.6-1.91**	**1.72:1.57-1.88**	**0.75:0.67-0.83**	**0.74:0.66-0.82**	**1.39:1.33-1.45**	**1.35:1.29-1.41**
WIMD at index date							*WIMD at index date*											
1	**1.7:1.63-1.78**	**1.64:1.57-1.71**	**1.53:1.19-1.94**	**1.53:1.19-1.95**	**1.67:1.59-1.75**	**1.61:1.53-1.69**	1.42:1.03-1.92	1.43:1.04-1.94	**1.54:1.21-1.94**	**1.49:1.17-1.88**	**1.54:1.47-1.62**	**1.48:1.41-1.55**	**1.49:1.26-1.75**	**1.45:1.23-1.71**	**0.69:0.56-0.84**	**0.67:0.55-0.81**	**1.28:1.19-1.37**	**1.23:1.14-1.32**
2	**1.66:1.59-1.74**	**1.62:1.55-1.69**	1.04:0.76-1.4	1.05-0.76-1.41	**1.74:1.66-1.83**	**1.69:1.61-1.78**	1.07:0.78-1.45	1.12:0.81-1.51	1.33:0.99-1.76	1.31:0.97-1.73	**1.62:1.54-1.69**	**1.57:1.5-1.64**	**1.81:1.53-2.13**	**1.77:1.5-2.09**	0.78:0.63-0.95	0.77:0.63-0.94	**1.27:1.17-1.38**	**1.24:1.14-1.34**
3	**1.69:1.62-1.76**	**1.63:1.56-1.7**	**1.71:1.26-2.29**	**1.74:1.28-2.33**	**1.67:1.59-1.75**	**1.6:1.53-1.69**	1.35:0.97-1.85	1.38:0.99-1.89	1.48:1.08-1.99	1.44:1.05-1.94	**1.61:1.53-1.68**	**1.54:1.47-1.62**	**1.66:1.4-1.95**	**1.62:1.37-1.91**	0.75:0.6-0.94	0.75:0.59-0.93	**1.43:1.32-1.56**	**1.39:1.27-1.51**
4	**1.65:1.58-1.73**	**1.6:1.53-1.68**	1.38:0.95-1.95	1.38:0.95-1.96	**1.7:1.61-1.79**	**1.64:1.56-1.74**	1.54:1.09-2.13	1.55:1.1-1.02	1.42:0.99-1.99	1.37:0.96-1.91	**1.63:1.55-1.71**	**1.57:1.5-1.66**	**1.79:1.5-2.13**	**1.76:1.47-2.09**	0.76:0.59-0.97	0.75:0.58-0.96	**1.4:1.27-1.54**	**1.35:1.23-1.49**
5	**1.72:1.65-1.8**	1**1.68:1.61-1.76**	1.39:0.94-1.99	1.41:0.96-2.03	**1.76:1.67-1.86**	**1.72:1.63-1.81**	1.22:0.84-1.72	1.25:0.86-1.78	1.61:1.09-2.33	1.58:1.06-2.29	**1.67:1.58-1.75**	**1.63:1.55-1.71**	**1.53:1.27-1.84**	**1.51:1.25-1.82**	0.97:0.76-1.22	0.96:0.75-1.21	**1.46:1.31-1.62**	**1.43:1.28-1.59**

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, CI: 95% Confidence Intervals, OR: odds ratios, SMI: Severe Mental Illness, SUD: Substance Use Disorder

Bold values show statistically significant IRR with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.7 Association of psychiatric diagnosis in cervical dystonia in relation to controls

	Diagnosis overall		**ADHD**		**Anxiety disorder**		**ASD**		**Conduct disorder**		**Depression**		**Eating disorder**		**SMI**		**SUD**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI [α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Cervical dystonia	**1.49:1.45-1.52**	**1.41:1.38-1.44**	**1.42:1.21-1.66**	**1.43:1.22-1.67**	**1.49:1.45-1.53**	**1.41:1.37-1.45**	**1.2:1.0:1.42**	1.23:1.03-1.46	**1.53:1.31-1.78**	**1.47:1.26-1.7**	**1.48:1.44-1.52**	**1.4:1.37-1.44**	**1.42:1.29-1.56**	**1.38:1.25-1.51**	**0.48:0.42-0.56**	**0.47:0.41-0.54**	**1.15:1.09-1.2**	**1.09:1.04-1.14**
Sex																		
Female	**1.6:1.55-1.65**	**1.51:1.47-1.55**	1.19:0.83-1.67	1.19:0.83-1.67	**1.55:1.5-1.6**	**1.47:1.42-1.52**	0.93:0.63-1.34	0.95:0.64-1.37	**1.56:1.23-1.96**	**1.47:1.16-1.85**	**1.57:1.52-1.62**	**1.48:1.44-1.53**	**1.44:1.29-1.6**	**1.4:1.26-1.55**	**0.46:0.38-0.55**	**0.45:0.37-0.54**	**1.19:1.11-1.27**	**1.13:1.06-1.21**
Male	**1.33:1.28-1.38**	**1.26:1.21-1.31**	**1.5:1.26-1.78**	**1.5:1.26-1.79**	**1.37:1.3-1.44**	**1.3:1.24-1.37**	1.3:1.06-1.57	1.32:1.08-1.61	**1.52:1.24-1.85**	**1.46:1.2-1.78**	**1.32:1.26-1.38**	**1.26:1.2-1.32**	**1.34:1.09-1.62**	1.31:1.07-1.59	**0.52:0.41-0.65**	**0.51:0.4-0.63**	**1.11:1.04-1.18**	1.05:0.98-1.13
Age at index date																		
< 20 years	**1.31:1.25-1.38**	**1.25:1.19-1.31**	1.27:1.49	1.25:1.05-1.48	**1.29:1.21-1.37**	**1.23:1.15-1.31**	1.16:0.96-1.39	1.17:0.97-1.4	**1.49:1.26-1.77**	**1.44:1.21-1.7**	**1.25:1.17-1.32**	**1.18:1.11-1.25**	**1.29:1.08-1.52**	1.24:1.05-1.46	0.78:0.55-1.07	0.74:0.52-1.02	1.13:1.02-1.35	1.07:0.97-1.18
≥ 20 years	**1.62:1.58-1.66**	**1.53:1.49-1.58**	1.12:0.72-1.67	1.15:0.74-1.72	**1.61:1.56-1.66**	**1.53:1.48-1.57**	0.55:0.31-0.92	0.55:0.3-0.91	1.04:0.73-1.43	0.97-0.68	**1.62:1.58-1.67**	**1.54:1.5-1.58**	**1.46:1.31-1.63**	**1.43:1.27-1.59**	**0.46:0.39-0.54**	**0.45:0.39-0.53**	**1.17:1.11-1.24**	**1.12:1.06-1.18**
WIMD at index date																		
1	**1.5:1.43-1.58**	**1.4:1.33-1.47**	**1.61:1.21-2.11**	**1.61:1.21-2.12**	**1.44:1.36-1.53**	**1.34:1.27-1.43**	1.52:1.06-2.14	1.54:1.07-2.17	**1.67:1.28-2.17**	**1.58:1.2-2.05**	**1.44:1.37-1.52**	**1.34:1.27-1.42**	1.19:0.96-1.47	1.15:0.93-1.41	**0.45:0.33-0.59**	**0.43:0.32-0.56**	1.01:1.01-1.2	1.04:0.95-1.13
2	**1.48:1.41-1.56**	**1.4:1.33-1.48**	0.97:0.66-1.38	0.97:0.66-1.38	**1.53:1.44-1.62**	**1.45:1.37-1.54**	0.78:0.5-1.16	0.82:0.52-1.21	1.35:0.96-1.86	1.31:0.93-1.8	**1.51:1.43-1.59**	**1.43:1.35-1.51**	**1.73:1.42-2.09**	**1.67:1.38-2.02**	**0.5:0.37-0.66**	**0.49:0.36-0.65**	1.12:1.01-1.23	1.07:0.96-1.17
3	**1.49:1.42-1.57**	**1.4:1.33-1.47**	**1.79:1.27-2.48**	**1.84:1.3-2.55**	**1.45:1.37-1.54**	**1.36:1.29-1.45**	1.23:0.83-1.78	1.26:0.85-1.83	1.54:1.08-2.15	1.47:1.03-2.05	**1.47:1.4-1.56**	**1.38:1.31-1.46**	**1.36:1.01-1.66**	1.31:1.06-1.6	**0.41:0.29-0.57**	**0.41:0.28-0.56**	**1.21:1.09-1.34**	1.14:1.03-1.27
4	**1.48:1.4-1.56**	**1.4:1.33-1.48**	1.38:0.9-2.06	1.38:0.9-2.06	**1.49:1.4-1.59**	**1.42:1.33-1.51**	1.38:0.91-2.02	1.39:0.91-2.04	1.48:0.99-2.15	1.4:0.94-2.04	**1.52:1.43-1.61**	**1.44:1.36-1.53**	**1.45:1.17-1.79**	**1.41:1.13-1.74**	**0.51:0.36-0.72**	**0.5:0.35-0.71**	**1.20:1.07-1.35**	1.15:1.02-1.29
5	**1.55:1.47-1.63**	**1.49:1.42-1.57**	1.46:0.94-2.19	0.99:0.96-1.02	**1.59:1.5-1.69**	**1.53:1.44-1.63**	1.21:0.78-1.8	1.26:0.81-1.87	1.69:1.08-2.56	1.65:1.05-2.49	**1.53:1.44-1.62**	**1.47:1.38-1.56**	**1.41:1.12-1.75**	**1.38:1.1-1.72**	**0.62:0.44-0.86**	**0.61:0.43-0.84**	**1.23:1.07-1.39**	1.18:1.04-1.35

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, CI: 95% Confidence Intervals, OR: odds ratios, SMI: Severe Mental Illness, SUD: Substance Use Disorder

Bold values show statistically significant IRR with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.8 Association of psychiatric diagnosis in blepharospasm in relation to controls

	Diagnosis overall		**ADHD**		**Anxiety disorder**		**ASD**		**Conduct disorder**		**Depression**		**Eating disorder**		**SMI**		**SUD**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Blepharospasm	**1.47:1.32-1.65**	**1.44:1.29-1.62**	0.42:0.07-1.29	0.42:0.07-1.29	**1.67:1.47-1.9**	**1.64:1.44-1.86**	0.67:0.17-1.76	0.68:0.17-1.78	0.62:0.15-1.61	0.61:0.15-1.58	**1.37:1.21-1.55**	**1.34:1.18-1.52**	1.1:0.63-1.76	1.08:0.62-1.74	0.87:0.48-1.44	0.86:0.47-1.42	1.15:0.9-1.43	1.12:0.88-1.4
Sex																		
Female	**1.41:1.22-1.62**	**1.4:1.21-1.61**	0.86:0.05-2.84	0.86:0.05-3.84	**1.58:1.35-1.84**	**1.57:1.35-1.84**	1.66:0.27-5.19	1.67:0.28-5.23	0.95:0.16-2.97	0.95:0.16-2.96	**1.27:1.09-1.47**	**1.25:1.08-1.46**	0.81:0.39-1.48	0.81:0.39-1.47	0.6:0.24-1.23	0.61:0.24-1.24	1.15:0.82-1.56	1.14:0.82-1.55
Male	**1.56:1.29-1.89**	**1.5:1.23-1.82**	0.29:0.02-1.29	0.29:0.02-1.29	**1.84:1.44-2.31**	**1.76:1.38-2.22**	0.33:0.02-1.45	0.33:0.02-1.47	0.38:0.02-1.68	0.37:0.02-1.63	**1.56:1.24-1.95**	**1.5:1.191.87**	2.06:0.81:4.23	2.01:0.79-4.13	1.36:0.58-2.65	1.33:0.57-2.59	1.18:0.83-1.62	1.13:0.8-1.55
Age at index date																		
< 20 years	0.89:0.56-1.36	0.9:0.56-1.39	-	-	1.09:0.59-1.83	1.11:0.61-1.9	1.433:0.24-4.52	1.44:0.24-4.53	2.24:0.55-5.94	2.25:0.55-5.98	0.66:0.33-1.16	0.66:0.33-1.19	0.62:0.04-2.79	0.63:0.04-2.81	3.3:0.54-10.43	3.38:0.56-10.74	0.75:0.23-1.79	0.77-0.24-1.84
≥ 20 years	**1.41:1.25-1.59**	**1.39:1.23-1.56**	1.96:0.32-6.14	1.98:0.33-6.2	**1.57:1.38-1.79**	**1.55:1.36-1.77**	0.9:0.05-4	0.89:0.05-3.98	-	-	**1.29:1.13-1.47**	**1.27:1.12-1.44**	1.22:0.68-1.98	1.2:0.68-1.96	0.68:0.35-1.18	0.68:0.35-1.17	1.13:0.88-1.41	1.11:0.89-1.4
WIMD at index date																		
1	1.54:1.11-2.12	1.58:1.14-2.19	-	-	**1.72:1.2-2.41**	**1.78:1.24-2.51**	-	-	2.19:0.36-6.91	2.24:0.37-7.08	1.29:0.91-1.81	1.33:0.93-1.87	1.05:0.17-3.29	1.06:0.17-3.32	1.19:0.29-3.15	1.21:0.3-3.19	1.54:0.92-2.43	1.58:0.94-2.5
2	**1.7:1.31-2.21**	**1.64:1.26-2.14**	-	-	**1.98:1.48-2.62**	**1.92:1.43-2.54**	-	-	-	-	**1.67:1.26-2.19**	**1.61:1.21-2.12**	1.21:0.3-3.2	1.19:0.29-3.13	0.97:0.24-2.56	0.96:0.24-2.53	1.12:0.65-1.8	1.08:0.62-1.74
3	**1.53:1.2-1.94**	**1.51:1.19-1.92**	-	-	1.43:1.07-1.88	1.41:1.05-1.87	-	-	1.05:0.06-4.68	1.03:0.06-4.63	1.37:1.05-1.78	1.36:1.03-1.76	1.67:0.59-3.65	1.65:0.59-3.61	0.97:0.24-2.54	0.96:0.24-2.53	1.26:0.74-1.99	1.24:0.73-1.97
4	**1.46:1.13-1.86**	**1.42:1.11-1.82**	-	-	**2.05:1.56-2.66**	**2.01:1.53-2.62**	-	-	-	-	1.41:1.07-1.85	1.38:1.04-1.81	1.73:0.62-3.79	1.7:0.6-3.72	0.76:0.13-2.37	0.75:0.12-2.34	0.82:0.41-1.46	0.8:0.4-1.43
5	**1.55:1.23-1.94**	**1.5:1.18-1.88**	-	-	**1.6:1.22-2.08**	**1.55:1.18-2.02**	-	-	-	-	**1.44:1.11-1.86**	1.39:1.07-1.8	-	-	0.73:0.12-2.29	0.72:0.12-2.25	1.61:0.93-2.58	1.57:0.91-2.51

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, CI: 95% Confidence Intervals, OR: odds ratios, SMI: Severe Mental Illness, SUD: Substance Use Disorder

[α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.9 Association of psychiatric diagnosis in tremor in relation to controls

	Diagnosis overall		**ADHD**		**Anxiety disorder**		**ASD**		**Conduct disorder**		**Depression**		**Eating disorder**		**SMI**		**SUD**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI [α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Tremor	**2.27:2.2-2.35**	**2.32-2.24-2.4**	1.34:1.05-1.7	1.34:1.05-1.7	**2.31:2.22-2.39**	**2.35:2.26-2.44**	**1.57:1.24-1.97**	**1.58:1.24-1.98**	1.31:1.02-1.66	1.32:1.02-1.66	**1.95:1.88-2.02**	**1.98:1.91-2.06**	**2.34:2.09-2.61**	**2.34:2.08-2.61**	**1.39:1.21-1.58**	**1.39:1.21-1.58**	**1.85:1.74-1.96**	**1.86:1.75-1.97**
Sex																		
Female	**2.25:2.15-2.35**	**2.29:2.19-2.39**	**2.05:1.32-3.05**	**2.05:1.32-3.05**	**2.28:2.17-2.38**	**2.31:2.2-2.42**	**1.89:1.2-2.82**	**1.9:1.21-2.84**	1.27:0.84-1.83	1.27:0.84-1.83	**1.85:1.77-1.94**	**1.88:1.79-1.96**	**2.34:2.05-2.67**	**2.34:2.05-2.66**	**1.51:1.28-1.78**	**1.51:1.28-1.78**	**1.7:1.56-1.85**	**1.7:1.56-1.85**
Male	**2.43:2.3-2.57**	**2.48:2.35-2.62**	1.11:0.82-1.47	.11:0.82-1.47	**2.56:2.4-2.73**	**2.61:2.45-2.78**	1.43:1.07-1.87	1.43:1.07-1.87	1.33:0.96-1.78	1.33:0.96-1.79	**2.31:2.17-2.45**	**2.35:2.21-2.5**	**2.42:1.92-3.01**	**2.42:1.92-3.01**	1.19:0.94-1.49	1.19:0.94-1.49	**1.98:1.82-2.14**	**2:1.84-2.16**
Age at index date																		
< 20 years	**1.99:1.82-2.16**	**2.23:2.03-2.43**	**1.98:1.51-2.56**	**2.0:1.52-1.58**	**2.22:2-2.46**	**2.44:2.2-2.71**	**2.08:1.56-2.71**	**2.06:1.55-2.69**	**1.84:1.35-2.44**	**1.89:1.39-2.51**	**1.72:1.55-1.9**	**1.88:1.69-2.09**	**1.99:1.51-2.57**	**2.06:1.56-2.65**	1.65:1.01-2.54	1.72:1.06-2.65	**1.3:1.08-1.55**	**1.36:1.13-1.63**
≥ 20 years	**2.24:2.16-2.33**	**2.26:2.18-2.35**	1.13:0.59-1.94	1.13:0.59-1.95	**2.22:2.14-2.32**	**2.24:2.15-2.33**	**1.9:1.18-2.9**	**1.89:1.18-2.89**	1.29:0.82-1.94	1.3:0.82-1.94	**1.9:1.83-1.97**	**1.91:1.84-1.99**	**2.49:2.19-2.82**	**2.48:2.19-2.81**	**1.29:1.11-1.48**	**1.28:1.11-1.48**	**1.89:1.77-2.01**	**1.89:1.78-2.01**
WIMD at index date																		
1	**2.27:2.1-2.44**	**2.32:2.15-2.5**	1.32:0.84-1.98	1.32:0.84-1.99	**2.27:2.1-2.45**	**2.31:2.14-2.5**	1.23:0.68-2.05	1.23:0.68-2.05	1.18:0.74-1.78	1.18:0.74-1.78	**1.81:1.68-1.95**	**1.84:1.7-1.99**	**2.23:1.75-2.79**	**2.22:1.75-2.78**	1.11:0.84-1.45	1.11:0.84-1.44	**1.63:1.46-1.82**	**1.63:1.46-1.82**
2	**2.2:2.04-2.37**	**2.26:2.1-2.44**	1.22:0.71-1.94	1.22:0.71:1.94	**2.32:2.14-2.51**	**2.38:2.2-2.58**	1.76:1.11-2.66	1.77:1.12-2.67	1.38:0.82-2.17	1.38:0.82-2.18	**1.9:1.76-2.05**	**1.96:1.8-2.11**	**2.1:1.61-2.7**	**2.11:1.61-2.71**	1.35:1.01-1.77	1.35:1.01-1.78	**1.67:1.47-1.89**	**1.69:1.49:1.92**
3	**2.37:2.19-2.55**	**2.42:2.24-2.61**	1.51:0.83-2.52	1.51:0.83-2.53	**2.36:2.17-2.56**	**2.4:2.21-2.61**	1.88:1.11-2.99	1.88:1.12-2.99	1.22:0.64-2.1	1.22:0.64-2.1	**2.01:1.86-2.18**	**2.04:1.88-2.22**	**2.52:1.96-3.19**	**2.52:1.96-3.19**	1.45:1.05-1.94	1.45:1.05-1.94	**2.08:1.82-2.36**	**2.09:1.83-2.37**
4	**2.26:2.09-2.45**	**2.28:2.1-2.47**	1.45:0.732.56	1.45:0.74-2.57	**2.3:2.11-2.52**	**2.32:2.12-2.54**	1.83:1.03-3.03	1.84:1.03-3.04	1.35:0.69-2.39	1.35:0.69-2.39	**1.99:1.82-2.16**	**1.99:1.83-2.17**	**2.76:2.14-3.52**	**2.75:2.13-3.51**	1.38:0.95-1.93	1.38:0.95-1.93	**2.04:1.75-2.35**	**2.03:1.75-2.35**
5	**2.25:2.08-2.43**	**2.28:2.11-2.47**	1.15:0.51-2.21	1.15:0.52-2.22	**2.24:2.05-2.44**	**2.27:2.07-2.48**	1.08:0.51-2.0	1.09:0.51-2.01	1.5:0.7-2.81	1.5:0.7-2.81	**2.07:1.9-2.25**	**1.07:1.06-1.07**	**2.08:1.55-2.75**	**2.08:1.55-2.75**	**1.85:1.33-2.52**	**1.85:1.33-2.51**	**2.03:1.71-2.38**	**2.03:1.71-2.38**

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, CI: 95% Confidence Intervals, OR: odds ratios, SMI: Severe Mental Illness, SUD: Substance Use Disorder

[α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.10 Association of psychiatric diagnosis in other dystonia in relation to controls

	Diagnosis overall		**ADHD**		**Anxiety disorder**		**ASD**		**Conduct disorder**		**Depression**		**Eating disorder**		**SMI**		**SUD**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI [α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Other	**1.99:1.69-2.35**	**2.1:1.78-2.48**	**3.67:1.67-6.91**	**3.66:1.66-6.89**	**1.73:1.43-2.08**	**1.82:1.5-2.19**	2.97:1.17-6.07	2.94:1.16-6.01	**3.19:1.36-6.22**	**3.28:1.4-6.41**	**1.84:1.55-2.19**	**1.95:1.63-2.32**	0.64:0.2-1.49	0.65:0.2-1.52	**3.61:2.33-5.32**	**3.67:2.37-5.4**	**1.98:1.49-2.57**	**2.05:1.55-2.66**
Sex																		
Female	**1.75:1.42-2.16**	**1.84:1.49-2.29**	**8.04:2.47-19.09**	**8.03:2.46-19.07**	**1.71:1.36-2.15**	**1.8:1.43-2.27**	**5.77:1.42-15.24**	**5.72:1.41-15.11**	2.21:0.37-6.89	2.31:0.38-7.23	**1.57:1.25-1.95**	**1.65:1.32-2.06**	0.84:0.26-1.95	0.85:0.26-2	2.14:1.02-3.91	2.18:1.04-3.98	0.99:0.56-1.6	1.02:0.58-1.66
Male	**2.52:1.94-3.26**	**2.64:2.03-3.44**	2.37:0.73-5.59	2.37:0.73-5.59	**1.84:1.31-2.54**	**1.92:1.35-2.65**	1.99:0.49-5.23	1.98:0.49-5.2	**3.88:1.38-8.49**	**3.96-1.4-8.67**	**2.59:1.95-3.42**	**2.72:2.04-3.6**	-	-	**6.13:3.47-10.03**	**6.22:3.51-10.16**	**3.1:2.2-4.26**	**3.23:2.29-4.46**
Age at index date																		
< 20 years	**3.18:2.07-4.89**	**4.34:2.75-6.84**	**5.93:2.3-12.55**	**6.11:2.37-12.95**	**2.82:1.68-4.54**	**3.64:2.13-6.02**	3.21:0.79-8.61	3.14:0.77-8.42	**5.66:1.98-12.67**	**6.32:.221-14.22**	**2.09:1.32-3.39**	**2.73:1.57-4.55**	0.92:0.05-4.13	1.03:0.06-4.64	**12.62:4.41-28.4**	**15.16:525-34.57**	**4.11:2.17-7.18**	**5.08:2.5-9.02**
≥ 20 years	**1.74:1.46-2.08**	**1.8:1.5-2.15**	4.52:0.75-14.21	4.49:0.74-14.12	**1.52:1.24-1.85**	**1.57:1.27-1.91**	**6.24:1.54-16.51**	**6.28:1.55-16.6**	2.71:0.45-8.48	2.81:0.46-8.79	**1.7:1.41-2.04**	**1.75:1.45-2.11**	0.6:0.15-1.56	0.6:0.15-1.57	**2.81:171-4.32**	**2.82:1.72-4.34**	**1.66:1.21-2.23**	**1.7:1.24-2.28**
WIMD at index date																		
1	**1.96:1.4-2.77**	**2.18:1.54-3.1**	4:0.98-10.66	4.01:0.98-1.68	1.49:1.01-2.16	1.63:1.09-2.37	2.01:0.11-9.06	0.99:0.96-1.02	2.47:0.41-7.81	2.63:0.43-8.34	1.5:1.05-2.13	1.65:1.14-2.36	0.59:0.03-2.62	0.61:0.03-2.73	**3.24:1.37-6.45**	**3.39:1.43-6.77**	**2.45:1.55-3.73**	**2.65:1.67-2.04**
2	**2.11:1.48-3.01**	**2.16:1.51-3.1**	3.46:0.57-10.96	3.45:0.57-10.96	1.57:1.04-2.33	1.6:1.05-2.38	3.69:0.61-11.71	3.69:0.61-11.72	1.83:0.1-8.23	1.84:0.1-8.27	**1.85:1.27-2.65**	**1.89:1.3-2.74**	0.74:0.04-3.3	0.74:0.04-3.31	**3.7:1.44-7.73**	**3.7:1.45-7.74**	1.73:0.93-2.96	1.75:0.94-3.0
3	**2.18:1.49-3.2**	**2.39:1.62-3.53**	2.99:0.17-13.54	2.95:0.17-13.35	**2.06:1.33-3.11**	**2.25:1.45-3.42**	-	-	5.69:0.93-18.16	6.03:0.99-19.28	**2.18:1.45-3.22**	**2.39:1.58-3.55**	0.89:0.05-3.98	0.93:0.05-4.16	**6.41:2.69-12.88**	**6.52:2.74-13.12**	1.84:0.86-3.44	1.95:0.91-3.66
4	1.49:0.97-2.24	1.53:0.99-2.31	3.6:0.2-16.34	3.58:0.2-16.28	1.48:0.88-2.38	1.53:0.9-2.46	6.76:1.11-21.66	6.73:1.1-21.59	3.37:0.19-15.29	3.45:0.2-15.7	1.45:0.9-2.27	1.49:0.92-2.34	1:0.06-4.48	1.01:0.06-4.55	2.23:0.37-7.06	2.24:0.37-7.72	0.96:0.29-2.29	0.97:0.3-2.34
5	**2.11:1.46-3.03**	**2.17:1.5-3.13**	3.37:0.19-15.29	3.37:0.19-15.27	**2.09:1.37-3.11**	**1.07:1.07-1.08**	2.81:0.16-12.69	2.8:0.16-12.64	3.91:0.22-17.78	3.94:0.22-17.92	**2.3:1.55-3.35**	**2.37:1.59-3.47**	-	-	2.014:0.33-6.36	2.02:0.33-6.4	2.24:1-4.31	2.27:1.01-4.37

Abbreviations: ADHD: Attention Deficit Hyperactive Disorder, ASD: Autism Spectrum Disorder, CI: 95% Confidence Intervals, OR: odds ratios, SMI: Severe Mental Illness, SUD: Substance Use Disorder

[α]ORs and CIs estimated by logistic regression and adjusted for time in study

4.3.6 Association between dystonia and psychiatric prescriptions

Anxiolytic prescriptions were almost two times higher (aOR: 1.61 [1.57–1.65]) in dystonia patients, while risk was lower but comparable for prescription of antidepressants and hypnotics (aOR [95% CI]: 1.39 [1.36–1.42] and 1.3 [1.26–1.33]) (Table 4.11). Interestingly, amongst dystonia overall and cervical dystonia (Table 4.12), risk of use of antipsychotics were reduced (aOR: 0.77 [0.72–0.82] and 0.54 [0.5–0.6]), whereas risk was comparable to controls in blepharospasm (Table 4.13) and increased in tremor and other dystonia (aOR: 1.3 [1.19–1.43], 1.98 [1.35– 2.8]) (Table 4.14 and 4.15, respectively). However, it is important to note that we excluded individuals who were prescribed an antipsychotic medication prior to their dystonia diagnosis so as not to include potential cases of drug-induced dystonia.

4.3.7 Comparative risk of psychiatric diagnosis and/or prescription of psychiatric medication

There was an increased risk of psychiatric diagnosis and prescription in those with dystonia across the entire study period, with this increasing in the year either side of dystonia diagnosis. A similar pattern was observed for anxiety and depression, and their associated oral medical therapies, while other psychiatric diagnoses (e.g. SMI and eating disorders) demonstrated a more consistent increased risk (Figure 4.11 and 4.12).

Table 4.11 Association of psychiatric prescription in dystonia in relation to controls

	Medication overall		**Antidepressant**		**Anxiolytic**		**Antipsychotic**		**Hypnotic**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Dystonia	**1.35:1.33-1.38**	**1.3:1.27-1.32**	**1.44:1.41-1.47**	**1.39:1.36-1.42**	**1.67:1.63-1.71**	**1.61:1.57-1.65**	**0.78:0.73-0.83**	**0.77:0.72-0.82**	**1.34:1.3-1.38**	**1.3:1.26-1.33**
Sex										
Female	**1.4:1.36-1.43**	**1.33:1.3-1.37**	**1.45:1.42-1.49**	**1.39:1.35-1.43**	**1.74:1.69-1.79**	**1.68:1.63-1.73**	**0.79:0.73-0.86**	**0.78:0.72-0.85**	**1.34:1.3-1.39**	**1.3:1.26-1.34**
Male	**1.32:1.28-1.36**	**1.27:1.23-1.32**	**1.47:1.42-1.52**	**1.43:1.38-1.48**	**1.55:1.49-1.62**	**1.5:1.44-1.57**	**0.76:0.69-0.85**	**0.75:0.67-0.83**	**1.34:1.27-1.4**	**1.3:1.24-1.36**
Age at index date										
<20 years	**1.33:1.26-1.39**	**1.29:1.23-1.36**	**1.33:1.26-1.4**	**1.29:1.23-1.36**	**1.51:1.39-1.64**	**1.46:1.35-1.59**	1.05:0.87-1.26	1.02:0.84-1.22	**1.36:1.24-1.48**	**1.32:1.2-1.44**
≥ 20 years	**1.41:1.38-1.44**	**1.35:1.32-1.38**	**1.51:1.48-1.54**	**1.45:1.42-1.48**	**1.73:1.69-1.78**	**1.67:1.63-1.72**	**0.76:0.71-0.81**	**0.75:0.7-0.81**	**1.36:1.32-1.4**	**1.32:1.28-1.36**
WIMD at index date										
1	**1.42:1.36-1.48**	**1.35:1.29-1.41**	**1.42:1.36-1.48**	**1.35:1.29-1.41**	**1.77:1.68-1.87**	**1.71:1.62-1.8**	**0.78:0.69-0.88**	**0.76:0.67-0.86**	**1.4:1.32-1.48**	**1.35:1.27-1.43**
2	**1.37:1.32-1.43**	**1.32:1.27-1.38**	**1.46:1.4-1.53**	**1.41:1.35-1.48**	**1.77:1.68-1.87**	**1.73:1.64-1.82**	**0.78:0.68-0.89**	**0.77:0.67-0.88**	**1.34:1.27-1.42**	**1.3:1.23-1.38**
3	**1.33:1.27-1.38**	**1.26:1.21-1.32**	**1.45:1.38-1.51**	**1.38:1.32-1.44**	**1.63:1.55-1.72**	**1.57:1.49-1.65**	**0.79:0.69-0.91**	**0.78:0.68-0.9**	**1.32:1.24-1.4**	**1.27:1.2-1.35**
4	**1.36:1.3-1.42**	**1.31:1.25-1.37**	**1.48:1.41-1.55**	**1.42:1.36-1.49**	**1.59:1.5-1.68**	**1.53:1.44-1.62**	**0.78:0.67-0.91**	**0.78:0.66-0.91**	**1.39:1.3-1.48**	**1.34:1.26-1.43**
5	**1.31:1.26-1.37**	**1.27:1.22-1.33**	**1.44:1.37-1.5**	**1.4:1.33-1.46**	**1.57:1.48-1.66**	**1.53:1.44-1.62**	0.78:0.67-0.92	0.78:0.66-0.92	**1.25:1.17-1.34**	**1.22:1.15-1.31**

Abbreviations: CI: Confidence Intervals, OR: Odds ratio

Bold values show statistically significant odds ratios with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.12 Association of psychiatric prescription in cervical dystonia in relation to controls

	Medication overall		**Antidepressant**		**Anxiolytic**		**Antipsychotic**		**Hypnotic**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Cervical dystonia	**1.19:1.16-1.22**	**1.11:1.09-1.14**	**1.29:1.26-1.32**	**1.21:1.18-1.24**	**1.56:1.52-1.6**	**1.48:1.43-1.52**	**0.57:0.52-0.61**	**0.54:0.5-0.6**	**1..17:1.13-1.21**	**1.11:1.08-1.15**
Sex										
Female	**1.28:1.24-1.31**	**1.19:1.15-1.22**	**1.35:1.32-1.39**	**1.27:1.23-1.3**	**1.66:1.61-1.72**	**1.58:1.52-1.63**	**0.57:0.51-0.64**	**0.56:0.5-0.62**	**1.21:1.16-1.26**	**1.15:1.1-1.19**
Male	1.06:1.02-1.1	1:0.96-1.04	**1.18:1.13-1.23**	**1.11:1.07-1.16**	**1.35:1.28-1.42**	**1.28:1.21-1.35**	**0.53:0.45-0.61**	**0.51:0.44-0.59**	1.09:1.03-1.16	1.04:0.98-1.11
Age at index date										
<20 years	**1.24:1.17-1.31**	**1.17:1.11-1.23**	**1.24:1.17-1.31**	**1.17:1.1-1.24**	**1.43:1.31-1.57**	**1.36:1.24-1.49**	0.86:0.69-1.06	0.82:0.65-1.01	**1.27:1.15-1.41**	**1.21:1.09-1.34**
≥ 20 years	**1.29:1.26-1.33**	**1.21:1.18-1.24**	**1.4:1.37-1.44**	**1.32:1.28-1.35**	**1.7:1.65-1.76**	**1.61:1.56-1.66**	**0.54:0.49-0.6**	**0.54:0.49-0.59**	**1.12:1.19-1.28**	**1.17:1.13-1.21**
WIMD at index date										
1	**1.25:1.19-1.32**	**1.15:1.09-1.21**	**1.27:1.21-1.34**	**1.17:1.11-1.23**	**1.64:1.54-1.74**	**1.54:1.45-1.64**	**0.57:0.48-0.67**	**0.54:0.46-0.64**	**1.26:1.18-1.35**	**1.19:1.11-1.27**
2	**1.22:1.16-1.28**	**1.14:1.08-1.2**	**1.32:1.26-1.39**	**1.24:1.18-1.31**	**1.66:1.56-1.76**	**1.57:1.48-1.68**	**0.65:0.55-0.77**	**0.63:0.53-0.75**	**1.18:1.09-1.26**	**1.12:1.04-1.2**
3	**1.16:1.11-1.22**	**1.08:1.03-1.13**	**1.29:1.23-1.36**	**1.2:1.14-1.26**	**1.52:1.43-1.61**	**1.42:1.134-1.51**	**0.51:0.42-0.62**	**0.51:0.41-0.62**	**1.13:1.06-1.21**	1.07:0.99-1.15
4	**1.18:1.12-1.25**	**1.11:1.06-1.18**	**1.31:1.24-1.38**	**1.24:1.17-1.31**	**1.5:1.4-1.6**	**1.42:1.32-1.51**	**0.51:0.41-0.64**	**0.51:0.4-0.63**	**1.19:1.1-1.28**	**1.14:1.05-1.23**
5	**1.16:1.1-1.22**	**1.11:1.05-1.17**	**1.28:1.21-1.35**	**1.22:1.16-1.29**	**1.5:1.4-1.6**	**1.43:1.34-1.53**	**0.51:0.41-0.64**	**0.51:0.4-0.64**	1.1:1.02-1.19	1.06:0.98-1.15

Abbreviations: CI: Confidence Intervals, OR: Odds ratio

Bold values show statistically significant odds ratios with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.13 Association of psychiatric prescription in blepharospasm in relation to controls

	Medication overall		**Antidepressant**		**Anxiolytic**		**Antipsychotic**		**Hypnotic**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Blepharospasm	**1.38:1.24-1.55**	**1.35:1.2-1.51**	**1.37:1.22-1.54**	**1.34:1.19-1.5**	**1.45:1.26-1.67**	**1.42:1.23-1.64**	0.96:0.67-1.32	0.95:0.66-1.31	**1.36:1.16-11.58**	**1.33:1.14-1.55**
Sex										
Female	**1.29:1.12-1.49**	**1.28:1.11-1.47**	**1.27:1.1-1.46**	**1.26:1.09-1.45**	**1.46:1.24-1.72**	**1.46:1.23-1.72**	0.93:0.59-1.39	0.93:0.59-1.39	1.29:1.07-1.55	1.28:1.07-1.54
Male	**1.52:1.25-1.83**	**1.45:1.19-1.75**	**1.53:1.25-1.87**	**1.47:1.19-1.79**	1.36:1.02-1.77	1.3:0.98-1.69	0.99:0.53-1.68	0.97:0.51-1.64	1.46:1.1-1.9	1.41:1.06-1.84
Age at index date										
<20 years	0.91:0.54-1.45	0.93:0.55-1.51	0.78:0.43-1.32	0.8:0.44-1.38	0.96:0.34-2.12	1:0.35-2.23	1.58:0.26-4.97	1.61:0.26-5.09	0.64:0.16-1.7	0.65:0.16-1.74
≥ 20 years	1.19:1.06-1.34	1.16:1.03-1.31	**1.22:1.08-1.37**	1.19:1.06-1.35	**1.26:1.09-1.46**	1.24:1.07-1.43	0.83:0.57-1.15	0.82:0.57-1.15	1.2:1.02-1.39	1.18:1.01-1.37
WIMD at index date										
1	1.05:0.76-1.45	1.07:0.77-1.48	1.08:0.78-1.5	1.11:0.79-1.55	1.63:1.1-2.35	1.69:1.13-2.44	0.89:0.32-1.96	0.9:0.32:1.98	1.25:0.8-1.88	1.28:0.82-1.93
2	**1.76:1.35-2.29**	**1.69:1.3-2.21**	**1.77:1.36-2.3**	**1.7:1.3-2.23**	**1.73:1.25-2.34**	**1.67:1.21-2.27**	0.83:0.33-1.71	0.81:0.32-1.68	1.6:1.13-2.21	1.55:1.09-2.14
3	1.36:1.07-1.72	1.34:1.05-1.7	1.24:0.96-1.58	1.22:0.94-1.56	1.24:0.9-1.67	1.22:0.88-1.66	0.66:0.24-1.44	0.66:0.23-1.43	1.37:0.98-1.86	1.35:0.97-1.84
4	**1.55:1.22-1.96**	**1.51:1.19-1.92**	**1.63:1.27-2.07**	**1.59:1.24-2.03**	1.52:1.12-2.04	1.49:1.09-2	1.37:0.65-2.52	1.37:0.65-2.5	1.4:0.99-1.92	1.37:0.97-1.89
5	1.41:1.13-1.75	1.35:1.08-1.7	1.42:1.12-1.79	1.37:1.08-1.73	1.43:1.06-1.9	1.38:1.02-1.84	1.31:0.62-2.4	1.31:0.62-2.39	1.36:0.98-1.85	1.32:0.95-1.8

Abbreviations: CI: Confidence Intervals, OR: Odds ratio

Bold values show statistically significant odds ratios with Bonferroni correction (p = 0.005). [α]Ors and CIs estimated by logistic regression and adjusted for time in study

Table 4.14 Association of psychiatric prescription in tremor in relation to controls

	Medication overall		**Antidepressant**		**Anxiolytic**		**Antipsychotic**		**Hypnotic**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Tremor	**1.83:1.77-1.89**	**1.86:1.8-1.93**	**1.89:1.83-1.95**	**1.93:1.86-1.99**	**1.94:1.86-2.02**	**1.97:1.89-2.05**	**1.3:1.19-1.43**	**1.3:1.19-1.43**	**1.78:1.7-1.86**	**1.79:1.71-1.87**
Sex										
Female	**1.77:1.7-1.85**	**1.79:1.71-1.88**	**1.75:1.68-1.83**	**1.78:1.7-1.86**	**1.93:1.84-2.03**	**1.96:1.86-2.06**	**1.33:1.18-1.49**	**1.32:1.18-1.48**	**1.73:164-1.83**	**1.74:1.65-1.83**
Male	**2.05:1.95-2.17**	**2.1:1.99-2.22**	**2.3:2.17-2.43**	**2.36:2.23-2.49**	**2.05:1.91-2.19**	**2.08:1.94-2.23**	**1.27:1.09-1.47**	**1.27:1.09-1.47**	**1.93:1.8-2.08**	**1.94:1.81-2.09**
Age at index date										
<20 years	**1.7:1.55-1.87**	**1.91:1.73-2.11**	**1.76:1.59-1.94**	**1.98:1.78-2.19**	**1.68:1.42-1.97**	**1.79:1.51-2.11**	**1.67:1.2-2.27**	**1.75:1.25-2.37**	**1.66:1.39-1.97**	**1.75:1.47-2.08**
≥ 20 years	**1.73:1.67-1.8**	**1.74:1.67-1.81**	**1.8:1.73-1.86**	**1.81:1.74-1.88**	**1.83:1.76-1.91**	**1.84:1.77-1.92**	**1.2:1.09-1.32**	**1.2:1.09-1.31**	**1.67:1.59-1.74**	**1.67:1.6-1.75**
WIMD at index date										
1	**1.87:1.73-2.01**	**1.9:1.76-2.05**	**1.82:1.69-1.96**	**1.86:1.72-2**	**2.04:1.87-2.22**	**2.06:1.9-2.25**	1.22:1.02-1.45	1.21:1.01-1.45	**1.7:1.55-1.86**	**1.7:1.55-1.86**
2	**1.79:1.66-1.93**	**1.85:1.71-1.99**	**1.83:1.7-1.98**	**1.9:1.76-2.05**	**2.04:1.87-2.23**	**2.09:1.92-2.28**	1.1:0.89-1.34	1.1:0.9-1.35	**1.77:1.61-1.94**	**1.8:1.64-1.98**
3	**1.86:1.73-2.01**	**1.89:1.75-2.04**	**1.95:1.8-2.1**	**1.99:1.84-2.15**	**1.97:1.81-2.16**	**2:1.83-2.19**	**1.45:1.19-1.76**	**1.45:1.19-1.76**	**1.83:1.66-2.01**	**1.84:1.67-2.02**
4	**1.89:1.75-2.05**	**1.91:1.76-2.07**	**1.96:1.81-2.13**	**1.98:1.82-2.15**	**1.83:1.66-2.01**	**1.84:1.67-2.03**	**1.45:1.15-1.8**	**1.45:1.15-1.79**	**1.96:1.77-2.16**	**1.96:1.77-2.16**
5	**1.72:1.59-1.86**	**1.74:1.61-1.88**	**1.87:1.72-2.02**	**1.89:1.75-2.05**	**1.74:1.58-1.92**	**1.76:1.59-1.94**	1.36:1.07-1.71	1.36:1.07-1.7	**1.64:1.47-1.82**	**1.64:1.47-1.82**

Abbreviations: CI: Confidence Intervals, OR: Odds ratio

Bold values show statistically significant odds ratios with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

Table 4.15 Association of psychiatric prescription in other dystonia in relation to controls

	Medication overall		**Antidepressant**		**Anxiolytic**		**Antipsychotic**		**Hypnotic**	
	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]	OR:95 % CI	OR:95 % CI[α]
Other	**2.09:1.77-2.46**	**2.23:1.89-2.64**	**1.93:1.63-2.27**	**2.06:1.74-2.43**	**2.71:2.27-3.23**	**2.89:2.41-3.45**	**1.96:1.34-2.77**	**1.98:1.35-2.8**	**1.83:1.49-2.24**	**1.9:1.54-2.32**
Sex										
Female	**1.86:1.5-2.31**	**1.98:1.6-2.48**	**1.64:1.32-2.02**	**1.74:1.41-2.16**	**2.61:2.09-3.25**	**2.79:2.22-3.49**	**1.7:1-2.69**	1.72:1.01-2.71	**1.56:1.19-2.01**	**1.62:1.24-2.09**
Male	**2.62:2.03-3.39**	**2.78:2.14-3.62**	**2.65:2.04-3.44**	**2.82:2.16-3.68**	**3.05:2.25-4.08**	**3.21:2.36-4.31**	**2.4:1.33-3.97**	**2.43:1.35-4.02**	**2.48:1.78-3.4**	**2.56:1.83-3.51**
Age at index date										
<20 years	**3.22:2.06-4.97**	**4.74:2.93-7.61**	1.55:0.88-2.58	2.05:1.13-3.52	**7.58:4.51-12.23**	**10.68: 6.18-17.82**	**6.03:2.11-13.51**	**7.17:2.5-16.25**	**4.7:2.48-8.21**	**5.83:3.04-10.37**
≥ 20 years	**1.77:1.48-2.12**	**1.84:1.53-2.2**	**1.81:1.51-2.16**	**1.88:1.57-2.25**	**2.23:1.84-2.69**	**2.32:1.91-2.81**	1.59:1.04-2.31	1.59:1.05-2.32	**1.52:1.22-1.89**	**1.56:1.25-1.93**
WIMD at index date										
1	**2.02:1.43-2.87**	**2.26:1.59-3.25**	1.68:1.2-2.36	**1.89:1.33-2.67**	**3.11:2.17-4.41**	**3.46:2.4-4.94**	1.87:0.88-3.48	1.95:0.92-3.63	**2.13:1.43-3.1**	**2.3:1.53-3.36**
2	**1.79:1.25-2.54**	**1.83:1.28-2.64**	1.64:1.14-2.34	1.69:1.17-2.42	**2.77:1.88-4.02**	**2.86:1.93-4.16**	1.02:0.31-2.42	1.02:0.31-2.43	1.16:0.68-1.86	1.17:0.69-1.89
3	**1.88:1.29-2.77**	**2.08:1.41-3.07**	**1.89:1.28-2.77**	**2.1:1.41-3.1**	**2.4:1.55-3.63**	**2.66:1.71-4.04**	**4.26:2.15-7.63**	**4.31:2.17-7.71**	2.01:1.24-3.14	**2.15:1.32-3.37**
4	**2.09:1.4-3.12**	**2.17:1.45-3.28**	1.86:1.23-2.79	**1.94:1.27-2.92**	**2.35:1.47-3.64**	**2.45:1.52-3.81**	0.87:0.14-2.76	0.88:0.14-2.77	1.57:0.89-2.62	1.6:0.9-2.68
5	**2.72:1.89-3.93**	**2.85:1.97-4.15**	**2.65:1.85-3.8**	**2.78:1.92-4.01**	**2.75:1.81-4.06**	**2.85:1.87-4.24**	2.01:0.71-4.45	2.02:0.71-4.46	**2.31:1.45-3.53**	**2.35:1.47-3.6**

Abbreviations: CI: Confidence Intervals, OR: Odds ratio

Bold values show statistically significant odds ratios with Bonferroni correction (p = 0.005). [α]ORs and CIs estimated by logistic regression and adjusted for time in study

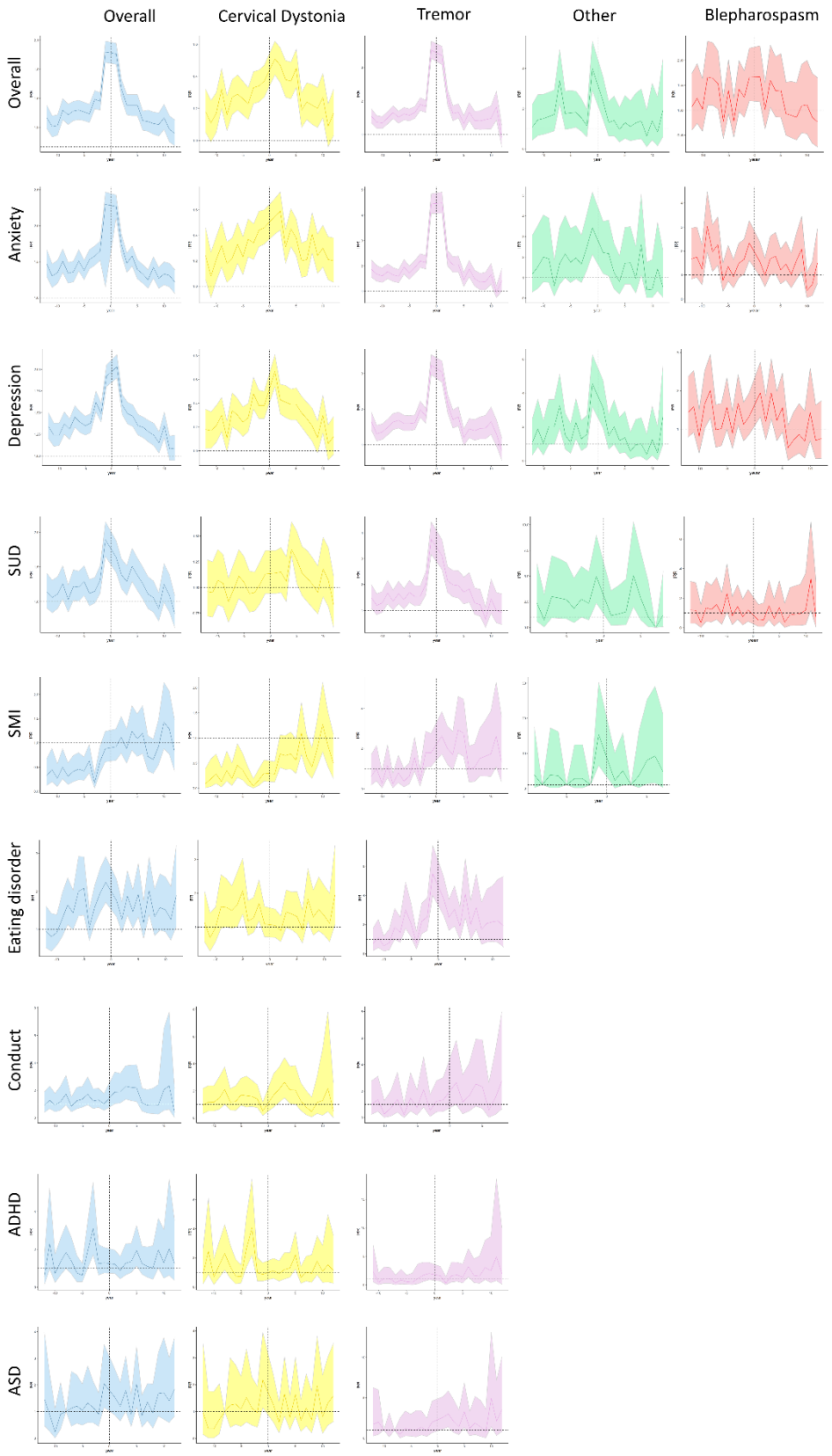

Figure 4.11 Trends in psychiatric diagnosis incidence rate ratios for dystonia subtypes in relation to controls with 95% confidence intervals

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder, ASD: Autism Spectrum Disorder, SMI: Severe Mental Illness

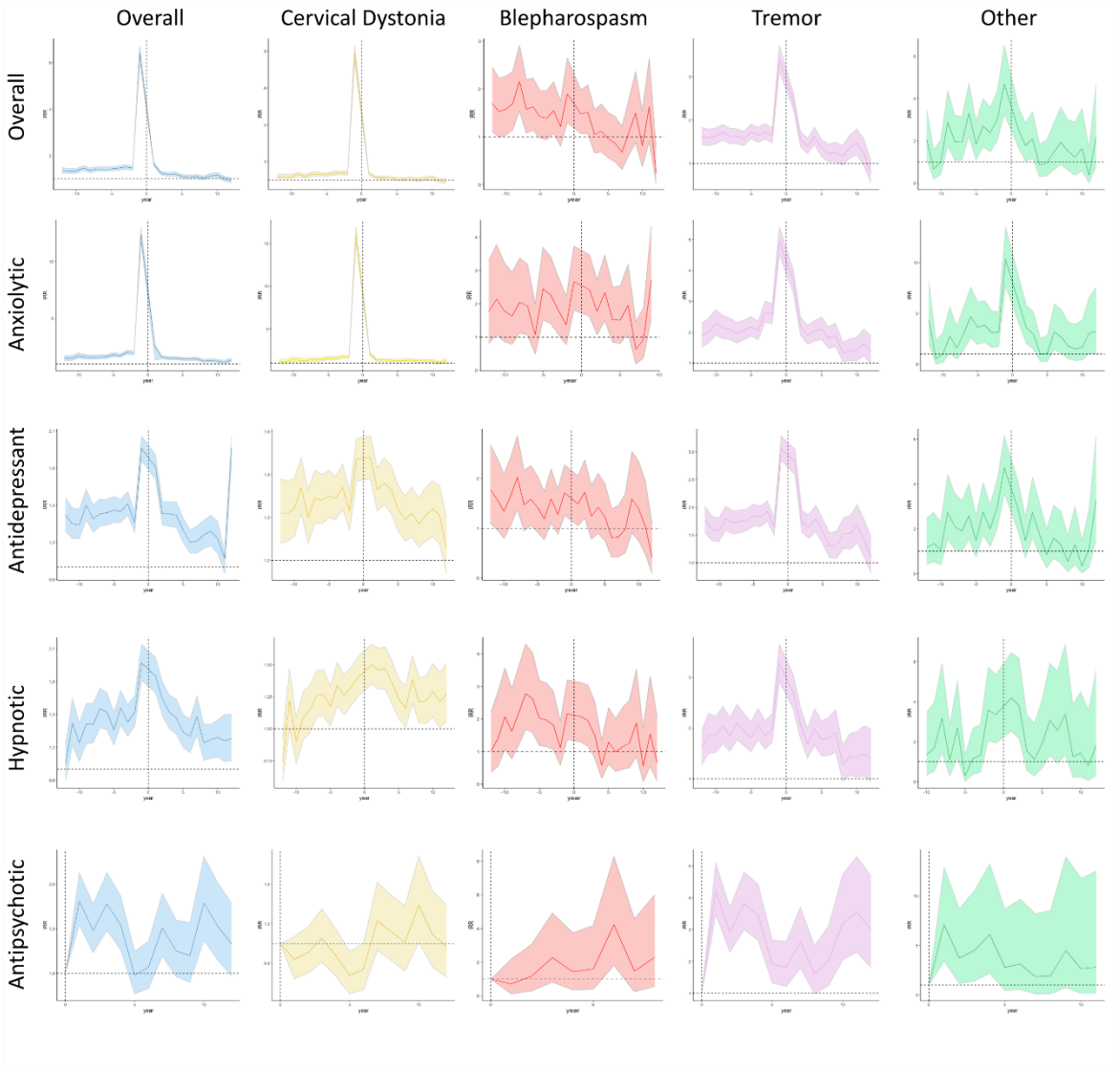

Figure 4.12 Trends in psychiatric prescription incidence rate ratios for dystonia subtypes in relation to controls with 95% confidence intervals

4.4 Discussion

This large, data linkage study demonstrates a significantly higher rate of psychiatric diagnoses and/or prescription of medication in individuals diagnosed with dystonia, compared to matched controls ($p < 0.001$). This difference was greater in the period pre-dating a dystonia diagnosis.

We found higher rates of all psychiatric disorders in those with idiopathic dystonia, with depression and anxiety being the most commonly diagnosed, and panic disorder (2.6%), specific isolated phobia (0.9%) and generalised anxiety (0.6%) the most common anxiety subtypes, comparable to that seen in multiple cross-sectional studies of idiopathic dystonia.[286,289,300,308,525] The rates of psychiatric diagnoses within the control population were in keeping with those estimated within the UK, including depression and anxiety disorders (21.4%),[559] ASD (0.5%)[560] and severe mental illness (0.7%).[561] Amongst the dystonia cohort and when broken down by subtypes, antidepressants and anxiolytics were the most frequently prescribed psychiatric medication. A higher number of individuals prescribed medication compared to those who received a diagnosis (56% vs 43%), potentially relating to the stigma associated with a psychiatric diagnosis, or that a prescription might imply a diagnosis.[562] Alternatively medications may have been prescribed for a non-psychiatric diagnosis such as neuropathic pain syndromes.

We noted higher rates of neurodevelopmental disorders and conduct disorder in the <20 dystonia group compared to the >20s, whilst depression, anxiety, SMI and SUD were increased in >20s. This likely reflects commonality in diagnoses: ASD, ADHD and conduct disorders are considered in childhood/adolescence and tend to lessen with age,[563] whereas rates of depression, anxiety and psychotic disorders are more pronounced in adults.[564] Although neurodevelopmental disorders can persist into adulthood, symptoms may be interpreted differently and this often results in misdiagnosis.[565,566]

Dystonia was also associated with a higher risk of all psychiatric diagnoses, with the exception of SMI, most notably anxiety disorder, eating disorder and depression (aOR: 1.64, 1.62 and 1.55, respectively). Anxiolytics, antidepressants and hypnotics were also associated with higher risk (aOR: 1.61, 1.39, 1.3, respectively), while

antipsychotics were associated with reduced risk (aOR: 0.77). These results are consistent with the single other population-based study undertaken to date in which increased risk for multiple psychiatric and neurodevelopmental disorders was observed, including depression, anxiety, ADHD and ASD.[525] The presence of a psychiatric diagnosis or psychiatric prescription however, doesn't appear to impact social deprivation, suggesting neither social drift nor causation is evident with dystonia, similarly observed in other neurological and psychiatric disorders.[561,567]

Our study is the first to investigate psychiatric co-morbidity both before and after dystonia diagnosis. The majority of work to date has been limited to the period after dystonia diagnosis, with preceding data relying on recall and anecdotal information. These studies have estimated rates of 40-69% of preceding mood disorders,[298–300] consistent with our findings in which 57% of new psychiatric diagnoses preceded the dystonia diagnosis. We also demonstrated a significantly increased risk of a psychiatric disorder immediately before and after dystonia diagnosis. This pattern is replicated across multiple specific diagnoses, particularly anxiety in which the risk of developing an anxiety disorder is highest in the five years leading to dystonia diagnosis. Although this may reflect the recognised diagnostic delay with dystonia (average 2 years),[391] onset of dystonia and psychiatric symptoms at a similar time point also potentially indicates common causative pathways or mechanisms. Similar temporal patterns were not observed across all diagnoses, for example the risk for SUD was increased in the two years leading to dystonia diagnosis and most prominent in the five years after dystonia diagnosis. Patterns also differed across subtypes of dystonia, those with blepharospasm and cervical dystonia were not at risk of eating disorders, while in the three years prior to a tremor diagnosis there was prominent risk. These results suggest that there may be a bidirectional relationship between psychiatric disorders and dystonia, particularly with mood disorders, whereby psychiatric symptoms may form a prodromal component of dystonia and following dystonia diagnosis there is an increased susceptibility for psychiatric diagnosis. This is also consistent with recent findings which support a susceptibility to psychiatric symptoms where enrichment of genes linked with psychiatric disorders, including OCD, depression and schizophrenia, were observed in co-expression modules enriched for dystonia-associated genes.[568]

There was a significantly higher rate of psychiatric medication prescription amongst those with dystonia compared to controls. Notably, there was 13.1-fold increase in anxiolytics prescribing in the year prior to dystonia diagnosis, particularly in those with cervical dystonia and other dystonia (IRR: 17 and 13.5, respectively), potentially reflecting the initial burden of a chronic disease diagnosis or again suggesting a potential common mechanistic pathway. However, it is important to note that the majority of prescribed anxiolytics were diazepam (92%), and GPs may prescribe diazepam because of its added benefit in the management of dystonia symptoms.[569] We sought to account for this by applying stringent exclusion criteria where individuals with dystonia who were prescribed a benzodiazepine were only considered to have a psychiatric prescription if their records also contained a psychiatric diagnoses code. This increased risk of psychiatric medication prescription gradually decreased over time, suggesting an absence of continued accumulation of psychiatric symptoms as a secondary consequence to a disabling motor disorder.

Several potential explanations for the association between dystonia and psychiatric disorders may exist. Firstly, a diagnosis of dystonia is delayed, on average, by two years from symptom onset. During this time, 50% of patients report a negative personal impact as a result of the delay,[391] with the psychological stressors experienced during this period contributing to both diagnosis and prescription of psychiatric medication. There is also considerable overlap in the cortical structures and neurotransmitters implicated in dystonia and psychiatric disorder pathogenesis. Disruption to monoaminergic neurotransmission, notably striatal dopaminergic and serotonergic pathways, has been identified across multiple models of psychiatric and dystonic disease, with evidence of lower numbers of striatal dopamine receptors, and striatal dopaminergic and midbrain serotonergic binding in adult-onset idiopathic focal cervical dystonia (AOIFCD) coupled with psychiatric symptoms.[182,378,379] Other structural and abnormalities within the prefrontal cortex, amygdala, hippocampus and thalamus have also been reported amongst these psychiatric disorders,[570–573] regions also implicated in dystonia.[165]

Although this study represents a step-change in the examination of psychopathology in those diagnosed with dystonia, potential limitations exist that are common to all

routinely collected data sources. Firstly, it is possible that we included a proportion of cases without dystonia as we were unable to obtain measures of specificity in our case ascertainment algorithm (see Section 3.4). We excluded individuals with potential secondary causes of dystonia, which may also have biased the control group. Limited motor treatment data was available for those diagnosed with dystonia, notably use of injectable botulinum toxin (BoNT), frequently used in the management of the motor symptoms of dystonia but also known to impact psychiatric symptoms in the same patient group.[574,575] We also had no access to the indication for prescribing, and whether the drug was dispensed or taken, and it is possible some drugs may have been prescribed for dystonic motor symptoms (e.g. diazepam). However, to account for this we excluded individuals with dystonia who were prescribed benzodiazepines and had no recorded psychiatric diagnoses. Although prescriptions issued in primary care are well recorded, psychiatric medication can also be prescribed in other healthcare contacts therefore the proportion of individuals prescribed psychiatric medication is likely to have been underestimated. Finally, individuals with dystonia may be more likely to seek medical treatment for a psychiatric problem than our control cohort without a neurological diagnosis, in turn this may explain increased incidence rates amongst the cases.

Our study demonstrates that idiopathic dystonia and specific subtypes of dystonia are associated with an increased risk for psychiatric disorders and medication prescription when compared to controls. Higher rates of anxiety and depression, and anxiolytic and antidepressant use, were observed across all dystonia subtypes. Psychiatric disorders generally pre-dated dystonia diagnosis, with incidence rates peaking 12-months prior to dystonia diagnosis. These findings may indicate that psychiatric disorders are either prodromal symptoms or reflect shared underlying pathophysiology. To a lesser extent, increased risk of psychiatric diagnoses and prescriptions were also noted following dystonia diagnosis, implying a potential bidirectional relationship. Further prospective work, both epidemiological and mechanistic models, is needed to better understand the association between dystonia and psychiatric symptomatology, with particular emphasis on early diagnosis and therapeutic intervention.

5 Sleep disturbance in Movement Disorders – insights, treatments and challenges

5.1 Introduction

Abnormal sleep and circadian rhythm disorders are seen in many patients with movement disorders, although they remain underdiagnosed and are a significant unmet need in clinical care. Sleep and circadian rhythms are generated from specific regulatory centres, including the forebrain, thalamus and midbrain dopaminergic neurons, regions also implicated in movement disorder pathogenesis.

The rate, nature and temporal pattern of these sleep disturbances vary across the different movement disorders. For example, in Parkinson's disease the rate of sleep disorders has been estimated to be as high as 98%, with REM behaviour disorder well established as pre-dating motor symptom onset.[576] In contrast, those with non-degenerative movement disorders, such as adult-onset idiopathic, isolated dystonia, may have poor sleep with evidence suggesting a link to psychiatric symptom severity (Section 1.18.4).[332]

This chapter provides an overview of normal sleep, the common sleep disorders, and the evidence to date for the patterns and prevalence across specific degenerative and non-degenerative movement disorders. We discuss the tools available for sleep assessment, the impact of medication used in motor symptom management upon sleep, and how disturbed sleep can affect daytime motor function. Finally, we highlight future challenges to the field, and general considerations in assessment and treatment of sleep disorders.

5.2 Sleep Structure, Anatomy and Physiology

Sleep cycles approximately every 90-120 minutes between an initial non-REM (NREM) stage (subdivided into N1-3 stages), followed by a rapid eye movement (REM/R) phase with a relative muscle atonia. Figure 5.1 summarises the typical hypnogram, although it is important to remember that with normal ageing, night awakenings increase, N3 decreases and total sleep time shortens.

Maintenance of the sleep/wake circuit is regulated by the fast-acting neurotransmitters glutamate and GABA, while an array of excitatory neurotransmitters are thought to have a modulatory role, including hypocretin/orexin

(lateral hypothalamus), histamine (tuberomammillary nucleus), acetylcholine (pedunculopontine and laterodorsal tegmentum), noradrenaline (locus coeruleus), dopamine (ventral periaqueductal grey matter) and serotonin (raphe nuclei) (Figures 5.2A-C). Sleep regulatory circuits are widespread throughout the brainstem and hypothalamus. GABAergic parvalbumin neurons in the basal forebrain arousal system and GABAergic neurons in the parafacial zone (PZ) of the medulla are essential for driving wakefulness, with the latter promoting sleep via inhibition of glutamatergic neurons in the parabrachial nucleus (PB). More recently, evidence suggests that GABAergic neurons in the lateral hypothalamus (LH) contribute to promoting wakefulness by inhibiting the thalamus and preoptic area. The ventrolateral preoptic area (VPLO) also contains GABAergic neurons, essential for promoting sleep via inhibition of the arousal system.

Glutamatergic REM-promoting neurons in the sublaterodorsal nucleus (SLD) are inhibited by GABAergic NREM-promoting neurons in the ventral periaqueductal grey (vPAG), while activation of GABAergic neurons in the ventral medulla which innervate vPAG promotes transition to REM sleep by disinhibition of the SLD. NREM sleep is driven by GABAergic neurons in the ventral periaqueductal grey (vPAG) and glutamatergic neurons located ventromedial to the superior cerebellar peduncle (SCP). These neurons suppress both wakefulness and REM sleep by inhibiting the SLD, with additional inhibition of the medial parabrachial nucleus by GABAergic neurons also promoting NREM sleep. Newer models of the sleep/wake circuit recognise that these interactions are modulated by several brain regions including the pedunculopontine (PPT), laterodorsal tegmental nuclei (LDT), projections from the medulla and the melanin-concentrating neuron system (MCH) (Figure 5.2A and 5.2B).[461]

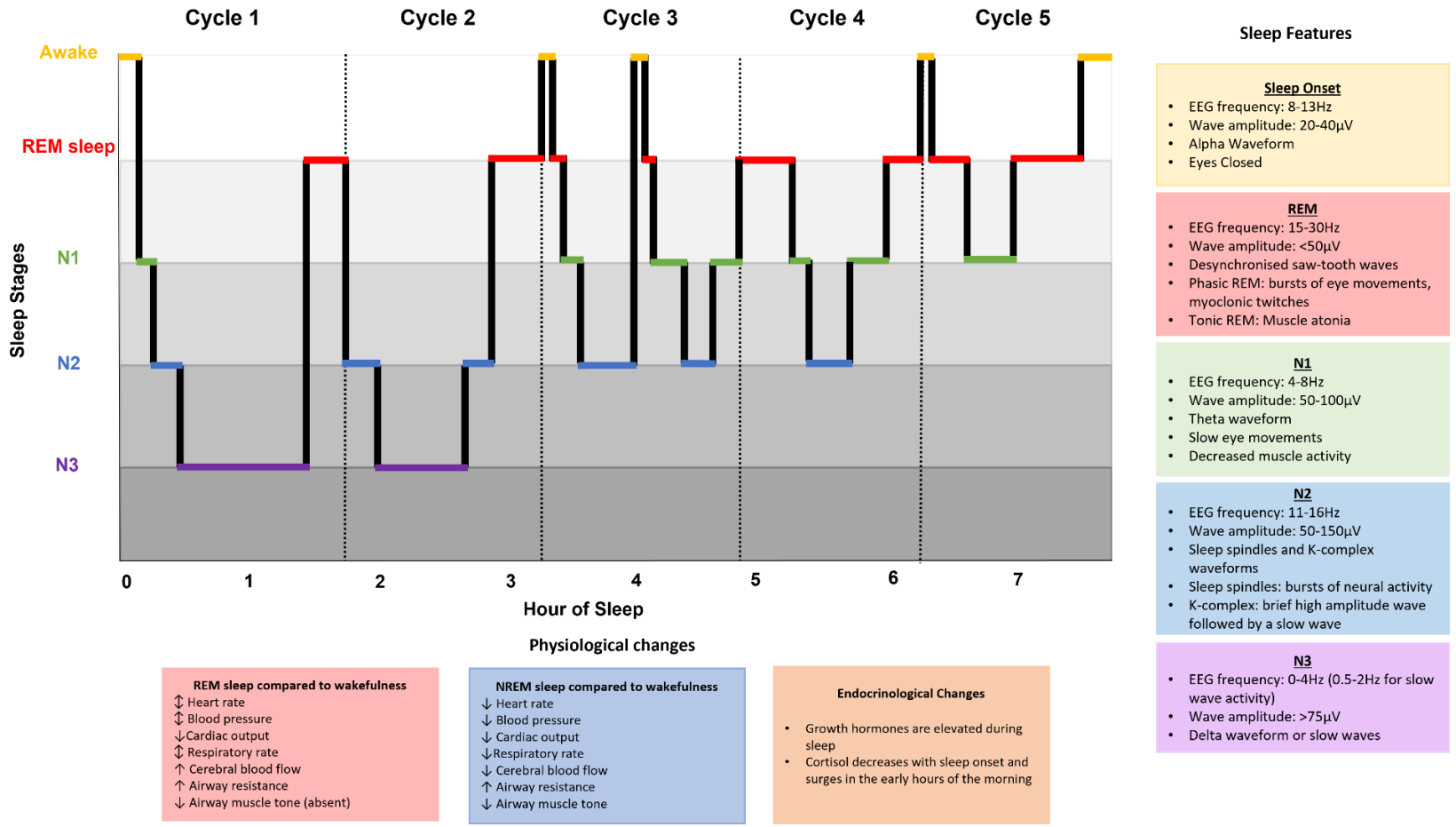

Figure 5.1 Sleep hypnogram illustrating a normal sleep cycle and physiological changes. NREM1/2/3: non-rapid eye movement sleep stages 1, 2 and 3

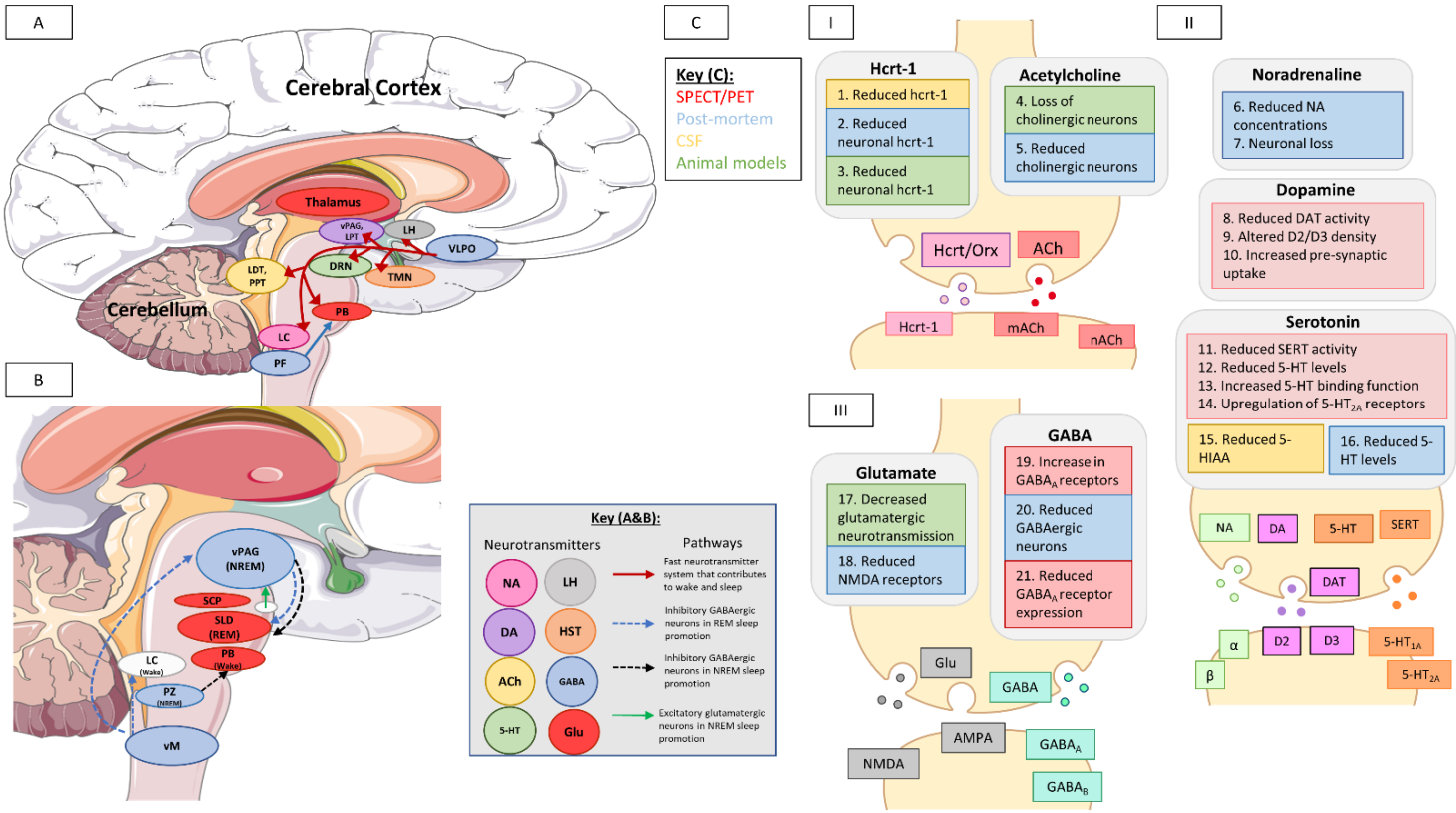

Figure 5.2 **(A)** Neurotransmitters and brain regions involved in the sleep-wake cycle **(B)** REM sleep circuitry: Hypothesised pathways include synucleinopathic degeneration in the SLD in DLB, in addition to Vm in PD, causing loss of REM sleep atonia and associated motor behaviours. Pathological changes to the LDT/PPN and LC in MSA may contribute to RBD. **(C)** Schematic of neurotransmitters involved in movement disorders in the context of sleep.

(I) Hypocretin/orexin and acetylcholine: 1: reduced hrct-1 in the CSF of NPC, PSP and PD, 2: reduced immunostaining of hcrt-1 neurons in MSA and HD patients, 3: decreased hcrt-1 in mouse models of HD, 4: deletion of torsinA protein was associated with cholinergic neuronal loss in dystonia, 5: cholinergic neuronal loss in the striatum of PD and PSP patients. (II) Monoamines: 6: reduced Na concentrations in dystonia

patients, 7: neuronal loss of Na neurons in PD, 8: reduced DAT in WD, NPC and Ts, and RBD patients who developed PD, 9: Reduced D3 receptors in PD associated with EDS, reduced D2 receptors in genetic carriers of DYT1, DYT6, DYT11 and NKX2.1, increased D2 receptors in TS, 10: Elevated DA uptake in TS, 11: Reduced SERT in PD, MSA and CD, 12: Reduced 5-HT levels in the DRN of CD patients, 13: increased 5-HT binding function in Ts patients, 14: Upregulation of 5-HT2A receptors in Ts cohorts, 15: reduced 5-HIAA in MD, 16: depleted 5-HT in raphe nuclei of MSA cases. (III) Glutamate and GABA: 17: reduced glutamatergic neurotransmission in animal mouse models of NPC, 18: reduced NMDA receptors in HD, 19: increase in GABAA receptors in HTT gene carriers and et patients, 20: Reduced GABAergic neurons in TS brains, 21: Reduced GABAA receptors in dystonia. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BF, basal forebrain; D2/3, Dopamine receptors; DA, dopamine; DAT, dopamine transporter; DRN, dorsal raphe nuclei; GABA, gamma aminobutyric acid; Glu, glutamate; Hcrt/Orx, hypocretin/orexin; HIAA, 5-hydroxyindoleacetic acid; HIST, histamine; LC, locus coeruleus; LDT, lateral dorsal tegmentum; LPT, lateral pontine tegmentum; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; NA, norepinephrine; nACh, nicotinic acetylcholine receptors; NMDA, N-methyl-D-aspartate; Pb, parabrachial nucleus; PPN, pedunculopontine nucleus; PPT, pedunculopontine; PZ, parafacial zone; SCP, superior cerebellar peduncle; SERT, serotonin transporter; SLD, sublaterodorsal nucleus; SN, substania nigra; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus; vM, ventromedial Medulla; vPAG, ventral Periaqueductal grey matter; VTA, ventral tegmental area.

5.3 Types of sleep disorders

The different forms of sleep disorders, as defined by the International Classification of Sleep Disorders (ICSD-3), their clinical features, diagnostic criteria, proposed underlying pathophysiology and currently suggested treatments are summarised in Table 5.1.

5.3.1 Diagnosing sleep disorders

Table 5.2 summarises the available sleep questionnaires. Sleep diaries and wrist actigraphy are often used for the diagnosis of insomnia and circadian rhythm disorders as well as population screening in research cohorts. The gold standard for objective sleep staging remains inpatient video polysomnography (PSG), involving video, electroencephalography, electromyography, and electrooculography. PSG is required for confirming the diagnosis of REM Sleep Behavioural Disorder (RBD), while PSG and multiple sleep latency test (MSLT) are used in the diagnoses of narcolepsy and other central hypersomnias.

5.3.2 Technology to aid diagnostic and therapeutic management

Development of consumer wearables is becoming recognised as a prospective clinical tool, aiding early diagnosis as well as the opportunity to monitor disease progression particularly, for example, in response to therapeutics. Actigraphy, an accelerometer validated to detect sleep/wake activity patterns, is particularly useful for documenting sleep-wake patterns for periods of days or weeks in the patient's own environment, as well as measuring physical activity during periods of wakefulness. Use of these wearable devices extends far beyond disease alone, potentially providing avenues to better understand the association between sleep and health, as well as opportunities to optimise interventions and reduce the adverse health impacts of poor sleep.

Table 5.1 Characteristic features of sleep disorders defined by the International Classification of Sleep Disorders (ICSD-3)

Sleep Disorder	Clinical Features	Diagnostic Criteria	Treatment	Proposed Pathophysiology
Chronic Insomnia	Difficulty falling asleep and/or maintaining sleep, with symptoms impacting daytime activity. Symptoms present on most nights for at least 3 months and occur at least three times per week.	Problems initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance going to bed on appropriate schedule or difficulty sleeping without parent/caregiver intervention. Sleep/wake complaints cannot be explained by inadequate opportunity or circumstances. In addition, fatigue, impaired performance, prone to errors/accidents	1st Line: CBT where available. Other treatments: Antihistamines, melatonin, benzodiazepines	1. Disinhibition of the VPLO 2. Impaired disengagement of cortical regions involved in executive control and attention 3. REM instability 4. Melatonin deficiency
Sleep Related Breathing Disorders				
Obstructive Sleep Apnoea	Chronic disorder characterised by snoring with episodes of upper airway collapse during sleep, waking with choking or breath holding. Associated fragmented, unrefreshing night sleep, insomnia and excessive daytime sleepiness. Risk factors: hypertension, type 2 diabetes mellitus and congestive cardiac failure.	PSG detecting ≥ 5/hour obstructive respiratory events alongside other criteria (e.g. partners reports of habitual snoring or breath interruptions) *or* ≥15/hour obstructive respiratory events during PSG.	CPAP: recommended first line therapy	1. Altered arousal threshold 2. Instability of ventilatory control 3. Increased glutamate and decreased GABA neurotransmission 4. Small pharyngeal airway
Central Sleep Apnoea	Abnormal brainstem ventilatory responses leading to reduced or absent respiratory effort, with no evidence of snoring. Results in insufficient/absent ventilation, frequent night-time awakenings and excessive daytime sleepiness. Common causes: opiate use and cardiac failure	PSG demonstrating ≥5/hour central apneas, number of central apnoeas is >50% of the total number of apnoeic and hypopneic episodes	CPAP treatment is less effective than in OSA.	1. Absence of ventilatory drive
Hypersomnolence				

Narcolepsy	Orexin/Hypocretin deficiency resulting in daytime sleepiness, sleep paralysis, hypnagogic hallucinations +/- cataplexy cause by instability in transitions between wake, NREM and REM sleep.	Narcolepsy Type 1: Diagnosed by the presence of one or both of i) cataplexy and a mean sleep latency of ≤8 minutes and ii) two or more sleep-onset REM periods (SOREMPs) on an MSLT or CSF hypocretin-1 concentrations below 110 pg mL^{-1} Narcolepsy Type 2: Daily periods of irrepressible need to sleep or daytime lapses into sleep confirmed with MSLT. Absence of cataplexy confirmed with CSF hypocretin-1 concentrations (>110 pg mL^{-1} or >1/3 of mean values obtained in normal subjects).	Amphetamine-like, Modafinil, Sodium oxybate	1. Unstable transitions between wake, REM and NREM sleep caused by loss of hypocretin neurons 2. Abnormal circadian regulation 3. Insufficient REM sleep 4. Hypothalamic lesions
Idiopathic Hypersomnia	Excessive daytime sleep and/or sleepiness, prolonged unrefreshing overnight sleep and difficulty waking occurring for at least 3 months.	MSLT shows fewer than two sleep onset REM periods or none if REM latency is ≤15 minutes. In addition to the presence of either an MSLT of ≤8 minutes, elevated total sleep time (12-14 hours) on PSG/wrist actigraphy or at least three daytime lapses into sleep associated with a sleep log (over seven nights).	Changes to routine, behavioural therapy, modafinil.	1. Abnormal neurotransmitter signalling of histamine, serotonin, dopamine and GABA
Parasomnias				
NREM Parasomnias	Confusional arousal, somnambulism and sleep terrors with incomplete/no recall. Predominantly arise during the first third of the night, during slow wave sleep.	Confusional arousal: Recurrent mental confusion on arousal/awakening, absence of fear, walking behaviour or hallucinations in association with episode. Sleep walking: Ambulation during sleep, difficulty arousing the patient during an episode, amnesia. Sleep terrors: PSG demonstrates tachycardia in associated with the episode and other sleep disorders e.g. nightmares, can be present.	Medical therapy used when episodes are frequent or violent. Melatonin and benzodiazepines, notably clonazepam, most commonly used.	1. Reduced regional perfusion in the frontal and parietal areas during N3 sleep 2. Activity in the thalamus and cingulate cortex during N3 sleep

REM Sleep Behaviour Disorder (RBD)	RBD occurs with loss of normal REM muscle atonia, resulting in dream enactment, often with injury to the patient/bed partner. Events tend to be memorable and associated with dreams.	Repeated episodes of sleep vocalisation and/or motor behaviours documented in video PSG during REM sleep or based on clinical history. PSG demonstrates REM sleep without atonia.	Melatonin and clonazepam, although no RCTs to date.	1. Dysfunction of the subcoeruleus nucleus, the medullary magnocellularis and the sublaterodorsal nucleus 2. Glutamatergic, GABAeric and cholinergic abnormalities
Sleep Related Movement Disorders				
Restless Leg Syndrome and Periodic Limb Movements During Sleep	Unpleasant sensation in the LL, affecting onset and maintenance of sleep. PLMS are periodic, repetitive LL movements typically co-occurring with RLS	RLS: Sensation begins or worsens during periods of rest (e.g. lying down), predominantly at night, which are relieved by movements. Symptoms should cause concern, sleep disturbance or impairment in important areas of functioning (e.g. physical, social). PLMS: PSG demonstrates PLMS with a frequency of >15h and causes significant sleep disturbance or impairs other important areas of functioning.	Dopamine agonists (rotigotine, pramipexole, ropinirole), gabapentin and pregabalin	1. Altered spinal circuits in sensory and motor processing areas 2. Dopaminergic and glutamatergic dysfunction 3. Iron deficiency

Abbreivation: AHI: Apnoea-Hypopnea index, CSF: Cerebral Spinal Fluid, GABA: Gama aminobutyric acid, LL: Lower Limb, N3: Non-rapid Eye Movement stage 3, NREM: Non-Rapid Eye Movement sleep, OSA: Obstructive Sleep Apnoea, PLMS: Periodic Limb Movements During Sleep, PSG: Polysomnography, QoL: Quality of Life, REM: Rapid Eye Movement sleep, RBD: REM Sleep Behaviour Disorder, RLS: Restless Leg Syndrome, VLPO: Ventrolateral Preoptic Nucleus

Table 5.2 Subjective and objective assessment measures and abbreviations of sleep questionnaires

Diagnostic Tool	Abbreviation	Measure
Apnea-Hypopnea Index	AHI	A measure of the number of apneas (pauses in breathing) or hypopneas (periods of shallow breathing) recorded during sleep. An AHI rating of <5 is considered normal
Athens Insomnia Scale	AIS	Insomnia symptoms
Basic Nordic Sleep Questionnaire	BNSQ	Sleep quality, medication use, daytime sleepiness, napping, snoring and general sleep habits
Berlin Questionnaire	BQ	Sleep apnea diagnosis
Bologna Questionnaire		Questions concerning excessive daytime sleepiness
Child Behaviour Checklist	CBCL	Completed by parents to detect behavioural problems
Epworth Sleepiness Scale	ESS	Daytime sleepiness
Fatigue Questionnaire	FQ	Fatigue severity
Fatigue Severity Scale	FSS	Impact of fatigue
Functional Outcomes of Sleep Questionnaire	FOSQ	Assess impact of daytime sleepiness on activities
Insomnia Severity Index	ISI	Impact and severity of Insomnia
International Restless Legs Syndrome Study Group	IRLSSG	Diagnostic criteria for RLS
John Hopkins Restless Leg Syndrome Severity Scale	JHRLSSG	Clinical scale assessing severity of restless leg syndrome
Maintenance of Wakefulness Test	MWT	A tool used measure ability to stay awake and alert during the daytime
Mayo Sleep Questionnaire	MSQ	Screens for RBD, PLMD, RLS, OSA, sleep walking and sleep-related leg cramps
Modified Fatigue Impact Scale	MFIS	Fatigue impact
Modified Simonds and Parraga Sleep Questionnaire	MSPSQ	Used to characterise sleep disturbances in young children
Morningness-eveningness Questionnaire	MEQ	Circadian rhythm
Multidimensional Fatigue Inventory	MFI	20-items designed to measure fatigue

Multidimensional Fatigue Symptom Inventory	MFSI	30 statements designed to assess fatigue by indicating the extent of symptoms experienced over a one-week period
Multiple Sleep Latency Test	MSLT	A diagnostic tool used to measure the time taken to fall asleep during a daytime nap. 15 to 20 minutes is considered normal
National Sleep Foundation's Sleep Satisfaction Tool		Sleep satisfaction
Non-Motor Symptoms Questionnaire	NMSQuest	Assesses non-motor symptoms in Parkinson's Disease including sleep disturbances such as nocturia, sleep initiation and maintenance, vivid dreams, RBD and RLS
Non-Motor Symptoms Scale for Parkinson's Disease	NMSS	Measures the severity and frequency of non-motor symptoms across nine domains including sleep/fatigue
Pittsburgh Sleep Quality Index	PSQI	Sleep quality over a one-month interval
Parkinson's Disease Sleep Scale	PDSS	Sleep disruption amongst PD patients
Parkinson's Disease Fatigue Scale	PFS	Fatigue and its impact on daily function amongst PD patients
Periodic Limb Movements Index	PLMI	Use to calculate the number of limb movements per hour during sleep. An index of <5 is considered normal
Polysomnography	PSG	An overnight sleep study used to diagnose sleep disorders through the use of electroencephalogram
REM Sleep Behaviour Disorder Screening Questionnaire	RBDSQ	RBD diagnosis
SCOPA-Sleep		Night-time sleep and daytime sleepiness for use amongst PD patients
Sleep Diary		Records sleep patterns and habits that can be useful in diagnosing sleep disorders
Sleep Disorders Questionnaire	SDQ	Measures sleep disturbance and sleep habits aimed to identify those at high risk of a sleep disorder (sleep apnea, narcolepsy, psychiatric disorders and periodic limb movement disorder)
Sleep Disturbance Scale for Children	SDSC	Evaluates sleep among children aged 13-18 years, differentiating disorders of sleep initiation and maintenance, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, excessive somnolence, and sleep hyperhidrosis

Stanford Sleepiness Scale	SSS	Quantifies sleepiness
The Sleep Disorders Questionnaire for HD	HDSQ	Evaluates sleep quality, motor activity, abnormal motor behaviour during sleep and other sleep disorders
Ullanlinna Narcolepsy Scale	UNS	Evaluate a variety of symptoms relating to narcolepsy

Abbreviations: OSA: Obstructive Sleep Apnea, PLMD: Periodic Leg Movement During Sleep, RBD: REM-behaviour disorder, RLS: Restless Leg Syndrome

5.4 Review of the evidence for sleep disturbance across degenerative and non-degenerative movement disorders

The literature search included the key words “sleep disturbances”, “sleep disorders”; “RLS”; “PLMS”; “sleep related breathing disorders”; “RBD”; “excessive daytime sleepiness”; “insomnia” in combination with degenerative movement disorders: PD, Dementia with Lewy bodies (DLB), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS), Huntington’s Disease (HD), Dentatorubral-pallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia (SCA), Anti-IgLON5 disease, Wilson’s Disease (WD), Niemann-Pick disease Type C (NPC), Neurodegeneration with Brain Iron Accumulation (NBIA) including: pantothenate kinase-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), Beta-propeller proteinassociated neurodegeneration (BPAN), mitochondrial membrane protein-associated neurodegeneration (MPAN) and fatty acid hydroxylase-associated neurodegeneration (FAHN), neuroacanthocytosis (NA) including: McLeod Syndrome (MLS) and Chorea-acanthocytosis (ChAc), and non-degenerative movement disorders: Dystonia, Essential Tremor (ET), Dystonic Tremor, Myoclonus (excluding myoclonus in relation to epilepsy), Tourette’s syndrome (TS), Tic Disorders and Benign Hereditary Chorea (BHC). Studies identified were divided according to cohort size and methods of assessment (Appendix 15-19). Only those involving PSG studies undertaken in case-control cohorts are discussed below and summarised in Tables 5.3 and 5.4. Where there is evidence, we have also sought to discuss potential underlying pathophysiological mechanisms.

5.4.1 Parkinsonism

5.4.1.1 Sleep disorders in Parkinson’s Disease

Sleep disturbance, which is typically multifactorial, is as high as 74-98% in individuals diagnosed with PD, with well documented evidence of parasomnias including RBD, periodic limb movement during sleep (PLMS) and sleep related breathing disorders. Many sleep symptoms are related to disease duration, for example, there are increased disturbances to sleep architecture, insomnia and somnolence in later disease stages compared to earlier timepoints. Two recent review

articles provide detailed oversight of the polysomnographic findings and therapeutic management of sleep disturbance in PD, and therefore we have only provided a brief overview below.[577,578]

RBD is well characterised in PD populations with longitudinal case-control studies identifying 73.5% of patients with idiopathic RBD (iRBD) develop a neurodegenerative disorder after 12-years.[579] Those patients diagnosed with PD and RBD tend towards more severe clinical features, including increased motor symptom severity, higher rates of axial symptoms, psychiatric symptoms, hallucinations, autonomic dysfunction, cognitive impairment and impulse control disorders, as well as a generally longer motor disease duration, when compared to PD patients without RBD.[580–582] Recent imaging studies of those with co-morbid PD and RBD demonstrate prominent loss of volume in the pontomesencephalic tegmentum, PPN network dysfunction and reduced signalling in the locus coeruleus compared to those with PD alone.[583–585]

Although often reported, systematic studies of RLS and PLMS have found conflicting results, but with close matching of control populations a general absence of RLS was observed, while use of actigraphy demonstrated high rates of PLMS. Evidence for the pathogenesis of PD and RLS is conflicting, some studies have reported reduced nigrostriatal dopaminergic activity in idiopathic RLS,[586] while one longitudinal imaging study demonstrated increased dopaminergic transporter availability in both the caudate and putamen to be associated with the presence of RLS.[587] It is also possible that RLS in PD is related to dopaminergic treatment rather than the disease itself. The prevalence of RLS in *de novo* PD patients is comparable to controls, with a longitudinal study showing significantly higher rates of RLS at 3 year follow-up than that at baseline in drug naïve patients.[588] Stimulation of the STN has also been shown to increase rates of RLS, with overstimulation of the dopaminergic system thought to resemble the clinical features of augmentation.[580]

Conflicting results have been found for rates of sleep apnea syndromes (SAS), with some studies identifying comparable AHI levels and a comparable risk of obstructive sleep apnea (OSA) and central sleep apnea (CSA), while elevated apnea-hypopnea indices (AHI) have also been reported at higher rates in those with PD compared to

controls.[589–592] However, several of these studies have not identified the typical oxygen desaturation profiles observed with OSAS, as well as the body mass indices (BMI) of those with PD being significantly lower compared to that of controls. These findings suggest that the sleep disordered breathing identified may represent nocturnal motor involvement of respiratory muscles or a precursor to later stage dysautonomia, rather than the more typical OSA observed in the general population.[593] Extensive loss of neurons, in particular within respiratory control structures such as the brainstem, may also contribute to respiratory disorders. PD patients show abnormal ventilatory response to hypoxia and hypercapnia suggesting involvement of the medulla, with neuronal and astrocyte reduction in the retrotrapezoid nucleus, nucleus of the solitary tract and pre-Bötzinger complex resulting in abnormal respiratory function in murine models of PD.[594]

Several studies have also reported reduced melatonin secretion in patients, with a case-control study showing a four-fold decrease in circulating melatonin levels in those with PD, and reduced melatonin rhythm amplitude in those with excessive daytime sleepiness.[595] These circadian disturbances are present in early disease stages and are often associated with cognitive decline and psychiatric disorders.[596] In addition, reduced expression of *Bmal1* (a clock gene) has been found to correlate positively with PD severity and PSQI scores, providing further evidence of a link between circadian rhythm and sleep disturbances.[597]

5.4.1.2 Sleep disorders related to motor symptoms in Parkinson's Disease

Studies involving PD cohorts (n=45) have shown a positive correlation between PLMS, daytime sleepiness and more severe motor rating scores and reduced mobility.[598] A number of studies have also established a strong link between iRBD and subsequent neurodegenerative disorders, with retrospective analysis of PSG data (n=59 PD patients) identifying faster motor progression in those with RBD (n=15) and REM sleep without atonia (RWA) (n=22) compared to those with preserved REM sleep atonia (n=22, p=0.015). However, this could also be due to increased disease severity and degeneration associated with RBD in PD patients.[599] Several studies also implicate cognitive impairment in the exacerbation of sleep disorders and altered sleep structure.[600] PD patients with primary sleep disorders (RBD and

insomnia) had significantly poorer global cognition, visuospatial and executive function in comparison to both unaffected controls and PD patients without sleep disorders.[601]

Table 5.3 Case–control polysomnography studies involving patients diagnosed with degenerative movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Huntington's Disease	Wiegand et al.[602]	1991	HD (12) HC (12); age- and gender-matched	Two nights of PSG	Patients had an increased sleep onset latency, reduced sleep efficiency, increased number of awakenings and reduced slow wave sleep compared to controls
Huntington's Disease	Wiegand et al.[603]	1991	HD (16) HC (16); age- and gender-matched	Two nights of PSG	HD patients had reduced sleep efficiency, increased sleep onset latency, reduced slow wave sleep and more time spent awake
Huntington's Disease	Neutel et al.[604]	2015	HD (29) HC (29); age- and gender-matched	v-PSG	Patients had longer total sleep and REM sleep onset latency. 2 patients had RWA. 7 patients had giant sleep spindles and one control
Huntington's Disease	Emser et al.[605]	1988	HD (10) HC (12); 7 volunteers, 2 patients with Menière's disease, and 3 patients with a peripheral nerve lesion	Two nights of PSG	HD and HC had no differences except for two patients who had a distinct reduction in slow wave sleep. Sleep spindle was also increased during N2 which correlated to duration of disease
Huntington's Disease	Lazar et al.[606]	2015	HD (38): premanifest gene carriers HC (36): age- and gender-matched controls	Two nights of PSG and MSLT, two weeks of Actigraphy	Gene carriers had more disrupted sleep, characterised by fragmented sleep profile: a decrease in REM sleep

Huntington's Disease	Cuturic et al.[607]	2009	HD (12) HC (12): unaffected relatives, age-gender- and race-matched	One night of PSG, ESS	ESS score had no significant difference between groups. Sleep latency was significantly longer in patients. Nocturnal SRBD were absent
Huntington's Disease	Arnulf et al.[608]	2008	HD (25) Narcolepsy (25) HC (25); age- and gender-matched	Overnight PSG, MSLT, ESS, clinical interview	HD patients had insomnia, earlier sleep onset, lower sleep efficiency, increased PLMS and shortened REM sleep, ESS was normal. 12% exhibited RBD
Huntington's Disease	Goodman et al. [609]	2011	HD (9) HC (10); age-, gender-, race- and BMI-matched	Three nights of v-PSG, MSLT, ESS, 14 nights of Actigraphy, FOSQ, MOS, BDI-2	FOSQ, ESS and MOS scores didn't differ from controls. Sleep architecture (lower percentage of REM sleep) and sleep efficiency differed compared to controls
Huntington's Disease	Piano et al.[610]	2015	HD (30) HC (30); age- and gender-matched	One night of v-PSG, ESS, IRLSSG, BQ, RBDSQ	Two patients reported RLS, 8 had scores ≥ 9.8 patients had high risk of OSA. 2 had pathological RBD. PSG showed no RWA and RBD. Disease duration correlated with ESS
SCA	Seshagiri et al.[611]	2018	SCA1 (6) SCA2 (5) SCA3 (7) HC (6)	Overnight PSG	Sleep spindle density significantly decreased in SCA
SCA	Rodríguez-Labrada et al.[612]	2019	SCA2 (20) SCA2 preclinical carriers (20) HC (20)	One whole night of PSG	Compared to controls sleep spindle density was significantly reduced in SCA2 and preclinical patients. Reduced spindle activity correlated with reduced N3 sleep in SCA2 patients
SCA	Rueda et al.[613]	2016	SCA 6 (12) HC (12); age-, gender- and BMI-matched	Overnight PSG	SCA6 had higher frequency of snoring, respiratory disorders and slow wave sleep compared to controls

SCA	Zanatta et al.[614]	2019	SCA 2 (17) HC (17); age-, BMI- and gender-matched	One night of v-PSG	Increased REM sleep in 70%, increased REM latency in 52%, increased OSA in 82% and absent REM density in 76%. Compared to controls SCA2 had reduced total sleep time, sleep efficiency, sleep latency, sleep N3 latency, REM quantity, N2 and N3 quantity. Disease progression correlated with a reduction in REM density and decreased sleep efficiency
SCA	Iranzo et al.[615]	2003	SCA3 (9) HC (9); age- and gender-matched	Overnight PSG, sleep questionnaire	55% of patients has RBD compared to no controls. SCA3 patients had reduced total sleep time, sleep efficiency, REM sleep percentage, increased WASO and PLMI compared to controls
SCA	Pedroso et al.[616]	2013	SCA3 (22) from 15 families HC (20)	Overnight PSG, RBDSQ, IRLSSG	SCA3 patients; 54% had RLS, 77% had PLMS, 73% had RWA and 59% had RBD
SCA	Velázquez-Pérez et al.[617]	2011	SCA2 (32) HC (32); age- and gender-matched	Two nights of v-PSG, ESS, sleep interviews – subjective sleep quality and dream recall, snoring, somniloquy and motor complaints during sleep	Reduced REM sleep percentage and REM density, an increase in RWA, PLMS in 37.5% of patients. 21.8% complained of insomnia vs 3% in HC and RLS diagnosed in 25% of patients compared to 3% in HC. No difference in ESS scores
SCA	Silva et al.[618]	2016	SCA3 (47) HC (47); age- and gender-matched	Overnight PSG, IRLSSG, RBDSQ, non-validated parasomnia questionnaire	SCA3 had higher frequency of arousals from slow wave sleep, parasomnia complaints, RWA, PLMI, percentage of N1 and N3 sleep
SCA	Chi et al.[619]	2013	SCA 3 (15) HC (16)	Overnight PSG, ESS	SCA3 patients had reduced sleep efficiency and percentage of REM sleep which negatively correlated with severity of ataxia. ESS was normal to controls
SCA	Reimold et al.[620]	2006	SCA1 (10) SCA2 (4) SCA3 (2) HC (9); age-matched – in PET only	Overnight PSG, ESS	RLS present in 25% of SCA1 and SCA2 patients, 100% of SCA3 patients. All RLS patients had abnormal PLMS score. One RLS had OSA. 1 SCA2 and SCA3 patient had EDS
SCA	London et al.[621]	2018	SCA 10 (23) HC (23)	One night of PSG, ESS	SCA10 patients had longer REM sleep and more REM arousal than controls. REM sleep onset correlated with disease duration

Wilson's Disease	Trindade et al.[622]	2017	WD (42) HC (42); age- and gender-matched	v-PSG, IRLSSG, ESS, PSQI, BDI	Sleep quality was worse compared to HC. WD patients showed lower sleep efficiency, less N2 sleep and more WASO and arousal compared to HC. WD with RLS showed significantly more PLM, more N1 sleep and a longer REM sleep latency
Wilson's Disease	Tribl et al.[623]	2015	WD (41) HC (41); age- and gender-matched	v-PSG, RBDSQ, PSQI, ESS, MSQ, clinical and sleep interviews	5 WD patients fulfilled the RBD criteria and had significantly higher values in RWA. RWA in WD patients without RBD was still significantly increased compared to controls
Wilson's Disease	Nevsimalova et al.[624]	2011	WD (55) HC (55); age- and gender-matched	PSG (24 WD and HC), ESS, RBDSQ, questionnaire concerning sleeping habits	13 WD patients fulfilled RLS criteria. WD patients were more prone to daytime napping accompanied by EDS and poor nocturnal sleep. Mean ESS as well as RBDSQ was higher than controls. TST was lower, with decreased sleep efficiency and increased wakefulness. WD had lower latency of N1 and N2 sleep. 14% had MSLT <8 minutes
Niemann-Pick Type C	Vankova et al.[625]	2003	Juvenile NPC (5) HC (12)	At least one night of PSG, MSLT	In all patients, sleep was fragmented and disorganised. Total sleep time and sleep efficiency was lower, shorter sleep latency and increased WASO

Abbreviations: BDI/−2, Beck's depression inventory; BQ, Berlin Questionnaire; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HC, healthy control; HD, Huntington's disease; HDSS, Hungtinton's Disease Sleepiness Scale; IRLSSG, International Restless Leg Syndrome Study Group; MSLT, Multiple Sleep Latency Test; MSQ, Mayo Sleep Questionnaire; NPC, Niemann-Pick disease Type C; OSA, obstructive sleep apneoa; PLMI, Periodic Limb Movement Index; PLMS, periodic limb movement during Sleep; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RBD, rapid eye movement sleep behaviour disorder; RBDSQ, Rapid Eye Movement sleep Behaviour Disorder Screening Questionnaire; REM, rapid eye movement sleep; RLS, Restless leg syndrome; RWA, rapid eye movement sleep without atonia; SCA, spinocerebellar ataxia; SRBD, sleep-related breathing disorder; v-PSG, video polysomnography; WASO, wake after sleep onset; WD, Wilson's disease.

5.4.1.3 Impact of treatment used in the management of motor symptoms on sleep

Dopaminergic Therapy

Night-time akinesia can worsen underlying disturbances to sleep. A placebo-controlled study of controlled release levodopa/carbidopa in PD patients (n=40) found improved nocturnal akinesia and therefore increased total hours slept, however immediate release preparations result in reduced total sleep time and lower rates of RBD related symptoms.[590] In contrast, several studies have shown that the use of dopamine agonists results in increased levels of nocturnal activity and higher levels of daytime sleepiness compared to levodopa therapy.[626] Sudden-onset sleep is sometimes described in PD and attributed to the sedative effects of dopamine agonists, with these 'sleep attacks' prompting safety concerns, particularly in relation to driving.[627] However, transdermal rotigotine patches have been shown to effectively aid sleep continuity, sleep stability and REM sleep, with comparable outcomes to pramipexole and superior to treatment with ropinirole.[628,629] Dopamine agonists are also licensed for use in the treatment of RLS and PLMS however, increasing recognition of impulse control disorder and augmentation as common side effects have limited their use, with pregabalin or gabapentin frequently used as alternatives.

Monoamine Oxidase Inhibitors

Rasagiline can be alerting with fatigue-related questionnaires completed by those with PD showing significant improvements to baseline scores at 12-weeks (n=16, $p=0.003$). Dopamine-naïve PD patients (n=1176) demonstrated dose-related improvements at week-36 compared to placebo (1mg $p=0.003$; 2mg $p<0.0001$), while PSG studies show increased sleep maintenance and lower WASO compared to controls.[630] Safinamide also improves sleep disorders in PD, likely due to its dual dopaminergic and glutaminergic mechanisms, while amphetamine-like derivatives of selegiline can worsen sleep quality by promoting the onset of insomnia.

Deep Brain Stimulation

PSG studies have noted improvements following subthalamic nuclei stimulation, with increased total sleep time, decreased WASO ($p<0.05$), and longer periods of

continuous sleep ($p<0.05$), while PPN stimulation – although experimental and performed in few patients – resulted in increased percentage REM sleep in both PD and PSP populations.[631] The efficacy of DBS in the management of sleep disorders in PD is conflicting, the majority of studies suggest that DBS has no impact on RBD[632], although restoration of REM-sleep without atonia has been noted.[633] Several studies have shown improvement in RLS symptoms following DBS,[634,635] while one study found that STN-DBS resulted in the emergence of RLS in 19% of those with PD.[580]

5.4.1.4 Therapeutics used in the management of sleep disorders in Parkinson's Disease

Wake-promoting agents

These include stimulants such as modafinil and methylphenidate, used to promote wakefulness in hypersomnolence. A recent meta-analysis demonstrated improvement in subjective sleepiness with modafinil, although no subjective improvement in fatigue or objective measures of sleepiness (MSLT or Maintenance of Wakefulness Test (MWA)).[636] Studies of other agents have also shown promising results with sodium oxybate ($GABA_B$ receptor agonist) decreasing ESS scores and increasing mean sleep latency, while methylphenidate resulted in a significant reduction to fatigue compared to placebo in PD populations.[637]

Melatonin

Melatonin is produced by the pineal gland with levels rising in darkness and acting as a key regulator of the sleep wake cycle. It has a short half-life at 30-60 minutes and is licensed to treat sleep onset insomnia as well as being used off license to treat RBD with PSG studies showing restoration of REM atonia, with case-controlled studies suggesting fewer side effects compared to clonazepam.[638] However, a recent placebo-controlled RCT found prolonged-release melatonin to have no significant impact on the subjective reporting of RBD symptoms.[639] Agomelatine, a synthetic melatonin analogue, initially developed for treatment of depression, has also been shown to alleviate sleep disturbances (PLMS and awakenings) in PD.[640]

Antidepressants and antipsychotics

Trazodone, a serotonin antagonist and reuptake inhibitor, is licensed for use in the treatment of insomnia in some countries. While there are no studies which evaluate its therapeutic use for sleep disorders within the PD population, effective doses within animal models alleviate dyskinesia and psychosis, but appear to cause sedation.[641] Other atypical anti-depressants including mirtazapine can be effective for insomnia due to potent anti-histamine effects but have also been reported to induce or aggravate RBD symptoms in PD cohorts, while use of doxepin in those with PD demonstrated substantial improvements to insomnia, sleep quality and fatigue. Commonly used for the management of hallucinations and delusions, quetiapine, clozapine and pimavenserin are not typically associated with the worsening of motor symptoms in movement disorders. While quetiapine leads to improvements in PD-related psychosis, it has not been shown to impact disturbances to sleep architecture. In contrast, preliminary data relating to pimavanserin (a novel 5-HT2A agonist) suggests improvements to nocturnal symptoms without worsening daytime sedation.[642] Finally, while there are no RCTs, clonazepam remains widely used in the treatment of RBD, in doses from 0.5mg to 2mg, although side effects of sedation at higher doses can be problematic.

5.4.1.5 Sleep disorders in Dementia with Lewy Bodies (DLB) and the impact of motor disease treatment on sleep

Fluctuating levels of alertness and REM sleep behaviour disorder form core diagnostic criteria for DLB, while PSG evidence of loss of REM atonia also forms a supportive diagnostic biomarker. RBD in DLB, is often experienced several years before the onset of cognitive decline with PSG studies indicating rates of RBD in DLB to be as high as 71%.[643] Case-control studies have also identified higher levels of PLMS, with sleep architecture abnormalities evident in 75%, predominantly in the form of REM sleep without atonia (44%).[643] Cholinesterase inhibitors (galantamine, donepezil and rivastigmine) used to treat cognitive decline in DLB have been shown to improve sleep quality, reduce fragmented sleep and reduce nocturnal activity.[644,645]

5.4.1.6 Sleep disorders in Multiple System Atrophy (MSA)

Sleep disorders are also well documented for multiple system atrophy (MSA). In brief, particularly high rates of RBD are reported (64-100%), with 76% (n=21) of one study reporting onset prior to their motor symptoms.[646] Respiratory stridor is also well-recognised, as well as being associated with more severe disease progression and sudden death. Case-control studies have identified increased rates of OSA and AHI levels >5, compared to controls with continuous positive airways pressure (CPAP) improving stridor and sleep apnea.[647] Disruption to subcortical serotonergic neurotransmission is considered to be a key pathophysiological contributor, with depletion of the serotonergic innervation of the raphe nuclei and neurodegeneration of regions involved in respiratory regulation – the brainstem ventral arcuate nucleus and pre-Bötzinger complex cells – considered central in pathogenesis.

5.4.1.7 REM sleep behaviour disorder in α-synuclein disorders

As outlined above, RBD is a recognised early clinical manifestation amongst the α-synucleinopathies; PD, MSA and DLB, often preceding disease onset by several years and representing a key prodromal marker.[648] Several imaging studies of those with iRBD have identified changes in multiple brainstem structures, namely the PPN, sublaterodorsal nucleus and laterodorsal tegmental region, with those without changes in these regions not observed to later develop PD.[649]

5.4.1.8 Sleep disorders in Progressive Supranuclear Palsy (PSP)

Studies to date suggest at least 60% of patients diagnosed with PSP report sleep disturbance, with insomnia being the dominant symptom. RBD and REM sleep without atonia also occur, but at lower rates (5-13%) than that seen in PD, with this not seeming to antedate motor disease onset.[650] Imaging studies show degeneration of REM-promoting structures, including the PPN and pontine tegmentum, as the likely cause.[651] A recent study also reported that patients diagnosed with PSP with Lewy type alpha-synucleinopathy were more frequently diagnosed with probable RBD compared to those with PSP without Lewy pathology.[652]

5.4.1.9 Sleep disorders in Corticobasal Syndrome (CBS)

Two small PSG studies reported sleep disorders in all of the patients involved, these included PLMS and/or RLS and sleep related breathing disorders including OSA and CSA. Alterations to sleep architecture were also observed, with patients showing decreases in sleep maintenance, total sleep time and REM sleep without atonia.[653,654]Although no studies have reported narcolepsy in CBS, there is evidence of reduced hypocretin in cerebral spinal fluid (CSF) compared to those with PD.[655]

5.4.2 Neurodegenerative Trinucleotide Repeat Disorders

5.4.2.1 Sleep disorders in Huntington's Disease (HD)

While sleep disturbance is a frequent complaint, with at least 90% of carers describing poor sleep, it remains less well characterised due to motor and psychiatric symptoms often dominating, as well as a lack of patient insight. Approximately two-thirds of patient cohorts report insomnia, describing difficulty falling asleep and maintaining sleep, with PSG showing increased sleep fragmentation, decreased N3 and REM compared to controls. Insomnia is often present early in disease, as well as being reported in pre-motor manifesting *HTT* carriers, and increasing with disease progression.[608] Reduced REM sleep (n=30) has also been shown to be inversely correlated with motor symptom severity ($p<0.05$), with cognitive impairment also implicated in the exacerbation of sleep disorders and altered sleep structure.[600]

Patients with HD also demonstrate strikingly abnormal circadian rhythms with both a delayed and irregular phase to sleep, with evidence from actigraphy monitoring, as well as abnormal melatonin and cortisol profiles. These changes are also consistently observed in animal models of disease, and are attributed to degeneration of the suprachiasmatic nucleus, hypothalamus and striatum.[656,657] They can also occur early in the condition and are associated with higher levels of cognitive impairment and anxiety.[658] Human post-mortem studies have shown a loss of orexin-releasing neurons in individuals diagnosed with HD, while transgenic HD mouse models suggest that changes to suprachiasmatic nucleus (SCN) circuitry are central in driving circadian disruption.[656]

5.4.2.2 Sleep in relation to the treatment of Huntington's Disease

Tetrabenazine, a monoamine reuptake inhibitor, is often used in the management of chorea associated with HD although daytime sleepiness is a commonly reported side effect. A study examining the effect of quetiapine (a partial D2 receptor antagonist) in those with HD found amelioration of their symptoms of insomnia, without any worsening of motor function.[659]

5.4.2.3 Sleep disorders in the Spinocerebellar Ataxias (SCAs)

A broad spectrum of sleep disorders is described amongst the spinocerebellar ataxias (SCAs), potentially representing widespread brain degeneration beyond the cerebellum. However, technical difficulties exist in measuring rapid eye movements in those who have developed impaired eye movements and saccades, with this likely accounting for some of the previous reports of abnormal or absent REM sleep. Individuals with SCA2 mutations often report good sleep quality but have abnormal PSG, including reduced N3 sleep and REM sleep.[612] NREM sleep appears to be the stage most severely affected in those with SCA3 and SCA6 mutations, with increased arousals from slow wave sleep and increased wake after sleep onset.[613,618] In contrast, a study of SCA10 patients found changes predominantly in REM sleep, including an increased number of REM sleep arousals.[621]

Overall, low rates (0-10%) of PLMS have been noted in those with SCA1 and SCA6 mutations, while higher rates and symptomatic RLS are more often seen in SCA3 cohorts (77%).[613] RLS is thought to reflect the basal ganglia involvement, with functional imaging supporting reduced striatal dopamine transporter activity in this region. Further investigation of the postsynaptic dopaminergic system has shown progressive loss of D2 receptors in the caudate, dorsal putamen and ventral striatum.[620]

Sleep-related breathing disorders have been identified in those with SCA2 and SCA6 mutations, including an increased central sleep apnea (CSA) index (events/h = 0.97) and AHI ($p=0.022$) in those with SCA2 mutations, and increased CSA events during sleep ($p=0.024$) and oxygen desaturations ($p=0.03$) in those with SCA6 mutations.[613] The underlying causative mechanisms remain unknown, although vocal paralysis

and dysphonia in combination with neurodegeneration of the supramedullary pathway and brainstem neurons have been proposed.[660]

5.4.3 Sleep disorders in Wilson's Disease and the impact of motor symptom treatment on sleep

Two video-PSG case-control studies have reported abnormal sleep architecture, with REM stages predominantly affected and a third demonstrating objective daytime sleepiness on MSLT and cataplexy-like epsiodes.[624,661] There is some limited evidence for higher rates of RLS amongst those with Wilson's disease compared to the general population, with 31% of a single cohort (n=42) meeting diagnostic criteria, and subsequent PSG demonstrating increased PLMS compared to controls ($p=0.009$).[622] Albeit in a single case-report, D-penicillamine resolved complaints of hypersomnia, while a case-control study identified higher rates of probable RBD found in those treated with D-penicillamine.[624,662]

5.4.4 Sleep disorders in Niemann Pick Type C

The heterogeneous and nonspecific clinical presentation of Niemann Pick Type C challenges its diagnostic process, although secondary cataplexy is an important and discriminatory clinical feature. A single, small (n=5) PSG study has been performed to date, with evidence of reduced total sleep time ($p<0.01$), sleep efficiency ($p<0.001$), shorter sleep latency ($p<0.01$), increased wake after sleep onset (WASO, $p<0.05$) and decreased REM sleep ($p<0.05$).[625] Reduced CSF hypocretin levels were also observed compared to controls, a feature also seen in narcolepsy and cataplexy, and consistent with hypothalamic dysfunction (Figure 2C).[625]

5.4.5 Sleep disorders in Anti-IgLON5 and the impact of disease treatment on sleep

Immunoglobulin-like cell adhesion molecule 5 (IgLON5) is a recently described disorder in which sleep disturbance is pronounced, as well as gait instability and movement disorders. The underlying aetiology of this disorder is thought to be a combination of neuroinflammation and neurodegeneration, with post-mortem evidence of hyperphosphorylated tau deposition.[663] The sleep disorders described include REM and NREM sleep parasomnias, sleep disordered breathing, namely

stridor and obstructive apnea, insomnia and hypersomnolence. Three PSG studies have identified altered sleep architecture, with evidence of undifferentiated NREM sleep and poorly structured N2 associated with abnormal behavioural manifestations.[664–666] Treatment of IgLON5 with intravenous steroids show normalised sleep onset and N1 and N2 stages, although marked abnormal sleep re-remerged three months later in spite of additional immunotherapy.[666]

Table 5.4 Case–control polysomnography studies involving patients diagnosed with non-degenerative movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Dystonia	Gadoth et al.[667]	1989	HPD (3) HC (11)	PSG over two nights (two patients, and one night in one patient and HC)	Sleep structure appeared to be normal in all subjects
Dystonia	Jankel et al.,[668]	1983	DMD (4) HC (4): age- and gender-matched	PSG over three nights	PSG showed increased sleep latency, reduced sleep efficiency, and unusually high voltage of sleep spindles (>100μV) sleep spindles during N2
Dystonia	Jankel et al.[669]	1984	DMD (9) HC (9): age- and gender-matched	PSG over three nights	All patients slept poorly, patients with advance stages of dystonia all displayed high-amplitude (>150μV) spindles during N2 and N3, increased sleep latency, less REM sleep, increased number of awakenings and poor sleep efficiency
Dystonia	Fish et al.[339]	1990	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10)	PSG over two nights	Four patients (taking benzodiazepines) with TD had increased sleep spindles more than both control groups. All patients with severe disease had abnormal sleep spindles
Dystonia	Fish et al.[670]	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10) Same sample as Fish et al., 1990	PSG over two nights	All patients and controls showed reduced EMG activity during REM sleep compared to wakefulness. Patients with secondary TD had fewer bursts of activity than normal subjects. RBD was absent in all groups

Dystonia	Fish et al.[671]	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10) Same sample as Fish et al., 1990	PSG over two nights	Movements were most frequent during awakening, proceeded by N1, with very few movements during N2 and REM sleep. Sleep-related movements in primary and secondary TD emerged after brief awakenings
Dystonia	Lobbezoo et al.[335]	1996	CD (9) HC (9) age- and gender-matched	PSG over two nights	PSG in CD patient were normal. Sleep was associated with an improvement of symptoms in CD, with abnormal cervical muscle activity decreasing immediately when lying down and then being abolished when transitioning to light NREM sleep
Dystonia	Antelmi et al.[337]	2017	CD (20) HC (22): age- and gender-matched	One full night of PSG, RLS, PSQI, ESS, BDI	PSQI showed significant reduction in sleep quality, and correlation with higher scores of BDI. ESS scores were normal. Difficulties in sleep efficiency and increased sleep latency and increased REM sleep latency. Patients had lower muscle amplitude contraction over the dystonic muscles compared to HC in slow wave sleep and REM sleep
Dystonia	Brüggemann et al.[338]	2014	DRD (23) HC (26): age-matched	PSG over one night, PSQI, ESS, SSS, FEPS-2, BDI, self-administered comorbidity questionnaire	Sleep quality, SSS and ESS was similar across groups. 6 patients underwent PSG, 2 had reduced sleep efficiency, 2 increased sleep latency, 5 increased REM latency, 4 had initiation problems and 4 had increased in numbers of arousal
Tic Disorders	Hashimoto et al.[672]	1981	TS (9) HC (9)	PSG	At all stages of sleep, body movements during sleep were more frequent in cases of TS. Twitch movements in REM sleep were significantly increased in TS. TS patients had increased total sleep time, REM sleep and NREM sleep
Tic Disorders	Stephens et al.[673]	2013	TS (20) TS+ADHD (21) HC (16) ADHD (33)	Two nights of PSG, respiration belt	Total number of leg movements higher in TS+ADHD group compared to TS only. Children with TS and ADHD had a significant higher number of arousals from slow wave sleep and total arousals
Tic Disorders	Kirov et al.[674]	2007	TS (18) TS+ADHD (18) ADHD (18) HC (18)	Two nights of PSG	TS patients had lower sleep efficiency and elevated arousal index in sleep. TS+ADHD patients had reduced sleep efficiency, elevated arousal index and increase in REM sleep

Tic Disorders	Kirov et al.[675]	2007	TS+ADHD (19) HC (19)	Two nights of PSG	Shorter REM sleep latency and increased REM sleep duration in patients with TS+ADHD
Tic Disorders	Kirov et al.[676]	2017	TS (21) ADHD/TS (21) ADHD (24) HC (22); age- and gender-matched	Two nights of PSG	Increased REM sleep and shorted REM latency in children with psychiatric disorders than controls
Tic Disorders	Voderholzer et al.[677]	1997	TS (7) HC (7); age- and gender-matched	Two nights of PSG	5/7 showed frequent PLMS in NREM and total sleep time significantly lower in TS group ($p<0.05$)
Tic Disorders	Cohrs et al.[678]	2001	TS (25); adults HC (11)	v-PSG over two consecutive nights	Patients with TS showed reduced sleep efficiency, total sleep time/time in bed, and percentage of slow wave sleep, as well as significantly prolonged sleep latency, significantly increased percentage of N1, percentage of time awake, and increased number of awakenings and sleep stage changes/hour sleep period time
Tic Disorders	Kostanecka-Endress et al.[679]	2003	TS (17); children HC (16); age-, gender-, IQ-matched	Two nights of PSG, CBCL sleep items (parent), semi structured interview with parents and patients	Children with TS demonstrated changes in sleep parameters, including longer sleep period time, longer sleep latency, reduced sleep efficiency, and prolonged wakefulness after sleep onset. Short arousal-related movements were increased in TS. Periodic limb movements during sleep were only seen in one TS patient

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BDI, Beck's Depression Inventory; CD, cervical dystonia; DRD, dopamine-responsive dystonia; EMG, electromyography; ESS, Epworth Sleepiness Scale; FEPS-2, Sleep-related Personality Traits Questionnaire; HC, healthy control; HPD, Hereditary Progressive Dystonia; NREM1/2/3, Non-Rapid Eye Movement Sleep stages; PLMS, Periodic Limb Movement during Sleep; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RBD, Rapid Eye Movement sleep Behaviour Disorder; REM, Rapid Eye Movement Sleep; RLS, Restless leg syndrome; TD, torsion dystonia; TS, Tourette's syndrome; v-PSG, video polysomnography.

5.4.6 Sleep Disorders in Dystonia

Disturbances to sleep have been reported in 40-70% of dystonia cohorts, with insomnia and abnormal movements during sleep (e.g. RLS) most commonly described, although several studies have also reported few or no disturbances to sleep.[337,351] A probable contributory role of the common psychiatric comorbidities (depression and anxiety in particular) to these sleep-related symptoms, is also likely and important to bear in mind. As such, varying changes in sleep architecture have been observed in distinct types of isolated idiopathic dystonia with PSG recordings of individuals with cervical dystonia (CD) (n=22), blepharospasm (BSP) (n=3), Meige Syndrome (n=7), and in combined genetic forms, such as *GCH1* mutation positive dopa-responsive dystonia (n=6), showing increased N1 phase (NREM) duration and reduced REM periods, compared to controls (Figure 5.3).[337,338]

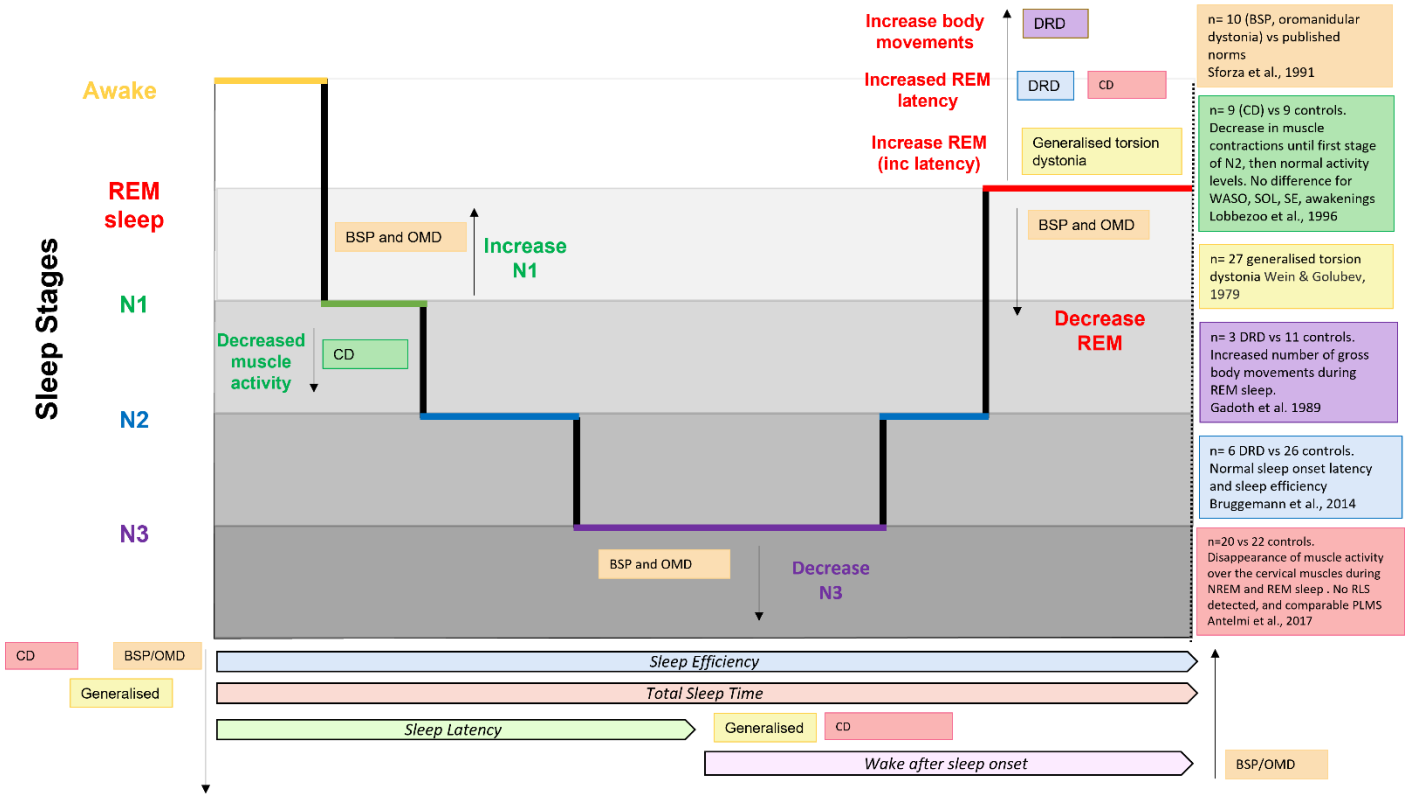

Figure 5.3 Polysomnography-based studies in dystonia

Abbreviations: BSP: Blepharospasm, CD: Cervical dystonia, DRD: Dopamine-responsive dystonia, NREM: Non-Rapid Eye Movement Sleep Stage (N1-N3), OMD: Oromandibular dystonia, PLMS: Periodic Limb Movements during Sleep, REM: Rapid Eye Movement Sleep Stage, RLS: Restless Leg Syndrome, SE: Sleep Efficiency, SOL: Sleep Onset Latency, WASO: Wake After Sleep Onset

5.4.6.1 Sleep in relation to the treatment of Dystonia

Levodopa has been shown to benefit sleep in those with G*CH1* mutation positive dopa-responsive dystonia, reducing rates of excessive daytime sleepiness, although also reducing total REM sleep.[680] Trihexyphenidyl has been reported to increase wakefulness and decrease REM sleep however, the drowsiness experienced at lower doses has limited its clinical use. Benzodiazepines are also often used in the management of dystonia, and as traditional hypnotics they decrease sleep latency but also suppress slow-wave sleep, lengthen REM sleep latency and can cause habituation with rebound insomnia. Also sometimes used, is gabapentin, an alpha 2 delta ligand that increases slow wave sleep, although when used during the day can be associated with drowsiness, fatigue and sedation. However, in children diagnosed with dystonia, gabapentin has been shown to reduce motor symptoms severity (n=69), as well as improve sleep quality and duration ($p<0.01$).[681]

5.4.7 Sleep Disorders in Essential Tremor

Sleep disturbances in ET are milder than those seen in PD, with a single PSG based study showing few objective changes compared to controls, in contrast to those with PD, although examination of the phenotypic heterogeneity amongst the ET cohort found that those PSG changes observed were most prominent in those with mild cognitive impairment.[682] A recent review, albeit using questionnaire only data, describes excessive daytime somnolence, RLS, insomnia and nocturia to be frequently reported by patients diagnosed with ET.[683] Once again, psychiatric comorbidities (anxiety in particular) likely play some role in contributing to the symptoms described.

5.4.7.1 Sleep in relation to the treatment of Essential Tremor

Commonly used in the treatment of essential tremor, beta-blockers often cause or worsen nightmares and restless legs, with 12 studies to date reporting rates of sleep disturbance between 12% and 60%.[684] Primidone has also been reported to have sedative side effects, including daytime sleepiness and tiredness (50%), often resulting in discontinuation of treatment (27%). As described above, Gabapentin, also sometimes used in the management of tremor, carries with it side effects that include drowsiness, fatigue and sedation.

5.4.8 Sleep in Tourette Syndrome

Many with Tourette's Syndrome (TS) have both insomnia and increased movements at night, during both REM and NREM stages, with studies of those with co-morbid attention deficit hyperactivity disorder (ADHD) reporting rates of sleep disorders to be as high as 80%.[685] Comparison with healthy controls has shown significant reductions in sleep efficiency ($p<0.05$) and total sleep time ($p<0.01$), while sleep latency ($p<0.05$) and WASO ($p<0.001$) were increased. In contrast, changes to the REM portion of sleep has varied between studies, with some reporting reduced periods (n=18/34), while others show increased or comparable levels to controls.[673] Other studies have sought to separate TS patients with and without symptoms of ADHD, with reduced REM sleep latency and increased REM sleep observed in both groups, while those with ADHD symptoms also had evidence of insomnia, RLS/PLMS and NREM parasomnias.[674] Interestingly, variants in the orexin-2/hypocretin-2 (OX2R) receptor gene, mutated in canine narcolepsy, have also been found to be present in those diagnosed with TS.[686]

5.4.8.1 Sleep in relation to the treatment of Tourette Syndrome

Albeit in only a small cohort of patients with tics (n=3), abnormal NREM sleep and sleep apnea resolved in two when treated with tetrabenazine.[687] A recent review article also noted that those treated with anti-psychotics (risperidone, aripiprazole and tiapride) were more likely to experience somnolence, sedation and sleep disturbance.[688]

5.5 Challenges in the field

As outlined above, increasing data suggests sleep disorders to be prevalent across the spectrum of movement disorders, although much of this work is limited by small, heterogenous cohorts. Larger studies often involve questionnaire-based assessments alone, while those that do involve PSG measurements vary in their approach with differences in single night versus multi-night assessments. The night-to-night variability typical of all sleep patterns questions the validity of single-night studies, particularly those undertaken in unfamiliar environments. To counter this, portable devices are now widely used in the home setting, allowing longer periods of

monitoring. Further work with these non-laboratory-based techniques is needed in order to establish more robust normative values on an individual and disorder-specific level.

While motor symptoms are usually considered as the first cause of sleep disturbance (e.g. dystonia in PD), it is important to recognise that comorbidities such as mood disorders and pain also have the potential to impact sleep. The relationship between depression and disturbed sleep is complex and bidirectional, for example, insomnia may be a direct result of depression or secondary to the movement disorder. Although few studies have addressed this issue, some have reported more impaired sleep (sleep maintenance insomnia) in patients with PD and depression than those without depression. Treatment of anxiety and depression should be managed as effectively as possible and may help consolidate the sleep/wake cycle.

Another important area for future understanding, and a potential avenue for therapeutic intervention is the glial-lymphatic (glymphatic) pathway, a highly organised fluid transport system moving CSF from the subarachnoid space to the peri-parenchymal interstitial fluid (ISF).[689] Murine studies have shown that glymphatic function increases during sleep, allowing for clearance of metabolic by products. Several studies have demonstrated that during disrupted or impaired sleep, these processes do not have sufficient time for normal clearance, leading to the accumulation of metabolites with subsequent impact on cognition and behaviour. Protein aggregates found in the glymphatic system include alpha-synuclein, as well as amyloid β (Aβ) observed in Alzheimer's disease. Dopamine and noradrenaline also appear to contribute to regulating ISF flow within the glymphatic system, resulting in feed-forward enhanced neurotransmission increasing dopamine and noradrenaline neurotransmission during wake states.[690]

5.6 Assessment and treatment considerations

A detailed discussion of the management of different sleep disorders is beyond the scope of this review, and only general guidelines are provided. An initial clinical history from both patient and bed partner wherever possible, alongside simple questionnaires, often allows good differentiation of many sleep disorders.

Consideration of the impact of motor symptom onset, severity and prescribed medication is also important. Co-morbid medical conditions that may cause or contribute to sleep disorders should be considered, for example primary treatment of psychiatric disorders may improve sleep-related symptoms. Sleep hygiene should be reviewed (e.g. caffeine use) and simple behavioural interventions considered in the first instance. CBT is recommended as standard therapy for the long-term management of insomnia, with digital forms of this treatment becoming increasingly available to broaden access and availability. Pharmacotherapy is effective in the treatment of moderate or severe RLS, with several clear treatment algorithms available, while extensive evidence supports the use of CPAP in the management of OSA, again aided by standardised therapy guidelines.

5.7 Conclusion

This review demonstrates that many patients with movement disorders also experience symptoms related to sleep disorders. Dysfunction of the medulla, raphe nuclei, pons and basal ganglia potentially form a shared underlying mechanism for both motor and sleep pathophysiology. For some, there are specific patterns to the sleep problems but for many, changes to sleep are multifactorial, involving medication side effects, motor and non-motor symptoms, suggesting the need for a systematic approach to assessment. Further work is needed to better understand the aetiology of sleep disturbances across distinct movement disorders in order to facilitate more targeted and effective therapeutic strategies, and to understand whether targeting poor sleep leads to clear improvements in motor outcomes. Future studies should be directed towards combining limited PSG assessment with far wider application of wearable or mobile home devices in order to identify robust digital biomarkers of utility in diagnosis and symptomatic monitoring.

6 Sleep disturbance in dystonia: An investigation using UK Biobank

6.1 Introduction

As highlighted in Chapter 5, sleep disorders are increasingly recognised as a common co-morbid trait in movement disorders, forming one of the most common non-motor symptoms (NMS) and affecting 40 – 70% of primary dystonia cohorts.[691,692] Compared to other NMS, few studies have evaluated sleep disturbance in dystonia, with these predominantly involving use of questionnaires. However, those studies undertaken to date report reduced quality of sleep and restless leg syndrome (RLS),[286,331,332,351,431,693,694] while daytime sleepiness is often at a level comparable to controls.[330–333]

Polysomnography (PSG), the gold standard tool in understanding changes to sleep architecture (see Section 5.3.1) has been used in only a few dystonia-related studies, frequently reporting few or no sleep disturbances. Amongst those with focal cranio-cervical dystonia three of these studies found a marked decrease in frequency and duration of muscle overactivity, but no complete resolution of the muscular hyperactivity observed in dystonia,[334–336] while the fourth found evidence of decreased sleep efficiency, increased sleep latency, increased rapid eye movement (REM) sleep latency and decreased activity over affected cervical muscles during non-rapid eye movement (NREM) and REM sleep, compared to controls.[337] A recent case-control studies in individuals with primary cervical dystonia observed increased sleep transition during REM and NREM (signifying increased cycling between REM sleep to NREM, increasing the potential for waking and sleep instability), reduced spindle maintenance and generation (spindles are important for sleep stability and allows progression to deeper sleep), increased delta power (associated with sleep duration and intensity, typically delta power decreases as sleep deepens and is enhanced after prolonged wakefulness) and reduced percentage REM sleep compared to controls, whilst a second observed comparable polysomnographic-derived sleep variables.[432,695] Other PSG based studies have found sleep fragmentation caused by spontaneous arousal and increased REM sleep latency in those with *GCH1* mutation-positive dopa-responsive dystonia.[338] Amongst patients diagnosed with primary and secondary torsion dystonia, a PSG investigation noted an increased number of sleep spindles in four of 24 the cases (17%) compared to control populations.[339]

However, multiple factors can influence sleep disturbance, including the co-existence of other NMS. Multiple studies have demonstrated the co-morbid nature of sleep and mental health disorders, with sleep disturbances considered a core secondary symptom of depression with abnormalities observed across all stages of sleep. Alterations in sleep architecture, particularly REM sleep, are also regarded as a distinctive neurological marker of depression, suggesting a complex bidirectional relationship between sleep and mental health disorders.[696] Co-morbid depression and anxiety is well recognised in dystonia, with evidence supporting a strong association between sleep and other NMS, although the nature and direction of the causal relationship remains uncertain.[331,694,697]

Pain is also widely associated with impaired sleep quality, with evidence again suggesting a bidirectional relationship. Several studies have demonstrated that pain is associated with insomnia, narcolepsy, obstructive sleep apnoea and reduced sleep duration, and those who present with both chronic pain and sleep disorders demonstrate a more severe clinical phenotype.[698] Although a bidirectional relationship has been observed, some evidence suggests that this relationship is more heavily weighted to sleep disturbance contributing to worsening pain, rather than vice versa.[699] Pain is well-established as a NMS in cervical dystonia, affecting up to 90% of patients.[700] It also appears to be a major contributor to impaired sleep quality amongst dystonia cohorts, with evidence of a relationship between sleep impairment and severity of pain.[333] Interestingly, the severity of dystonia does not appear to be associated with impaired sleep quality,[331,351,694,697] further supporting the notion that dystonia-related sleep disturbances are not related to pain or muscle contraction.[337]

To date, evidence remains unclear whether sleep disturbances are primary NMS in dystonia or a secondary phenomenon relating to psychiatric/pain disturbances, or secondary to overactivity of dystonic muscles. However, multiple levels of emerging evidence increasingly suggests that it forms a primary phenotypic component, with these including i) there is considerable overlap in the anatomical regions implicated in both symptom groups, including the cortex, brainstem and basal ganglia,[701,702] ii) several neurotransmitters are involved in the co-ordination of smooth movements and the maintenance of the sleep/wake cycle, including GABA, glutamate, acetylcholine and the monoamines; dopamine and serotonin, with these already

shown to also play a role in dystonia pathogenesis.[197,379,703], iii) the co-morbidity of RLS and cervical dystonia has led to speculation of shared features of dopamine abnormalities in the basal ganglia as a central underlying pathophysiology, a distinct overlap of both disorders.[333]

As outlined above, pain and mood disorders are thought to exacerbate sleep disturbances, although pain intensity and unpleasantness decreased by 50% overnight[430] and poor sleep quality persists when controlling for anxiety and depression.[332] One study found sleep impairment was correlated with severity of pain in patients with CD, supporting the notion that overactive muscles could contribute to sleep impairments.[333] In contrast, a single study found botulinum toxin (BoNT) did not improve sleep, despite improvements in motor severity,[332] and impaired sleep has been shown to persist in the absence of excess muscle activity.[337] Together, these results suggest that sleep disturbances are, at least in part, unrelated to the other aspects of the clinical phenotype (motor and non-motor) and are likely intrinsic to dystonia in a proportion of patients.

Although PSG remains the gold-standard objective measure of sleep stages, wrist actigraphy and accelerometer devices, validated to detect sleep/wake activity patterns, are increasingly being used to assess sleep parameters in movement disorders, particularly over extended time periods.[704–707] Actigraphy also has the potential to provide opportunities to optimise interventions, as well as assess the effects of medications used to manage motor symptoms in movement disorders. However, to date, no studies have used actigraphy to examine sleep quality in dystonia.

As discussed in Chapter 3, linked healthcare data allows prospective and longitudinal analysis of many chronic disorders, including multiple neurological conditions. Use of data from several sources has the potential to generate detailed information, particularly research into the aetiology and temporal patterns of non-motor symptoms which is currently lacking in dystonia. The UK Biobank (UKBB) is a large population-based study of over half a million adults which contains multiple types of detailed clinical data, including raw acceleration data, self-reported symptom questionnaires, primary care records and hospital admissions (see Section

2.4). This presents a unique opportunity to assess sleep disturbances in multiple forms of dystonia within this population, as well as examine the extent to which sleep is associated with other non-motor symptoms frequently observed in dystonia, including pain and psychiatric disorders.

In this chapter, through use of both symptom questionnaire and accelerometer data, we explore whether there is evidence of an excess of sleep disturbance in individuals diagnosed with dystonia. Secondly, we will seek to determine whether there is any relationship between patient-reported sleep symptoms and objective accelerometer-derived measures, and finally we'll seek to determine whether there is a relationship between sleep and measures of psychiatric symptoms, pain and physical activity in dystonia cohorts.

6.2 Methods

6.2.1 Data collection

Data was analysed from the UKBB (Section 2.2) (Multi-centre Research Ethics Committee [MREC] reference: 21/NW/0157) released to Cardiff University as part of project 13310. As outlined previously, the UKBB is a prospectively recruited cohort of over 500,000 adults aged between 40-69 years who were registered with the NHS. Participants who expressed the view that they would want to be withdrawn should they lose mental capacity or die were excluded. Baseline data was collected between 2006 and 2010 during face-to-face interviews and touchscreen questionnaires, including physical and cognitive measures, extensive lifestyle and health-related data (see Section 2.2). Samples of blood, saliva and urine were also collected to perform genotyping, haematological and biochemistry assays. Additional data has been incorporated into the UKBB over the years, including imaging, eye measures, tests of hearing and arterial stiffness, cardiorespiratory fitness, physical activity (acceleration) data over 7-days and completion of regular online questionnaires related to diet, occupational history, pain, cognitive function, digestive health and mental health.[708] More recently, linkage data has been obtained through electronic health-related records from the UK NHS including death, cancer and hospital admissions for the entire cohort, and primary care records are available for approximately 45% of the participants.

6.2.2 Study cohort

Individuals with dystonia were identified using International Classification of Diseases version 10 (ICD-10) codes (hospital records) or Read Code version 2 (primary care records), shown in Table 2.2. Dystonia codes were previously validated in Chapter 3 and demonstrated a sensitivity of 79%. Those with primary and potential secondary causes of dystonia were excluded, as described in Table 2.2. The control cohort were derived from participants matched for both age and gender.

6.2.3 Psychiatric symptoms and diagnoses

We identified individuals as having been diagnosed with a psychiatric disorder if their records contained a Read Code version 2 (primary care records) or ICD-10 code (Data field 41202 or 41204; hospital records) denoting a recognised psychiatric disorder. ICD-10 codes included symptomatic, mental disorders (F00-F09), mental and behavioural disorders due to psychoactive substance use (F10-F19), schizophrenia, schizotypal and delusional disorders (F20-F29), mood [affective] disorders (F30-F39), neurotic, stress-related and somatoform disorders (F40-F48), behavioural syndromes associated with physiological disturbances and physical factors (F50-F59), disorders of adult personality and behaviour (F60-F69), disorders of psychological development (F83-F89), other behavioural and emotional disorders with onset usually occurring in childhood (F98) and adolescence, and unspecified mental disorder (F99). We included primary care codes for depression, anxiety, severe mental illness (SMI; schizophrenia, schizotypal and delusional disorders, bipolar disorder, other mood-related and other severe mental illness), substance use disorder (SUD), eating disorders, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and conduct disorder. Read codes and ICD-10 codes are available in Table 3.2. Psychiatric symptoms were determined from the systematic and standardised mental health questionnaires used as part of the UKBB assessment, as has been described in previous UKBB studies.[709] Multiple questionnaires are available in the UKBB (Mental Health Questionnaire) however, we chose to focus on those outlined in Table 6.1 focusing on symptoms of depression, anxiety and tension. Possible outcomes to each question included: yes, no, and those who answered ‘Do not know’ or ‘Prefer not to answer’ were excluded

from further analysis. The other psychiatric questionnaires were not used for this analysis owing to the poor completion rate within the dystonia cohort (e.g. completion rate for the Mental Health Questionnaire was 437/1572, <30%).

6.2.4 Pain components

During an initial assessment visit, participants were asked whether they had experienced any pain in the last month (yes/no). If pain was indicated, they were then asked which bodily region was affected, followed by whether they had general body pain for more than three months (Table 6.2). Although other pain assessments are available in the UKBB (experiences of pain [Data Field: 120000 – 120127], chronic pain (>three months) including headaches [Data Field: 3799], facial pains [Data Field: 4067], neck/shoulders [Data Field: 3404], back pain [Data Field: 3571], stomach/abdominal pain [Data Field 3741], hip pain [Data Field: 3414] and knee pain [Data Field: 3773]), we used the questionnaires detailed in Table 6.2 owing to high completion rate (1565, 99.6%) and the opportunity to separate out the pain symptoms to distinct body regions.

6.2.5 Sleep behaviours

In keeping with multiple previous studies of sleep involving UKBB data, determination of sleep quality was made through responses to five self-reported sleep behaviours, with these then used to generate a sleep score,[710] detailed in Table 6.3. These were categorised as: i) chronotype, whether they consider themselves a morning or evening person: low risk: morning, high risk: evening ii) sleep duration, reported hours of sleep in 24h hours: low risk: 7-8 hours per day, high risk: <7 hours or ≥9 hours iii) insomnia: trouble falling asleep at night, low risk: never/rarely, high risk: sometimes and usually iv) excessive daytime sleepiness: likeliness to dose or sleep during the day, low risk: never/rarely or sometimes, high risk: often or all of the time v) snoring: participants who reported a partner, close relative or friend complaining about snoring, low risk: no, high risk: yes. For each low risk factor a score of one was given and the total summed, with higher scores indicating a healthier sleep pattern. Sleep patterns were defined as: healthy (≥4), intermediate (2 or 3), and poor (≤1). Participants who answered ‘Do not know’ or ‘Prefer not to answer’ were excluded from further analysis.

Table 6.1 UK Biobank questions related to psychiatric symptoms and responses

Symptom	Description	Data Field	Question	Response
Psychiatric	Mood swings	1920	Does your mood often go up and down?	Yes/No/Do not know/Prefer not to answer
	Miserableness	1930	Do you ever feel 'just miserable' for no reason?	Yes/No/Do not know/Prefer not to answer
	Irritability	1940	Are you an irritable person?	Yes/No/Do not know/Prefer not to answer
	Fed-up feelings	1960	Do you often feel 'fed-up'?	Yes/No/Do not know/Prefer not to answer
	Nervous feelings	1970	Would you call yourself a nervous person?	Yes/No/Do not know/Prefer not to answer
	Worrier/anxious feelings	1980	Are you a worrier?	Yes/No/Do not know/Prefer not to answer
	Tense/'highly strung'	1990	Would you call yourself tense or 'highly strung'?	Yes/No/Do not know/Prefer not to answer
	Worry too long after embarrassment	2000	Do you worry too long after an embarrassing experience?	Yes/No/Do not know/Prefer not to answer
	Suffers from 'nerves'	2010	Do you suffer from 'nerves'?	Yes/No/Do not know/Prefer not to answer
	Loneliness/isolation	2020	Do you often feel lonely?	Yes/No/Do not know/Prefer not to answer
	Guilty feelings	2030	Are you often troubled by feelings of guilt?	Yes/No/Do not know/Prefer not to answer
	Seen doctor (GP) for nerves, anxiety, tension or depression	2090	Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression?	Yes/No/Do not know/Prefer not to answer
	Seen a psychiatrist for nerves, anxiety, tension or depression	2100	Have you ever seen a psychiatrist for nerves, anxiety, tension or depression	Yes/No/Do not know/Prefer not to answer

Table 6.2 UK Biobank questions related to pain symptoms and responses

Description	Data Field	Question	Response
General pain for > three months	2956	Have you had pains all over the body for more than 3 months?	Yes/No/Do not know/Prefer not to answer
Pain type(s) experienced in last month	6159	Are you troubled by pain or discomfort, either all the time or on and off, that has been present for more than 3 months?	Headache Facial pain Neck or shoulder pain Back pain Stomach or abdominal pain Hip pain Knee pain Pain all over the body None of the above

Table 6.3 UK Biobank questions related to sleep disturbances and responses

Description	Data Field	Question	Response
Sleep duration	1160	About how many hours sleep do you get in every 24 hours? (please include naps)	1-23 hours, Do not know, Prefer not to answer
Morning/evening person (chronotype)	1180	Do you consider yourself to be?	Definitely a morning person, More a morning person than an evening person, More an evening person than a morning person, Definitely an evening person, Do not know, Prefer not to answer
Insomnia/sleeplessness	1200	Do you have trouble falling asleep at night or do you wake up in the middle of the night?	Never/rarely, Sometimes, Usually, Prefer not to answer
Snoring	1210	Does your partner or a close relative or friend complain about your snoring?	Yes, No, Do not know, Prefer not to answer
Daytime dozing/sleepiness (narcolepsy)	1220	How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)	Never/rarely, Sometimes, Often, All of the time, Do not know, Prefer not to answer

6.2.6 Acceleration collection and processing

Physical activity was extracted from 100Hz raw triaxial acceleration data obtained via Axivity AX3 wrist-worn accelerometers in 103,712 participants enrolled in the UKBB between June 2013 and December 2015 (see Section 2.4.1).[476] Data was collected continuously over seven days, whilst participants continued with their normal daily activities. Data was derived by processing raw accelerometer data (5-second epoch time series) from Continuous Wave Accelerometer (CWA) files, a binary format developed by Axivity. CWA files were processed and analysed using R package GGIR (version 2.3-0; http://cran.r-project.org).[478] This package allows for the estimation of the sleep period window from accelerometer data by detecting periods of non-movement using the Distribution of Change in Z-Angle (HDCZA) algorithm.

Processing of data including calibration, resampling and epoch generation has been described elsewhere (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/PhysicalActivityMonitor.pdf).[476] In brief, acceleration signals were calibrated to local gravity using stationary periods in ten second windows where all three axials had a standard deviation of <13mg. Stationary periods were then used to optimise the gain and offset for each axis to fit a unit gravity sphere using ordinary least squares linear regression. Although the accelerometer was setup to record at 100Hz, sample rates can fluctuate between 94-104Hz. Therefore, valid data was resampled to 100Hz using linear interpolation, except for interruptions lasting longer than 1 second which were set to missing. The sample level Euclidean norm minus one (ENMO) of the acceleration in the three raw signals were calculated to quantify the acceleration related to the movement registered (expressed as mg).[479] A fourth order Butterworth low pass filter with a cut-off frequency of 20Hz was used to remove machine noise. Five second epochs were generated by combining the sample level data, allowing for description of the overall level and distribution of physical activity intensity. An empirical cumulative distribution function from all available five second epochs were generated to represent the distribution of time spent in different levels of physical activity intensity.[480] Non-wear time was removed, this was defined as consecutive episodes lasting for at least 60 minutes. The same standard deviation thresholds to identify

stationary episodes were applied, as described above in the calibration process. A .csv file summarising physical activity and sleep variables for each participant were generated. We used the autocalibration feature of the GGIR package to calibrate measurements from individual accelerometers.[477] These thresholds have shown good accuracy for sleep detection without the use of a sleep diary compared to PSG.[711] Participants were excluded if they had fewer than three days recorded data (>16 hours per day) or if they failed calibration (> 0.01g). Derived sleep features and physical activity (Table 6.4) measures were average across valid days.

Table 6.4 Sleep features and physical activity and their definitions

Variable	Definition
Sleep	
Sleep onset	Median start time of sleep period, expressed as hours since the midnight of the previous night
Waking time	Median end time of sleep period, expressed as hours since the midnight of the previous night
Sleep duration	Total duration of sleep bouts during the primary sleep period
Time in bed	Difference between sleep onset and wake time
Sleep efficiency	Sleep duration/time in bed
Wake after sleep onset (WASO)	Duration of wake bouts during sleep period
Number of nocturnal sleep episodes	Number of wake bouts during sleep period
Number of naps	Number of sleep periods outside sleep period
Duration of longest sleep	Length of longest sleep bout during sleep period
Physical activity	
Overall physical activity	Average acceleration over 24-hour day in milligravity (mg)
Daytime physical activity	Average acceleration during the waking day in milligravity (mg)
Sleep time physical activity	Average acceleration during the sleep period in milligravity (mg)
Total inactive	Total minutes within waking hours spent inactive (<40mg)
Total light activity	Total minutes within waking hours spent in light activity (40-100mg)
Total moderate activity	Total minutes within waking hours spent in moderate activity (100-400mg)
Total vigorous activity	Total minutes within waking hours spent in vigorous activity (>400mg)
One-minute bouts of moderate-to-vigorous activity	Segments for which the acceleration within moderate-to-vigorous activity for one minute
30-minute bouts of inactivity	Segments for which the acceleration is defined as inactive for 30-minutes
Least active five hours	Average acceleration during the five least active hours
Move active five hours	Average acceleration during the five most active hours

6.2.7 Statistical Analysis

All statistical analyses were performed using R (version 4.0.1). Categorical data was compared between groups using chi-square test. The normality of data was examined, and all were found to deviate from the normal distribution. Mann-Whitney U tests were therefore used to assess any difference in cases and controls, with Bonferroni corrections applied for multiple comparisons. Associations between physical activity, psychiatric and pain diagnoses, and accelerometery outcomes, were assessed using linear regression analysis. Concordance between self-reported sleep properties and accelerometery-derived sleep measures were also examined using linear regression. All analyses undertaken were adjusted for age at recruitment and sex.

6.3 Results

6.3.1 Cohort

A total of 1,572 individuals were identified as having been diagnosed with dystonia (Table 6.4). The control group was formed matching to both age ($p = 0.789$) and gender ($p = 0.471$) and consisted of 24,012 participants (14,889 females and 9,123 males). For analysis of self-reported data, the dystonia cohort was split based on specific diagnoses (Table 6.5), and idiopathic familial dystonia, idiopathic non-familial dystonia and idiopathic orofacial dystonia were excluded due to their small sample sizes. The 'other' dystonia subgroup was too small to be analysed independently and was combined with the 'unspecified' subgroup for further analysis.

6.3.2 Symptomatic reported characteristics

Overall, a significantly higher number of those diagnosed with dystonia reported insomnia (cases: 80.5% vs controls: 79.4%, $p = 0.006$), sub-optimal sleep duration (<7 hours >8 hours) (cases: 38.2% vs controls: 32.1%, $p < 0.001$) and increased daytime sleepiness (4.7% and 2.9%, $p <0.001$) when compared to controls (Table 6.6). Similar patterns of sleep abnormalities were noted in dystonic tremor patients, whilst only reduced sleep duration ($p = 0.003$) was significantly different to controls in those with other/unspecified dystonia. Poor sleep patterns were observed amongst the overall cohort, and more specifically other/unspecified dystonia and dystonic

tremor subtypes ($p < 0.001$, $p = 0.04$, and $p = 0.03$, respectively). The overall cohort ($p < 0.001$), cervical dystonia ($p < 0.001$) and dystonic tremor ($p < 0.001$) cohorts were also found to have poorer sleep scores in comparison to controls.

Table 6.5 Age and gender in the overall dystonia cohort (n=1572), dystonia diagnostic subgroups and control cohort (n=24,012) for those with clinical data alone

Diagnosis	N	Age			Gender	
		Mean	Standard Deviation	Range	Male	Female
Dystonia	1,572	59	8.1	40-70	583	989
Idiopathic Familial Dystonia	3	57.9	3.5	41-68	1	2
Idiopathic Non-familial Dystonia	1	58	-	-	0	1
Cervical Dystonia	775	55.8	8.1	40-70	283	492
Idiopathic Orofacial Dystonia	6	47.7	8.8	40-64	3	3
Blepharospasm	131	60.4	7.3	42-70	40	91
Idiopathic torsion dystonia	1	47	-	-	0	1
Writer's cramp	4	53.8	2.5	51-57	1	3
Myoclonic dystonia	1	61	-	-	1	0
Tremor	488	59.6	7.7	40-70	201	287
Other Dystonia	8	54.9	5.9	47-65	2	6
Dystonia Unspecified	154	57.5	8.1	41-70	51	103
Control	24,012	59	8.1	40-70	9,123	14,889

Table 6.6 Baseline self-reported sleep pattern characteristics for both the overall dystonia group (n=1569) and control cohort (n=23,942) for those with clinical data alone

	Dystonia		**Cervical Dystonia**		**Blepharospasm**		**Tremor**		**Dystonia, Unspecified**		**Control**
	n (%)	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**
Sleep											
Insomnia	1263/1569 (80.5%)	0.006**	621/775 (80.1%)	0.210	104/131 (79.4%)	1	403/486 (82.9%)	0.011*	120/153 (78.4%)	1	18421/23942 (76.4%)
Chronotype	554/1395 (39.7%)	0.575	283/695 (40.7%)	0.495	42/118 (35.6%)	1	179/433 (41.3%)	0.845	47/131 (35.9%)	1	7997/21289 (37.6%)
Sleep Duration	594/1553 (38.2%)	$2.63x10^{-6}$ ***	267/772 (34.6%)	0.789	46/129 (35.7%)	1	208/478 (43.5%)	$7.50x10^{-7}$ ***	68/149 (45.6%)	0.003**	7639/23825 (32.1%)
Snoring	550/1423 (38.7%)	0.303	282/716 (39.4%)	0.413	44/113 (38.6%)	1	163/440 (37.0%)	1	54/136 (39.7%)	1	8029/22213 (36.1%)
Daytime sleepiness	72/1553 (4.7%)	$4.61x10^{-4}$ ***	30/769 (3.9%)	0.570	3/126 (2.4%)	1	29/481 (6.0%)	$4.03x10^{-4}$ ***	10/153 (6.5%)	0.065	683/23855 (2.9%)
Sleep Pattern											
Health Sleep pattern	402/1249 (32.2%)	$4.90x10^{-4}$ ***	208/642 (32.4%)	0.016*	34/99 (34.3%)	0.639	116/379 (30.6%)	0.011*	37/114 (32.5%)	0.350	7306/19674 (37.1%)
Intermediate sleep pattern	766/1249 (61.3%)	0.049*	397/642 (61.8%)	0.095	57/99 (57.6%)	0.939	237/379 (62.5%)	0.124	67/114 (58.8%)	1	11502/19674 (58.5%)
Poor sleep pattern	81/1249 (6.5%)	$7.67x10^{-4}$ ***	37/642 (5.8%)	0.121	8/99 (8.1%)	0.083	26/379 (6.9%)	0.030*	10/114 (8.8%)	0.042*	866/19674 (4.40%)
Sleep score	3(2-4)	$9.16x10^{-8}$ ***	3(2-4)	$4.37x10^{-4}$ ***	3(2-4)	0.517	3(2-4)	$3.01x10^{-5}$ ***	3(2-4)	0.056	3(3-4)

p-values are determined through comparison of the respective dystonia group vs control group and are represented as post Bonferroni correction for multiple comparisons
*p<0.05; **p<0.01; ***p<0.001

6.3.3 Symptomatic reported data and accelerometer data

Of the dystonia cohort, accelerometer data was available for 241 (15%) individuals with dystonia (159 female, 82 male), with the mean age at examination for this group being 58 years (Table 6.7). Due to the small sample size, the dystonia cohort was analysed as a single group. The control cohort consisted of 15,768 age- and sex-matched controls ($p = 0.07$, $p = 0.1$, respectively) (11,131 female, 4,637 male), with a mean age of 58 years. Distribution and density of accelerometer data for both cohorts are shown in Figure 6.1.

Amongst those with both symptom reported and accelerometer data, individuals with dystonia were significantly more likely to have poor self-reported sleep patterns and reduced sleep scores compared to controls (7.4% vs 3.2%, $p < 0.001$) (Table 6.8). In contrast to the entire dystonia cohort, no other significant differences were found which may be attributed to differences in cohort size. However, in keeping with the overall dystonia clinic cohort, individuals with cervical dystonia had poorer sleep patterns (9% vs 3.2%, $p <0.001$). We also observed elevated daytime sleepiness amongst those with unspecified dystonia (11.8% vs 2.2%, $p = 0.007$), whilst suboptimal sleep duration was not observed.

Accelerometer derived measures found that those with dystonia had a significantly later bedtime (cases: 23:45, controls: 23:32, $p <0.001$), spent less time in bed (7.2 vs 7.4 $p =0.002$) and reduced sleep duration (6.5 vs 6.7, $p =0.001$) compared to controls (Table 6.9). Visual outputs reported by GGIR are shown in Figure 6.2 and 6.3 for cases and controls respectively, with these providing an interpretable overview of sleep patterns and aiding in the identification of nights with poor sleep.

The accelerometer data also demonstrated that those with dystonia were less active during waking hours than controls, evident with the reduction in daytime acceleration (mg; cases: 38 vs controls 39, $p <0.001$) (Table 6.8). During the daytime, total time spent in light, moderate and vigorous activity was comparable to controls (258.8 and 260, $p =0.4$, 94.6 and 95.7, $p = 0.9$ and 2.13 and 2.31 $p = 0.17$, respectively). Inactive time and 30-minute bouts of activity were also similar between both cohorts (inactive minutes; cases: 629.6 and controls 633.8, $p = 0.84$,

322.3 and 333.89 bouts of 30-minutes activity, $p = 0.93$), both groups spent almost 6 hours of the day in 30-minute inactivity bouts.

Table 6.7 Age and gender in the overall dystonia cohort (n=241), dystonia diagnostic subgroups and control cohort (n=15,768) for those with clinical and accelerometer data

Diagnosis	N	Age			Gender	
		Mean	Standard Deviation	Range	Male	Female
Dystonia	241	57.5	7.9	40-70	82	159
Idiopathic Familial Dystonia	2	62	0	-	0	2
Idiopathic Non-familial Dystonia	-	-	-	-	-	-
Cervical Dystonia	128	56.6	7.6	41-70	47	81
Idiopathic Orofacial Dystonia	2	43	1.4	42-44	0	2
Blepharospasm	14	60	8.18	42-68	4	10
Idiopathic torsion dystonia	-	-	-	-	-	-
Writer's cramp	1	57	-	-	0	1
Myoclonic dystonia	-	-	-	-	-	-
Tremor	75	59	8.1	40-70	27	48
Other Dystonia	1	57	-	-	0	1
Dystonia Unspecified	17	57.1	9	43-69	4	13
Control	15,768	58.4	7.8	40-69	4,637	11,131

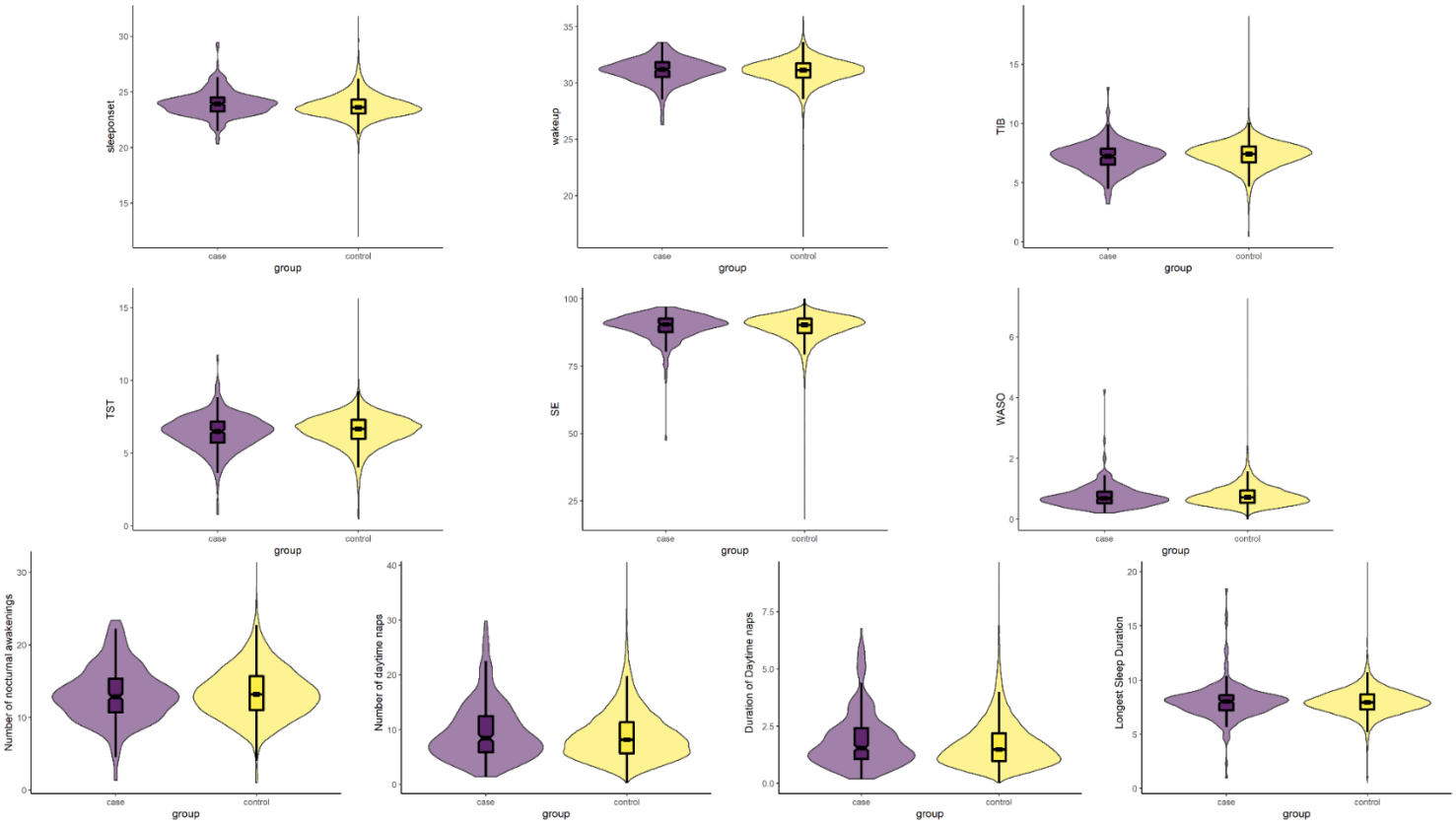

Figure 6.1 Violin plots showing density and distribution of data

Abbreviations: SE: Sleep efficiency; TIB: Time in bed; TST: Total sleep time; WASO: Wake after sleep onset

Boxplots show the median, 95% confidence interval of the median, the quartiles, and outliers. Onset of sleep expressed as hours since the midnight of the previous night. Waking time (after sleep period) expressed as hours since the midnight of the previous night

Table 6.8 Baseline self-reported sleep pattern characteristics for both the overall dystonia group (n=241) and control cohort (n=15,763) for those with clinical and accelerometer data

	Dystonia		**Cervical Dystonia**		**Blepharospasm**		**Tremor**		**Dystonia, Unspecified**		**Control**
	n (%)	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**	**n (%)**
Sleep											
Insomnia	179/241 (74.3)	0.4	95/128 (74.2)	0.53	8/14 (57.1)	0.086	63/75 (84)	0.13	10/17 (58.8)	0.08	12071/15763 (76.6)
Chronotype	89/218 (40.8)	0.09	46/115 (40)	0.3	6/13 (46.2)	0.41	29/68 (42.6)	0.21	6/15 (40)	0.7	5029/14238 (35.3)
Sleep Duration	79/240 (32.9)	0.11	46/128 (35.9)	0.054	3/14 (21.4)	0.57	25/75 (33.3)	0.33	5/16 (31.25)	0.79	4443/15727 (28.3)
Snoring	83/225 (36.9)	0.22	52/124 (41.9)	0.035	5/12 (41.7)	0.52	18/70 (25.7)	0.2	5/14 (35.7)	0.83	4857/14725 (33)
Daytime sleepiness	9/241 (3.7)	0.1	4/128 (3.1)	0.47	0/14 (0)	0.58	3/75 (4)	0.28	2/17 (11.8)	**0.007**	343/15740 (2.2)
Sleep Pattern											
Healthy Sleep pattern	79/203 (38.9)	0.48	42/111 (37.8)	0.45	6/11 (54.5)	0.38	4/63 (6.3)	0.43	5/13 (38.5)	0.83	5500/13290 (41.4)
Intermediate sleep pattern	109/203 (53.7)	0.62	59/111 (53.2)	0.63	4/11 (36.4)	0.2	36/63 (57.1)	0.78	8/13 (61.5)	0.66	7366/13290 (55.4)
Poor sleep pattern	15/203 (7.4)	**0.0008**	10/111 (9)	**0.0006**	1/11 (9.1)	0.27	23/63 (36.5)	0.16	0/13 (0)	0.51	424/13290 (3.2)
Sleep score	3 (2 – 4)	**0.05**	3 (2-4)	**0.02**	4 (2-4)	0.83	3 (3-4)	0.32	3 (3-4)	0.78	3 (3-4)

Table 6.9 Accelerometer derived estimates of sleep variables and day-time physical activity

Accelerometery	**Dystonia**	**Controls**	**p-value**
Sleep			
Bedtime	23:55 (01:14)	23:37 (01:14)	**0.0008845**
Wake-up time	07:11 (01:41)	07:08 (01:16)	0.49
Time in bed (hours)	7.24 (1.37)	7.44 (1.3)	**0.00187**
Sleep duration (hours)	6.5 (1.43)	6.7 (1.31)	**0.001**
Sleep efficiency (%)	90.5 (5)	90.4 (5.3)	0.55
WASO	0.69 (0.37)	0.72 (0.41)	0.089
Number of nocturnal awakenings	12.8 (4.67)	13.2 (4.67)	0.47
Number of daytime naps	8.47 (6.67)	8.2 (5.67)	0.098
Duration of daytime naps	1.55 (1.35)	1.48 (1.21)	0.055
Duration of longest sleep bout	8 (1.4)	8 (1.4)	0.81
Physical activity	240	15,636	
Overall physical activity (mg)	27.5 (10.15)	28.14 (10.55)	0.1299
Daytime acceleration (mg)	37.95 (14.47)	38.59 (15.03)	**<2.2e-16**
Sleep time acceleration (mg)	3.98 (1.53)	3.97 (1.68)	0.8177
Inactive time (minutes)	629.6 (149)	633.81 (130.74)	0.84
Light time (minutes)	258.77 (72.08)	260.02 (75.82)	0.4
Moderate time (minutes)	94.56 (60.61)	95.68 (58.74)	0.9
Vigorous time (minutes)	2.13 (2.9)	2.31 (3.73)	0.17
Bouts of 30 minutes inactivity	322.33 (202.11)	333.89 (193.37)	0.93
Bouts of 1-minute MVPA	38.36 (36.74)	36.71 (37.81)	0.74
Least active 5 hours (mg)	3.74 (1.68)	3.53 (176)	0.23
Most active 5 hours (mg)	58.77 (21.9)	60.35 (24.35)	0.02

Abbreviations: MVPA: Moderate-vigorous physical activity, WASO: Wake after sleep onset

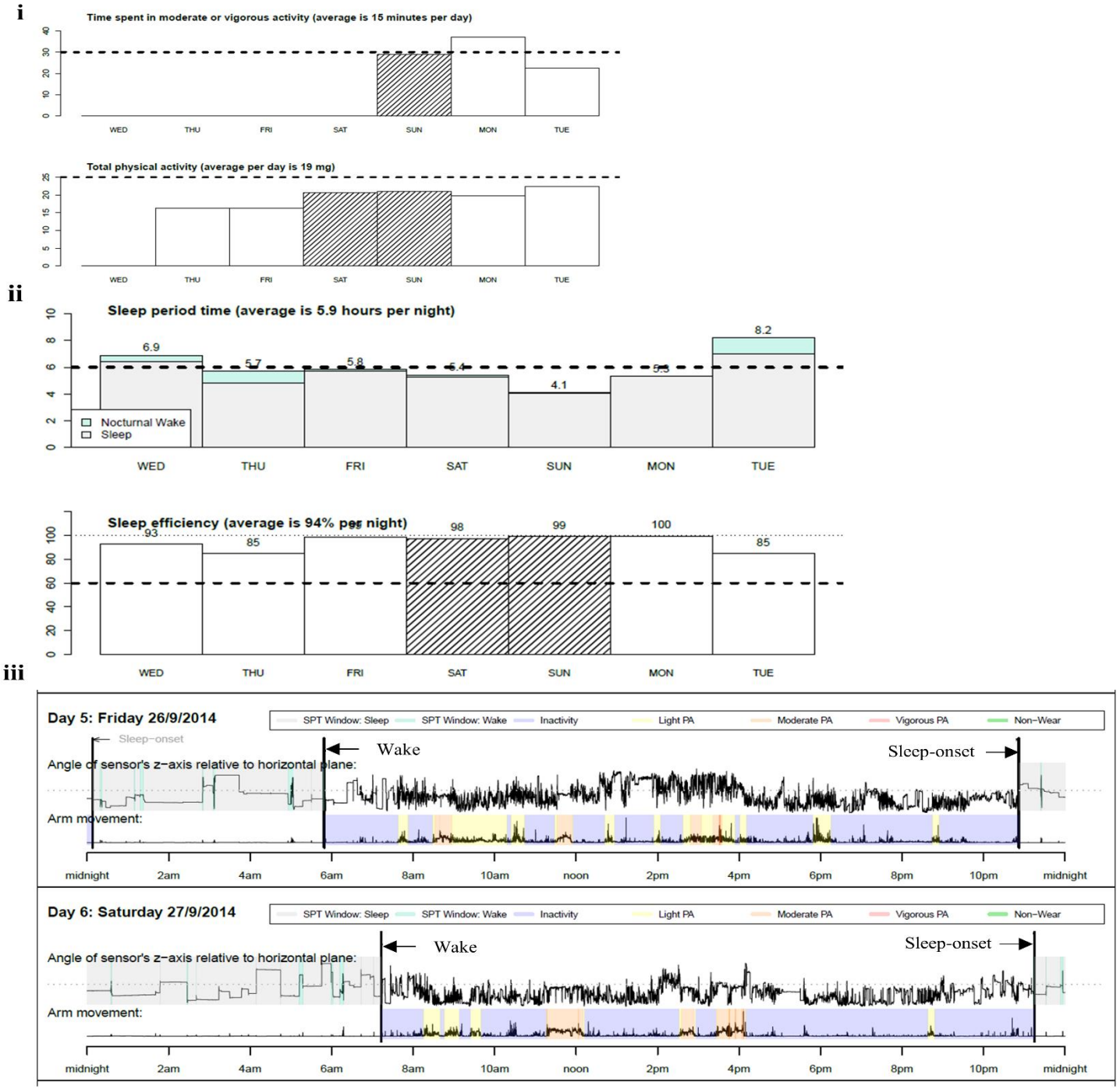

Figure 6.2 Visual output reported by GGIR in the dystonia cohort

i) Bar plots with information on key physical activity and sleep variables **ii)** Bar plots with some sleep variables **iii)** Visual summary of physical activity and sleep patterns

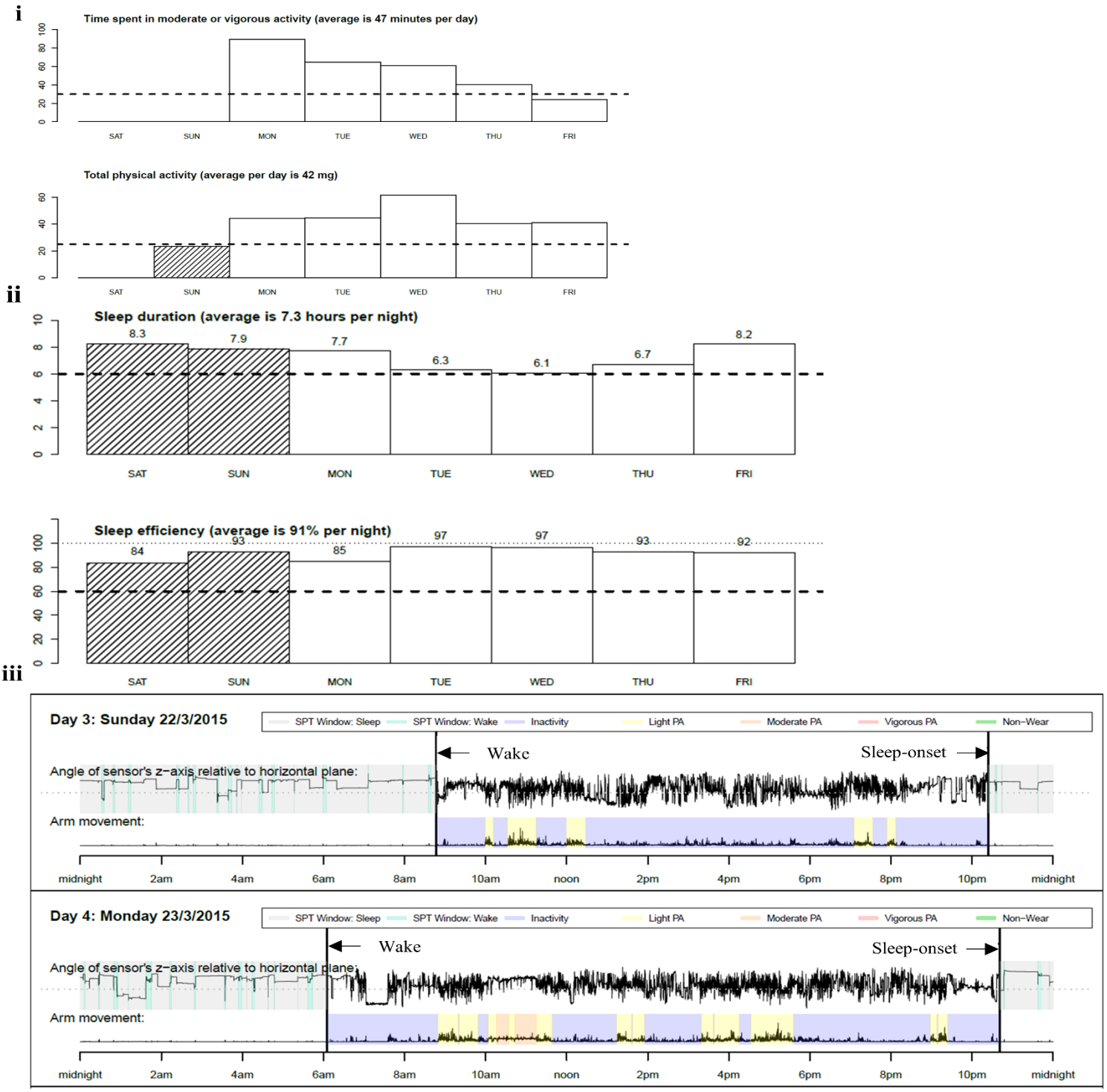

Figure 6.3 Visual output reported by GGIR in the control cohort

i) Bar plots with information on key physical activity and sleep variables **ii)** Bar plots with some sleep variables **iii)** Visual summary of physical activity and sleep patterns

6.3.4 Association between self-reported and accelerometer-based sleep variables

Linear regression analysis identified self-reported sleep variables to be weakly associated with their respective accelerometer derived sleep measures, these included self-reported chronotype with accelerometery derived sleep and wake time ($\beta = 0.3$, $p < 0.001$; $\beta = 0.2$, $p < 0.001$, respectively), as well as self-reported and accelerometery sleep duration ($\beta = 0.2$, $p < 0.001$) (Table 6.10, Figure 6.4). Other associated variables included insomnia and daytime naps ($\beta = 0.2$, $p < 0.001$), nocturnal awakenings ($\beta = -0.1$, $p = 0.02$), and sleep onset ($\beta = 0.2$, $p = 0.007$), and number of nocturnal awakenings ($\beta = 0.3$, $p <0.001$). Snoring and daytime sleepiness were not associated with any accelerometer-derived variables.

6.3.5 Association between psychiatric/pain diagnoses and accelerometery sleep variables

Number of waking naps and duration of naps were associated with a psychiatric diagnosis after adjusting for age and sex ($\beta = 2$, $p = 0.001$, 0.2, $p < 0.001$, respectively). There were no associations between self-reported pain or psychiatric symptoms and any of the other accelerometer derived sleep variables (Table 6.12, Figure 6.5).

6.3.6 Association between physical activity and accelerometery sleep variables

After adjusting for age and sex, several accelerometer-determined measures of physical activity were associated with accelerometer derived sleep measures (Table 6.14, and Figure 6.6). In those with dystonia, daytime activity was associated with earlier bedtimes ($\beta = -0.211$, $p = 0.001$), reduced number of waking naps ($\beta= -0.452$, $p <0.001$) and duration of waking naps ($\beta= -0.452$, $p <0.001$). Total time spent in light ($\beta = -0.443$, $p <0.001$ and $\beta = -0.378$, $p < 0.001$), moderate ($\beta = -0.293$, $p < 0.001$ and $\beta = -0.290$, $p <0.001$) and vigorous activity ($\beta = -0.178$, $p = 0.005$ and $\beta = -0.194$, $p = 0.002$) was associated with reduced number and duration of waking naps. 30-minute bouts of inactivity were associated with later sleep times ($\beta = 0.336$, $p <0.001$), reduced time in bed ($\beta= -0.342$, $p <0.001$), reduced total sleep time ($\beta = -0.342$, $p < 0.001$) and increased number and duration of wake time naps ($\beta = 0.6$, $p < 0.001$). Interestingly, time spent being inactive and 30-minute bouts of inactivity

were weakly associated with a reduced number of nocturnal awakenings ($\beta = -0.25$, $p < 0.001$, $\beta = -0.185$, $p = 0.003$, respectively).

Table 6.10 Associations between subjective and accelerometer derived sleep variables in dystonia cohort

Sleep variable	Sleep onset	Wake time	TIB	TST	SE	WASO	Number of nocturnal awakenings	Number of waking naps	Duration of daytime naps	Duration of longest sleep bout
Sleep duration	-0.16 [-0.29, -0.04] (0.0109)	**0.201 [0.08, 0.33] (0.0018)**	**0.338 [0.22, 00.46] (7.64e-08)**	**0.223 [0.17, 0.27] (<2e-16)**	0.089 [-0.04, 0.22] (0.34)	0.031 [-0.1, 0.16] (0.63)	**0.241 [0.12, 0.36] (0.000166)**	-0.117 [-0.24, 0.01] (0.0709)	-0.093 [-0.22, 0.03] (0.149)	0.169 [0.04, 0.3] **(0.0085)**
Snoring	-0.006 [-0.14, 0.13] (0.931)	0.05 [-0.08, 0.18] (0.454)	0.049 [-0.08, 0.18] (0.462)	0.015 [-0.04, 0.07] (0.58)	-0.041 [-0.17, 0.09] (0.54)	0.075 [-0.06, 0.21] (0.265)	0.008 [-0.12, 0.14] (0.909)	-0.067 [-0.2, 0.06] (0.31)	-0.056 [-0.19, 0.0] (0.404)	0.03 [-0.10, 0.16] (0.654)
Daytime sleepiness	0.017 [-0.11, 0.14] (0.795)	0.012 [-0.12, 0.14] (0.849)	-0.005 [-0.13, 0.12] (0.933)	-0.021 [-0.07, 0.03] (0.408)	0.039 [-0.09, 0.17] (0.548)	-0.042 [-0.17, 0.08] (0.51)	-0.073 [-0.2, 0.05] (0.257)	0.076 [-0.05, 0.20] (0.24)	0.124 [0, 0.25] (0.554)	0.109 [-0.02, 0.24] 0.092
Chronotype	**0.348 [0.22, 0.47] (1.38e-07)**	**0.177 [0.05, 0.31] (0.0088)**	**-0.1,83 [-0.31, -0.05] (0.00687)**	-0.068 [-0.12, -0.02] (0.0109)	0.059 [-0.08, 0.19] (0.388)	-0.092 [-0.23, 0.04] (0.175)	-0.076 [-0.21, 0.06] (0.262)	0.098 [-0.04, 0.23] (0.147)	0.104 [-0.03, 0.24] (0.125)	-0.102 [-0.24, 0.03] (0.133)
Insomnia	**0.18 [0.05, 0.31] (0.005)**	0.084 [-0.04, 0.21] (0.192)	-0.095 [-0.22, 0.03] (0.141)	**-0.066 [-0.12, -0.02] (0.00957)**	-0.061 [-0.19, 0.07] (0.543)	0.025 [-0.10, 0.15] (0.699)	-0.163 [-0.29, -0.04] (0.11)	**0.226 [0.10, 0.35] (0.000418)**	**0.237 [0.11, 0.36] (0.00021)**	0.075 [-0.05, 0.20] (0.25)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and symptomatic sleep. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.005)

Table 6.11 Adjusted associations between subjective and accelerometer derived sleep variables in dystonia cohort

Sleep variable	Adjusted sleep onset	Adjusted wake time	Adjusted TIB	Adjusted TST	Adjusted SE	Adjusted WASO	Adjusted number of nocturnal awakenings	Adjusted number of waking naps	Adjusted duration of daytime naps	Adjusted duration of longest sleep bout
Sleep duration	-0.19 [-0.32, -0.06] (0.00367	**0.194 [0.07, 0.32] (0.0029)**	**0.358 [0.24, 0.48] (2.54e-08)**	**0.228 [0.18, 0.28] (<2e-16)**	0.046 [-0.08, 0.17] (0.47)	0.077 [-0.05, 0.2] (0.23)	**0.296 [0.18, 0.42] (2.06e-06)**	-0.11 [-0.23, 0.02] (0.08)	**-0.096** [-0.22, 0.03] (0.1338)	**0.189 [0.06, 0.32] (0.0039)**
Snoring	-0.02 [-0.15, 0.11] (0.77)	0.035 [-0.1, 0.17] (0.60)	0.049 [-0.08, 0.18] (0.467)	0.014 [-0.04, 0.07] (0.61)	-0.063 [-0.19, 0.07] (0.33)	0.094 [-0.04, 0.22] (0.15)	0.008 [-0.12, 0.14] (0.903)	-0.029 [-0.15, 0.10] (0.65)	-0.023 [-0.15, 0.1] (0.718)	0.024 [-0.11, 0.16] (0.722)
Daytime sleepiness	0.015 [-0.11, 0.14] (0.81)	0.014 [-0.11, 0.14] (0.83)	-0.005 [-0.13, 0.13] (0.967)	-0.021 [-0.07, 0.03] (0.406)	0.032 [-0.09, 0.16] (0.61)	-0.034 [-0.16, 0.09] (0.59)	-0.058 [-0.18, 0.07] (0.356)	0.068 [-0.06, 0.19] (0.28)	0.114 [-0.01, 0.24] (0.0693)	0.116 [-0.01, 0.24] (0.072)
Chronotype	**0.348 [0.22, 0.47] (1.31e-07)**	**0.173 [0.04, 0.31] (0.0105)**	**-0.186 [0.32, -0.05] (0.0061)**	-0.067 [-0.12, -0.01] (0.012)	0.063 [-0.07, 0.19] (0.406)	-0.099 [-0.23, 0.03] (0.14)	-0.097 [-0.23, 0.03] (0.141)	0.114 [-0.02, 0.24] (0.08)	0.122 [-0.01, 0.25] (0.0671)	-0.111 [-0.24, 0.02] (0.103)
Insomnia	**0.173 [0.05, 0.3] (0.00721)**	0.08 [-0.05, 0.21] (0.21)	-0.092 [-0.22, 0.04] (0.156)	-0.069 [-0.12, -0.02] (0.007)	-0.083 [-0.21, 0.04] (0.192)	0.046 [-0.08, 0.17] (0.47)	**-0.141 [-0.26, -0.02] (0.0242)**	**0.229 [0.11, 0.35] (0.000108)**	**0.235 [0.11, 0.36] (0.00016)**	0.083 [-0.04, 0.21] (0.2)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and symptomatic sleep. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.005). Adjusted for sex and age

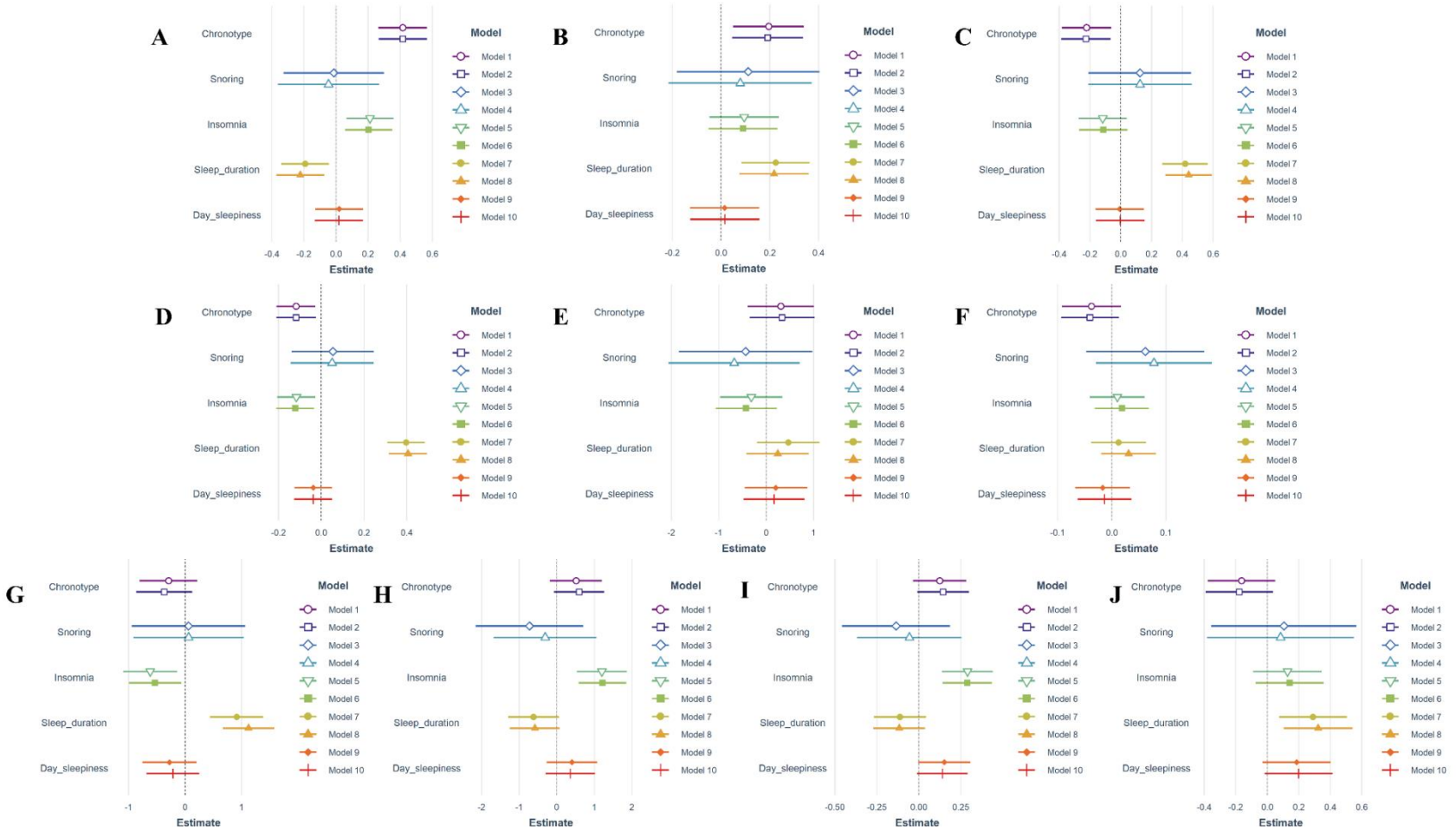

Figure 6.4 Forest plots showing linear regression models for symptomatic and accelerometer derived sleep measures

Odd numbered models are unadjusted and even numbered models are adjusted for age and sex. **A:** Sleep onset, **B:** wake time, **C:** time in bed, **D:** total sleep time, **E:** sleep efficiency, **F:** wakefulness after sleep onset, **G:** number of nocturnal awakenings, **H:** number of waking naps, **I:** duration of waking naps, **J:** duration of longest sleep

Table 6.12 Association between psychiatric diagnoses and pain and accelerometer sleep outcomes

Sleep variable	Sleep onset	Wake time	TIB	TST	SE	WASO	Number of nocturnal awakenings	Number of waking naps	Duration of waking naps	Duration of longest sleep bout
Pain	-0.022 [-0.15, 0.11] (0.73)	-0.004 [-0.13, 0.12] (0.95)	0.016 [-0.11, 0.14] (0.8)	0.015 [-0.11, 0.14] (0.82)	-0.008 [-0.14, 0.12] (0.91)	0.001 [-0.13, 0.13] (0.98)	0.057 [-0.07, 0.18] (0.38)	0.012 [-0.12, 0.14] (0.85)	0.07 [-0.06, 0.2] (0.28)	0.015 [-0.11, 0.14] (0.82)
Psychiatric diagnosis	0.126 [0, 0.25] (0.05)	0.01 [-0.12, 0.14] (0.88)	-0.113 [-0.24, 0.01] (0.08)	-0.09 [-0.22, 0.04] (0.16)	0.043 [-0.08, 0.17] (0.505)	-0.06 [-0.19, 0.06] (0.33)	-0.084 [-0.21, 0.04] (0.19)	0.157 [0.03, 0.28] (0.0146)	**0.18 [0.05, 0.31] (0.00507)**	-0.09 [-0.22, 0.04] (0.16)
Psychiatric symptom	0.078 [-0.05, 0.2] (0.23)	-0.012 [-0.14, 0.12] (0.85)	-0.086 [-0.12, 0.04] (0.18)	-0.099 [-0.23, 0.03] (0.127)	-0.074 [-0.2, 0.05] (0.25)	0.047 [-0.08, 0.17] (0.46)	-0.079 [-0.21, 0.05] (0.22)	0.094 [-0.03, 0.22] (0.14)	0.048 [-0.08, 0.18] (0.457)	-0.099 [-0.23, 0.03] (0.127)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and pain/psychiatric symptoms. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.005)

Table 6.13 Adjusted associations between psychiatric diagnoses and pain and accelerometer sleep outcomes

Sleep variable	Adjusted sleep onset	Adjusted wake time	Adjusted TIB	Adjusted TST	Adjusted SE	Adjusted WASO	Adjusted number of nocturnal awakenings	Adjusted number of waking naps	Adjusted duration of waking naps	Adjusted duration of longest sleep bout
Pain	-0.036 [-0.17, 0.09] (0.58)	-0.027 [-0.16, 0.10] (0.68)	0.008 [-0.12, 0.14] (0.9)	0.007 [-0.12, 0.14] (0.92)	-0.02 [-0.15, 0.11] (0.76)	0.004 [-0.12, 0.13] (0.96)	0.021 [-0.11, 0.15] (0.75)	0.075 [-0.05, 0.2] (0.24)	0.13 [0, 0.26] (0.04)	0.007 [-0.12, 0.14] (0.92)
Psychiatric diagnosis	0.12 [-0.01, 0.25] (0.06)	-0.005 [-0.13, 0.12] (0.94)	-0.121 [-0.25, 0.01] (0.06)	-0.098 [-0.23, 0.03] (0.14)	0.037 [-0.09, 0.16] (0.56)	-0.063 [-0.19, 0.06] (0.32)	-0.113 [-0.24, 0.01] (0.07)	**0.201 [0.08, 0.32] (0.00131)**	**0.22 [0.1, 0.34] (0.000437)**	-0.098 [-0.23, 0.03] (0.135)
Psychiatric symptom	0.069 [-0.06, 0.2] (0.29)	-0.02 [-0.15, 0.11] (0.73)	-0.086 [-0.21, 0.04] (0.185)	-0.104 [-0.23, 0.02] (0.11)	-0.093 [-0.22, 0.03] (0.14)	0.063 [-0.06, 0.19] (0.32)	-0.073 [-0.2, 0.05] (0.243)	0.113 [0.01, 0.24] (0.071)	0.061 [-0.06, 0.19] (0.33)	-0.104 [-0.23, 0.02] (0.11)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and symptomatic sleep. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.005). Adjusted for sex and age.

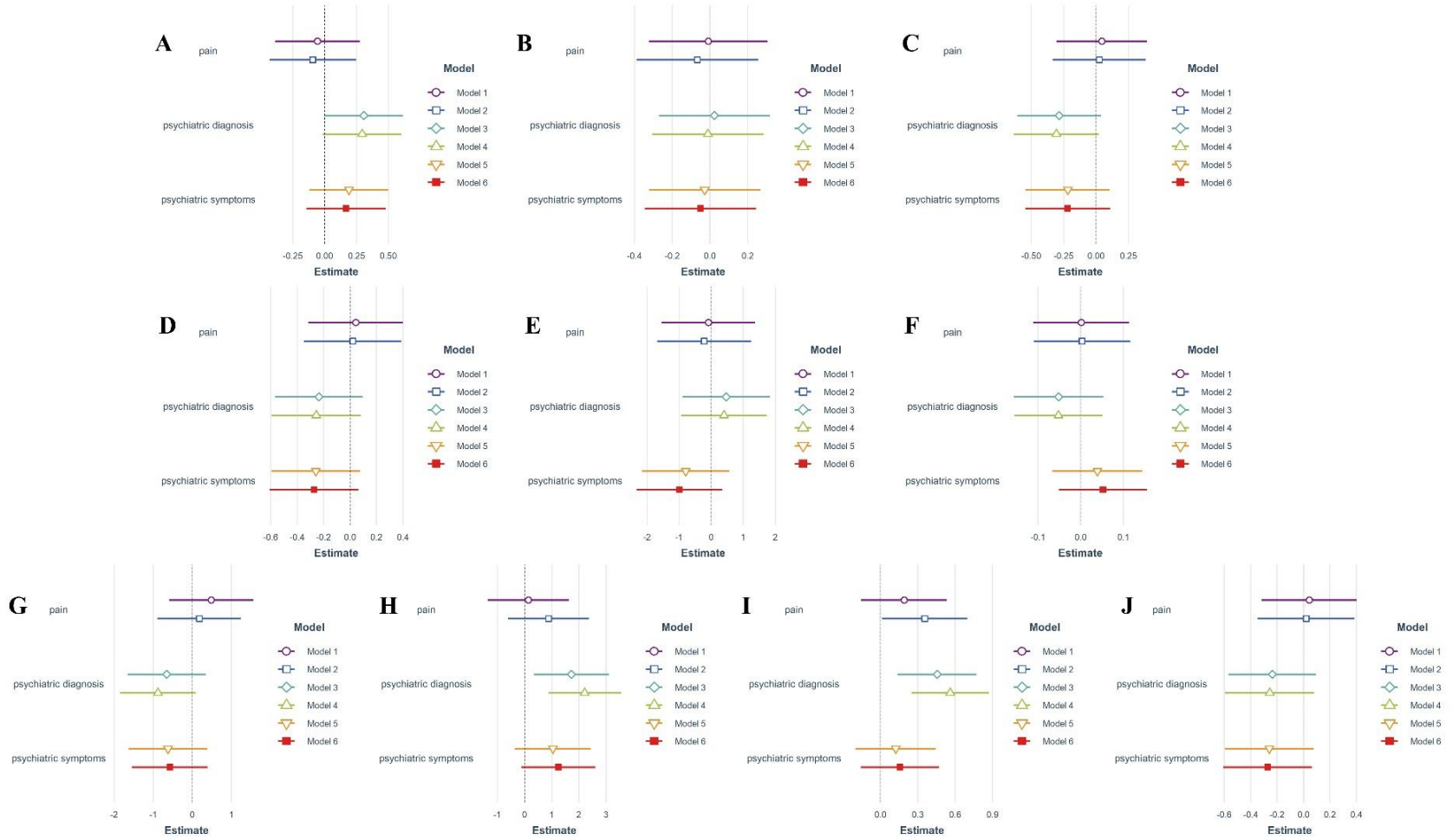

Figure 6.5 Forest plots showing linear regression models for pain and psychiatric disorders, and accelerometer derived sleep variables

Odd numbered models are unadjusted and even numbered models are adjusted for age and sex. **A:** Sleep onset, **B:** wake time, **C:** time in bed, **D:** total sleep time, **E:** sleep efficiency, **F:** wakefulness after sleep onset, **G:** number of nocturnal awakenings, **H:** number of waking naps, **I:** duration of waking naps, **J:** duration of longest sleep

Table 6.14 Association between physical activity and accelerometer derived sleep outcomes

Sleep variable	Sleep onset	Wake time	TIB	TST	SE	WASO	Number of nocturnal awakenings	Number of waking naps	Duration of waking naps	Duration of longest sleep bout
Overall physical activity (mg)	-0.092 [-0.22, -0.04] (0.156)	-0.109 [-0.24, 0.02] (0.0917)	-0.01 [-0.14, 0.12] (0.87)	-0.011 [-0.14, 0.12] (0.866)	0.018 [-0.11, 0.15] (0.78)	0.002 [-0.13, 0.13] (0.97)	0.022 [-0.11, 0.15] (0.73)	**-0.425 [-0.54, -0.31] (5.88e-12)**	**-0.406 [-0.52, -0.29] (6.01e-11)**	-0.065 [-0.19, 0.06] (0.314)
Daytime acceleration (mg)	**-0.194 [-0.32, -0.007] (0.00248)**	-0.017 [-0.14, 0.11] (0.789)	**0.171 [0.05, 0.3] (0.007)**	0.167 [0.04, 0.29] (0.0095)	0.071 [-0.06, 0.2] (0.27)	-0.001 [-0.13, 0.13] (0.985)	0.13 [0.0, 0.26] (0.04)	**-0.484 [-0.6, -0.37] (1.74e-15)**	**-0.482 [-0.59, -0.37] (2.4e-15)**	0.074 [-0.05, 0.2] (0.255)
Inactive time (minutes)	**0.369 [0.25, 0.49] (3.86e-09)**	-0.145 [-0.27, -0.02] (0.025)	**-0.48 [-0.6, -0.37] (1.59e-15)**	**-0.457 [-0.57, -0.34] (9.29e-14)**	-0.148 [-0.27, -0.02] (0.022)	-0.048 [-0.18, 0.08] (0.464)	**-0.242 [-0.37, -0.12] (0.000157)**	**0.614 [0.51, 0.71] (< 2e-16)**	**0.626 [0.53, 0.73] (<2e-16)**	**-0.272 [-0.39, -0.15] (2e-05)**
Light time (minutes)	0.035 [-0.09, 0.16] (0.592)	-0.077 [-0.20, 0.05] (0.234)	-0.103 [-0.23, 0.02] (0.11)	-0.082 [-0.21, 0.05] (0.208)	0.033 [-0.09, 0.16] (0.607)	-0.059 [-0.19, 0.07] (0.361)	-0.0.92 [-0.22, 0.04] (0.155)	**-0.443 [-0.56, --0.33] (6.19e-13)**	**-0.396 [-0.49, -0.25] (3.63e-09)**	-0.128 [-0.25, 0.0] (0.0476)
Moderate time (minutes)	-0.114 [-0.24, 0.01] (0.0783)	-0.084 [-0.21, 0.04] (0.197)	0.034 [-0.09, 0.16] (0.603)	0.03 [-0.09, 0.16] (0.612)	0.024 [-0.1, 0.15] (0.713)	0.00 [-0.13, 0.13] (0.997)	0.039 [-0.09, 0.17] (0.547)	**-0.337 [-0.46, -0.22] (8.74e-08)**	**-0.331 [-0.45, -0.21] (1.57e-07)**	-0.013 [-0.14, 0.11] (0.844)
Vigorous time (minutes)	-0.058 [-0.19, 0.07] (0.369)	0.006 [-0.12, 0.13] (0.928)	0.062 [-0.07, 0.19] (0.338)	0.075 [-0.05, 0.2] (0.25)	0.054 [-0.07, 0.18] (0.405)	-0.045 [-0.17, 0.08] (0.491)	0.136 [0.01, 0.26] (0.0359)	**-0.175 [-0.3, -0.05] (0.00663)**	**-0.199 [-0.32, -0.07] (0.00194)**	0.034 [-0.09, 0.16] (0.595)
Bouts of 30 minutes inactivity	**0.302 [0.18, 0.42] (1.93e-06)**	-0.047 [-0.17, 0.08] (0.465)	**-0.332 [-0.45, -0.21] (1.43e-07)**	**-0.216 [-0.26, -0.17] (<2e-16)**	-0.072 [-0.20, 0.05] (0.264)	-0.066 [-0.19, 0.06] (0.31)	**-0.198 [-0.32, -0.07] (0.002)**	**0.711 [0.62, 0.80] (<2e-16)**	**0.710 [0.62, 0.8] (<2e-16)**	-0.130 [-0.26, 0.0] (0.044)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and symptomatic sleep. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.007)

Table 6.15 Adjusted association between physical activity and accelerometer derived sleep outcomes

Sleep variable	Adjusted sleep onset	Adjusted wake time	Adjusted TIB	Adjusted TST	Adjusted SE	Adjusted WASO	Adjusted number of nocturnal awakenings	Adjusted number of waking naps	Adjusted duration of waking naps	Adjusted duration of longest sleep bout
Overall physical activity (mg)	-0.083 [-0.24, 0.02] (0.107)	-0.133 [-0.26, 0.00] (0.00429)	-0.019 [-0.15, 0.11] (0.78)	-0.019 [-0.15, 0.11] (0.779)	0.012 [-0.12, 0.14] (0.852)	0.001 [-0.13, 0.13] (0.98)	-0.015 [-0.14, 0.11] (0.818)	**-0.389 [-0.50, -0.27] (2.22e-10)**	**-0.372 [-0.49, -0.25] (1.96e-09)**	-0.083 [-0.21, 0.05] (0.212)
Daytime acceleration (mg)	**-0.211 [-0.34, -0.08] (0.00127)**	-0.036 [-0.17, 0.09] (0.58)	0.17 [0.04, 0.3] (0.01)	0.169 [0.04, 0.3] (0.0108)	0.075 [-0.05, 0.2] (0.246)	-0.01 [-0.14, 0.12] (0.876)	0.089 [-0.04, 0.21] (0.164)	**-0.452 [-0.56, -0.34] (7.62e-14)**	**-0.452 [-0.57, -0.34] (1.34e-13)**	0.062 [0.1, 0.2] (0.354)
Inactive time (minutes)	**0.394 [0.28, 0.51] (3.43e-10)**	-0.129 [-0.26, 0.00] (0.0474)	**-0.495 [-0.61, -0.38] (<9.39e-16)**	**-0.459 [-0.57, -0.34] (1.51e-13)**	-0.124 [-0.25, 0.00] (0.051)	-0.070 [-0.20, 0.06] (0.275)	**-0.246 [-0.37, -0.13] (7.45e-05)**	**0.588 [0.49, 0.69] (< 2e-16)**	**0.608 [0.51, 0.71] (<2e-16)**	**-0.269 [-0.39, -0.14] (3.07e-05)**
Light time (minutes)	0.014 [-0.12, 0.14] (0.838)	-0.116 [-0.17, -0.07] (0.146)	-0.10 [-0.23, 0.03] (0.132)	-0.092 [-0.22, 0.04] (0.164)	-0.013 [-0.14, 0.11] (0.837)	-0.015 [-0.14, 0.11] (0.812)	-0.051 [-0.18, 0.07] (0.42)	**-0.443 [-0.56, -0.33] (2.16e-13)**	**-0.378 [-0.49, -0.26] (1.06e-09)**	-0.133 [-0.26, 0.0] (0.044)
Moderate time (minutes)	-0.132 [-0.26, 0.00] (0.0467)	-0.111 [-0.24, 0.02] (0.095)	0.026 [-0.11, 0.16] (0.697)	0.027 [-0.11, 0.16] (0.692)	0.019 [-0.11, 0.15] (0.768)	-0.004 [-0.13, 0.12] (0.954)	-0.005 [-0.13, 0.12] (0.933)	**-0.293 [-0.41 -0.17] (3.22e-06)**	**-0.290 [-0.41, -0.17] (5.03e-06)**	-0.031 [-0.16, 0.1] (0.642)
Vigorous time (minutes)	-0.042 [-0.17, 0.09] (0.523)	0.014 [-0.12, 0.14] (0.836)	0.054 [-0.08, 0.19] (0.416)	0.083 [-0.05, 0.21] (0.214)	0.103 [-0.02, 0.23] (0.112)	-0.095 [-0.22, 0.03] (0.144)	0.081 [-0.04, 0.21] (0.207)	**-0.178 [-0.3, -0.05] (0.00525)**	**-0.194 [-0.32, -0.07] (0.00251)**	0.03 [-0.01, 0.16] (0.652)
Bouts of 30 minutes inactivity	**0.336 [0.21, 0.46] (1.85e-07)**	-0.024 [-0.15, 0.11] (0.72)	**-0.342 [-0.47, -0.22] (1.21e-07)**	**-0.307 [-0.43, -0.18] (2.5e-06)**	-0.051 [-0.18, 0.08] (0.43)	-0.085 [-0.21, 0.04] (0.19)	**-0.185 [-0.31, -0.06] (0.0035)**	**0.684 [0.459, 0.78] (< 2e-16)**	**0.69 [0.60, 0.78] (< 2e-16)**	-0.12 [-0.25, 0.01] (0.069)

Abbreviations: SE; sleep efficiency, TIB; time in bed, TST; total sleep time, WASO; wakefulness after sleep onset

Linear regression effects sizes (standardised beta coefficient), [confidence intervals (95%)], (p-value) for association between each accelerometer derived sleep measure and symptomatic sleep. Bold p-values represent significant associations as post Bonferroni correction for multiple comparisons (<0.007).

Adjusted for sex and age

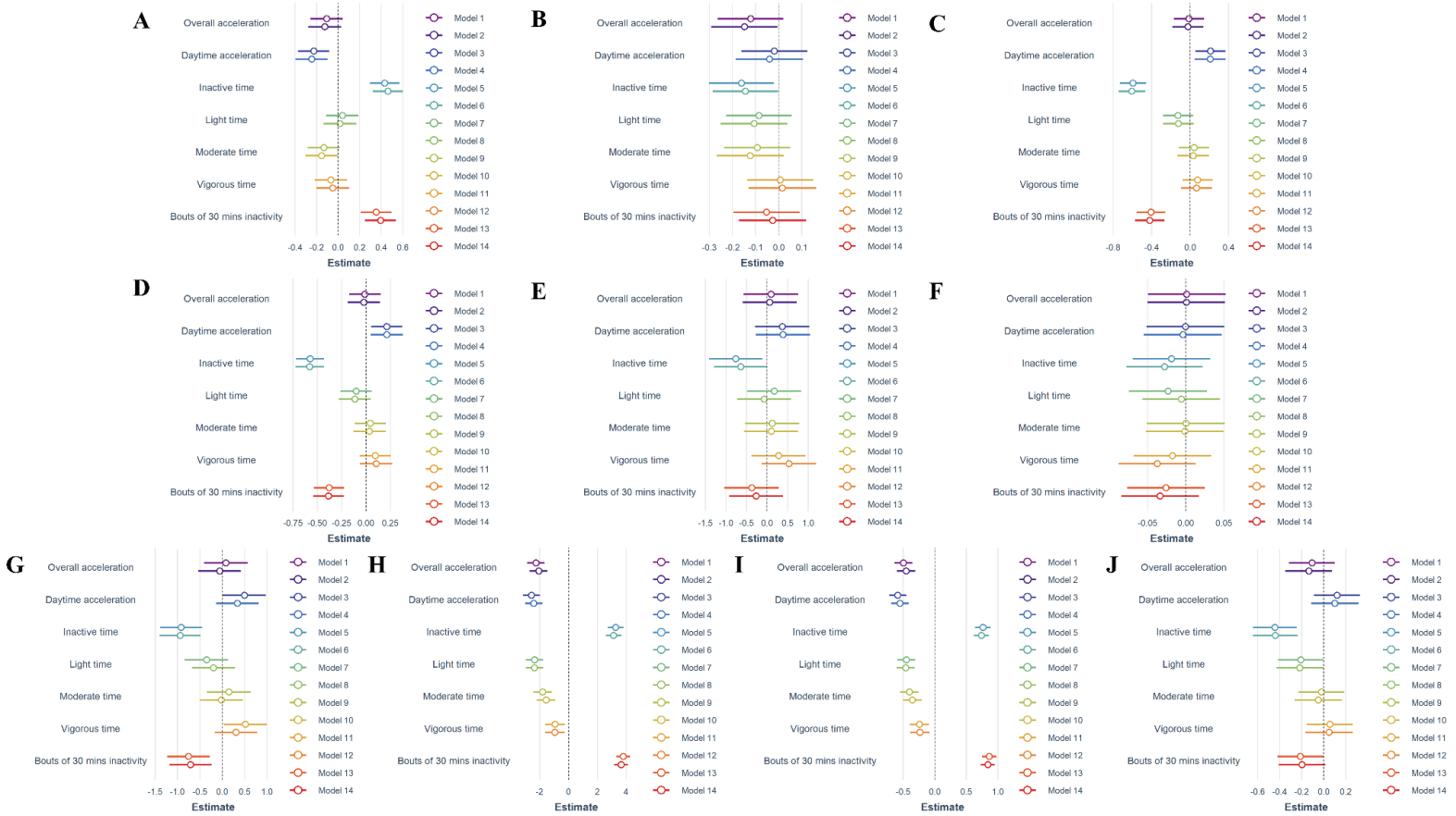

Figure 6.6 Forest plots showing linear regression models for physical activity and accelerometer derived sleep variables

Odd numbered models are unadjusted and even numbered models are adjusted for age and sex. **A:** Sleep onset, **B:** wake time, **C:** time in bed, **D:** total sleep time, **E:** sleep efficiency, **F:** wakefulness after sleep onset, **G:** number of nocturnal awakenings, **H:** number of waking naps, **I:** duration of waking naps, **J:** duration of longest sleep

6.4 Discussion

Here we have analysed the combination of participant reported sleep data alongside the more objective accelerometer measurements, to investigate whether there is any evidence for differences in sleep quality between individuals diagnosed with dystonia, and age and sex matched controls in the UKBB. Amongst the overall dystonia cohort, there was evidence of self-reported insomnia, suboptimal sleep duration (<7 hours, >8 hours), increased daytime sleepiness and poor sleep patterns in comparison to controls. These patterns were not replicated across different subtypes of dystonia: suboptimal sleep duration, increased daytime sleepiness and insomnia were noted in dystonic tremor, whilst suboptimal sleep duration was observed in the unspecified forms of dystonia. Within this dystonia cohort, accelerometer data was also captured for 241 individuals, the largest dystonia accelerometery dataset to date. Here, we found that individuals with dystonia had significantly later sleep times, reduced time in bed and shorter sleep duration, in comparison to controls. There was also evidence of poorer self-reported sleep patterns in those with dystonia, particularly cervical dystonia and increased daytime sleepiness only in the unspecified category of dystonias. Interestingly, we only found evidence of associations between psychiatric diagnoses and the number and duration of waking naps, with no other associations observed between the accelerometer derived sleep variables and symptoms of pain or psychiatric disturbance. As expected, several accelerometer-determined measures of physical activity were associated with accelerometer derived sleep measures. Daytime activity was associated with earlier bedtimes amongst those with dystonia, whilst time spent being inactive was associated with later bedtimes. Daytime acceleration was also associated with reduced number and duration of waking naps, whereas time inactive was associated with increased number and duration of waking naps, reduced time in bed, total sleep time and shorter sleep bouts. Total time spent in light, moderate and vigorous activity was associated with reduced number and duration of waking naps. We noted a weak association between time spent being inactive and periods of inactivity and a reduced number of nocturnal awakenings.

Amongst the entire dystonia cohort (n=1,572), sleep disturbances were consistently reported in the questionnaire captured dataset. In comparison to controls, there was

evidence of insomnia, suboptimal sleep duration and excessive daytime sleepiness. These findings were also observed in those with dystonic tremor, and to an extent unspecified dystonia, whereby only suboptimal sleep duration was noted. Poor sleep patterns were also evident in the overall cohort, in particular those with unspecified forms of dystonia and dystonic tremor. In contrast to previous studies, there was no evidence of sleep disturbance in those with cervical dystonia.[332,431,694] Less evidence of sleep disturbance was also observed amongst the smaller cohort (questionnaire and accelerometer sleep data (n=241)) with evidence of poorer sleep patterns in the overall and cervical dystonia cohorts, and increased daytime sleepiness in the unspecified group, compared to controls. Poor sleep patterns amongst the dystonia cohort were the only self-reported variable common to both dystonia cohorts which may be attributed to differences in cohort size. Typically, standardised sleep questionnaires such as the PSQI and ESS have been employed as screening tools in dystonia studies, in spite of them being designed to identify specific types of sleep disturbance (e.g. excessive daytime sleepiness), which may account for these differences. Further, the UKBB used only a single question for five aspects of sleep, potentially not allowing for the depth of symptom information needed to identify sleep disturbances.

To date, this is one of the first studies to have examined accelerometer data in patients diagnosed with dystonia. We found that patients with dystonia had a significantly later bedtime, reduced sleep duration and spent less time in bed compared to controls. Although PSG studies do not directly report time spent in bed, a single study has reported increased sleep latency in dystonia cohorts which could be interpreted as similar to our findings.[337] Another recent PSG study also confirmed shorter sleep duration in those with cervical dystonia compared to controls (470.52 ± 55.05 min vs 474.0 ± 73.5), however this did not reach statistical significance ($p = 0.95$).[432] Of the available PSG studies, few polysomnographic abnormalities have been reported, with the abnormalities that have been observed usually affecting sleep architecture e.g. reduced REM sleep.[337,432] Although we were unable to analyse the sleep stages in detail, these results demonstrate the usefulness of accelerometers in identifying and exploring relationships between sleep and dystonia.

Within the dystonia cohort, subjective sleep variables were associated with their respective accelerometer measure, including sleep duration and subjective chronotype, and objective sleep onset and wake time. The consistency in reported and measured outcomes is further supported by a single PSG-based study showing significant correlations between SE and sleep onset latency (SOL), and Pittsburgh Sleep Quality Index (PSQI) scores.[337] However, a mixed picture was observed as to whether sleep symptom reporting was accurately mirrored in the findings from the accelerometer measurements. The domains in which less consistency was observed may in part due to the up to 7-year interval between baseline assessment and accelerometery data capture in some cases (average 5.9 years), as well as the well-recognised differences that emerge between subjective and objective sleep measures.[712,713]

In contrast to previous literature, we found no association between pain or psychiatric symptoms and accelerometer determined sleep disturbances, although psychiatric disorders were associated with an increased number and duration of daytime naps. This finding is consistent with previous findings which have observed excessive daytime sleepiness (measured by the Epworth Sleepiness Scale) amongst psychiatric patients compared to controls.[714] Several PSG and questionnaire-based studies have shown that pain and mood disorders are associated with sleep impairment amongst dystonia cohorts,[332,432,694] with a recent review suggesting sleep quality was more prominently associated with depressive symptoms than motor symptoms.[692] It is possible that the small sample size (n =13) amongst PSG-based studies may account for the association, whilst accelerometer data may provide a balance between accuracy and cohort size. Further, the rate and severity of the psychiatric/pain symptoms may have altered during the 7-year interval between baseline self-reported behaviours and the period of accelerometer data capture. Alternatively, sleeping patterns may have changed, especially as we did not account for seasons at time of accelerometer data collection. Further studies involving concordant sleep symptom and accelerometer data capture are needed, as well as adjustments for seasonal variation and therapies used in the management of the motor symptoms of dystonia.

We found several associations between physical activity and accelerometer-derived sleep measures in the dystonia cohort. Our findings are consistent with existing evidence suggesting strong associations between physical activity and sleep.[715] Time spent in moderate activity was 95 minutes/day which is higher than expected, world health organisation (WHO) recommend 150 minutes/week,[716] but this may capture sporadic arm movements which cannot be separated from true physical activity. For this reason, it is sometimes more informative to evaluate bouts of activity however, 1-minute bouts of moderate-vigorous physical activity (MVPA) and 30-minute bouts of inactivity did not differ between the dystonia cohort and controls. However, within the dystonia cohort bouts of inactivity were significantly associated with later sleep time, reduced TIB, TST, reduced number of nocturnal awakenings and an increased number and duration of daytime naps. However, the latter may reflect the limitations of defining inactivity using accelerometers (i.e. periods of inactivity may be incorrectly identified as naps). Future studies investigating physical activity profiles in dystonia cohorts may be helpful in further refining these findings.[717–719] Taken together, these findings suggest that physical activity can promote healthy sleep in those with dystonia, although we cannot rule out reverse causality where healthy sleeping habits promote a more active lifestyle, further work will be needed to better understand this association.

Whilst this study benefits from the extensive longitudinal information collected on a large scale within the UKBB, as well as allowing for accelerometer derived sleep measures, there are several limitations that need to be considered. Firstly, the UKBB is a volunteer-based sample and is not likely to represent the general population.[720] Since the individuals with dystonia volunteered to participate, it is possible that they experience fewer symptoms that would interfere with participation, potentially not providing a representative example of individual diagnosed with dystonia in the wider population. This is particularly relevant in the context of sleep disturbance as those who experience more severe dystonic symptoms may experience increased sleep impairments.[432] Secondly, individuals who volunteered to wear the accelerometer device may have deemed themselves more likely to tolerate the device and therefore have fewer sleep impairments which again may have biased the results. Thirdly, we also excluded individuals with potential neurological causes of dystonia, which may have biased the control cohort as there is mounting evidence linking

sleep disorders and neurological disorders more widely.[721] Fourth, the accelerometer-based sleep measurement is not as accurate as the gold-standard polysomnography which may account for the relatively high median sleep efficiency. Several newer algorithms allow for modelling of more complex sleep parameters by using accelerometers alongside PSG, as well as incorporating variables such as heart rate and pulse oximetry.[493,722] Lastly, we were unable to confirm a clinical diagnosis due to the anonymity of the dataset, diagnoses were only confirmed by self-report, therefore it is possible that we included a proportion of individuals without dystonia. However, we sought to address this by using a published algorithm to identify dystonia cases from within both primary and secondary care data sets which has been shown to have a sensitivity of 79% in identifying those with dystonia (see Section 3.2.3, Figure 3.1).[723]

The present findings add to a growing body of evidence of sleep disturbances in individuals diagnosed with dystonia, as well as demonstrating the capacity of accelerometry measurements in providing more detailed information about sleep patterns at scale. Individuals with dystonia were found to go to sleep earlier, spend less time in bed and shorter sleep duration compared to controls, highlighting the need for sleep disturbances to be considered as part of routine clinical assessment. However, although accelerometery was able to identify sleep impairments in dystonia, using this approach we were unable to examine in detail sleep architecture such as REM and NREM sleep. Monitoring of sleep may also be important for prevention and treatment of non-motor symptoms in dystonia, particularly as inactivity was associated with poorer sleep architecture. Our findings provide a platform for future investigations including patterns of physical activity, sleep and sedentary behaviour in dystonia. Future studies should address the association between sleep, mental health and pain, as well as employing a longitudinal study design to examine how sleep parameters vary across neurotoxin treatment cycles in dystonia.

7 Sleep in cervical dystonia: an evaluation using subjective and objective measures

7.1 Introduction

As outlined in Chapters 5 and 6, sleep plays a vital role in maintaining health, as well as contributing to a high quality of life.[724] Poor sleep is associated with reduced cognitive function and can contribute to multiple psychiatric and medical disorders, including depression, anxiety, cardiovascular disease and diabetes mellitus.[725] As discussed in Chapter 5 (section 5.3.1), polysomnography (PSG), a laboratory-based, overnight sleep study involving electroencephalography (EEG), electrooculogram (EOG), and electromyogram (EMG), represents the 'gold standard' means of determining sleep structure and sleep quality, as well as objective measures of NREM and REM sleep stages (see section 5.2). However, PSG can be expensive and time consuming, with limitations in being able to extrapolate findings from single night recordings in an unfamiliar environment to the wider context of sleep. Sleep questionnaires and diaries are inexpensive and easily used on a large scale. However, for frequent behaviours such as sleep, people are unlikely to be able to recall specific details of sleep episodes unless they are irregular behaviours. Instead, they rely on retrospective recall and estimations which are subject to error (e.g. rounding to the nearest hour or half-hour) and reporting biases.[726] Agreement between sleep diaries and PSG is acceptable (kappa = .87), with high sensitivity and specificity (92.3% and 95.6%) demonstrated,[727] with a week of sleep diaries sufficient to achieve adequate stability of sleep variables amongst older adults.[728] The sleep diary is a useful tool, but should be used with caution due to the differences observed in age groups, ethnicity, depressive symptoms and use of medication that affects sleep.[729]

Given the chronic nature of dystonia, greater understanding of sleep in these patients, particularly any potential disruption to normal sleep patterns would require a monitoring system that was low-cost, minimally intrusive and requires minimal input from the patients themselves. In recent years, wrist-worn sensors have become widely available and increasingly affordable. Actigraphy is a simple non-invasive device that measures body movement (to estimate sleep parameters), usually worn on the non-dominant wrist. The accelerometer outputs an analogue electrical voltage in response to motion, which is sampled at a specific frequency, with the data then processed to obtain information relating to movement frequency, duration and intensity.[730] Dependent on the device, acceleration data can be stored in several different modes: i) Zero Crossing Mode (ZCM), which measures how many times

per minute the voltage signal crosses a threshold value (usually close to zero) ii) Time Above Threshold (TAT) indicates the amount of time per epoch that the signal is above a set threshold iii) proportional integration mode (PIM), also known as digital integration, calculates the area under the curve for each epoch or iv) raw acceleration.[731]

The introduction of functions such as measures of heart rate and heart rate variability, light detectors, and high-resolution movement sensing through triaxial accelerometers make accelerometers an attractive alternative to polysomnography (PSG) to undertake analysis at a larger scale and outside of the setting of a sleep laboratory. Advanced devices use microelectromechanical systems (MEMS), yielding raw triaxial accelerometery at high sample rates, involving linear acceleration along three refence axes allowing an accurate reconstruction of the movement and position.[732] However, the accuracy depends on the quality of the sensor and the performance of the algorithms in scoring sleep by sensed movement.

Although there is no recommended specific sleep/wake scoring algorithm, several have been developed. Actigraphy has high sensitivity in detecting sleep (0.87 – 0.99) but lacks specificity (0.28 – 0.67).[733] Early validated methods most commonly used to process actigraphy data focus only on correlation and accuracy of a given device (e.g. Webster algorithm, Sadeh algorithm and Cole-Kripe algorithm).[734–736] Although these demonstrate high rates of agreement in comparison to PSG, large differences between devices persisted and sensitivity and specificity measures were not assessed.[734] Further, these algorithms use pre-processed data onboard the device as a 30-second aggregate known as an activity count. In the mid-2000s, technological advances resulted in a new generation of accelerometers which were sensitive to gravitational acceleration, enabling unprocessed data to be stored in the device and processed offline. As a result, the next generation of algorithms aimed to improve actigraphy scoring by using raw triaxial sensor data, in turn allowing for improved sensitivity and reduced variability between different devices. Access to raw data has increased the ability to standardise analysis across studies, allowing a more meaningful comparison. Machine learning techniques have also been incorporated into the latest algorithms, allowing for optimisation of models through use of a training phase. Utilisation of these dedicated algorithms outputs a range of variables

including total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), fragmentation index and number of awakenings, whilst newer algorithms enable differentiation of sleep stages, such as REM and NREM.[737]

A promising example of a sleep staging technique uses cardiac activity, most notably heart rate (HR) or heart rate variability (HRV). Cardiovascular functions play an essential role in sleep and differ when transitioning into and out of sleep, and between different sleep stages. Transitions between wake, NREM and REM are accompanied by changes in HRV characteristics including HR, Low-Frequency power, High-Frequency power and LF/HF ratio (low-to-high frequency ratio which can be used to quantify the changing relationship between sympathetic and parasympathetic nerve activities i.e the degree of sympatovagal balance). HRV-based algorithms allow three or four sleep stage classifiers, and demonstrate encouraging results compared to PSG.[493,722,738,739] The majority of algorithms are developed using ECG data, with the potential to apply this technique using alternatives such as photoplethysmography (PPG) in wrist-worn devices. PPG is widely used in consumer devices, however in many of these devices it is not possible to access the raw PPG data. To date, only two studies have incorporated raw PPG signals to develop sleep staging algorithms in healthy participants,[493,738] whilst a third has trained and validated their algorithm in individuals diagnosed with a sleep disorder.[740]

As with any technique, actigraphy has its own limitations. Although standard devices have been extensively validated against PSG, they tend to overestimate sleep parameters including total sleep time and sleep efficiency.[741] In general, actigraphy also shows poor accuracy for determining sleep stages, compared to PSG, for example the Fitbit Surge demonstrated 69% and 62% accuracy with light and deep sleep respectively, and 72% for REM sleep.[738] Actigraphy devices (Actiwatch Spectrum), specific for motion detection, demonstrate slightly improved accuracy values: 65.7% for N1 and N2, 82.5% for N3, and 75.3% for NREM and 78.9% for REM.[739] However, other difficulties exist, with one of the most prominent limitations in actigraphy research being the lack of agreed data-processing algorithms or protocol, resulting in inconsistent reporting of sleep parameters across

the literature. Finally, many companies employ their own algorithms and only offer processed data such as steps, sleep onset and offset. The algorithms are often not published in detail, further compromising generalisability between studies.

Actigraphy-based research to date has focused on developing and validating actigraphy models in healthy controls, although the outcomes of these are often not generalisable in the investigation of disease, and in particular movement disorders.[742] These more specific difficulties relating to movement disorders are caused by disorder-related motion that produces data then scored as being awake, when PSG recordings would classify it as sleep, underestimating total sleep time and sleep efficiency. In spite of this, there have been several studies that have used actigraphy in the study of movement disorders, with this work aimed at: i) investigating validity, ii) identifying sleep disorders, iii) evaluating treatment monitoring and iv) potential use as diagnostic aids (e.g. RBD in Parkinson's disease). These findings have been discussed in a recent literature review in Parkinson's disease,[743] results for other movement disorders are shown in Table 7.1.

Coupled with actigraphy, longitudinal monitoring can also be achieved using Patient-Reported Outcomes (PROs) or Patient-reported Outcome Measures (PROMs). Here participants are prompted to complete questionnaires capturing disease specific symptoms using standardised questionnaires. The use of PROs can lead to improved patient communication with care providers, engagement, satisfaction, and better health outcomes by capturing the dynamic changes in symptomology whilst fully capturing the patient's own perceptions and experiences not always addressed in a clinical setting. However, this approach is often more complex in individuals diagnosed with neurological disorders due to potential limitations in their ability to interact with these assessment measures although previous work has generally shown high rates of feasibility and adherence (77%).[744] One example of a PROs in sleep studies are sleep diaries, recommended as the gold standard for subjective sleep monitoring, and are typically completed over a one week period.[745] However, as previously mentioned, sleep diaries are usually limited by relying on an individual's ability to estimate their own sleep times, and similar to other PROs, are prone to recall bias.

This study seeks to undertake a more detailed investigation of sleep in the largest cohort of individuals diagnosed with AOIFCD to date. Using a mobile application (app) (Oxygen by Aparito), we assessed the feasibility of remote measures using smartphones and smartwatches in people diagnosed with AOIFCD compared to unaffected controls. The app receives recorded sensor data during daily life, as well as delivering a comprehensive collection of self-administered PROs to capture motor and non-motor symptoms related to dystonia. These include questionnaires relating to sleep and other non-motor symptoms such as pain, anxiety and quality of life. Our primary objective was to identify sleep disturbances in individuals with AOIFCD by comparing the accelerometer determined sleep-variables to controls, as well as to evaluate the concordance between the subjective PROs and objective accelerometer measures amongst the cohorts.

Table 7.1 Actigraphy in movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Huntington's disease	Hurelbrink et al	2005	HD (8) HC (8)	Actiwatch-Neurologica, ESS, Huntington's Disease Sleep Scale, PDSS, sleep diary	Patients showed more activity and high acceleration movements. Actigraphy was cable of assessing movements in HD patients during sleep
Huntington's disease	Goodman et al	2010	HD (9) HC (10)	vPSG, Actiwatch, ESS, Functional Outcomes of Sleep Questionnaire, Medical Outcomes Study Scale, Horne Ostberg	PSG confirmed actigraphy findings;
Huntington's disease	Lazar et al	2015	HD (38) pre-manifesting gene carriers HC (36) age- and sex-matched	2 nights of PSG, MSLT, Actiwatch, sleep diaries	Actigraphy did not show any differences in sleep parameters compared to controls, although PSG did detect sleep abnormalities
Huntington's disease	Townhill et al	2016	HD (13) HC (9)	Actiwatch, EEG, sleep diary	All periods of sleep agreed with the Actiwatch, however, periods of night-time wakefulness agreed poorly with EEG recordings, whereby multiple periods of wakefulness demonstrated by the Actiwatch corresponded to sleep periods on the EEG

Huntington's disease	Maskevich et al	2017	HD (7) gene carriers	PSG, Jawbone UP2, Fitbit One, Actiwatch Spectrum Pro, PSQI, ISI	In comparison to PSG, all three devices significantly overestimated total sleep time and sleep efficiency, whilst Jawbone UP2 and Fitbit underestimated wake after sleep onset. Watches were highly sensitive in determining sleep but low specificity in identifying wake
Huntington's disease	Bartlett et al	2019	HD (32) pre-manifesting HC (29) age- and sex-matched	Sleep diary, GT3X+ ActiGraph, PSQI, ESS	Pre-manifesting HD individuals exhibited decreased sleep efficiency and increased number of awakenings and wake after sleep onset compared to controls. No evidence of associations between hypothalamic volume and circadian rhythm
Progressive Supranuclear Palsy	Walsh et al	2016	PSP (17) HC (17)	Micro SleepWatch, Action4, sleep diary	Compared to controls, PSP patients had significantly reduced percentage sleep during up and increased during down periods, with reduced down period duration and increased fragmentation during this period
Dementia Lewy Body	Kanemoto et al	2020	DLB (22)	Actiwatch-L, sleep diary	Total sleep time and body activity during sleep wee associated with severity of hallucinations in patients with DLB

Dystonia-parkinsonism	Leu-Semenescu et al	2010	Generalised dystonia-parkinsonism (1) sepiapterin reductase deficiency	Actiwatch-Mini, PSG, sleep interview, sleep diary, ESS	Actigraphy showed marked changes in more regular sleep following treatment. Prior to treatment sleep-wake period was 11.8 ± 5.3 hours
Tourette's Disorder	Ricketts et al	2021	TD (14) HC (20) age- and sex-matched	Actiwatch, sleep diary, Diagnostic Interview for Sleep Patterns and Disorders, PSQI, Morningness-Eveningness Questionnaire-Revised, ESS	Adults with TD exhibited significantly longer sleep-onset latency, lower sleep efficiency and greater sleep fragmentation than healthy controls. Following morning light therapy, actigraphy demonstrated no change in sleep variables
Anti-IgLON5	Gaig et al	2019	IgLON5 (4) HC (9)	v-PSG, MSLT, actigraphy	Actigraphy showed a 10-fold increase in nocturnal activity compared to controls. Decrease in nocturnal activity was observed following treatment

Abbreviations: DLB: Dementia with Lewy Body, EEG: Electroencephalogram, ESS: Epworth Sleepiness Scale, HC: Healthy control, HD: Huntington's Disease, ISI: Insomnia Severity Index, MSLT: Multiple Sleep Latency Test, PD: Parkinson's Disease, PDSS: Parkinson's Disease Sleep Scale, PSG: Polysomnography, PSP: Progressive Supranuclear Palsy, PSQI: Pittsburgh Sleep Quality Index, SCOPA-S: Scales for Outcomes in Parkinson's Disease – Sleep, TD: Tourette's disorder

7.2 Methods

7.2.1 Participants

Participants diagnosed with AOIFCD and those with no known neurological deficits (control cohort) were recruited via the Welsh Movement Disorders Research Network (see Section 2.2). Standardised questionnaires were used to collect baseline clinical information, including sex, date of birth, current medication use and receipt of any ongoing treatment with botulinum toxin injections (BoNT) (Appendix 5 Q1-Q14). Participants were required to own an Apple iPhone, with this being required owing to poor data capture with the use of Android devices. Participants were reimbursed for their time with a one-off £10 Amazon voucher.

7.2.2 Study design

PROs were answered via a mobile application (app, Oxygen by Aparito). Participants received a notification when PROs for each 24-hour period became available. The wearable device (Vivosmart 4, Garmin) was also paired to the app, allowing wearable data to sync to the mobile via Bluetooth. To encourage the syncing of the data, PROs were strategically placed throughout the day. The frequency of the PROs are shown below in Figure 7.1.

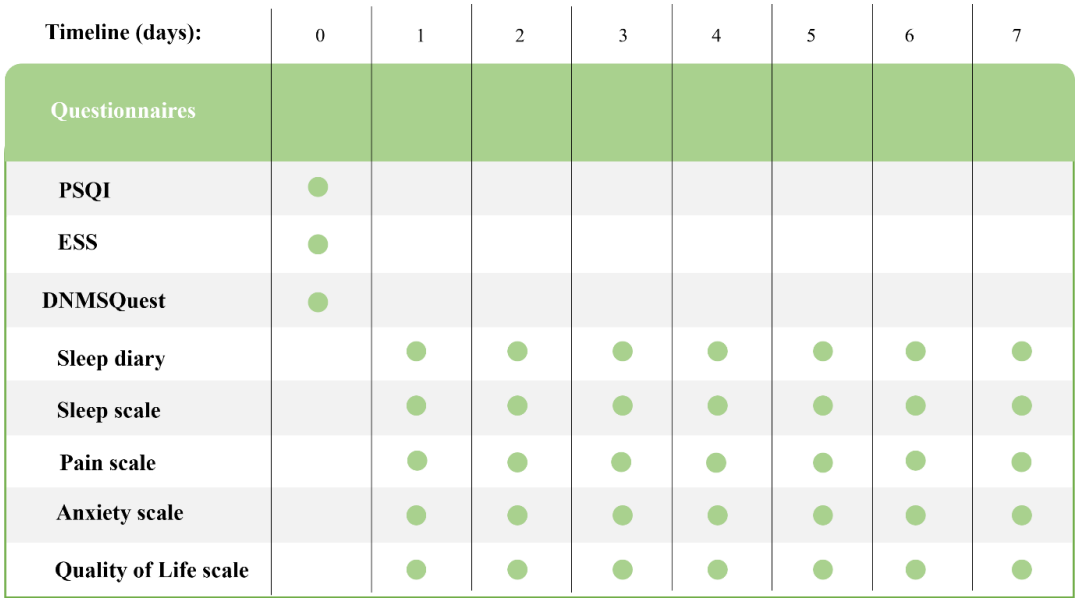

Figure 7.1 Frequency of questionnaires

Abbreviations: DNMSQuest: Dystonia Non-Motor Symptoms Questionnaire, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index

7.2.2.1 Sleep and non-motor questionnaires (PROs)

The study design and questionnaires are described in more detail in Section 2.5.3.

Pittsburgh Sleep Quality Index (PSQI)

Quality of sleep was measured by the Pittsburgh Sleep Quality Index (PSQI), a widely sleep questionnaire used to assess sleep quality and disturbances relating to sleeping habits during the past month.[489,490] In addition to differentiating 'poor' from 'good' sleepers (>5 indicates poor sleep quality), it also measures seven components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction based on a 0 to 3 scale.

Epworth Sleepiness Scale (ESS)

Excessive daytime sleepiness was assessed by means of the Epworth Sleepiness Scale (ESS), participants are instructed to rate the chances of dozing/falling asleep during eight different activities, with each item based on a 0 to 3 scale.[491] A score of 11 or more is considered suggestive of excessive sleepiness.

Dystonia non-motor symptoms questionnaire (DNMSQuest)

Non-motor symptoms were measured using the dystonia non-motor symptoms questionnaire (DNMSQuest), a 14-item self-completed questionnaire examining sleep, autonomic symptoms, fatigue, emotional well-being, stigma, activities of daily living and sensory symptoms.[492] Four questions directly relating to dystonia were removed for the control cohort (Q7 "Do you suffer from loss of self-confidence due to stigma of visible dystonia?", Q10 "Do you experience unpleasant sensations such as numbness, tingling or pins and needles in the body area or nearby the body area of your dystonia?", Q12 "Does your dystonia affect your vision?", Q13 "Do you suffer from pain of the body area or near to the body area of your dystonia?"). For these questions, controls were given '0' meaning that total score remained out of 14 for controls.

Sleep diary

A useful tool in identifying sleep habits, self-reported questions included time of going to bed, approximately how long it took them to fall asleep, how many times

they woke in the night and the duration of the wakeful period, the time they woke in the morning and the time they rose in the morning.

Visual Analogue Scales (VAS)

Following initial standardised baseline questionnaires, daily experience of sleep, pain, anxiety, quality of life for the day before was obtained using a scale (1 – 10). Daily questions included: Last night, how well did you sleep (1 being poor, 10 being good)? Yesterday, how much pain did you experience (1 being no pain, 10 being the worst pain possible)? Yesterday, how anxious were you (1 being no anxiety, 10 being extremely anxious)? Yesterday, to what extent did your physical health or emotional problems interfere with your normal social activities? (1 being no interference, 10 extreme interference)?

Wrist-worn device

Participants wore a consumer-grade, MEMS triaxial accelerometer wearable (Vivosmart 4, Garmin) (Figure 7.2) on their non-dominant wrist for seven days, coinciding with the sleep diary and non-motor symptoms recording. Devices were worn continuously, except for charging during which the device needed to be removed. A maximum of ten hours non-wear time was acceptable to meet the minimum requirement of fourteen hours of recorded data. Although there is little consistency of the recommended daily wear time, a common approach is to require ten or more hours/day of wear time to be considered valid day, with sixteen hours being the upper limit. However, some research suggests a minimum wear of thirteen hours/day should be implemented.[746] Data was sampled at a rate of 1Hz. In addition to triaxial acceleration, heart rate, step count and pulse oximetry were recorded.

Figure 7.2 Garmin Vivosmart 4 wearable device

7.2.3 Sleep/wake algorithm

Details of the published algorithm and datasets used to determine sleep stages in the data captured in this study are described in Sections 2.2.5 and 2.2.6. In brief, the training of the model was done using either the 7-14 days of raw triaxial acceleration and heart rate data obtained from Walch et al. (2019) (n= 31)[493] or the 7 days of actigraphy-derived activity counts and heart rate derived from PSG data accessed from the Multi-ethnic Study of Atherosclerosis (MESA) dataset (n = 1,835).[494,495] Due to differences in cohort size, both datasets were tested to compare the impact of sleep/wake and sleep stage detection.

7.2.4 Predictive models

Four commonly used machine learning algorithms were utilised using Python's sklearn (version 0.20.3) to compare different classification algorithms, these included logistic regression, *k*-nearest neighbours, random forest and neural net. Details and hyperparameters of the classifiers can be found in Section 2.5.7.

7.2.5 Algorithm training/validation

Training and testing of the models has been described in Section 2.5.8. Briefly, models were trained and tested using Monte Carlo cross-validation, the dataset was randomly split 50 times into a training set (approximately 70% of the subjects) and testing set (~30%). Receiver operating characteristics (ROC) curves and precision-recall curve demonstrate the ability of each algorithm, each curve represents the

average across all 50 training and test sets. Higher area under the ROC curve (AUC) suggests that the model is better able to distinguish classes. Bland-Altman plots visualise the differences between classifier and PSG values (*y*-axis) versus PSG values (*x*-axis).

7.2.6 Performance measures

Agreement between the predicted classes and PSG sleep stages were assessed using accuracy, AUC and Cohen's kappa coefficient of agreement (κ). When calculating kappa, the true positive rates for the binary classes (sleep/wake) and accuracy values for the three classes (wake/NREM/REM) were used as the threshold values. In the three classes, kappa was calculated using the average over the data splits of the kappa value using the thresholds that generate the highest accuracy (kappa).

7.2.7 Data processing and analysis

Triaxial data was pre-processed, filtered and calibrated by Garmin. Outcomes were averaged across valid days. We derived sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE), REM sleep minutes and NREM sleep minutes from our raw triaxial acceleration and heart rate data using Walch's algorithm.

7.2.8 Statistical analysis

Walch's algorithm was written and ran using Python (Python Software Foundation, http://www.python.org). The overall score of baseline standardised questionnaires (PSQI, ESS and DNMSQuest) were compared using a *t*-test or Mann-Whitney U. Mean scores of sleep measures from the wrist-worn device and sleep diary were calculated per participant and compared between groups using a Mann-Whitney U test.[498–502] Agreement between sleep measures derived from the wrist-worn device and sleep diary were assessed using Bland-Altman plots and intraclass correlation coefficient (ICC) and compared using a paired *t*-test. We evaluated the relations between the wrist-worn sleep parameters and the sleep PROs using a repeated measures correlation.

7.3 Results

7.3.1 Algorithm performance

Tables 7.3 and 7.4 show sleep/wake performance for each classifier between the predicted sleep stages using PSG, acceleration and heart rate data, and using the MESA or Walch et al dataset, respectively. ROC curves summarising the performance of each classifier are shown in Figure 7.3 and precision-recall plots are shown in Figure 7.4. Performance metrics of wake/NREM/REM trained classifiers are detailed in Tables 7.5 and 7.6. Figure 7.5 shows the PR curves summarising classifier performance for wake/NREM/REM metrics. Bland-Altman plots demonstrating the differences between classifier and PSG values are presented in Figure 7.6 and 7.7.

7.3.2 Sleep/wake classification

When classifying sleep/wake with the MESA dataset, precision was lowest across all classifiers when using only the heart rate feature. Interestingly, motion and heart rate combined performed poorer than motion when the fraction of sleep epochs scored correctly (sensitivity) was held at 90% across all classifiers (Table 7.3). Specificity ranged between 46% – 49%, with the logistic regression classifier performing the worst. Performance was improved by approximately 14% using the motion only feature compared to the combined features, 60% – 63% of wake epochs were scored correctly when using a 90% threshold. Three classifiers, logistic regression, random forest and neural net performed similarly scoring 63% of wake correctly. AUC was worse when using heart rate only and greatest when using motion only, in particular when logistic regression was used as a classifier (AUC = 0.851), although the difference between types of classifiers was limited. Similarly, only small differences were noted between AUC and features for motion and heart rate and motion. For example, the AUC of the random forest classifier for motion and HR was 0.851, only 4% higher than the AUC of the motion-only feature (AUC = 0.807).

Similar to classifiers trained with the MESA dataset, precision was lowest when HR was the only feature used (Table 7.4). In contrast, motion and HR combined performed better than the motion only feature when sensitivity was held at 90% across all classifiers. Specificity was higher than that observed in the MESA dataset,

ranging between 53% – 55% when using combined features, however improvements to specificity were much lower in comparison to the motion only feature (0 – 4%). In terms of specificity, the neural network classifier performed best when using the motion and HR feature, although there were only marginal differences (<1%) between the classifiers. Again, AUC was similar across classifiers, with the logistic regression classifier leading (AUC = 0.844).

7.3.3 Wake/NREM/REM classification

ROC curves were generated to analyse the wake/NREM/REM classification performance (Figure 7.5). Using a threshold that makes the fractions of NREM and REM equally correctly classified does not necessarily achieve the highest accuracy because time spent in NREM sleep is longer than REM sleep. As a result, the fraction of NREM sleep will be proportionally more accurate than REM sleep classification. Accuracy, corresponding κ values and AUC are shown in Table 7.5 and 7.6.

When training classifiers, heart rate by itself, closely followed by motion was the poorest predictor of NREM and REM. Heart rate appears to play a much more important role in the classification of NREM and REM compared with sleep/wake. For example, the AUC was greater when predicting wake/NREM and REM sleep compared to sleep/wake in the *k*-nearest neighbours, random forest and neural net classifiers when trained with the Walch data. The inclusion of heart rate improved accuracy REM classification by approximately 8% in both datasets when used in addition to motion, whilst findings were more inconsistent in NREM classification. NREM accuracy was worsened by the inclusion of heart rate in the logistic regression and random forest classifiers in the MESA dataset, whereas NREM accuracy was only reduced in the *k*-nearest neighbours classifier when using the Walch dataset.

In the MESA dataset, the wake/NREM/REM *k*-nearest neighbours, logistic regression and neural net classifiers achieved the same accuracy (0.66) when using combined features (HR and motion), however the neural net provided the highest κ corresponding value (0.3) and AUC (0.739). In both datasets, inclusion of motion

and heart rate features improved the classifiers' ability to differentiate wake/NREM/REM stages (AUC was highest). Interestingly, AUC was higher in classifiers trained with the Walch dataset, however small sample sizes can reduce power and accuracy of the algorithm therefore algorithms trained from the MESA dataset were favoured.

Table 7.2 Sleep/wake performance by each classifier using acceleration and heart rate data from the MESA dataset

Classifier	Features	Precision	Wake correct (specificity)	Sleep correct (sensitivity)	κ	AUC
Logistic regression	HR	0.829	0.330	0.8	0.203	0.667
			0.184	0.9	0.170	
			0.135	0.93	0.150	
			0.100	0.95	0.130	
	Motion	0.854	0.747	0.8	0.545	0.851
			0.631	0.9	0.547	
			0.579	0.93	0.531	
			0.533	0.95	0.51	
	HR and motion	0.888	0.612	0.8	0.399	0.783
			0.463	0.9	0.398	
			0.399	0.93	0.377	
			0.345	0.95	0.351	
k-nearest neighbours	HR	0.795	0.330	0.8	0.137	0.619
			0.184	0.9	0.101	
			0.135	0.93	0.082	
			0.100	0.95	0.070	
	Motion	0.812	0.731	0.8	0.531	0.819
			0.596	0.9	0.513	
			0.531	0.93	0.484	
			0.472	0.95	0.448	
	HR and motion	0.898	0.650	0.8	0.431	0.807
			0.483	0.9	0.416	
			0.410	0.93	0.389	
			0.350	0.95	0.355	
Random forest	HR	0.83	0.396	0.8	0.202	0.667
			0.241	0.9	0.167	
			0.190	0.93	0.147	
			0.150	0.95	0.128	
	Motion	0.851	0.748	0.8	0.547	0.851
			0.632	0.9	0.548	
			0.579	0.93	0.530	
			0.533	0.95	0.508	
	HR and motion	0.902	0.654	0.8	0.434	0.807
			0.489	0.9	0.422	
			0.418	0.93	0.396	
			0.359	0.95	0.365	

Neural net	HR	0.827	0.398	0.8	0.204	0.667
			0.245	0.9	0.171	
			0.191	0.93	0.150	
			0.153	0.95	0.131	
	Motion	0.853	0.745	0.8	0.545	0.850
			0.63	0.9	0.546	
			0.578	0.93	0.529	
			0.533	0.95	0.508	
	HR and motion	0.901	0.654	0.8	0.434	0.806
			0.489	0.9	0.422	
			0.418	0.93	0.396	
			0.359	0.95	0.365	

Abbreviation: AUC: Area under curve, HR: Heart rate, κ: Cohen's kappa coefficient of agreement

Fraction of true sleep epochs (sensitivity) and fraction of true wake epochs (specificity), AUC and Cohen's kappa averaged across trials

Table 7.3 Sleep/wake performance by each classifier using acceleration and heart rate data from the Walch dataset

Classifier	Features	Precision	Wake correct (specificity)	Sleep correct (sensitivity)	κ	AUC
Logistic regression	HR	0.963	0.45	0.8	0.144	0.716
			0.310	0.9	0.177	
			0.260	0.93	0.187	
			0.225	0.95	0.194	
	Motion	0.979	0.720	0.8	0.277	0.843
			0.535	0.9	0.336	
			0.465	0.93	0.355	
			0.407	0.95	0.363	
	HR and motion	0.979	0.723	0.8	0.281	0.844
			0.549	0.9	0.347	
			0.477	0.93	0.366	
			0.417	0.95	0.372	
k-nearest neighbours	HR	0.954	0.394	0.8	0.115	0.669
			0.253	0.9	0.133	
			0.195	0.93	0.127	
			0.147	0.95	0.113	
	Motion	0.968	0.681	0.8	0.256	0.790
			0.486	0.9	0.301	
			0.409	0.93	0.308	
			0.348	0.95	0.310	
	HR and motion	0.977	0.714	0.5340.8	0.283	0.833
			0.534	0.9	0.343	
			0.463	0.93	0.360	
			0.409	0.95	0.369	
Random forest	HR	0.956	0.417	0.8	0.128	0.684
			0.276	0.9	0.152	
			0.226	0.93	0.156	
			0.190	0.95	0.158	
	Motion	0.974	0.694	0.8	0.272	0.826
			0.519	0.9	0.332	
			0.451	0.93	0.350	
			0.400	0.95	0.358	

	HR and motion	0.977	0.688	0.8	0.266	0.827
			0.527	0.9	0.334	
			0.462	0.93	0.356	
			0.407	0.95	0.365	
Neural net	HR	0.964	0.454	0.8	0.144	0.716
			0.310	0.9	0.176	
			0.258	0.93	0.185	
			0.225	0.95	0.193	
	Motion	0.979	0.721	0.8	0.279	0.843
			0.541	0.9	0.341	
			0.469	0.93	0.359	
			0.412	0.95	0.368	
	HR and motion	0.979	0.711	0.8	0.275	0.836
			0.541	0.9	0.342	
			0.48	0.93	0.368	
			0.424	0.95	0.378	

Abbreviations: AUC: Area under curve, HR: Heart rate, κ: Cohen's kappa coefficient of agreement

Fraction of true sleep epochs (sensitivity) and fraction of true wake epochs (specificity), AUC and Cohen's kappa averaged across trials

Table 7.4 Sleep stage classification accuracy across different classifiers in the MESA dataset

Classifier	Features	Accuracy	Wake correct	NREM correct	REM correct	κ	AUC
Logistic regression	HR	0.605	0.6	0.352	0.353	0.125	0.611
	Motion	0.691	0.6	0.572	0.36	0.436	0.738
	HR and motion	0.658	0.6	0.474	0.473	0.282	0.716
k-nearest neighbours	HR	0.577	0.6	0.299	0.299	0.045	0.584
	Motion	0.677	0.6	0.445	0.49	0.416	0.705
	HR and motion	0.655	0.6	0.496	0.495	0.29	0.725
Random forest	HR	0.603	0.6	0.351	0.352	0.124	0.620
	Motion	0.691	0.6	0.572	0.36	0.437	0.739
	HR and motion	0.602	0.6	0.497	0.495	0.274	0.733
Neural net	HR	0.603	0.6	0.349	0.350	0.128	0.619
	Motion	0.691	0.6	0.475	0.463	0.436	0.738
	HR and motion	0.662	0.6	0.507	0.507	0.299	0.739

Abbreviation: AUC: Area under curve, HR: Heart rate, κ: Cohen's kappa coefficient of agreement

NREM and REM correct relate to the fraction of NREM and REM epochs scored correctly when a threshold is chosen so they are as close as possible, while maintaining the fraction of correctly scored wake epochs at 0.6

Table 7.5 Sleep stage classification accuracy across different classifiers in the Walch dataset

Classifier	Features	Accuracy	Wake correct	NREM correct	REM correct	κ	AUC
Logistic regression	HR	0.691	0.6	0.390	0.390	0.035	0.655
	Motion	0.706	0.6	0.542	0.294	0.090	0.724
	HR and motion	0.702	0.6	0.578	0.578	0.096	0.747
k-nearest neighbours	HR	0.668	0.6	0.365	0.364	0.070	0.641
	Motion	0.691	0.6	0.582	0.278	0.068	0.655
	HR and motion	0.696	0.6	0.565	0.566	0.141	0.753
Random forest	HR	0.673	0.6	0.376	0.376	0.216	0.659
	Motion	0.694	0.6	0.520	0.332	0.084	0.709
	HR and motion	0.660	0.6	0.579	0.579	0.242	0.775
Neural net	HR	0.701	0.6	0.391	0.391	0.031	0.678
	Motion	0.707	0.6	0.348	0.562	0.090	0.700
	HR and motion	0.712	0.6	0.592	0.593	0.112	0.774

Abbreviation: AUC: Area under curve, HR: Heart rate, κ: Cohen's kappa coefficient of agreement

NREM and REM correct relate to the fraction of NREM and REM epochs scored correctly when a threshold is chosen so they are as close as possible, while maintaining the fraction of correctly scored wake epochs at 0.6

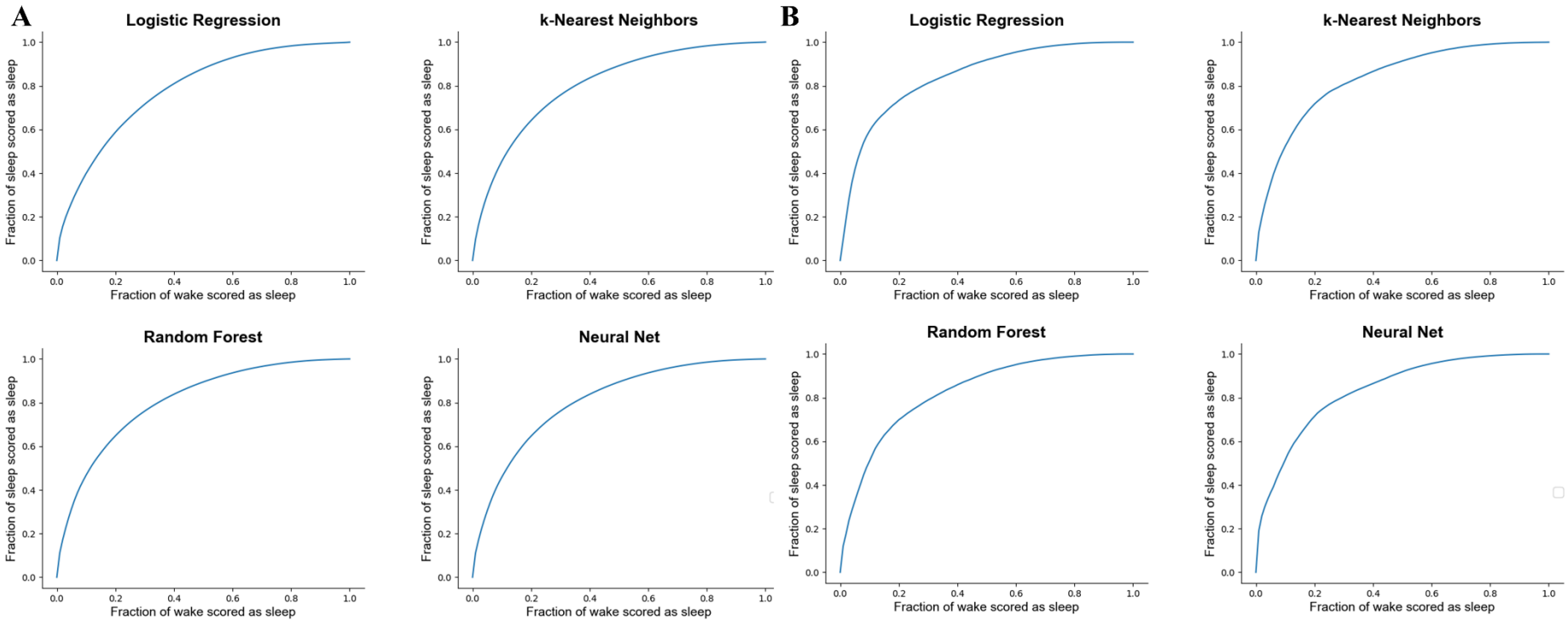

Figure 7.3 ROC curves across several classifiers for classifying sleep/wake using motion and heart rate from the **A)** MESA dataset and **B)** Walch dataset

The *x*-axis represents the fraction of true wake epochs incorrectly classified as sleep and the *y*-axis represents the fraction of true sleep epochs correctly classified as sleep

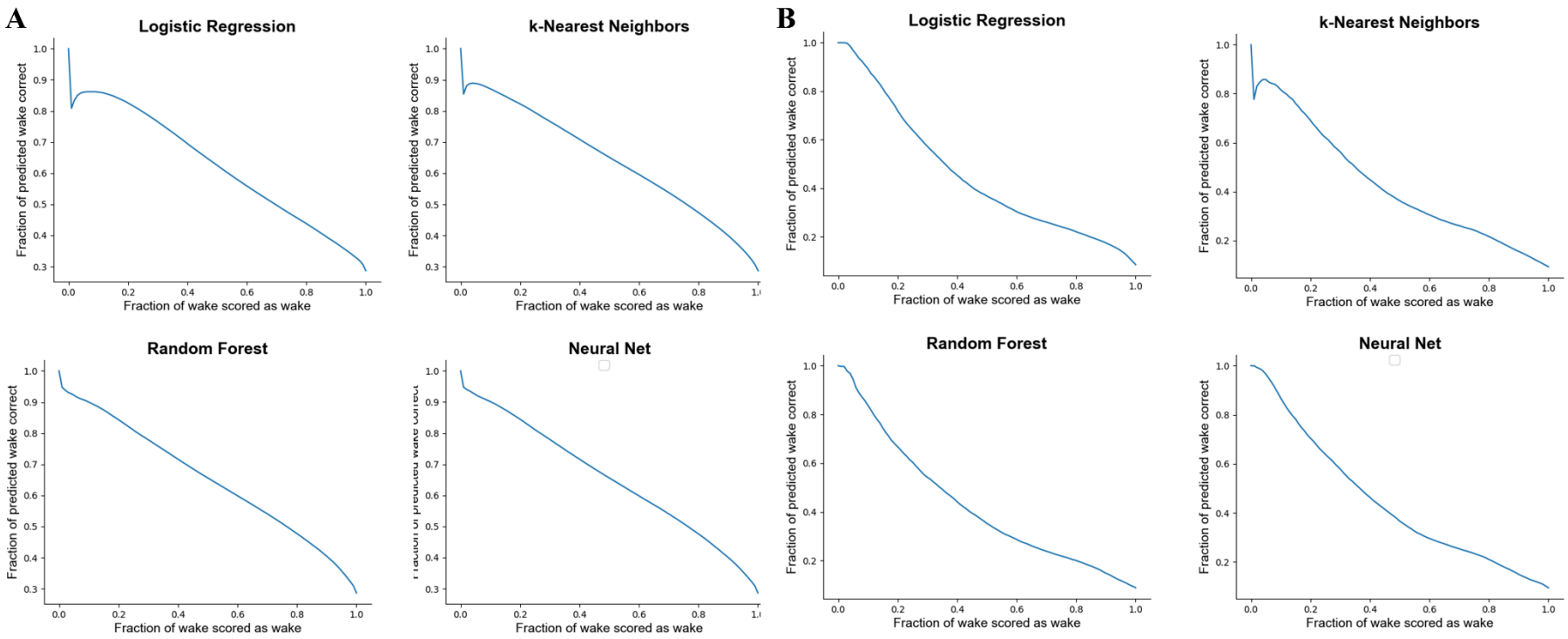

Figure 7.4 Precision-recall curves across classifiers for differentiating sleep and wake using motion and heart rate from the **A)** MESA dataset and **B)** Walch dataset

The *x*-axis represents the fraction of the true wake epochs correctly classified as wake and the *y*-axis represents the fraction of all epochs correctly labelled wake that were truly wake

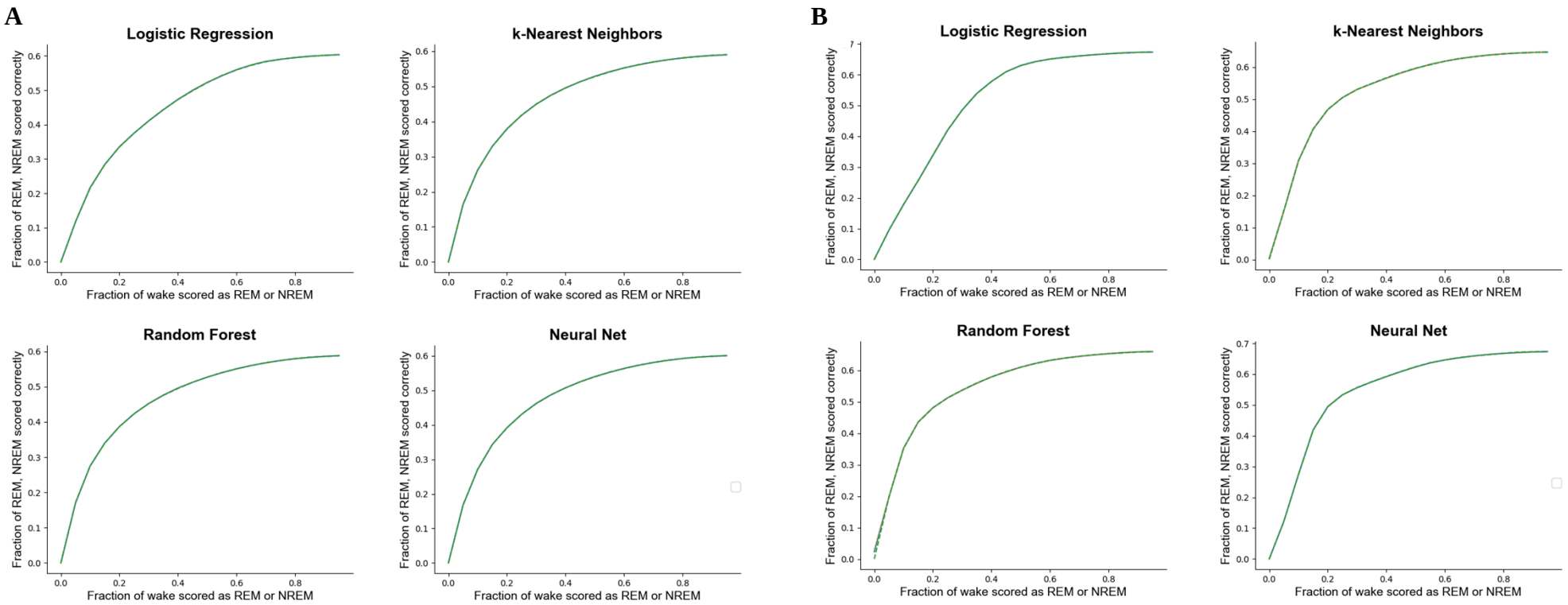

Figure 7.5 ROC curves across classifiers for classifying wake/NREM/REM using the **A)** MESA dataset **B)** Walch dataset

The *x*-axis represents the fraction of wake epochs classified incorrectly, with wake epochs classified as either NREM or REM sleep counting as a false positive. The *y*-axis represents REM and NREM accuracy rates. A binary search was performed to find the value that minimised the differences between REM and NREM accuracy

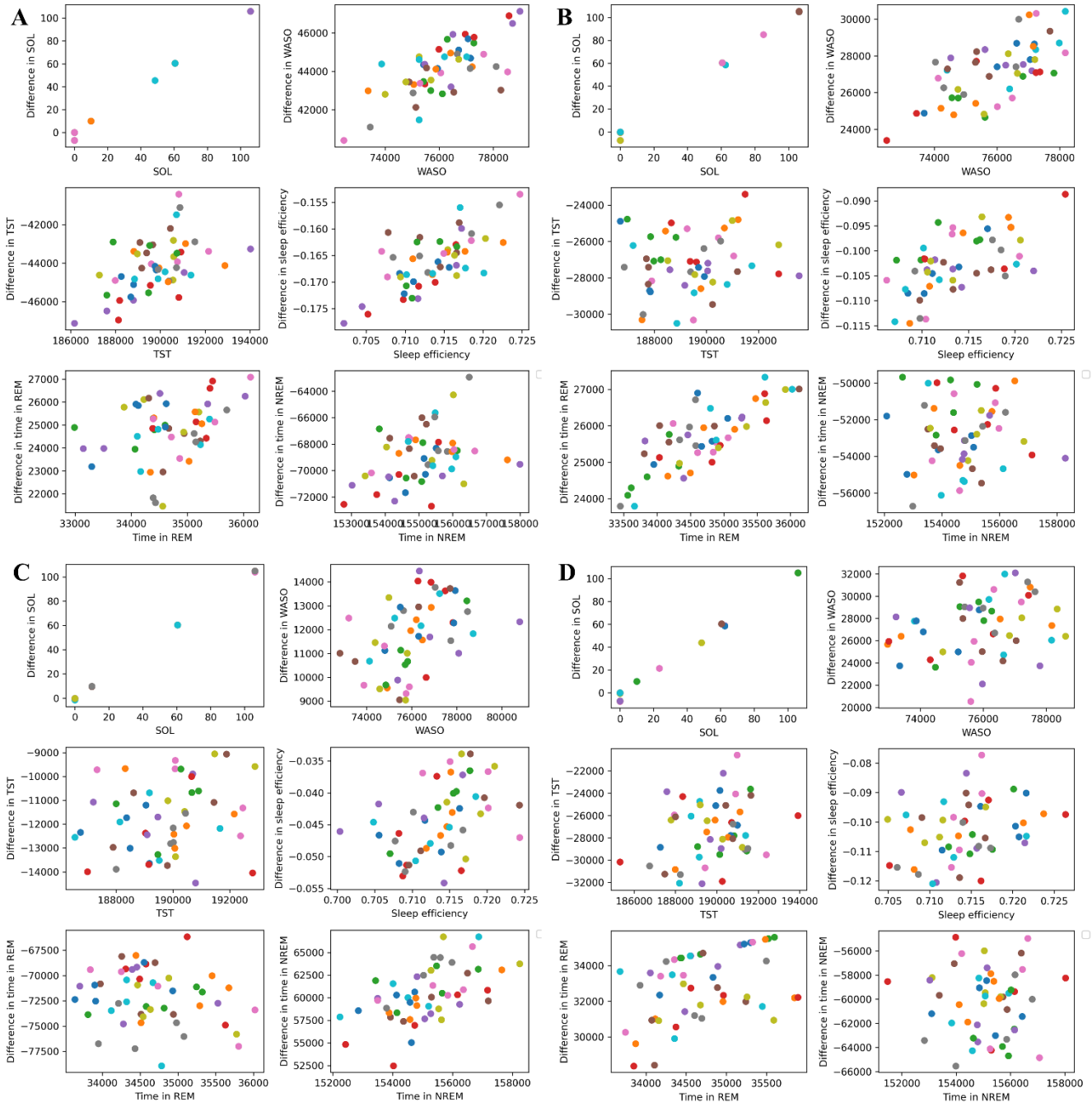

Figure 7.6 Bland-Altman plots for sleep parameters predicted by several classifiers using the MESA dataset

The difference in classifier-produced sleep variables versus PSG values are plotted on the versus PSG values are plotted on the *y*-axis and the corresponding PSG values are plotted on the *x*-axis for classifiers **A)** logistic regression **B)** *k*-nearest neighbours **C)** random forest **D)** neural net

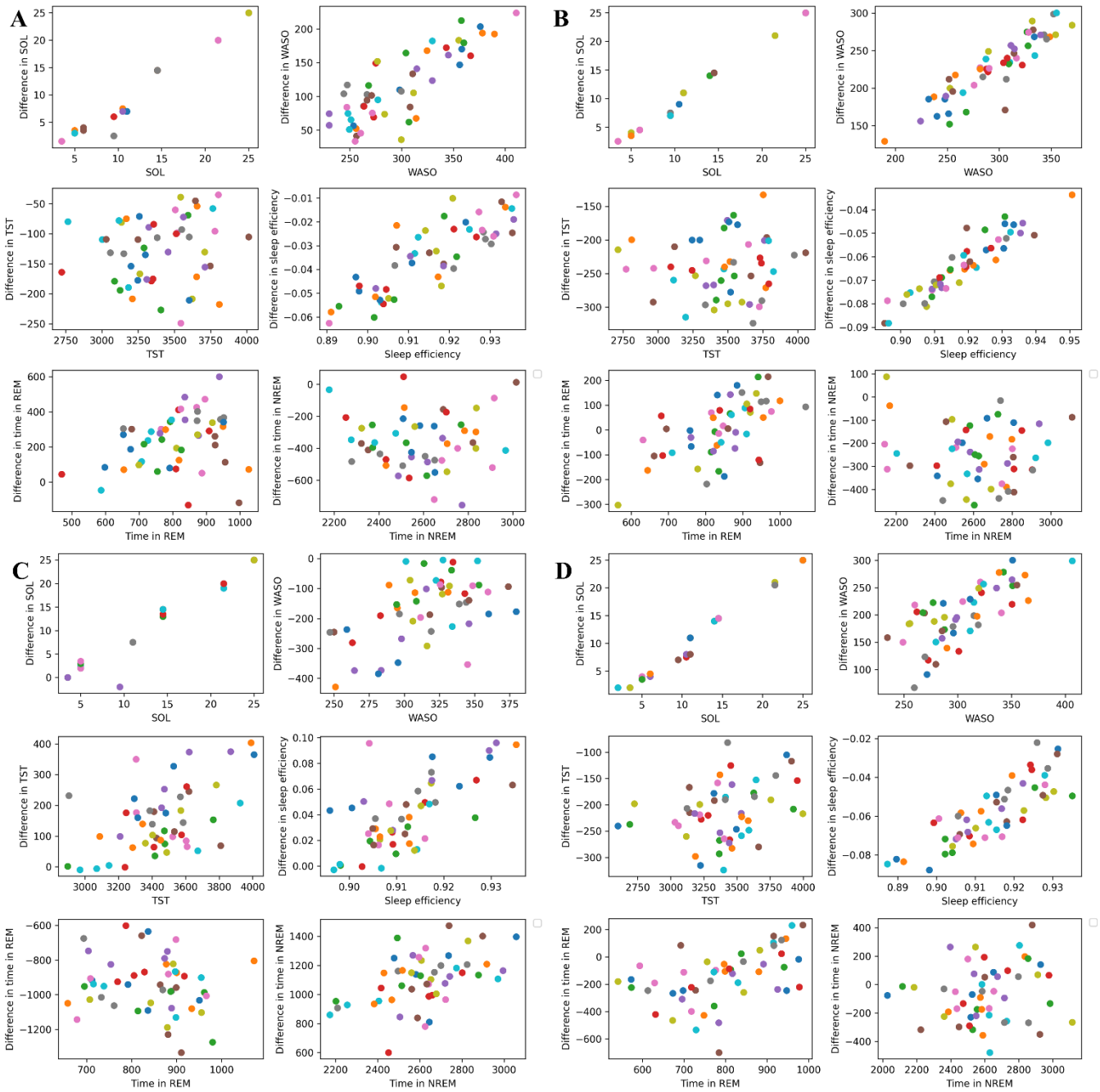

Figure 7.7 Bland-Altman plots for sleep parameters predicted by several classifiers using the Walch dataset

The difference in classifier-produced sleep variables versus PSG values are plotted on the *y*-axis and the corresponding PSG values are plotted on the *x*-axis for classifiers **A)** logistic regression **B)** *k*-nearest neighbours **C)** random forest **D)** neural net

7.3.4 Cohort

50 individuals diagnosed with adult-onset isolated, focal cervical dystonia (AOIFCD) (M:14, F: 36) and 47 age- and sex-matched controls (M:16, F:31) with no neurological deficits were recruited. Table 7.7 summarises their demographic and clinical characteristics.

Table 7.6 Summary of the demographics and clinic data of participants

Demographics		**AOIFCD**	**Controls**	**p-value**
Number of participants		50	47	
Age (median, range)		59 (32 – 73)	61 (38 – 80)	0.13
Sex	Female (%)	36	31	0.67
	Male (%)	14	16	
Medication (%)				
	Amantadine	1 (2)	0 (0)	
	Amitriptyline	4 (8)	1 (2)	
	Atenolol	1 (2)	0 (0)	
	Bisoprolol	0 (0)	1 (2)	
	Cetirizine	2 (4)	0 (0)	
	Circadin (melatonin)	1 (2)	0 (0)	
	Citalopram	2 (4)	1 (2)	
	Clonazepam	4 (8)	0 (0)	
	Diazepam	2 (4)	0 (0)	
	Fluoxetine	1 (2)	2 (4)	
	Gabapentin	5 (10)	0 (0)	
	Hyoscine	1 (2)	0 (0)	
	Mirtazapine	1 (2)	1 (2)	
	Nortriptyline	1 (2)	0 (0)	
	Pregabalin	2 (4)	0 (0)	
	Promethazine	1 (2)	0 (0)	
	Propranolol	2 (4)	0 (0)	
	Sertraline	6 (12)	2 (4)	
	Topiramate	0 (0)	1 (2)	
	Trihexyphenidyl	2 (4)	0 (0)	
	Venlafaxine	2 (4)	0 (0)	
	Zopiclone	0 (0)	1 (2)	
	Botulinum toxin (%)	45 (90)	-	

7.3.5 Subjective self-reports

Standardised questionnaires

Those with AOIFCD reported increased levels of excessive daytime sleepiness ($p = 0.04$) and impaired sleep quality ($p = 0.03$) in comparison to controls (Table 7.8). On closer inspection individuals with AOIFCD had significantly increased daytime dysfunction ($p = 0.001$) and use of sleep medication ($p = 0.001$) as measured by the PSQI. The DNMSQuest revealed elevated non-motor symptoms amongst the dystonia cohort ($p<0.001$), with evidence of increased levels of fatigue ($p < 0.001$),

autonomic symptoms ($p < 0.001$), sensory symptoms ($p < 0.001$), stigma ($p < 0.001$), impaired emotional well-being ($p = 0.001$), and impaired activities of daily living ($p < 0.001$).

Sleep diary

There were no significant differences between cases and control groups in the self-reported sleep measures, including SOL, TST, TIB, SE, WASO and number of nocturnal awakenings (Table 7.9). Self-reported sleep onset latency in dystonia cohort neared significance ($p = 0.06$).

7.3.6 Wearable-derived sleep variables

We used the neural net classifier trained using motion and heart rate from the MESA dataset to test our raw triaxial data gathered from the wrist-worn devices (accuracy = 0.662, AUC = 0.739). Sleep measures estimated by the wearable device are shown in Table 7.10. In comparison to the controls, those with AOIFCD were found to have significantly longer total sleep times (cases: 435 minutes vs controls: 388 minutes, $p = 0.004$) and total time spent in NREM (cases: 360 minutes vs controls: 325 minutes, $p = 0.009$) compared to controls. Sleep onset latency, wake after sleep onset, sleep efficiency and total time spent in REM sleep were comparable between the cohorts. Pearson's correlation demonstrated no relation between time since last BoNT injection and TST ($r = -0.03$, $p = 0.86$) and time spent in NREM sleep ($r = -0.04$, $p = 0.79$).

Table 7.7 Questionnaire results obtained from AOIFCD and control groups

	AOIFCD (n = 48)	**Controls (n = 45)**	**p-value**
PSQI score	6.5 (0 – 15)	5 (1 – 15)	**0.03**
Sleep quality	1 (0 – 3)	1 (0 – 3)	0.47
Sleep onset latency	1 (0 – 3)	1 (0 – 3)	0.22
Sleep duration	0 (0 – 3)	0 (0 – 3)	0.76
Sleep efficiency	1 (0 – 3)	1 (0 – 3)	0.88
Sleep disturbance	1 (0 – 2)	1 (0 – 2)	0.07
Use of medication	0 (0 – 2)	0 (0 – 1)	**0.001**
Daytime dysfunction	1 (0 – 3)	1 (0 – 2)	**0.001**
Number with impaired sleep (%)	27 (56)	21 (47)	0.47
ESS	N = 49	N = 47	
ESS total score	5 (0 – 17)	4 (0 – 19)	**0.04**
Number with abnormal ESS (%)	7 (14)	5 (11)	0.82
Normal (%)	42 (86)	42 (89)	0.82
Mild (%)	3 (6)	3 (6)	1
Moderate (%)	1 (2)	0 (0)	1
Severe (%)	3 (6)	2 (4)	1
DNMSQuest	N = 49	N = 47	
Total score	7 (0 – 13)	2 (0 – 10)	**<0.001**
Number with impaired sleep (%)	41 (84)	32 (68)	0.08
Impaired sleep quality (%)	33 (67)	27 (57)	0.32
Insomnia (%)	32 (65)	25 (53)	0.23
Number with impaired fatigue (%)	37 (76)	11 (23)	**<0.001**
Number with autonomic symptoms (%)	24 (49)	6 (13)	<**0.001**
Number with impaired emotional well-being (%)	34 (69)	17 (36)	**0.001**
Number with sensory symptoms (%)	44 (90)	0 (0)	**<0.001**
Number with impaired AODL (%)	31 (63)	9 (19)	**<0.001**
Number with stigma (%)	34 (69)	0 (0)	**<0.001**

Abbreviations: AOIFCD: Adult-onset, isolated focal cervical dystonia, DNMSQuest: Dystonia Non-Motor Symptom Questionnaire, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index

Mann-Whitney U comparison. Impaired sleep is considered a PSQI global score ≥6, abnormal ESS >11

Table 7.8 Self-reported sleep diary data for AOIFCD and controls

Sleep diary measures	AOIFCD (n = 50)	Controls (n = 46)	p-value
Sleep onset latency (minutes) [α]	22.1 (19.8)	14.1 (14.6)	0.06
Total sleep time (minutes) [α]	443.9 (68.5)	441.5 (74.6)	0.79
Time in bed (minutes) [β]	530.4 (70.1)	530 (49.1)	0.98
Wake after sleep onset (minutes) [α]	15.1 (29.3)	19.8 (20.5)	0.66
Number of nocturnal awakenings [α]	2 (1.5)	1.9 (0.9)	0.96
Sleep efficiency (%)[α]	86.5 (13.9)	84.9 (8.2)	0.79

[α]Mann-Whitney U test to compare cases and controls reported as median and interquartile range (IQR), [β]t-test to compare cases and controls reported as mean and standard deviation (SD)

Table 7.9 Wearable-derived sleep data in AOIFCD patients compared to controls

	AOIFCD (n = 48)	**Controls (n = 43)**	**p-value**
Sleep onset latency (minutes)	0.96 (1.9)	1 (1.6)	0.7
Total sleep time (minutes)	435 (104.4)	388.2 (66.9)	**0.0038**
Wake after sleep onset (minutes)	134.8 (116)	147.4 (51.9)	0.21
Sleep efficiency (%)	75.3 (21.4)	72.6 (9.1)	0.08
Total REM (minutes)	61.9 (57.1)	59.2 (41.2)	0.71
Total NREM (minutes)	359.5 (107.4)	325.2 (86.4)	**0.0089**

Abbreviations: NREM: Non-Rapid Eye Movement Sleep, REM: Rapid Eye Movement Sleep

Mann-Whitney U test to compare cases and controls reported as median and interquartile range (IQR)

7.3.7 Agreement between wearable-device and sleep diary derived sleep parameters

The relationship between sleep outcomes measured by the wrist-worn device and sleep diary values are presented in Table 7.11. All measures were significantly different between the two approaches for both cohorts, with the exception of the measurement of TST in the dystonia cohort ($p = 0.81$). Both groups overestimated SOL compared to the wearable device (cases: diary: 18 minutes vs wearable: 0.96 minute, $p < 0.001$, controls: sleep diary: 15 minutes vs wearable: 1 minute, $p < 0.001$), underestimated WASO (cases: diary: 15.7 minutes vs wearable: 134.8 minutes, $p < 0.001$, controls: diary: 20 minutes vs 147.4 minutes, $p < 0.001$), and self-reported elevated sleep efficiency (cases: diary: 86% vs wearable 75%, $p < 0.001$, controls: 84% vs 73%, $p < 0.001$), with these values broadly similar between the two groups. There was no agreement between measures, except for poor agreement between TST in both cohorts (dystonia: ICC =0.4 and controls: ICC = .1) and WASO in the dystonia cohort (ICC =0.3). Again, correlation was poor between the wearable-device and self-reported sleep variables. Measures of TST and SE showed very weak correlations amongst the dystonia cohort ($r = 0.1$ and $r = 0.09$, respectively), whilst WASO and SE demonstrated very weak correlations in the control cohort ($r = 0.2$ and $r = 0.08$, respectively).

Bland-Altman plots for TST, SOL, SE and WASO demonstrated differences between the measures in the dystonia cohort (Figure 7.8) and control group (Figure 7.9). When compared with sleep diaries, the wearable device underestimated TST (limits of agreement: -206.8 – 207.9), SE (limits of agreement: 61.4 – 102.6) and SOL (limits of agreement: -20.9 – 69.7), overestimated WASO (limits of agreement: -41.8 – 225.2) in both the dystonia and control group.

7.3.8 Association between wearable-derived sleep parameters and sleep PROs

Amongst both cohorts, repeated correlations showed no association between subjectively rated sleep disturbance and wearable-derived sleep parameters ($p > 0.05$) (Table 7.12). Interestingly, there was a trend towards increased time spent in REM sleep and self-reported sleep disturbance in the control group ($p = 0.06$).

Table 7.10 Agreement between sleep parameters measured by wearable-device and sleep diary in dystonia cohort

	Wearable-device	**Sleep diary**	**Mean comparison[α]**	**Bland-Altman**	**Reliability**	**Correlation[β]**
Dystonia cohort				Limits of agreement	ICC	*r*
Sleep onset latency (minutes)	0.96 (1.9)	18 (19.9)	**<0.001**	-20.9 – 69.7	0	-0.002
Total sleep time (minutes)	435 (104.4)	445 (91.9)	0.81	-206.8 – 207.9	0.4	0.11
Wake after sleep onset (minutes)	134.8 (116)	15.7 (30.6)	**<0.001**	-41.8 – 225.2	0.3	0.002
Sleep efficiency (%)	75.3 (21.4)	86 (12.4)	**<0.001**	61.4-102.6	0	0.09
Control cohort						
Sleep onset latency (minutes)	1 (1.6)	15 (18.9)	**<0.001**	-44.5 – 97.8	0	-0.04
Total sleep time (minutes)	388.2 (66.9)	443.5 (82.3)	**0.005**	-219.1 – 275.7	0.1	0.04
Wake after sleep onset (minutes)	147.4 (51.9)	20 (23.2)	**<0.001**	-248 – 34.7	0	0.2
Sleep efficiency (%)	72.6 (9.1)	84 (7.5)	**<0.001**	60.6 – 102.2	0	0.08

Abbreviations: ICC: intraclass correlation coefficient

[α]Wilcoxon signed rank test was used for mean comparison of non-normally distributed data, reported as median and interquartile range (IQR)

[β]Repeated measures correlation

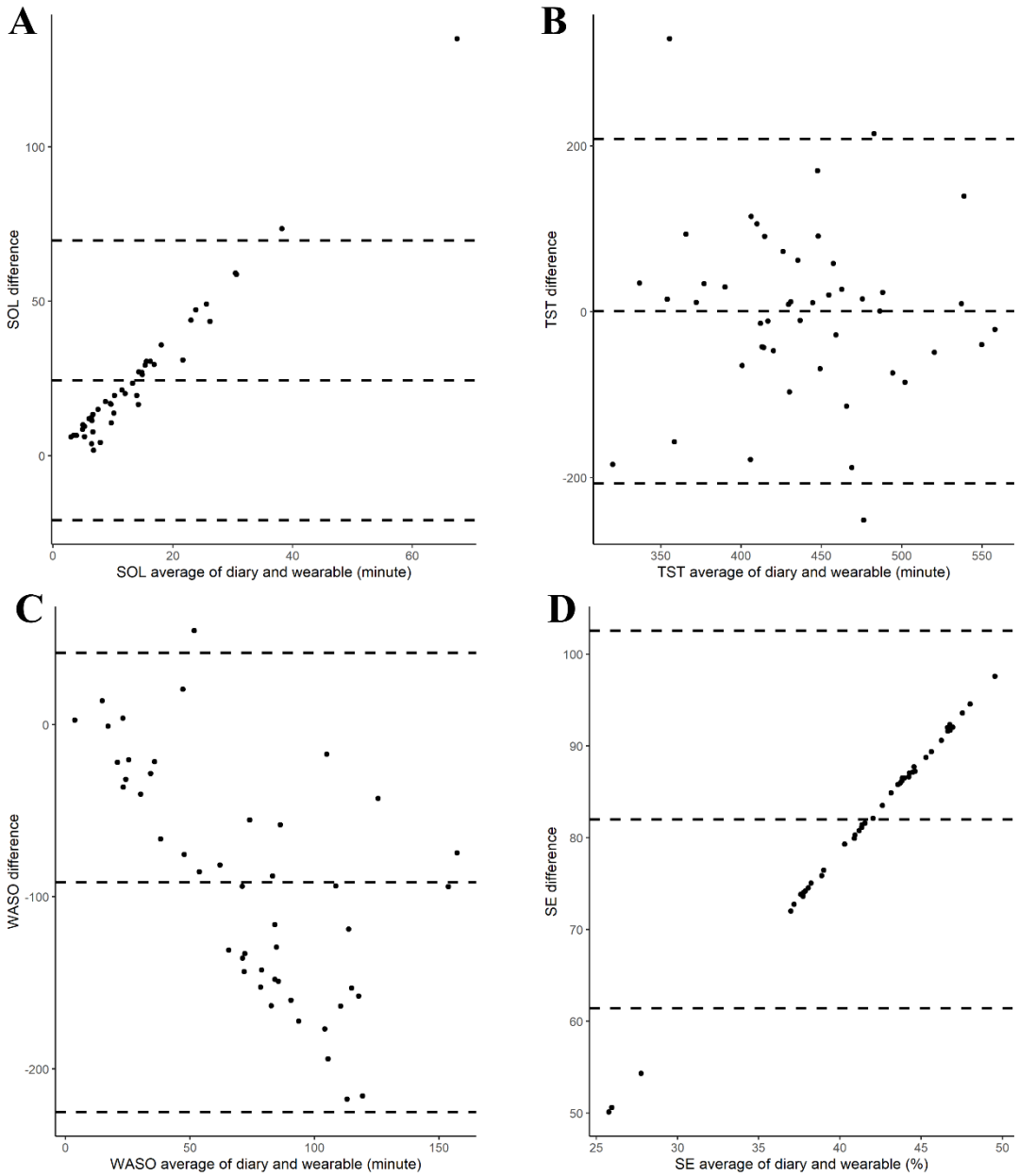

Figure 7.8 Bland-Altman plots for (A) sleep onset latency, (B) total sleep time, (C) wake after sleep onset and (D) sleep efficiency in dystonia cohort

Abbreviations: SE: Sleep efficiency, SOL: Sleep onset latency, TST: Total sleep time, WASO: Wake after sleep onset

The *y*-axis represents the difference between the two measures (diary – wearable) and the *x*-axis shows the average of both measures. The central dashed horizontal line represents the mean difference between both methods, accompanied by two horizontal dashed lines that demonstrate the 95% limits of agreement (mean difference ± 1.96 standard deviation)

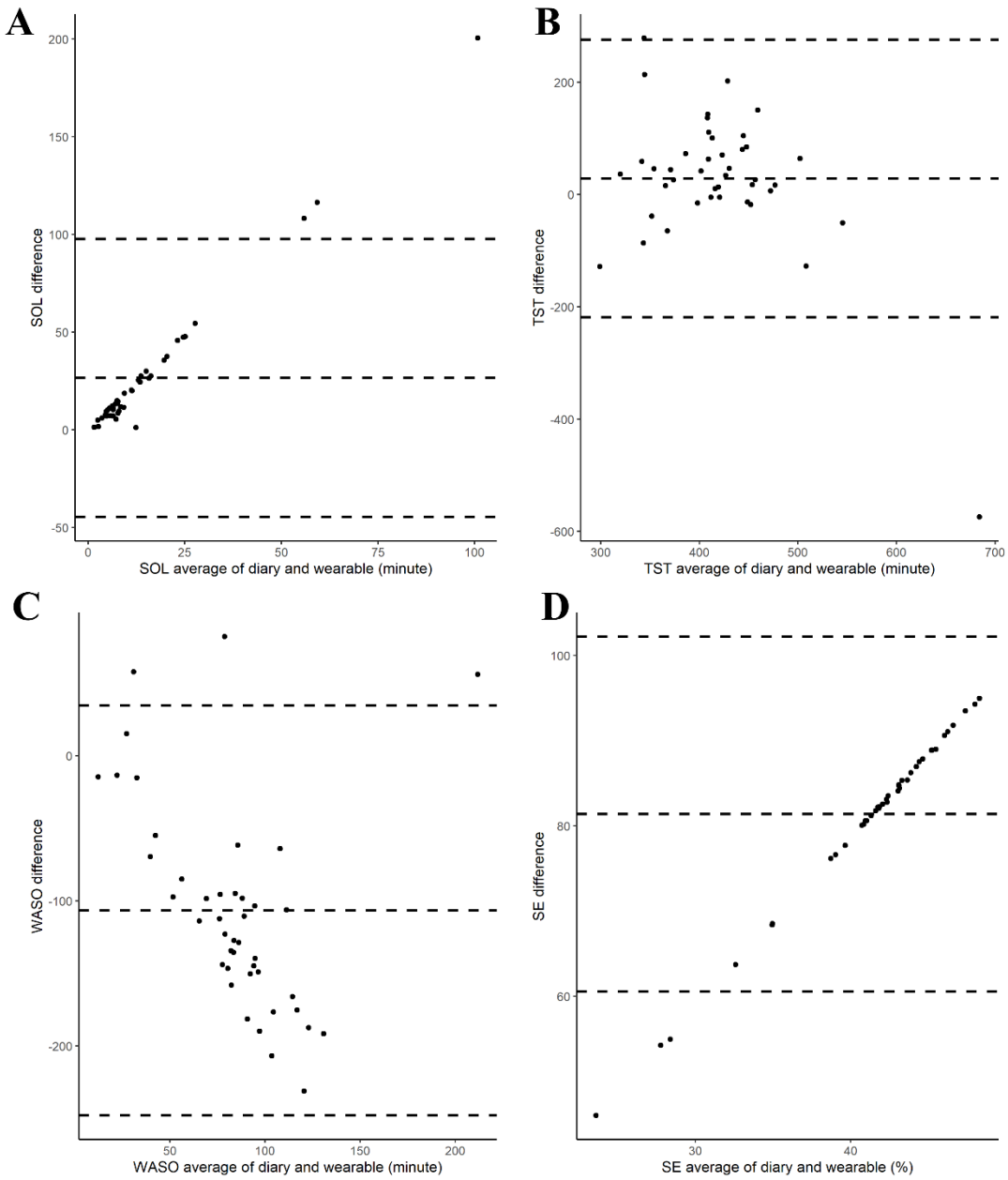

Figure 7.9 Bland-Altman plots for (A) sleep onset latency, (B) total sleep time, (C) wake after sleep onset and (D) sleep efficiency in control cohort

Abbreviations: SE: Sleep efficiency, SOL: Sleep onset latency, TST: Total sleep time, WASO: Wake after sleep onset

The *y*-axis represents the difference between the two measures (diary – wearable) and the *x*-axis shows the average of both measures. The central dashed horizontal line represents the mean difference between both methods, accompanied by two horizontal dashed lines that demonstrate the 95% limits of agreement (mean difference ± 1.96 standard deviation)

Table 7.11 Repeated measures correlation coefficient between wearable-derived and sleep PROs

	AOIFCD (n = 45)		**Control (n = 43)**	
Wearable-device parameters	**Sleep PRO (*r*)**	**p-value**	**Sleep PRO (*r*)**	**p-value**
Sleep onset latency	0.13	0.11	0.06	0.53
Total sleep time	-0.07	0.38	0.008	0.93
Wake after sleep onset	-0.03	0.69	0.004	0.97
Sleep efficiency	0.01	0.99	0.05	0.59
NREM (minutes)	-0.07	0.35	0.11	0.26
REM (minutes)	0.05	0.53	0.17	0.06

Abbreviations: NREM: Non-Rapid Eye Movement sleep, REM; Rapid Eye Movement

7.4 Discussion

These findings represent the first comprehensive study of wrist-worn devices in a cohort of individuals diagnosed with AOIFCD. We evaluated objective and subjective sleep measures using a wrist-worn wearable device, validated sleep questionnaires (PSQI, ESS, DNMSQuest) and sleep diary in both the recruited AOIFCD cohort and matched control group. Wearable-device derived sleep measurements found those diagnosed with dystonia experienced significantly longer total sleep time and increased time spent in NREM sleep compared to controls, while all other measures were comparable between the two groups. These differences were replicated in the questionnaire captured data with elevated PSQI and ESS scores between the two groups. The dystonia specific DNMSQuest scores were, overall, significantly higher in the dystonia cohort, as well as demonstrating higher levels of fatigue within the dystonia group. There was poor agreement between total sleep time derived from the wearable-device and the sleep diary in the dystonia cohort, but not in the control group. No other sleep parameters obtained from the wearable-device were comparable to the sleep diary, nor correlated with the sleep PRO.

Non-motor symptoms were significantly more common in AOIFCD compared to controls. Of those with AOIFCD, 98% (48/49) individuals reported at least one NMS and at least five in 76% (37/49). Fatigue was the most prominent sleep-related impairment (76%) in the dystonia cohort, there was also evidence of increased sensory symptoms (90%) and impaired emotional well-being (69%). Interestingly, we observed similar burden of sleep quality and insomnia between the groups. Although the DNMSQuest is not a detailed questionnaire specific to sleep disorders, it does highlight the burden of NMS in AOIFCD.

Interestingly, we found evidence of excessive daytime sleepiness, as measured by the ESS. To date, a single study has found presence of excessive daytime sleepiness in cervical dystonia,[330] with the majority of studies finding no evidence of excessive daytime sleepiness.[286,330–333,351] In line with previous literature, we found evidence of impaired sleep quality (PSQI) score, with evidence of increased use of sleep medication and daytime dysfunction. Prior studies have found inconsistencies in self-reported sleep qualities amongst those with cranio-cervical dystonia,[692] some

have found increased PSQI scores,[286,331,333,351,747] while others have found PSQI scores comparable to controls,[748] particularly when controlling for depression and anxiety.[694] Although it is difficult to determine the cause of these discrepancies, it cannot be ruled out that impaired sleep quality occurred as a side effect of medication used to manage dystonic symptoms. However, these scores often have poor correlation with polysomnographic and actigraphic parameters and may not be indicative of sleep disturbances especially as they are prone to recall bias.[749] Further, these questionnaires were designed to assess generic sleep habits and specific sleep disorders such in a detailed manner, they were not designed to screen sleep in movement disorders. For example, the PSQI is heavily weighted towards sleep habits and does not adequately cover other sleep disturbances such as REM Sleep Behaviour Disorder (RBD) common in Parkinson's Disease. Lastly, there is limited knowledge of their reliability and validity in AOIFCD, although the PSQI does demonstrate some sensitivity to change in PD cohorts.[750]

Expanding on the results found in Chapter 6, this work, to our knowledge, is the first to use activity monitors to analyse sleep stages in detail in dystonia. TST and time spent in NREM sleep derived from the wearable-device were significantly increased amongst the AOIFCD cohort compared to controls. Of the few polysomnographic studies to date, evidence suggests reduced muscle activity when in a relaxed state (i.e. lying down) and during sleep in those with cranio-cervical dystonia compared to controls.[335–337] It is possible that TST was elevated amongst the dystonia cohort as it may have been misclassified as a sleeping state due to this reduced muscle activity. In addition, PSG-studies have identified no differences in TST between dystonia and control cohorts,[337,432] and sleep diary data found no significant differences in TST between AOIFCD and control cohorts in this study.

Interestingly, PSG-based studies have previously reported REM sleep changed in dystonia,[337,432] however, several oral medical therapies sometimes used in the management of the motor symptoms of dystonia (e.g. trihexyphenidyl and benzodiazepines) have been linked with decreased REM sleep duration.[751,752] with these studies reporting 48% prescribed trihexyphenidyl and 24% clonazepam within their cohorts.[432] By contrast, only 8% and 4% of the cohort recruited in this study were prescribed clonazepam or trihexyphenidyl, respectively, likely due to the

majority being recruited via neurotoxin services, with their motor symptoms predominantly managed through injectable botulinum toxin and potentially providing an explanation for the lack of observable difference in REM sleep here.

In line with our findings of increased NREM sleep in the AOIFCD cohort, a single study noted increased N1 sleep in those with cranial dystonia,[336] with a second trending towards increased N1 percentage ($p = 0.079$).[432] The serotonergic raphe and brainstem are typically involved in NREM maintenance, both of which have been implicated in dystonia pathophysiology.[452] Interestingly, this imaging study also showed sleep disturbances were related to increased serotonergic binding potential in the dorsal raphe nucleus, caudate nucleus and hippocampus. Abnormally enhanced excitability of brainstem circuits has been demonstrated in cervical dystonia[411] and in a number of sleep disorders including NREM-sleep parasomnias[753] and restless leg syndrome.[754] Elevated rates of RLS have also been reported in dystonia cohorts.[333] Interestingly, brainstem circuits are not only important for controlling sleep/wake state, but have also been implicated in the modulation of pain during sleep.[755] Brainstem abnormalities amongst those with cervical dystonia may explain why pain intensity is reportedly low during sleep and early morning, gradually increasing during the course of the day.[335] Taken together, these findings suggest that shared underlying mechanisms may give rise to abnormal sleep architecture and cervical dystonia.

Significant differences were noted between wearable and diary estimates of the sleep variables across both cohorts, whereby the wearable-device underestimated SOL and overestimated WASO when compared to sleep diaries. These findings are consistent with previous work,[756,757] and has also been evident in evaluating sleep in other neuropsychiatric disorders, such as bipolar disorder.[758] Methodological differences potentially contribute to a portion of these discrepancies, for example subjective recall may not be as accurate in ageing adults and those with cognitive impairment, with previous studies of AOIFCD indicating impairments to executive function.[759] In addition, temporal differences are also likely to contribute, with individual recall of nocturnal awakenings differing substantially from mathematical evaluation of 30-second epochs.[760]

It is important to emphasise that actigraphic parameters are a function of the device and the algorithm used to analyse data, therefore validation findings are unique and different algorithms applied to the same data can produce different findings. A single study assessing the Garmin vivosmart found low to moderate correlation to TST and TIB recorded in sleep diaries, but SE and WASO were not related.[761] Again, although we found similar outcomes, it is important to emphasise that the above study used Garmin generated parameters, whilst we have derived sleep measures from raw triaxial data. Our results suggest these parameters may not be suitable for clinical investigations but do provide insightful indications of changes to normal sleep patterns.

In addition to standardised questionnaires, we used daily VAS to examine perceptions of sleep quality. Single-item sleep quality assessments are practical when measures are taken frequently, for example in daily sleep diaries. Consistent with previous findings in patients with advanced cancer, the self-reported sleep PROMs (sleep diary) did not correlate with any wearable measures which suggests that a single Likert scale rating sleep is not detailed enough to capture sleep abnormalities.[762] Despite this, several studies have validated single-item measures of sleep quality.[763] It is difficult to distinguish whether discrepancies were caused by erroneous interpretation of inactivity as sleep by the wearable or the patients' inability to self-report sleep. Use of PSG in future studies would help address this. Moreover, sleep quality is a complex phenomenon which includes several aspects of sleep; therefore, it can be difficult to measure, and differences between subjective and objective measures may be explained by the measuring of different dimensions of sleep quality, especially as we did not address how individuals defined sleep quality. A previous study in older adults also highlighted that perceived sleep quality is different from objective sleep quality,[764] therefore patients' experience of sleep may be more important than objective measures. Although in our cohort PRO response rates were high, it is possible that those with severe dystonic motor symptoms may have increased difficulty answering PROs because of complex symptom burden. Future studies should obtain motor symptom severity to account for this.

Other relevant confounders of sleep disturbance include physical activity and sedentary behaviour.[765,766] Individuals with AOIFCD may have more sleep disturbances than the general population because of their sedentary lifestyle caused by associated disabilities (e.g. pain) and worsened dystonic symptoms that follow physical exertion.[767] Future studies should use actigraphy to investigate physical activity in dystonia and its impact on sleep, particularly as it might be more effective in reducing sleep disturbances than medications.

One of the main limitations of this study was the lack of simultaneously captured PSG data, the gold-standard for sleep studies. As a result, we were unable to compare sensitivity and specificity of the sleep algorithm used. Future studies of dystonia cohorts would aim to include weeklong sleep diary and actigraphy measurements, together with an overlapping night of PSG measurements to allow for epoch-by-epoch comparison. Difficulties also emerged in ensuring syncing data between the wearable device and the app. This was primarily due to volume of data collected, meaning that passively syncing was not possible and resulted in loss of several nights of data for participants (416/679, 61.3%). Further, sampling frequency had to be reduced to 1Hz (hertz) to prolong battery life. Although there is no optimal sampling frequency to use when collecting raw triaxial data previous studies have typically used sampling frequencies between 30 and 100Hz.[768] Reduced sampling frequency (25Hz) does demonstrate strong correlations to 100Hz sampling rates (r > 0.96), however it has been shown to affect the processing of data to activity count and demonstrates reduced overall acceleration.[769,770] In addition, wearable data capture was limited to participants owning an iPhone due to poorer data capture with android devices and therefore limited participant recruitment. The wearable device used was consumer grade and may not be as accurate as validated actigraphs, however, although we were unable to compare the Garmin device to actigraphic measures, we used the raw triaxial data rather than brand specific algorithms for improved generalisability. Further previous studies using FitBit devices suggest sleep variables are comparable to actigraph devices amongst adolescents.[771]

Sleep diaries and sleep PROs rely upon subjective perception, which may be affected by recall bias. Although all sleep-related PROs were triggered at 8AM, participants did not necessarily complete the PRO at this time. A longer recall period could

introduce higher levels of bias and may have been a contributing factor to the differences between sleep diary and wearable-device sleep measures. Several participants (cases and controls) were prescribed medications that can affect sleep including antidepressants, benzodiazepines and anticholinergics. We did not correct for this, and this may account for differences in sleep variables. Lastly, we did not control for time of BoNT injections which may have affected sleep quality, although it is important to note that the literature suggests sleep quality does not improve in spite of reduced dystonia severity.[332]

We have shown the potential feasibility of using wearable-devices in estimating sleep measures, at scale, amongst those diagnosed with AOIFCD. Altered sleep quality and sleep architecture were present in those with AOIFCD, in particular we found evidence for increased TST and NREM sleep. These findings suggest that previously reported disruptions to brainstem circuitry and serotonin neurotransmission may contribute to both motor and sleep pathophysiology, as well as indicating the need for more routine evaluation of sleep disturbances in the clinical management of dystonia. Here we demonstrate the benefits of extracting sleep parameters from raw accelerometry traces. Findings from this study emphasise the need for sleep researchers and clinicians to consider the use of methodology when interpreting findings. Dystonia research would benefit from comparison studies of actigraphic and PSG variables, as well as the affects medication used to manage dystonia have on sleep.

8 Concluding remarks

8.1 Summary

This thesis has sought to determine the key epidemiological characteristics of dystonia, as well as to make use of a variety of technological platforms in gaining greater insights into the co-morbid non-motor symptoms, more specifically psychiatric disorders and sleep disturbance. Using a clinically validated case-ascertainment algorithm, I have evaluated these epidemiological and clinical characteristics across dystonia cohorts derived from multiple sources, including the SAIL databank, the UK Biobank and the Move Wales cohort. This work has focused on establishing the prevalence and incidence rates of dystonia, determining social deprivation and mortality characteristics (Chapter 3) and psychiatric disorders (Chapter 4). In Chapter 5, I have reviewed the growing literature demonstrating the relationship between sleep and movement disorders (Chapter 5), more specifically evaluated sleep disturbances in overall dystonia (Chapter 6) and adult-onset cervical dystonia (Chapter 7) utilising medical grade actigraphy and consumer grade accelerometer devices. In this final chapter I will review the key findings of this thesis and highlight areas for future work. I will discuss how the results from this study may impact our understanding of the aetiology, phenotype, and pathogenesis of dystonia, as well as areas of potential future research.

8.2 SAIL studies

The results presented in Chapters 3 and 4 demonstrate the ability to conduct retrospective healthcare studies at a population level. Linkage of national datasets can be used to facilitate detailed population-level analysis of disorders across the clinical spectrum, as well as examining the burden of the disorder through measures of health and social outcomes. The key areas of advantage of this approach are the substantial uplift in cohort size used during analysis, compared to prospectively recruited cohorts, as well as the access to clinical data pre- and post-diagnosis of interest, without the need for reliance on patient recall. In addition, the central most barrier to identifying a clinical cohort is its diagnostic accuracy. However, having established this algorithm, this then provides a platform that allows for application to other similarly coded cohorts. This work has also highlighted the opportunities that exist in identifying patients from both GP and hospital records.

8.2.1 Validation of dystonia algorithm

This work provides a validated algorithm for identifying individuals with dystonia using anonymous healthcare records. No previous studies have developed such an algorithm. As described in Chapter 3, we were able to robustly develop and validate our case ascertainment algorithm through use of a reference population of individuals with a confirmed clinical diagnosis. Our optimised algorithm had a sensitivity of 79%, with the reference population predominantly identified from primary healthcare records alone (0.9% identified from hospital records). Given that a diagnosis of dystonia typically takes place within a secondary or tertiary neurology care setting, it is likely that this reflects transcribing of these diagnoses from out-patient clinical letters by those in General Practice. The low level of hospital reported diagnosis is potentially due to the few, if any, acute admissions directly relating to dystonia, and therefore even in the context of co-morbid pathology, is unlikely to be included in documents such as the discharge summary. This distinction in reporting rates was consistent across both SAIL and UKBB cohorts, and is an important result for future research involving GP dystonia diagnosis codes.

8.2.2 Prevalence and incidence of dystonia

To this point, the prevalence of dystonia has remained largely unknown, with a wide variety of reported values dependent on country, ethnicity, subtype of dystonia and study design (Table 3.1). Prior to my work, there were no studies specifically focused on the Welsh population, and no recent studies in the United Kingdom. To address this, our study aimed to establish the incidence and prevalence of adult-onset idiopathic dystonia over a 24-year period, using Welsh national care registry data and patient records available in the SAIL databank.

A single record-linkage study in North England estimated prevalence rates of 38.1/100,000 in focal dystonia.[397] However, the number of cases ascertained were relatively small and limited to specific catchment areas, making these studies vulnerable to local clusters. Our results suggest an overall prevalence of 1220/100,000/year (1.2%), which given the unbiased nature of the case identification, suggests a more accurate population-based value. Population coverage of this study was relatively high (data from 80% of GPs and 100% of Welsh

hospitals was available for the period included within the study), which may in part explain the higher prevalence compared to existing studies. Previous linkage-based studies in European countries such as Finland and Sweden,[81,505] have also found elevated point prevalence (44/100,000) and incidence (34 per million person-years) of dystonia in comparison to prior epidemiological rates.[3,391] The prevalence and incidence rates of dystonia increased in yearly comparisons from 1994 to 2017, this likely reflects the aging population, increased recognition and awareness of dystonia, and improved availability of neurological services. The median age at diagnosis (42 years) and proportion of males to females (1:1.7) were comparable with previous studies, in spite of methodological differences and variable prevalence estimates.[390] Although other parts of the UK have similar healthcare systems, further work is required to determine whether these results are generalisable to the remainder of the UK. The next logical step would be to apply the same algorithm to the English population using the Clinical Practice Research Datalink (CPRD), however only 30% of English general practices contribute to the GOLD database (October 2019), and 10% to the more recently established Aurum database (June 2019).[772]

To continue this work, future studies should examine prevalence and incidence rates in different subtypes of dystonia, as well as investigate rates across different geographical locations of Wales. Regional factors are thought to be involved in the prevalence rates of blepharospasm, correlating with sun exposure,[83] while amongst patients with Parkinson's Disease, incidence rates are significantly higher in urban compared to rural areas,[773] therefore it is possible that a similar trend exists in dystonia. In addition, there may be genetic isolates which may contribute to dystonia-inducing gene mutations enriched in particular areas. Longer-term follow-up studies where gene/environmental exposures, individual characteristics (e.g. smoking, body mass index) and dystonia diagnoses are obtained may further our understanding of the relationship between environmental and genetic risk factors in dystonia.

8.2.3 Social deprivation and mortality

Data from specific sections of the SAIL databank can also be used to measure the potential social impact of dystonia, in particular, to explore whether there is evidence

of social drift in relation to being given a clinical diagnosis of dystonia. Although much of the research in dystonia focuses on the motor and non-motor symptoms, there is some evidence to suggest that dystonia affects productivity, employment and age of retirement, with pain, social phobias and severity of the motor symptoms impacting work and retirement status.[529,774,775] Our work is the first to directly examine social deprivation in dystonia by comparing deprivation at time of diagnosis up to a possible 24-year follow-up period through use of WIMD quintiles. Unexpectedly, we were unable to find any evidence of social drift following a diagnosis of dystonia, similarly, there was no evidence of change in social status prior to a dystonia diagnosis, potentially indicating little or no impact of social causation in giving rise to dystonia. These findings can provide individuals with dystonia assurance that this diagnosis is unlikely to impact them socioeconomically, while also highlighting that existing a proportion of those diagnosed with dystonia experience pre-existing deprivation, and may need additional support in access care, services and treatment.

Deprivation is difficult to measure, and although WIMD is considered one of the more comprehensive scores available, it as an area level measure and therefore does not cover every aspect of deprivation. There can be individuals living in deprived areas who would not be considered deprived, and vice versa. For example, around 1 in 5 income deprived people live in the 10% most deprived areas.[776] Similarly, for people who develop dystonia in densely populated areas, such as major cities, there may minimal residential movement and therefore markers of social drift may appear to be limited. For these reasons, the ability to measure individual level deprivation scores could provide more detailed insight. There is potential to link patient records to earnings, benefits and tax records which could have the potential to examine deprivation in more detail. Within SAIL, WIMD decile scores are also available, and it is possible that there may have been evidence of social drift having used smaller groups.

No increased risk of premature death was observed in this cohort, with rates comparable to the general population in Wales (35.9% and 31.7%, respectively). Median age at death in males and females also matched life expectancy in Wales (dystonia: 78 years (males) and 82 years (females), Wales: 78.5 years (males) and

82.3 years (females). The most common causes of death included respiratory disorders, circulatory disorders, cancers or dementias, again, in keeping with the leading causes of death registered in England and Wales. These findings are consistent with current views that there is no evidence to suggest increased or earlier mortality in individuals diagnosed with dystonia.

8.2.4 Psychiatric disorders

This work demonstrates that psychiatric comorbidities form part of the clinical phenotype of idiopathic dystonia, in keeping with multiple previous prospectively recruited cohorts.[282,283,286,525,540] More than half of the cohort presented with psychiatric disorders, a significantly higher proportion than the matched control group. Depression and anxiety were the most commonly diagnosed disorders in the overall dystonia cohort (31% and 26%, respectively) and were observed in both childhood (<20 years) and adult-onset (≥20 years) forms of dystonia. Consistent with the single other population-based study undertaken to date, dystonia was associated with a higher risk of all psychiatric diagnoses,[525] most notably anxiety disorder, depression and eating disorders.

Psychiatric diagnoses and prescriptions were recorded at higher rates prior to the date of dystonia diagnosis, compared to those made afterwards. However, there was an increased risk of psychiatric diagnosis and prescription in those with dystonia across the entire study period, particularly in the years either side of a dystonia diagnosis. This may reflect diagnostic delay (average two years),[391] initial burden of the disease or potentially indicates common pathophysiological mechanisms. The increased risk of a psychiatric diagnosis and prescription of medication for treatment of these disorders gradually decreased over time, suggesting an absence of continued accumulation of psychiatric symptoms as a secondary consequence to a disabling motor disorder. Our work suggests that those with a dystonia diagnosis have an increased risk of psychiatric diagnosis, further supported by recent work suggesting an increased psychiatric susceptibility in dystonia, whereby enrichment of genes linked with psychiatric disorders, including obsessive-compulsive disorder, depression and schizophrenia were observed in co-expression modules enriched for dystonia-associated genes.[568]

To continue this work, future studies could investigate phenotypic profiles amongst different subtypes of dystonia. It would be of particular interest to differentiate genetically defined and sporadic forms of dystonia, to establish whether these are unique features to those with DYT mutations or a wider characteristic of dystonia. This would provide further understanding of the mechanisms and pathogenesis of this disorder. Few studies have explored, in detail, the links between psychiatric comorbidity and dystonia motor symptom severity, which coupled with longitudinal studies of changes in dystonic and psychiatric symptoms could shed further light on the important temporal relationship between these two elements of the disorder.

8.3 Sleep in dystonia

A review of the available literature investigating sleep disturbances in dystonia found that self-reported sleep quality is lower than that reported by unaffected control cohorts. Estimates of sleep disturbances were between 40% and 70%, with depression more prominently associated with impaired sleep than the motor symptoms. Interestingly, sleep quality did not improve following neurotoxin treatment, in spite of improved motor function.[332] These findings suggest that sleep disturbances are another primary non-motor symptom in dystonia, rather than secondary to muscular overactivity or pain. Varying results have been demonstrated in polysomnography-based (PSG) studies including decreased sleep efficiency, increased sleep latency, reduced REM sleep and changes to spindle maintenance and generation.[432,695]

8.4 Subjective and accelerometer-derived sleep measures in the UK Biobank

Amongst the entire UKBB dystonia cohort (n=1569) self-reported insomnia and daytime sleepiness was higher than that of the control population, with additional evidence of suboptimal sleep duration (< 7 hours or > 8 hours). Suboptimal sleep was also evident amongst the individual subtypes of dystonia including dystonic tremor and unspecified forms of dystonia, whilst excessive daytime sleepiness and insomnia was reported amongst those with dystonic tremor. Accelerometer data was available for a proportion of the dystonia cohort (n=241, 15%). Amongst this smaller cohort, only excessive daytime sleepiness was observed amongst those with

unspecified forms of dystonia. Poor self-reported sleep patterns were reported in the overall dystonia cohort and cervical dystonia in comparison to controls. Accelerometer data identified individuals diagnosed with dystonia had later bedtimes, spent less time in bed and suboptimal sleep duration, consistent with previous work in which both self-reported and objective alterations in sleep architecture have been identified.[337,432]

The present study used data available from the UK Biobank and was unable to investigate associations in direct concordance with self-reported and accelerometer-derived sleep variables due to the time differences in data collection (average 5.9 years). To continue this work, future studies would include a more detailed assessment of self-reported sleep using validated questionnaires (e.g. PSQI and ESS) collected concurrently with accelerometer data. As raw triaxial data is collected through accelerometers, it is possible to utilise several algorithms, future studies should employ newer accelerometer algorithms which details sleep stages.

8.5 Subjective and consumer grade wearable devices in AOIFCD

Consistent with the outcomes derived from the UKBB analysis, my work prospectively recruiting a cohort of patients diagnosed with AOIFCD and undertaking remote analysis of their sleep quality using consumer grade wearable devices, demonstrated altered sleep quality and architecture compared to a matched control group. Increased NREM sleep provided the most striking difference, an interesting finding given that two recent PSG studies identified reduced REM sleep and increased REM sleep latency.[337,432] However, the former study reported (n=13) increased N1 (NREM sleep stage) sleep trending towards statistical significance ($p = 0.07$),[432] while a third PSG study reported increased N1 sleep.[336] It is possible that the small sample (n=13) accounts for differences in REM and NREM sleep structure, whilst our wearable data in a larger cohort (n = 50) provides some balance between accuracy and cohort size. Although this study represents the largest cohort to date, longitudinal monitoring of a much larger cohort, in conjunction with PSG would aid our understanding of the nature and impact of sleep disturbances in AOIFCD. In addition, this would allow us to investigate the impact of 12-weekly neurotoxin

injections on sleep, as well as other non-motor symptoms such as depression and anxiety, which too can secondarily impact sleep.

Other areas of future work would be to combine clinical assessment, genetic analysis, accelerometer use and PSG, to explore whether distinct Mendelian inherited mutations in dystonia genes differentially affect sleep quality, as well as whether more subtle differences in motor phenotype are seen to exacerbate sleep more than others. Wearable-devices are also able to measure daytime activity, this could be of interest given that physical activity can improve sleep quality, and previous studies suggest those with cervical dystonia are less active compared to controls.[767] Finally, another area of work would be to undertake MRI brain imaging studies (potentially including both functional and microstructural approaches), in conjunction with more prolonged periods of wearable device usage, aimed at identifying differences in specific brain regions, or networks, that may be observed between those determined to have impaired sleep quality and those without.

8.6 Implications for dystonia

A large proportion of individuals with dystonia present with non-motor symptoms including depression, anxiety and sleep disturbances. The impact that these symptoms have on quality of life indicates the importance of taking non-motors into account during clinical assessment, developing dystonia-specific questionnaires and evaluating new treatments for dystonia. Moreover, more than half of individuals diagnosed with psychiatric co-morbidities in our SAIL cohort, developed these symptoms prior to onset of the motor dystonic symptoms. These findings support the hypothesis that psychiatric co-morbidity represents a primary phenotypic component of dystonia, at least in the majority, rather than a secondary reactive response.

To date, there is limited work that has been aimed at addressing the efficacy of oral medications in managing the non-motor symptoms in dystonia. Although BoNT treatment has been shown to impact both mental health and pain symptoms, there is some evidence to suggest selective serotonin re-uptake inhibitors can worsen dystonia,[360] although psychiatric symptoms improved following treatment.[363] Recognition of non-motor symptoms in clinical settings may lead to novel

therapeutic targets that allow for combined management of motor and non-motor symptoms, and potentially a recognition of those targets which may worsen one or other of these symptoms.

8.7 Study limitations

8.7.1 Dystonia epidemiological characteristics determined using data from the SAIL databank

While it was possible to calculate the sensitivity (79%) for the case-ascertainment algorithm used to identify the dystonia cohort, the absence of a control cohort prevented calculation of the specificity, potentially allowing for a proportion of individuals without dystonia to be included in our cohort. However, in order to attempt to mitigate against this, stringent exclusion criteria was applied, covering all diagnoses that may be included as a differential diagnosis in this clinical setting. Although coding is considered relatively accurate in the UK,[535] it is possible that codes might represent a misdiagnosis or be inaccurate, and coding variation is recognised to exist between GP practices. Individuals with mild symptoms may not seek medical advice which could lead to an underestimation of prevalence and incidence rates. In addition, further clinical detail such as the severity of the motor symptoms or age at onset isn't included in healthcare data, limiting some of our interpretation. My data analysis within the SAIL databank also only included those seeking care via the NHS, and not those treated in the private sector. Private healthcare however, only includes a small fraction of the total care provided in the UK with this estimated to be approximately 11%[777] and given the chronic nature of the disorder, fewer patients diagnosed with dystonia are likely to access their healthcare via this route.

8.7.2 Psychiatric disorders in healthcare data

As discussed above, anonymised healthcare databank contains little to no detail of the more specific components of individual diagnoses. Secondary care records contain appointment details, although often lack the reason for the appointment, resulting in very limited data being available in relation to the use of injectable botulinum toxin (BoNT). Alongside use in the management of dystonia, BoNT is known to improve non-motor symptoms, including psychiatric symptoms,[575] and as

a result this approach does not capture the impact of BoNT on the non-motor symptoms. Within primary care records there is no indication as to the clinical indication for the prescription of individual drugs, and there is no way of determining whether individual prescriptions were dispensed or taken. Many medications also demonstrate pleural roles in the disorders or symptoms that they are used to manage, for example diazepam, used as a muscle relaxant and in the treatment of anxiety. During the course of this thesis, I have sought to mitigate these multiple potential confounders, detailing them in the methods (Chapter 2) and individual chapters (Chapter 4), with one such example being the use of benzodiazepines, where these were prescribed in the absence of a documented psychiatric diagnosis, they were then considered to be prescribed for a non-psychiatric problem, and therefore not included in the overall analysis of psychiatric co-morbidity.

8.7.3 UK Biobank

The UK Biobank is the largest known public accelerometry data set, where a dystonia cohort can be identified to determine differences in sleep quality in comparison with and unaffected control cohort. In spite of this, multiple limitations exist including; 1) the UK Biobank is unlikely to be representative of the general population. Recruitment was via individuals self-selecting the participate and therefore likely biases more towards those with fewer co-morbidities, leading to an overall lower disease burden within the dataset, 2) I excluded individuals based only on neurological disorders in the control cohort, while multiple other medical co-morbidities may have impacted sleep quality and reduced physical mobility, 3) there was a time lag (up to 7 years) between collection of the accelerometry and questionnaire (psychiatric and sleep) data, which obscures whether participants had changes in sleep quality and psychiatric symptoms contemporaneously. 4) Accelerometer-based measures are not as accurate as PSG, the gold standard in sleep research. Moreover, accelerometry alone cannot distinguish sleep stages (REM and NREM sleep), input from other physiological measures such as heart rate variability is also required, which was not recorded within this dataset.

8.7.4 Consumer grade wearable devices and sleep

A key limiter to my work in the prospective recruitment of individuals diagnosed with AOIFCD and use of a consumer grade wearable device in the measurement of their sleep quality was the lack of simultaneous PSG. For this reason, we were unable to determine sensitivity and specificity of the sleep algorithms that were used. As with any method, accelerometry has limitations which limit its practical usefulness. Firstly, the majority of sleep/wake algorithms are validated in normal populations, with specificity potentially therefore being lower in clinical populations such as those with movement disorders, with specificity lower than 60% likely to compromise evaluation of sleep parameters.[778] Therefore combined actigraphy data over multiple nights is recommended. Some researchers suggest at least four to five nights although this is yet to be established.[779] Due to technological syncing difficulties, only 61% of the recruited cohort achieved four or more nights, and therefore constrains some of the conclusions from this work. Another key limitation across the field of wearable devices and sleep analysis is the lack of standardised protocols and analytic methods, resulting difficulties in comparing results across multiple data capture devices and algorithms. It is in large part due to this lack of consistency of approach that a complementary assessment method, such as sleep diaries or PSG, are used as an additional marker during analysis. This study employed a commercially available sleep tracker, an inexpensive alternative to medical grade devices which has become a popular alternative in sleep research. However, previous studies have shown their inability to accurately capture sleep parameters, with devices differing significantly from results derived from PSG or actigraphy.[780] Although there are significant limitations to using accelerometers as a research tool, there may be a role for commercially available devices within a clinical setting. For example, they may be able to provide within-subject changes to sleep behaviour that are more apparent than self-reported measures. Lastly, we did not control for patients who were prescribed medications that can affect sleep quality and architecture due to the small cohort size. Antidepressants, benzodiazepines and anticholinergics are often prescribed to manage motor and non-motor symptoms in dystonia, but also impact sleep. Future studies should seek to recruit larger patient cohorts in order to allow for adjustments such as these.

8.8 Future directions

This work, arguably the SAIL databank work is direction setting in the dystonia field. SAIL provides multiple avenues for further understanding of the spectrum of dystonic disorders. Our understanding derived from linked data can be augmented further by linking with additional data sources.

8.8.1 Genetic data

The case-ascertainment algorithm could be used to create a dystonia register within the SAIL databank, and other link databases such as the UK Biobank, to facilitate further research. Future work should involve linking a cohort with exome data from Welsh patients collected as part of the Welsh Movement Disorder Research Network to the SAIL databank. Next Generation Sequencing (NGS) genetic data provides detail genetic analysis on an individual level that would allow exploration or potential trends in co-morbidities and phenotypes within dystonia subtypes, including both rare, highly penetrant variants (such as the Mendelian inherited genes identified as causative in dystonia) and the more common, low penetrance observed in polygenic disease. Already known examples of this variation include *SGCE* mutations in Myoclonus Dystonia, associated with higher rates of anxiety and OCD,[306] suggesting that it is likely that those with dystonia-associated mutations may present with different clinical profiles. Another avenue would be to use non-motor features such as temporal discrimination to identify endophenotypes of non-manifesting gene carriers, this may allow us to segregate patients with similar clinical profiles, as well as the potential to identify new genetic causes of dystonia.

8.8.2 Comorbidities

Future studies could use the SAIL databank to investigate other clinical co-morbidities amongst dystonia cohorts, particularly as thyroid diseases appear to be more frequent in dystonia populations.[781] Mild abnormalities in cardiovascular regulation, heart rate and blood pressure variability have also been identified in patients with CD,[782] where cardiovascular autonomic imbalance was associated with comorbid depression.[783] Other comorbidities include degenerative changes in the cervical spine, soft tissue disorders, essential tremor, neck tension, dental caries and abdominal and pelvic pain.[774] Dystonia severity is not well recorded in GP records,

and so there needs to be focus on enriching datasets with more detailed information on disease status, allowing for investigations of associations between comorbidities and severity. To address this, a subset of the SAIL cohort could be clinically reviewed and linked to the databank.

8.8.3 Education

To expand on the work carried out in this thesis, educational attainment available within the SAIL databank could be compared in those with dystonia and controls. Several studies have demonstrated cognitive deficits in dystonia,[315,318,324,784] which are not accounted for by motor severity.[319] Although not a direct measure of IQ, it would be possible to evaluate educational attainment, and to explore whether changes within dystonia cohorts has a secondary impact on social deprivation. This too would aid in establishing pathways for scholastic support for those with childhood-onset dystonia, as well as identifying those who might benefit most from early intervention.

8.8.4 Sleep

Sleep disturbances are prominent in dystonia and can give insight into the shared mechanisms underlying both sleep and the movement disorder. There are few available PSG studies and no previous accelerometer studies investigating sleep quality in dystonia. Although we were able to demonstrate that accelerometery is able to detect sleep disturbance in dystonia, future studies should perform overnight PSG-studies whilst individuals with dystonia wear an accelerometer device to validate the actigraphy measurements. This type of study would allow us to evaluate the sensitivity and specificity of sleep/wake algorithms in dystonia cohorts and provide the opportunity to adapt algorithms as required.

Given the importance of non-motor symptoms in dystonia, future studies should consider using standardised questionnaires and a broader spectrum of non-motor patient reported outcomes. Dystonia is often managed using BoNT over a 12-week period, a longitudinal study should be employed to examine how sleep parameters vary across therapeutic cycles. Motor disability can also impact utilisation of devices and apps, as we did not directly evaluate disease severity it is possible that this

affected compliance. Future studies will need to address feasibility across a spectrum of disease severity, as well as associations between sleep disturbances.

8.9 Clinical care pathways

The burden of non-motor symptoms in dystonia is considerable, in particular sleep and psychiatric disorders have a detrimental impact on quality of life. Increased emphasis on the management of non-motor symptoms is needed, and the impact of their treatment should be evaluated. One possible option would be to develop a team of multi-professionals including psychologists and physiotherapists, developing novel care pathways in dystonia that allow for evaluation, recognition and appropriate therapeutic intervention across the complete spectrum of manifested symptoms.

8.10 Conclusion

My work has shown dystonia to be one of the most common chronic movement disorders (estimated prevalence of 1.2%) and observed at rates in the general population that are comparable to other, more extensively evaluated, neurological disorders, such as Parkinson's disease (1.1 -1.6%)[785] and epilepsy (1.1-1.2%).[786,787] The findings presented in this study provide an insight into how technology can be used to explore in detail the non-motor symptoms in dystonia, with advances in our view and approach to the analysis of 'big data' enabling much larger scale understanding and exploration of disorder specific traits, as well as indications of phenotypic heterogeneity within individual clinical populations. Accelerometer-based devices have provided additional, at home, mechanisms to evaluate sleep at scale, but similar technological approaches could be harnessed for future work, for example in monitoring timing and compliance with oral medical therapy, daytime physical activity, amount of daylight and screentime exposure during the day, enabling more accurate analysis of key clinical traits and their interaction with the surrounding environment.

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APPENDICES

1 SAIL application

For SAIL use
Ref. No.

Secure Anonymised Information Linkage (SAIL)

Information Governance Review Panel (IGRP) Application Form

SAIL IGRP Application Form

The following form has been designed to collect the information needed for the information governance approval process for work involving the SAIL databank. The information you provide will facilitate consideration of your enquiry. Guidance notes on completing this form can be found at:

https://www.saildatabank.com/wp-content/uploads/Guidance_Notes_for_SAIL_IGRP_Application_4https://www.saildatabank.com/wp-content/uploads/Guidance_Notes_for_SAIL_IGRP_Application_4-1.docx1.docx

SAIL Feasibility Agreement

All projects require a SAIL Feasibility Agreement to be completed and signed before proceeding to IGRP.

This agreement will have been developed as part of the initial project scoping process with a SAIL analyst.

Do not continue with this form until you have had your project scoping discussion. Please provide the agreement number: 0768

1a. Provide contact details of project lead:

Name: Kathryn Peall

Job title: MRC Clinician-Scientist Fellow, Clinical Senior Lecturer and Honorary Consultant Neurologist

Organisation: Cardiff University

Address: Neuroscience and Mental Health Research Institute, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ

Tel:

02920

688338

Fax:

Email: PeallKJ@cardiff.ac.uk

1b. Provide contact details of the lead contact from any other organisation who will be accessing the data:

	Name	Job title	Organisation
1			
2			
3			
4			

2. **Provide full title of the project:** Investigating the clinical and social characteristics of dystonia

3. **Provide details on who is commissioning the project:** Dystonia Medical Research Foundation

4. **Provide the aim of the project, including anticipated outcomes:**

Background

Our main research interest is dystonia – a common, yet under recognised movements disorders – present both in isolation (primary dystonia), and as part of neurodegenerative movement disorders (for example Parkinson's disease and Huntington's disease). In addition to the motor phenotype, non-motor symptoms (notably psychiatric symptoms) are a recognised component of the dystonia clinical phenotype. To date, little work has sought to address the true reported prevalence of dystonia, prescribing practices and the impact that the disorder and its management has on day-to-day living.

Aims:

To better understand the clinical and social features associated with dystonia. This will be done through:

a) Identification of the prevalence of dystonia diagnosed in Wales, and rates of associated medical comorbidities
b) prescribing practices for the treatment of motor symptoms in dystonia
c) prescription of medication for the treatment of non-motor symptoms in dystonia – with particular emphasis on the use of anti-depressants and anxiolytics
d) Use other forms of therapy e.g. physiotherapy and Deep Brain Stimulation (DBS)

15) Anecdotal evidence supports that individuals with dystonia often have difficulty accessing the work place owing to both motor and non-motor symptoms, and therefore we would plan to investigate whether there was any link between the clinical disorder and social deprivation

Anticipated outcomes

a) identification of the number of individuals diagnosed with Dystonia currently registered with SAIL
b) identification of potential associated medical co-morbidities not currently recognised
c) Comprehensive understanding of past and current medical therapy
d) Estimates of those having received DBS, and other treatments e.g. physiotherapy
e) Indication of the breadth of social demographic of those with dystonia.

We aim to publish this work in high-impact, peer-reviewed publications, as well as to develop clinical service provision within Wales.

Please include a copy of the protocol/plan for the proposed work with SAIL, including the contact details of any co-applicants when you return your completed form.

5. Provide a lay summary of the project: Dystonia is the third most common movement disorder worldwide, and is caused when opposite muscle groups are over active, causing pain, spams and abnormal body positions and postures. The most common part of the body to be affected is the neck or arms, but the legs and body can also be affected, particularly in children. As well as problems with movement, research studies have also shown that people with dystonia often have psychiatric symptoms, particularly depression and anxiety. The combination of difficulties with movement and mood often result in problems with work and education, having a big impact on day-to-day living. Although dystonia is common, it is often difficult to diagnose, with individuals waiting months or years before receiving a diagnosis and treatment. The treatment itself can also be complex, with physiotherapy, medication and surgery available.

Our aim with this project is to better understand: a) the number of people with a diagnosis of dystonia in Wales, b) the number and types of medication they've

received to treatment the movement and mood symptoms, c) whether they've received other forms of treatment, for example physiotherapy and surgery,

15) how this has impacted their day-to-day living, particularly access to jobs.

7. Provide information on the relevant permissions you have obtained or that are being sought:			
	Obtained	*Being sought*	*Not required*
Research ethics	[☒]	[☐]	[☐]
Please state the name of the committee that is being applied to/ has given approval, as applicable:			

Research ethics committee: **REC Wales.**
Study Title: Move Wales: Welsh Movement Disorders Research Network
REC reference: 14/WA/0017
IRAS project ID: 146495

If you have ticked 'not required' please specify the reasons:

☐ The project will use only anonymised data, and therefore research ethics review is not required.
☐ Other:

	Obtained	*Being sought*	*Not required*
Independent peer review	[☒]	[☐]	[☐]

Please state the name of the peer reviewing organisation that is being applied to/ has given approval, as applicable:
Peer reviewing organisation: **The Dystonia Society UK, and Dystonia Medical Research Foundation**

If you have ticked 'not required' please specify the reasons:

	Obtained	*Being sought*	*Not required*
Permission from data-holding organisation to use their datasets	[☒]	[☐]	[☐]

Please state the name of the data provider that is being applied to/ has given approval, as applicable:
Data organisation: **Cardiff Movement Disorders Service for which I am the clinical lead. All data uploaded will be from participants consented to the Welsh Movement Disorders Research Network.A data sharing agreement has also been completed.**

If you have ticked 'not required' please specify the reasons.

☐ The project uses only SAIL unrestricted core datasets and/or data held by the project.
☐ Other:

Please note that it is the responsibility of the project lead to ensure that the relevant permissions are obtained.

15. **Provide an outline of the public engagement strategy for the study, or a brief explanation why there is not public engagement:** Pre-project engagement:
Working alongside our research team is the movement disorders patient and public involvement group. This includes inidviduals diagnosed with a range of movement disorders, including dystonia. This project has been discussed, and supported particularly in its breadth and potential to better understand dystonic disorders.

This project has also been discussed at a recent regional Dystonia UK lay group meeting (21st March 2018, University Hospital of Wales, Cardiff), together with a number of members of the national Dystonia UK team. The consensus was that this was much needed work, and would provide an impetus for further, potentially national and international projects of its kind.

Engagement with the public (results and outcomes):

As a medical advisor to The Dystonia Society UK, and lead of the Cardiff movement disorders service, myself and my team are uniquely positioned to maximise the output from this work. We would aim to communicate the findings at both local and national Dystonia UK meetings, as well as through the weekly Dystonia UK ebulletin and annual print newsletter (estimated membership 70,000). This has already been discussed with the Society (locally and nationally), with support from the CEO and lay members.

Engagement with professionals (results and outcomes):

We aim to present this work at local, national and international conferences, and to publish this work in high-impact, peer-reviewed journals.

8a. Provide a prospective start date for the work involving SAIL: (dd/mm/yy)
01/06/2018

8b. Provide anticipated end date of the project: (End date OR time duration after approval) 31/12/2019

9a. Provide details of data you require access to for the proposed work with SAIL?

Please list:

The SAIL datasets you require information from

Outpatient

Primary Care GP

Welsh Demographic Service

Patient Episode Database for Wales

The information needed from each dataset

Outpatient

details of contact with specialist services, which would include previous/ongoing review within neurologic services, as well as specific treatments delivered within the out-patient sector, such as neurotoxin therap

Primary Care GP

for the identification of individuals with a diagnosis of dystonia, details of other documented medic disorders, listed medication

Welsh Demographic Service

WIMD quintile, WIMD score and Townsend score to address questions relating to whether social deprivatio is linked with the disorder, and whether this could potentially be due to social causation or social drift.

Patient Episode Database for Wales

to identify inpatient epsiodes principally related to treatment – for example Deep Brain Stimulation, or some settings neurotoxin injection – both recognised and important treatments for dystonia

Please indicate the time period for which data is requested

January 1st 2000 to December 31st 2017

Please indicate the geographic area for which data is requested All

Wales

Please indicate demographic criteria for the data requested (age, gender, etc.) All

inidviduals diagnosed with dystonia. No restrictions of age or gender.

9b. Will you be providing any other dataset(s) to be incorporated into the SAIL databank?

Yes [☒] No [☐]

If yes:

Provide the name of the dataset(s): Cardiff Movement Disorders dataset

Provide details of the contents of the dataset(s): This will include 100 cases known to our clinical service with a diagnosis of dystonia – this will be used for validation of the dataset.

9c. Provide an outline of your analysis plan including the anticipated outputs: Analysis will be undertaken by experience members of the Welsh Movement Disorders Research Network using the R statistical software programme. Using a variety of statistical analysis techniques, we will aim to look for:

evidence of an association between dystonia and other medical co-morbidities

rates of prescription of individual medications for motor and non-motor symptom, 465ndividua

simultaneous prescription of multiple medications. We will also look for evidence of a correlation between use of medication for motor symptoms and use of anti-depressants/anxiolytics, as well as differences in prescription of anti-depressants/466ndividuall based on 466ndividual of motor symptoms.
rates of attendance of physiotherapy and neurology outpatient services, and whether this correlates with prescribed medication
descriptor of Townsend score across the whole cohort, and whether any association exists between this and prescribed medication – motor and non-motor symptom treatment 466ndividually and in combination.

9d. Are the results/methods developed likely to have other potential applications?

Yes [☒] No [☐]

If yes, please specify: The results obtained from this study are likely to have a number of potential future applications:
development of clinical management guidelines for addressing motor and non-motor symptoms in primary and secondary care
development of non-medication treatments in the management of dystonia e.g. physiotherapy. The results from this work have the potential to form a framework for the application of future research funding to develop targeted treatment plans, similar to that which has been achieved with Parkinson's disease
opportunity for greater public awareness of dystonia and its implications to daily living both inside and outside the home.

10a. Please indicate your plans for publishing the results of your project, e.g. target journal or intended recipients of report:

As outlined in the engagement section above. Targeted journals will be those with a large readership of general physicians, neurologists, movement disorders specialists and those working in allied professions.

10b. What are the potentially sensitive issues that need to be taken into account when publicising the findings of the project?

Please outline the issues and your proposed solutions:

This is difficult to anticipate at this point as the frequency of dystonia diagnosis beyond those receiving ongoing treatment is not known in any population group. However, there exists a potential of only small numbers being linked with specific co-morbid diagnoses or treatments. If this were to be the case, we would aim to report the results in a way that has less potential for disclosure, avoiding

e.g. frequency tables linking the diagnosis of dystonia with other diagnoses.

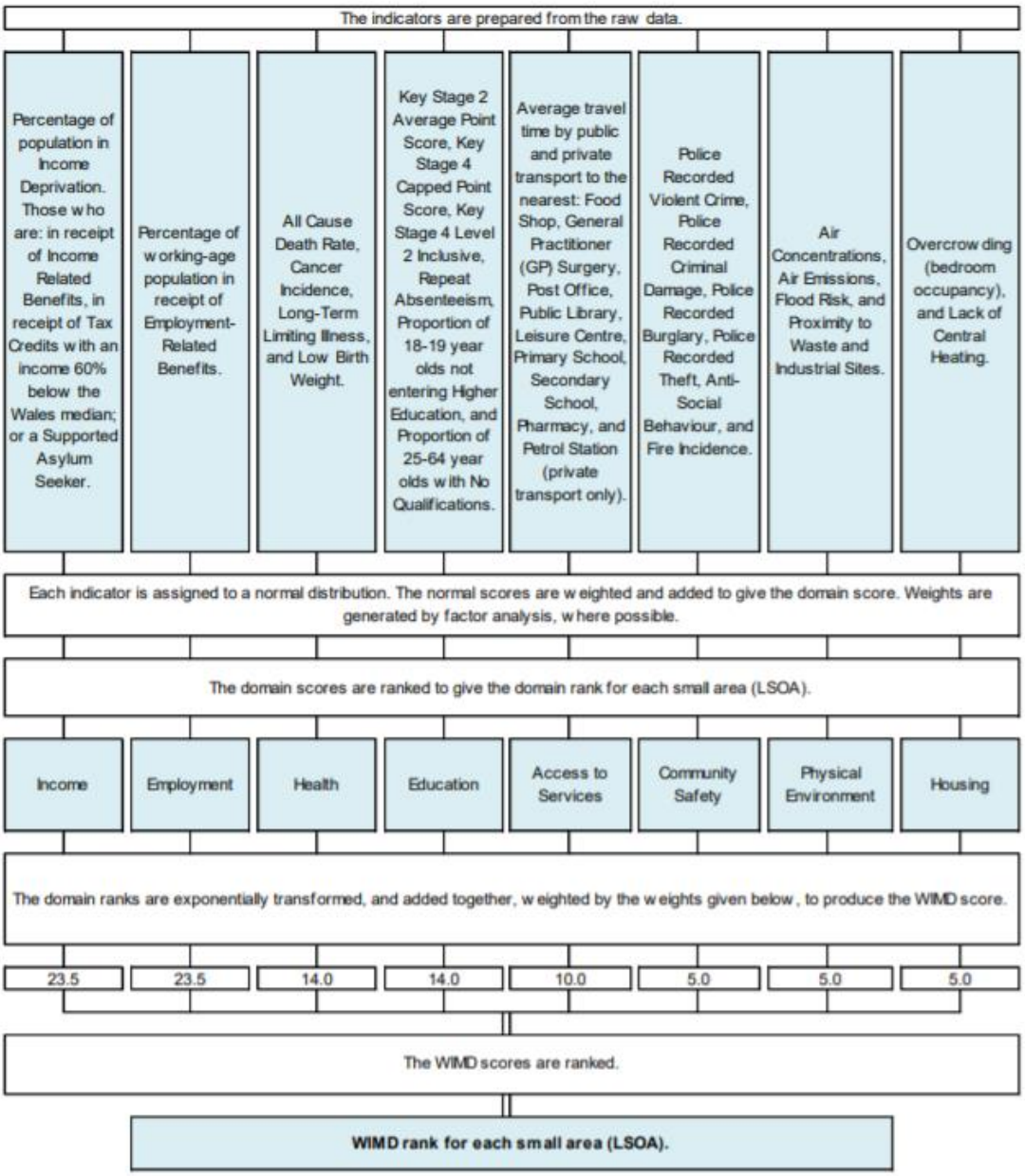
What to do next

Please return your completed form and supporting documents by email to Cynthia McNerney, Information Governance Coordinator c.l.mcnerney@swansea.ac.uk

Thank you.

2 Welsh Index of Multiple Deprivation (2014)

The following diagram provides a more detailed description of how WIMD is calculated.



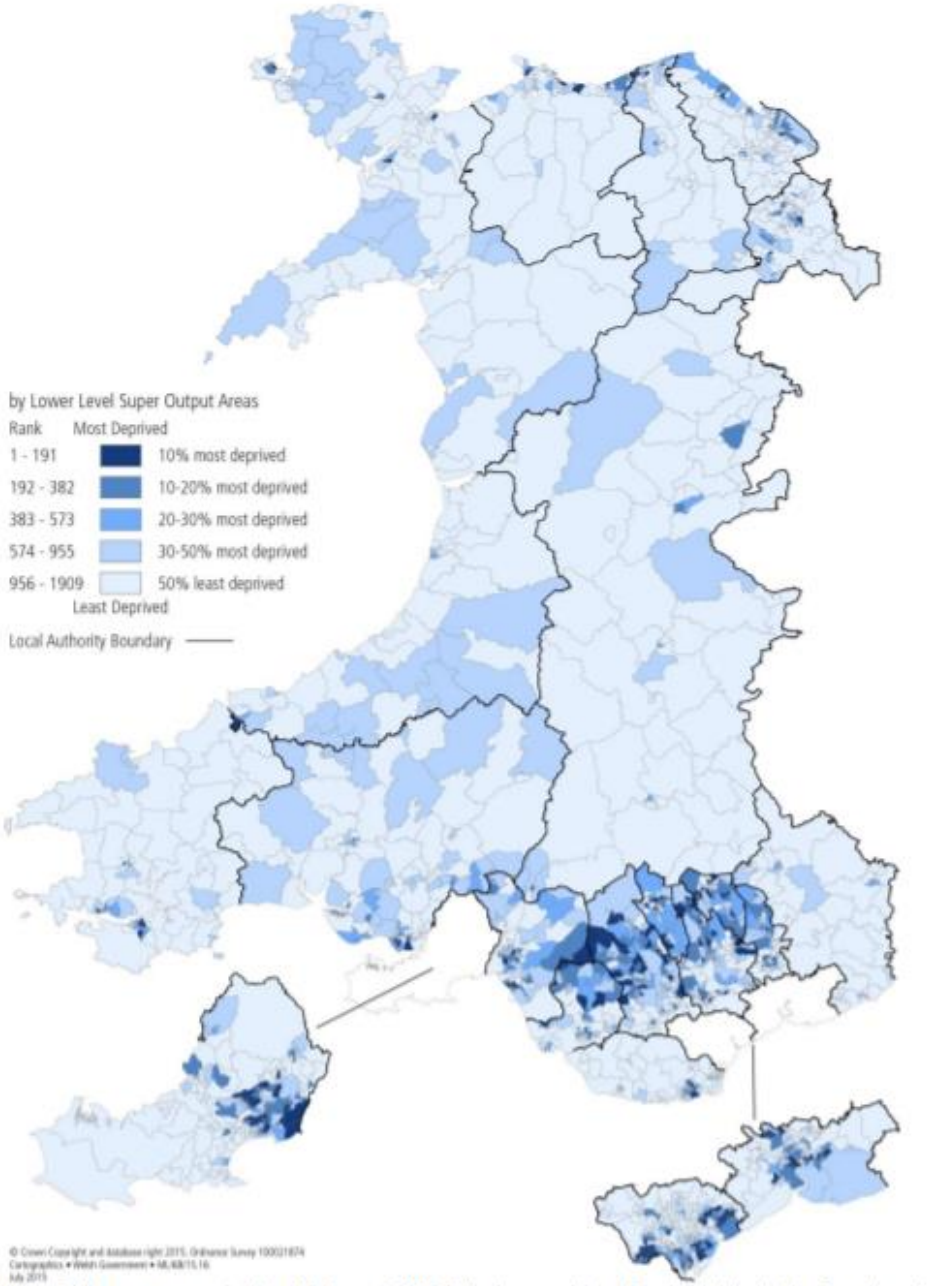
WIMD is constructed from a weighted sum of the deprivation score for each domain. The weights reflect the importance of the domain as an aspect of deprivation, and the quality of the indicators available for that domain. The domain weights for WIMD 2014 are:

Income	23.5%
Employment	23.5%
Health	14.0%
Education	14.0%
Access to Services	10.0%
Community Safety	5.0%
Physical Environment	5.0%
Housing	5.0%

The overall methodology used within WIMD 2014 is the same as used for WIMD 2011. The domains have also remained the same. There have been a small number of changes to individual indicators (or the inclusion of new indicators) within the Income, Education, Access to Services, Community Safety, Physical Environment and Housing domains; as well as some technical changes to some of the individual domains.

Welsh Index of Multiple Deprivation 2014

Welsh Index of Multiple Deprivation



Note: This map was revised on 12 August 2015 following provision of revised data by the Department for Work and Pensions (DWP).

12

3. Participant information sheet

3.1 Move Wales participant information sheet for individuals with a movement disorder

Move Wales: Welsh Movement Disorder Research Network (WMDRN)

Research Participant Information Sheet

We would like to invite you to participate in our research project. This project aims to study the causes of a wide range of movement disorders. We are inviting people diagnosed as having these disorders and unaffected volunteers.

What is the aim of the study?

We aim to identify variation in inherited material (DNA, Genes) that may cause, or increase the risk of movement disorders. This may occur when many people in a family are affected by a similar movement disorder but also sometimes occur when only one person is affected. We will also study blood markers that may help in diagnosis or in monitoring disease progression. This may improve our ability to diagnose these disorders and help in the development of new treatments.

Why have I been asked to participate?

You have been asked to participate because you have one of the disorders included in this study.

How can I participate?

If you would like to take part in the study we will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form or complete an electronic version of the consent form using a tablet device. You will be able to choose whichever method of consent you prefer and a member of the research team will be available to assist you throughout.

As part of this form we will ask for your consent to review your clinical notes and investigations, your permission to carry out a clinical assessment that may also include a video taped examination that can be reviewed by other specialists from other Universities and NHS organisations. We will also ask for your consent to take, store and analyse a blood sample for genetic and chemical analysis. If it is not possible to take a blood sample we may ask you to provide a saliva (spit) sample. You may also be asked if you're willing to provide a skin sample (biopsy), if so, the procedure will be carried out by a doctor specifically trained in this technique.

Study procedures will usually be performed by a member of the Cardiff University research team but may from time to time be performed by external collaborators who are not employed directly by Cardiff University (for example, NHS staff or students). All collaborators working on the study will have received appropriate training and will be appropriately qualified to perform study procedures and take samples from you.

We would also like to see how you are getting on over the next few years, in particular how you've responded to any treatment. We will send you a small pack of questionnaires once a year that we would be grateful if you could return in the SAE provided. If you would like, we can always go through these with you on the phone. As well as this we would also like to review how your health is generally. This will involve asking if you've developed any additional health problems, whether you have seen any other specialists, had contact with any other health services (for example, community physiotherapy) and whether you have been admitted to a care or nursing home, or any other health facility.

Some patients undergo surgery as part of their treatment (e.g. Deep Brain Stimulation). If you were to receive surgery we would be very interested to see how you respond, both in terms of the movement disorder and pain, sleep, mood and quality of life. In this case we would like to repeat the assessment at 3, 6, 12 and 18 months after your surgery. This would again involve a videotaped assessment of your movements and the same questionnaires.

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How will the blood sample be taken?
We will take approximately 35ml of blood from a vein in your arm. This is a standard procedure that takes place routinely in hospitals. There may be some minor discomfort and there are very small risks of bruising or local infection, both of which can be treated. If it is not possible to take a blood sample we may ask you to provide a saliva (spit) sample. This will involving spitting into a small, specifically designed container. In some cases we may ask to take a buccal cell sample as well. This will involve swabbing the inside of you cheek and using this sample for further genetic analysis.

How will the skin sample (biopsy) be taken?
The skin sample will be taken by a doctor trained to carry out this procedure. The doctor will re-check that you're willing to undergo the procedure, review your medical history and check any current medication that you may be taking. They will then select an area of skin from which to take the sample (usually the top of the arm or top of the leg). A local anaesthetic injection will be used to numb the skin in this area. This may cause some stinging of the skin, but this which usually resolves quickly. Once the skin is numb, a sample of the skin will be obtained using a specifically designed tool (punch biopsy). This will remove a sample of skin that is approximately half a centimetre wide. The wound will then be stitched using dissolvable stitches and a dressing placed over the top. There may be some discomfort around this site as the anaesthetic wears off, but this should improve over the next day or so. You will be given written information regarding the care of the wound and the doctor will go through this with you on the day of the procedure. There is a small risk of infection at the site of the wound, so should you experience any problems after the procedure, please contact the study doctor (details at the bottom of this information sheet) or your GP.

What will happen to my blood/saliva/skin sample after that?
Inherited material (e.g. DNA, RNA, Genes) as well as other parts of the blood (e.g. serum, plasma) will be extracted from the blood/saliva sample at a local facility. On some occasions we may need to send the sample to a commercial company that specialises in this process. Your sample will be anonymised throughout and the extracted material returned to the research team at the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University. In addition, a "cell line" may be created from the blood/skin sample. This means that a) new cells can be grown more than once from the original sample to make sure there is enough genetic material is available for future research, and b) disease relevant cell models can be created to investigate the function of genes that cause movement disorders. The cell lines will be anonymously coded and stored for an indefinite period.

The sample will be treated as a gift for research, stored and used in on-going and future projects. Your tissue may be retained at the end of this study for use in future research within the UK and abroad. At this stage we do not know what the research will involve but some of it could include further genetic research, animal research or use in the commercial sector. On the consent form you will be given the option to opt out of all future research. At no point will your tissue be sold.

How does the analysis work?
We will analyse the inherited material (DNA, genes) to see if new genes changes, which may directly cause the disorder, are present. We will also investigate whether common variants (common DNA changes) increase the risk of the disorder in the population and/or change the characteristics of the disorder. The main studies will be carried out by the Cardiff University research team involved in this project. To ensure that your contribution has its maximum impact, we may also work with collaborating groups in other high quality studies. All tissue will be supplied anonymously to researchers; only Dr Peall will be able to identify which tissue samples you donated. The recipients of the tissue will not be supplied with your name or any other identifiable information and will not be able to identify you from the tissue.

Can I receive direct results of my genetic analysis?
No. The tests in this study are performed on a research basis and cannot be used for clinical purposes. In some circumstances the research tests may indicate that future NHS based genetic or chemical testing may be useful in accurately diagnosing the disorder you have and in determining the risk to other family members. You can choose whether you wish to be informed about this in advance. If you do choose to be informed of future test development, we will arrange for you to be given appropriate genetic advice. This will be discussed with you by your doctor, a member of the Cardiff University clinical team who arranged the original research blood sample, or by Dr Kathryn Peall. Currently these types of tests do not lead to any new treatments or changes in your current treatment, although this may change in the coming years.

Can outside bodies (for example, insurance companies) access the research tests?
No. Each sample will be given a specific code. The link between this code and your name will be kept confidential. Coded samples (i.e. without your name) may be shared with other research groups for analyses. Any information collected during the study will be kept confidential, aside from enabling us to inform you about the development of new tests as described above. We will store the assessment and test results on a secure, confidential database. This will enable us to analyse the information collected during this study. When this study is complete we will continue to hold the data on our computer.

What will happen to the results of the study?
We plan to publish any results in scientific journals. Your name will not be mentioned in any publication. We will make regular reports to funding bodies and patient groups as well as providing updates in our annual newsletter.

What will happen to the information?
The clinical information collected during the study and your personal details will be kept in a clinical database on an NHS computer system. This computer network routinely holds personal details and test results for hospital networks. An anonymised, coded database holding personal and genetic data, without personal details, will be held on Cardiff University research computers, may be held by collaborators at other sites and may be made publicly available to enable combined analysis of samples from large patient series around the world.

What will happen to my samples at the end of the study?
As movement disorders are rare, any samples from patients with these disorders are extremely valuable and they will be invaluable to other research projects on these disorders. With your consent, we would like to store any left over samples anonymously for use in subsequent projects.

What are the benefits of participating?
We may learn more about your condition. We cannot promise that the study will help you but the information we get may help to better treat people with similar conditions in the future.

What happens if I chose not to participate?
Participation in the study is voluntary and choosing not to take part will not affect your current or future treatment in any way.

What happens if I don't want to carry on with the study?
Participation in this study is voluntary and you are free to withdraw at any time without giving a reason and without your medical care or legal rights being affected. If you do withdraw your consent your tissue will not be used further in this study and will be destroyed according to locally approved practices. Any tissue, or results derived from tissue, that has already been used prior to the withdrawal of consent will continue to be used in this study.

You may also withdraw your consent for the storage and future use of samples at any point. If you do withdraw your consent your tissue will not be used in any subsequent studies and will be destroyed according to locally approved practices. Any tissue already distributed for use in research prior to the withdrawal of consent will continue to

be used in that study and any tissue remaining at the end of the study will be destroyed.

Who can I contact about this study?

Dr Kathryn Peall
MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Maindy Road, Cathays, Cardiff, CF24 4HQ.
Tel: 029 20 688336
Email: **movementdisorders@cardiff.ac.uk**

(Please note that this is a non-secure email address. If wishing to discuss confidential information please email use with your contact number and a convenient time for us to phone, alternatively feel free to phone us directly)

3.2 Global Myoclonus participant information sheet for individuals with Myoclonus dystonia and primary dystonia

Participant information sheet for adults with other primary Dystonia conditions
(Version 3, Dated 26/02/2018)

Re: Clinical Study Short Title of Study:
Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study

West Midlands – Edgbaston Research Ethics Committee **Ref: 18/WM/0031**

Invitation to join study

1 You are being invited to take part in a research study. Before you decide whether or not you would like to participate, it is important for you to understand why the research is being done and what it will involve.
- *Part 1 tells you the purpose of this study and what will happen to you if you take part.*
- *Part 2 gives you more detailed information about the conduct of the study.*

2 Please take time to read the following information carefully. Talk to others about the study if you wish. The following person can give you independent advice, or can be your point of contact for any complaints relating to the study:
Dr Samantha Loveless
Telephone Number: +44 (0)29 2074 3454 Email: lovelesss1@cardiff.ac.uk

Part 1: About the Study

3 ***What is the purpose of the study?***
We are trying to understand the complete spectrum of symptoms that individuals with forms of primary Dystonia experience and how this impacts on day-to-day living. By comparing information from people with forms of primary Dystonia with people who have Myoclonus Dystonia and healthy controls, we hope that our study will improve the understanding of Dystonia's and help find better treatments in the future.

If you decide to take part, we will ask you to provide us with some basic information about you, your movement difficulties and general health. We will also ask you to complete a series of online cognitive tests and further questionnaires that will assess psychiatric factors, quality of life, quality of sleep and pain in order to help us better understand this disorder and to answer these important research questions.

4 ***Why have I been chosen?***
You have been chosen to participate in this study because you are at least 18 years of age and you have been referred to the Myoclonus Dystonia research group at Cardiff University, with a form of primary dystonia.

5 ***Do I have to take part?***
Participating in this study is completely voluntary; it is up to you if you choose to sign up or not. Your treatment will not be affected if you do not take part in the study.

6 ***What will I have to do?***
Taking part is voluntary; it's up to you if you choose to sign up. Your treatment will not be affected if you don't take part.

If you join us, you'll be asked whether you would be willing to:

- Provide us with your contact details (e.g. address, email address and phone number) and some personal information (e.g. date of birth, ethnic group and employment status).
- Answer some questions about your physical health and lifestyle. This will take approximately 10-15 minutes.
- Complete cognitive tests and further questionnaires that will assess psychiatric factors, quality of life, quality of sleep and pain. This could take up to 60 minutes or longer depending on how many times you return to the questionnaires. You will have the option of returning to the questionnaires as often as you wish. You will also be able to complete the survey in the comfort of your home/place of residence.
- Allow us to access and use the information in your routinely collected NHS records. This is to gain further details about the kinds of symptoms and treatments you have had. We would also like to look at your records in the future to see if there has been any change in your health.
- Allow us to contact you in the future about other studies that you may want to partake in. There will be no obligation for you to take part in these future opportunities.
- Allow us to contact you every 12 months to invite you to provide more information about your mental and physical health and lifestyle.
- Allow us to share anonymous information with other researchers if they have scientific and ethical approval for the questions that they would like to answer.

We will use your answers, together with the information from your NHS records, to improve our understanding of Dystonia and help find better treatments in the future.

Once you have joined, you can choose if you want to take part in any of the questionnaires, studies, or events that we tell you about when we get in touch with you.

Part 2: Detailed Information

7 *Who is doing the study?*

The Global Myoclonus Dystonia Registry and Non-Motor Study is funded by the Dystonia Medical Research Foundation, and is led by the research group at Cardiff University in the United Kingdom. The clinical lead for this study is Dr. Kathryn Peall.

8 *How can I join the study?*

You will have the opportunity to join the study once you have read through and understand the information.

9 *What are the possible benefits of taking part?*

We hope that learning more about Dystonia and the range of symptoms that people experience, will lead to new ways of treating the disorder. However, these remain long-term aims and you will not benefit directly from taking part in this study.

10 *Who will have access to my information?*

Only members of the team directly involved in the study and authorised by the Principal Investigator will have access to your details, and only they will contact you directly. These members are all aware of the laws that safeguard your privacy at every stage, as they have received adequate training in maintaining patient confidentiality in trials.

Your personal information will be kept confidential during the course of the research, in accordance with the Data Protection Act 1998 or General Data Protection Regulation, as applicable. This will be achieved by assigning a unique study code to your data when you register for the study.

Your name and identifying information will not be passed on to anyone, apart from extenuating circumstances when you may need to be referred for further treatment by clinicians outside of the team.

The team at Cardiff University may link the anonymised collected data to other routinely collected, anonymised datasets (such as those held in the Secure Anonymised Information Linkage [SAIL] databank), in order to answer future questions relating to Myoclonus Dystonia. In order that the data from this study can have maximum beneficial impact on research, we envisage sharing of your anonymised data with collaborating research groups and institutions in the UK and internationally. Other potential collaborators will also be able to apply for access to your anonymised data that we collect, provided that they have a clear outline of their research question.

11 *What questions will I be asked now?*

When you agree to take part and sign up, you will be asked to provide contact details and some other information about yourself such as your age and ethnic group. You will also be asked to answer some questions about your general and mental health, as well as some questions relating to lifestyle.

You will then be asked to complete a series of online cognitive tests and questionnaires that will assess a range of non-motor symptoms associated with Dystonia (such as anxiety, depression, pain, sleep problems).

The cognitive tests will be operated via the Cambridge Cognition Web-based Testing service. Cambridge Cognition Limited has set up and manages this application as part of this research study. When you use this application, you will be asked to provide information and conduct cognitive tests relevant to this research study. The privacy policy tells you what will happen to the information that is gathered by this application. Please take the time to read this policy. You can view this policy at:
http://download.camcog.com/Documentation/Privacy_Policies/WBT/ACA/ACA_WBT_Privacy_Policy.pdf

You can complete all questionnaires in your own time from home. As there will be a save and exit option, you will be able to re-visit the questionnaires as often as you like. Some of these questions will ask about very personal feelings therefore, if a question appears too intrusive, you will have the option of clicking on the "I do not wish to answer this question" option.

If any of the questions make you overly anxious, depressed, suicidal or causes a panic attack, please see your general practitioner or local specialist. In an emergency, please seek urgent medical help.

12 *How often will I be contacted?*

With your consent, we will contact you every 12 months to ask you questions about your general and mental health, and lifestyle. Sometimes we will ask for information that you haven't given before. Sometimes we will ask you the same questions as before so that we can see how your lifestyle and health are changing over time.

As well as this regular contact, the study team may contact you from time to time to ask you to take part in new studies. These contacts will normally be to everyone registered to this study, but it may also be because of something that you have told us about (for example, your age). These studies may be conducted by other research teams. We will give you more information about these studies, including why the research is being carried out, what you might be asked to do, and how to sign up. It is up to you to decide whether you want to take part in these new studies. It won't affect your participation in the overall Myoclonus Dystonia Study if you prefer not to get involved.

3.3 Global Myoclonus participant information sheet for controls

Participant information sheet for healthy volunteers / healthy spouses
(Version 3, Dated 26/02/2018)

Re: Clinical Study Short Title of Study:
Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study

West Midlands – Edgbaston Research Ethics Committee **Ref: 18/WM/0031**

Invitation to join study

1 You are being invited to take part in a research study. Before you decide whether or not you would like to participate, it is important for you to understand why the research is being done and what it will involve.
- *Part 1 tells you the purpose of this study and what will happen to you if you take part.*
- *Part 2 gives you more detailed information about the conduct of the study.*

2 Please take time to read the following information carefully. Talk to others about the study if you wish. The following person can give you independent advice, or can be your point of contact for any complaints relating to the study:
Dr Samantha Loveless
Telephone Number: +44 (0)29 2074 3454 Email: lovelesss1@cardiff.ac.uk

Part 1: About the Study

3 ***What is the purpose of the study?***
We are trying to understand the complete spectrum of symptoms that individuals with movement disorders (known as Myoclonus Dystonia and other forms of primary Dystonia) experience and how this impacts on day-to-day living. By comparing information from people who have forms of primary Dystonia or Myoclonus Dystonia with healthy controls, we hope that our study will improve the understanding of Dystonia's and help find better treatments in the future.

If you decide to take part, we will ask you to provide us with some basic information about you and your general health, in order to help us better understand this disorder and to answer these important research questions. We will also ask you to complete a series of online cognitive tests and further questionnaires that will assess psychiatric factors, quality of life, quality of sleep and pain in order to help us better understand this disorder and to answer these important research questions.

4 ***Why have I been chosen?***
You have been chosen to participate in this study because you are at least 18 years of age, and either:
- The healthy spouse of a patient who has been referred to the Myoclonus Dystonia research group at Cardiff University, with a form of primary dystonia; OR
- A healthy volunteer for this study, who does not have any movement disorders or psychiatric conditions.

5 ***Do I have to take part?***
Participating in this study is completely voluntary; it is up to you if you choose to sign up or not.

6 *What will I have to do?*

Taking part is voluntary; it's up to you if you choose to sign up. If you join us, you'll be asked whether you would be willing to:

- Provide us with your contact details (e.g. address, email address and phone number) and some personal information (e.g. date of birth, ethnic group and employment status).
- Answer some questions about your physical health and lifestyle. This will take approximately 10-15 minutes.
- Complete cognitive tests and further questionnaires that will assess psychiatric factors, quality of life, quality of sleep and pain. This will take up to 60 minutes or longer depending on how many times you return to the questionnaires. You will have the option of returning to the questionnaires as often as you wish. You will also be able to complete the survey in the comfort of your home/place of residence.
- Allow us to access and use the information in your routinely collected NHS records. This is to gain further details about the kinds of symptoms and treatments you have had. We would also like to look at your records in the future to see if there has been any change in your health.
- Allow us to contact you in the future about other studies that you may want to partake in. There will be no obligation for you to take part in these future opportunities.
- Allow us to contact you every 12 months to invite you to provide more information about your mental and physical health and lifestyle.
- Allow us to share anonymous information with other researchers if they have scientific and ethical approval for the questions that they would like to answer.

We will use your answers, together with the information from your NHS records, to improve our understanding of Dystonia and help find better treatments in the future.

<u>Part 2: Detailed Information</u>

7 *Who is doing the study?*

This study is funded by the Dystonia Medical Research Foundation, and is led by the research group at Cardiff University in the United Kingdom. The clinical lead for this study is Dr. Kathryn Peall.

8 *How can I join the study?*

You will have the opportunity to join the study once you have read through and understand the information.

9 *What are the possible benefits of taking part?*

Collecting data from healthy controls like yourself will allow us to compare data from healthy controls with those who have movement disorders, such as Myoclonus Dystonia and other forms of dystonia. We hope that learning more about Dystonia conditions and the spectrum of symptoms that people experience, will lead to new ways of treating the disorders. However, these remain long-term aims.

10 *Who will have access to my information?*

Only members of the team directly involved in the study and authorised by the Principal Investigator will have access to your details, and only they will contact you directly. These members are all aware of the laws that safeguard your privacy at every stage, as they have received adequate training in maintaining patient confidentiality in trials.

Your personal information will be kept confidential during the course of the research, in accordance with the Data Protection Act 1998 or General Data Protection Regulation, as applicable. This will be achieved by assigning a unique study code to your data when you register for the study. Your name and identifying information will not be passed on to anyone.

The team at Cardiff University may link the collected data to routinely collected, anonymised datasets (such as those held in the Secure Anonymised Information Linkage [SAIL] databank), in order to answer future questions relating to Myoclonus Dystonia. In order that the data from this study can have maximum beneficial impact on research, we may share your anonymised data with collaborating research groups and institutions in the UK and internationally. Other potential collaborators will also be able to apply for access to your anonymised data that we collect, provided that they have a clear outline of their research question.

11 What questions will I be asked now?

When you agree to take part and sign up, you will be asked to provide contact details and some other information about yourself such as your age and ethnic group. You will also be asked to answer some questions about your general and mental health, as well as some questions relating to lifestyle.

You will then be asked to complete a series of online cognitive tests and questionnaires that will assess levels of Obsessive-Compulsive Disorder (OCD), anxiety, depression, sleep disturbance and pain. These questionnaires have been separated into three parts (Part 2a, Part 2b and Part 3). You can complete these in your own time from home. As there will be a save and exit option, you will be able to re-visit the questionnaires as often as you like. Some of these questions will ask about very personal feelings therefore, if a question appears to be too intrusive, you will have the option of clicking on the "I do not wish to answer this question" option.

The cognitive tests will be operated via the Cambridge Cognition Web-based Testing service. Cambridge Cognition Limited has set up and manages this application as part of this research study. When you use this application, you will be asked to provide information and conduct cognitive tests relevant to this research study. The privacy policy tells you what will happen to the information that is gathered by this application. Please take the time to read this policy. You can view this policy at:
http://download.camcog.com/Documentation/Privacy_Policies/WBT/ACA/ACA_WBT_Privacy_Policy.pdf

12 How often will I be contacted?

You will only complete the questionnaires on one occasion. However, the study team may contact you from time to time to ask you to take part in new studies. These contacts will normally be to everyone registered to this study, but it may also be because of something that you have told us about (for example, your age). These studies may be conducted by other research teams. We will give you more information about these studies, including why the research is being carried out, what you might be asked to do, and how to sign up. It is up to you to decide whether you want to take part in these new studies. It won't affect your participation in the overall Myoclonus Dystonia Study if you prefer not to get involved.

13 How long will it take?

First you need to join the study. This involves reading this information and then giving your consent. Take as much time as you need to decide whether you wish to take part. If you want to participate in the study, it should take about 5 minutes to give your consent.

Once you have given your consent, completing a series of questions relating to your mood, memory, sleep, pain and quality of life should take up to 60 minutes to finish. We know that we get the best data if you are able to complete these questions in one go, but if for some reason this isn't possible then you

can come back to the website later, as you can save your answers once you have finished a set of questions.

14 Can I decline or withdraw from the study?

You do not have to take part in this study. If you do decide to take part you are still free to withdraw at any time without giving a reason. If you decide to withdraw from this study, all details you have provided will be destroyed. These will not be used further in the research.

15 What happens when the study is finished?

This is a long-term study that will allow us to learn a lot about Myoclonus Dystonia and other primary Dystonia conditions and their related symptoms. The information you provide will be stored for use on a long-term basis (at least 15 years). The team at Cardiff University may link the collected data to routinely collected, anonymised datasets (such as those held in the Secure Anonymised Information Linkage [SAIL] databank), in order to answer future questions relating to Myoclonus Dystonia.

You will not have any claim to any future commercial use of the results from the study in which your data has been used. To make best use of the resources, we will share data (anonymised to exclude any personal details) with different groups of researchers from the NHS, universities and commercial companies, throughout the world. However, we would stress that those organisations will never obtain access to personal/identifying information (for example, your name, address, date of birth).

16 Who has reviewed the study?

Ethical approval has been obtained from the West Midlands – Edgbaston Research Ethics Committee (Ref: 18/WM/0031), and NHS (Research and Development) permission has also been obtained. If you have further questions about the study, please contact the study team

Welsh Movement Disorders Research Network
Neuroscience and Mental Health Research Institute,
Hadyn Ellis Building,
Maindy Road,
Cardiff CF24 4HQ
Telephone number: 0044 29 20 688338
Email: movementdisorders@cardiff.ac.uk

If you would like to discuss this study with someone independent of the study, or you have any complaints in relation to the study, please contact:

Dr Samantha Loveless
Lab Manager
Neurology Academic Department,
B4-C4 Link Corridor,
University Hospital of Wales,
Heath Park,
Cardiff,
CF14 4XW
Telephone Number: 0044 (0)29 2074 3454
Email: lovelesss1@cardiff.ac.uk

4 Consent forms

4.1 Move Wales consent form for adults with movement disorders and controls

Move Wales: Welsh Movement Disorder Research Network (WMDRN)

Consent Form: for all participants over 16 years consenting to participate in the study

Study Number:

Participant:

Date of Birth:

Date:

Name of Researcher: **Initial boxes to agree**

1. I have read and understood Version 3 of the Move Wales (WMDRN) patient information sheet and been given a copy to keep. I have had the opportunity to ask questions about the project and I understand why the research is going to be done and any foreseeable risks involved. ☐
2. I understand that my participation is voluntary and that I am are free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to give a sample of blood/saliva/buccal cells for research in the above project. This sample will be used to study inherited material (DNA, RNA), the blood chemistry (plasma, serum) and creation of cell lines. ☐
4. I agree to give a sample of skin (skin biopsy) for research in the above project. This sample will be used in the creation of cell lines to study the function of genes known to cause movement disorders. ☐
5. I give permission for my medical records, including investigations, X-Rays and scans to be looked at confidentially by members of the Cardiff University research team who would not normally be involved with my clinical care. ☐
6. I give permission for ongoing collection of my health related information, including contact with other health services/specialists/institutions. ☐
7. If possible, I would like to be informed or research results that might indicate that a test could be developed which may be of use to me or my family. ☐

MoveWales_Consent_Case_v3
29/10/2019

8. I agree that the DNA and blood samples that I have given can be looked after and stored for use in current and future projects, as described in the information sheet. ☐

9. I agree that my own doctor (GP and/or hospital) can be informed of my involvement in this study if they have not already been involved. ☐

10. I agree that my clinical details can be stored in a clinical research database on the NHS hospital computer network and understand that a separate anonymised Cardiff University research database will be used to store research results. The anonymised DNA information may be made publicly available to enable large-scale analysis. ☐

11. I am happy to be contacted by telephone/letter/email to obtain more information or about future research projects (please delete any means by which you wish not to be contacted) ☐

12. I give permission for a videotape examination, in which I am personally identifiable, to be stored as part of my clinical assessment and to be used for teaching and research purposes. ☐

Thank you for your participation in this study

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

4.2 Myoclonus Dystonia Registry and Dystonia Non-Motor Symptoms Study for adults with primary dystonia

Global Myoclonus Dystonia Registry and Dystonia Non-Motor Symptoms Study

Consent Form for all adult participants with other forms of Primary Dystonia

Study Number:

Name of participant: Code Number:

Date of Birth:

Date: Name of Researcher:

		Initial boxes to agree
1.	I have read and understood Version 3 of the *Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study* participant information sheet and been given a copy to keep. I have had the opportunity to ask questions about the project. I understand why the research is going to be done and any foreseeable risks involved.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I agree to join the registry by providing contact details (name, postcode, email address, phone number) and some details about myself (such as my gender, date of birth, ethnic group, details about my dystonia symptoms, general health problems and current/past treatment methods).	
4.	I agree to complete some questionnaires about my lifestyle, mental and general health.	
5.	I consent to the use of the information I provide as part of this study and consent to the use of my information in accordance with Cambridge Cognition's privacy policy.	
6.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Cardiff University, from regulatory authorities, or from the NHS Trust/Health Board, where relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
7.	I allow the team at Cardiff University to link the information I provide to routinely collected, anonymised datasets (such as those held in the Secure Anonymised Information Linkage (SAIL) databank, in order to answer future research questions related to Myoclonus Dystonia. I understand that the data within any such dataset will be fully anonymised by allocating my details with a unique code, and I would not be identifiable in any way.	
8.	I agree that my details can be stored in a clinical research database on the NHS hospital computer network for 15 years.	

Other forms of dystonia_MD Registry and NMS Study_Consent_v3 26/02/2018

9.	I agree that my own doctor (GP and/or hospital) can be informed of my involvement in this study if they have not already been involved, as a matter of courtesy.	
10.	I agree to being contacted by the study team who will provide updates about the Myoclonus Dystonia Registry research, and inform me about other studies that I may want to take part in (for example, via your Move Wales newsletters).	
11.	I agree to being contacted every 6-12 months or so by the study team to invite me to provide updated information about my physical and mental health, and lifestyle.	
12.	I give permission to the team at Cardiff University to share my anonymised information with other researchers.	
13.	I agree to being withdrawn from the study if I lost the capacity to provide consent in the future. If this occurs, I agree for you to retain any identifiable and non-identifiable data that I provided before losing capacity to provide my consent.	
14.	I am happy to be contacted by telephone/letter/email to obtain more information or about future research projects (please delete any means by which you wish to not be contacted).	

Thank you for your participation in this study

Name of Participant	Date	Signature

Name of Researcher	Date	Signature

4.3 Myoclonus Dystonia Registry and Dystonia Non-Motor Symptoms Study consent form for controls

Global Myoclonus Dystonia Registry and Dystonia Non-Motor Symptoms Study

Consent Form for all adult healthy participants

Study Number:

Name of participant: Code Number:

Date of Birth:

Date: Name of Researcher:

		Initial boxes to agree
1.	I have read and understood Version 3 of the *Global Myoclonus Dystonia Registry and Non-Motor Symptoms Study* participant information sheet and been given a copy to keep. I have had the opportunity to ask questions about the project. I understand why the research is going to be done and any foreseeable risks involved.	
2.	I understand that my participation as a control subject for this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I agree to provide my contact details (name, postcode, email address, phone number) and some details about myself (such as my gender, date of birth, ethnic group).	
4.	I agree to complete some questionnaires about my lifestyle, mental and general health.	
5.	I consent to the use of the information I provide as part of this study and consent to the use of my information in accordance with Cambridge Cognition's privacy policy.	
6.	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Cardiff University, from regulatory authorities, or from the NHS Trust/Health Board, where relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
7.	I allow the team at Cardiff University to link the information I provide to routinely collected, anonymised datasets (such as those held in the Secure Anonymised Information Linkage (SAIL) databank, in order to answer future research questions related to Myoclonus Dystonia. I understand that the data within any such dataset will be fully anonymised by allocating my details with a unique code, and I would not be identifiable in any way.	
8.	I agree that my details can be stored in a clinical research database on the NHS hospital computer network for 15 years.	

9.	I agree to being contacted by the study team who will provide updates about this study, and inform me about other studies that I may want to take part in (for example, via your Move Wales newsletters).	
10.	I give permission to the team at Cardiff University to share my anonymised information with other researchers.	
11.	I agree to being withdrawn from the study if I lost the capacity to provide consent in the future. If this occurs, I agree for you to retain any identifiable and non-identifiable data that I provided before losing capacity to provide my consent.	
12.	I am happy to be contacted by telephone/letter/email to obtain more information or about future research projects (please delete any means by which you wish to not be contacted).	

Thank you for your participation in this study

Name of Participant	Date	Signature

Name of Researcher	Date	Signature

5 Myoclonus Dystonia Registry Questionnaire for adults with primary dystonia

Global Myoclonus Dystonia and Non-Motor Symptoms Study Questionnaire Pack (REC: 18/WM/0031)

Enter your diagnosis: _____

Enter date of completing questionnaire pack: _____

Preliminary Questions about you

1. **What is your date of birth?**

2. **How old are you?**

3. **What was your age of onset of Myoclonus Dystonia/Dystonia symptoms?**

4. **What is your gender?**

5. **Please write here your General Practitioner (GP) contact details (Name and Address):**

6. **Please state the ethnic origin of yourself, your mother and your father by ticking below:**

		Yours	Mother	Father
White	British			
	English			
	Welsh			
	Scottish			
	Irish			
	Northern Irish			
	Gypsy or Irish Traveller			
	Any other white background			

Asian	Indian			
	Pakistani			
	Bangladeshi			
	Chinese			
	Any other Asian background			

Mixed/ Multiple ethnic groups	White and Black Caribbean			
	White and Black African			
	White and Asian			
	Any other mixed or multiple ethnic backgrounds			

Black/ Black British	African			
	Caribbean			
	Any other Black/African/Caribbean background			

Other ethnic group	Arab			
	Any other ethnic group			

Unknown	Unknown

7. **What was the highest level of education that you completed? Select from the list below:**

   Secondary School (left school at 16 years of age)

   6th Form College (left school/college at 17 or 18 years of age)

   University (Undergraduate)

   University (Postgraduate)

8. **What is your current state of employment?**

   Employed (including being on temporary leave from work for any reason)

   Self-employed or freelance

   Out of work and looking for work

   Out of work but not looking for work

   A homemaker

   A student

   Retired

   Volunteering

   Unable to work (including those receiving Disability Living Allowance)

9. **What is your marital status?**

Single

Unmarried but have a partner

Married

Divorced

Widowed

<u>About your family history and your general health</u>

10. Please state your Family History (i.e. known key conditions experienced by your immediate family – mother, father, siblings, aunts, uncles)

11. Do you have any other problems with your general health?

Yes **No**

IF YES, please select the condition(s) from the list below:

Heart:	☐ Ischaemic Heart Disease; ☐ Irregular heart rhythms; ☐ Prosthetic heart valve; ☐ Cardiac failure; ☐ Congenital Cardiac Malformation ☐ Cerebrovascular disease; ☐ High blood pressure
Lungs:	☐ Chronic obstructive pulmonary disease (COPD)/Chronic obstructive airway disease (COAD); ☐ Asthma
Kidneys:	☐ Chronic kidney disease; ☐ Chronic kidney disease with high blood pressure
Liver:	☐ Chronic liver disease
Transplant:	☐ Transplanted (any) organ; ☐ Pre-transplant/ chemo /bisphos assessment
Epilepsy	☐ Epilepsy
Diabetes:	☐ Diabetes type 1; ☐ Diabetes type 2
Infectious disease:	☐ HIV disease; ☐ Hepatitis B; ☐ Hepatitis C; ☐ Other infectious disease
Bleeding disorders:	☐ Bleeding disorders; ☐ Long-term anticoagulant therapy; ☐ Sickle-cell disease
Osteoporosis:	☐ Bisphosphonate therapy; ☐ Congenital malformation of skull/face bones
Cancer:	☐ Cancer current disease; ☐ History of malignant disease
Drug dependence:	☐ Alcohol dependence; ☐ Cannabis dependence; ☐ Cocaine dependence; ☐ Heroin/methadone dependence; ☐ Drug dependence (combination)
Endocrine:	☐ Endocrine disorder; ☐ Disease of digestive system
Autoimmune:	☐ Autoimmune disease; ☐ Arthritis
Other	☐ **Please state:**

About your lifestyle

12. How much do you smoke per day?

None **Less than 10** **11-20** **Greater than 20**

13. How much alcohol do you drink per week (units/week)? Please refer to the image below for the drink measurements equivalent to 1 unit:

None **Less than 14** **14-21** **Greater than 21**

<u>Botox treatment</u>

15. a) Are you receiving Botox treatments for your dystonia symptoms?

Yes **No** **No, I am a healthy volunteer**

IF YES: b) How effective has this Botox treatment been for you?

Very effective

Somewhat effective

Not effective

Has made my symptoms worse

15) How frequently are you having the Botox treatment?

Once a month

Once every 3 months

Once every 6 months

Once a year

Other (please state)

15. **a) Have you previously had Deep Brain Stimulation (DBS), or been referred for DBS?**

Yes **No**

IF YES: b) How effective has this Deep Brain Stimulation been for you?

Very effective

Somewhat effective

Not effective

Has made my symptoms worse

<u>Current medications</u>

16. a) Are you currently taking any medications for your dystonia symptoms?

Yes **No**

IF YES: b) What medication(s) are you currently taking (including doses)?

1
.
2
.
3
.
4
.

5.

15) Please rate the level of effectiveness of each medication:

	Very effective	Somewhat effective	Not effective	Has made my symptoms worse
Medication 1				
Medication 2				
Medication 3				
Medication 4				
Medication 5				

Previous treatments

17. a) Have you had any previous treatments (including Botox or Deep Brain Stimulation) for your dystonia symptoms?

Yes **No**

b) IF YES: What previous treatments have you received, including doses?

1

2

3

4

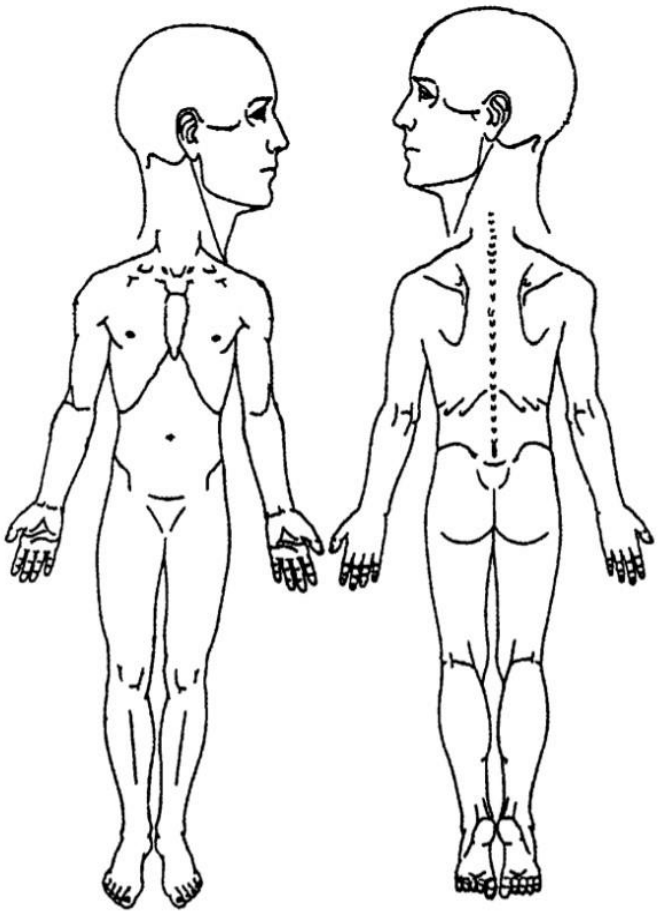
5

15) Please rate the level of effectiveness of each medication:

	Very effective	Somewhat effective	Not effective	Has made my symptoms worse
Medication 1				
Medication 2				
Medication 3				
Medication 4				
Medication 5				

Location of your dystonia symptoms

17. Please circle on the diagrams below the parts of your body that are affected by your dystonia symptoms.



Are your symptoms on the feft or right side of the body, or both?

Left **Right** **Both**

18. Tremor Symptoms

As part of your symptoms, do you experience a tremor?

No **Yes**

Please indicate the areas of your body affected by tremor (select all that apply):

Head/Neck **Trunk**

Vocal Cords **Pelvis**

Left Arm **Left Leg**

Right Arm **Right Leg**

Left Hand

Right Hand

Modified Dystonia movement and disability scales

The Burke-Fahn-Marsden dystonia scales

Dystonia disability scale

Speech		
0	Normal	
1	Slightly involved, easily understood	
2	Some difficulty in understanding	
3	Marked difficulty in understanding	
4	Complete or almost complete anarthria	
Handwriting		
0	Normal	
1	Slight difficulty; legible	
2	Almost illegible	
3	Illegible	
4	Unable to grasp to maintain hold on pen	
Feeding		
0	Normal	
1	Use ‘tricks’; independent	
2	Can feed but not cut	
3	Finger food only	
4	Completely dependent	
Hygiene		
0	Normal	
1	Clumsy; independent	
2	Need help with some activities	
3	Need help with most activities	
4	Need help with all activities	
Dressing		
0	Normal	
1	Clumsy; independent	
2	Need help with some activities	
3	Need help with most activities	
4	Need help with all activities	

Walking		
0	Normal	
1	Slightly abnormal; hardly noticeable	
2	Moderately abnormal; obvious to naïve observer	
3	Considerably abnormal	
4	Need assistance to walk	
5	Wheel-chair bound	
	Total	

Modified Unified Myoclonus Rating Scale

SECTION 1: MYOCLONUS PATIENT QUESTIONNAIRE
15. Reading (silently) ☐ 0 My ability to read is normal. ☐ 1 I have slight difficulty reading. ☐ 2 I have moderate difficulty reading. ☐ 3 I have great difficulty reading. ☐ 4 I cannot read.
B. Eating ☐ 0 I eat normally. ☐ 1 I can eat by myself, but with effort. ☐ 2 I can feed myself but others must cut my food. ☐ 3 I can only feed myself finger food. ☐ 4 I am dependent on others to feed me.
C. Drinking ☐ 0 I drink normally. ☐ 1 I can drink from a cup but I need to be careful. ☐ 2 I need a special cup to drink, or I use two hands. ☐ 3 I must use a straw to drink. ☐ 4 I cannot drink by myself.

D. Swallowing

☐ 0 I swallow without difficulty.

☐ 1 I choke occasionally.

☐ 2 I choke frequently and have difficulty swallowing.

☐ 3 I am unable to swallow firm foods.

☐ 4 I cannot swallow soft foods or liquids.

E. Arising

☐ 0 I arise from a chair without difficulty.

☐ 1 I arise from a chair with some difficulty.

☐ 2 I arise from a chair with significant difficulty, but I do not require assistance.

☐ 3 I need help to arise from a chair.

☐ 4 I cannot arise from a chair unless I am pulled up.

F. Standing

☐ 0 I can stand by myself without any difficulty.

☐ 1 I can stand by myself but I am a little unsteady.

☐ 2 I can stand by myself but I am quite unsteady.

☐ 3 I can stand only if someone holds on to me.

☐ 4 I cannot stand even if I am assisted.

G. PATIENT GLOBAL ASSESSMENT

☐ 0 I have no disability.

☐ 1 I have mild disability but I function independently.

☐ 2 I have moderate disability. I depend on others to help me.

☐ 3 I have marked disability. There are many things I cannot do even with help.

☐ 4 I am completely disabled. I am totally dependent on others.

Mini Screen (MMS)

Section A – Please circle "yes" or "no" for each question.

1. Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks? ..... Yes No
2. In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time? ..... Yes No
3. Have you felt sad, low, or depressed most of the time for the last two years? ..... Yes No
4. In the past month, did you think that you would be better off dead or wish you were dead? ..... Yes No
5. Have you ever had a period of time when you were feeling up, hyper, or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) ..... Yes No
6. Have you ever been so irritable, grouchy, or annoyed for several days, that you had arguments, had verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared to other people, even when you thought you were right to act this way? ..... Yes No

Section B – Please circle "yes" or "no" for each question.

7. Have you had one or more occasions when you felt intensely anxious, frightened, uncomfortable, or uneasy, even when most people would not feel that way? Did these intense feelings get to be their worst within ten minutes? (If the answer to both questions is "yes," circle "yes"; otherwise circle "no.") ..... Yes No
8. Do you feel anxious or uneasy in places or situations where you might have the panic-like symptoms we just spoke about? Or do you feel anxious or uneasy in situations where help might not be available or escape might be difficult? Examples: ○ being in a crowd, ○ standing in a line, ○ being alone away from home or alone at home, ○ crossing a bridge, ○ traveling in a bus, train, or car? ..... Yes No
9. Have you worried excessively or been anxious about several things over the past six months? (If you answer "no" to this question, answer "no" to Question 10 and proceed to Question 11.) ... Yes No
10. Are these worries present most days? ..... Yes No
11. In the past month, were you afraid or embarrassed when others were watching you or when you were the focus of attention? Were you afraid of being humiliated? Examples: ○ speaking in public, ○ eating in public or with others, ○ writing while someone watches, ○ being in social situations. ..... Yes No

12. In the past month, have you been bothered by thoughts, impulses, or images that you couldn't get rid of that were unwanted, distasteful, inappropriate, intrusive, or distressing? Examples: ○ being afraid that you would act on some impulse that would be really shocking, ○ worrying a lot about being dirty, contaminated, or having germs, ○ worrying a lot about contaminating others, or that you would harm someone even though you didn't want to, ○ having fears or superstitions that you would be responsible for things going wrong, ○ being obsessed with sexual thoughts, images, or impulses, ○ hoarding or collecting lots of things, ○ having religious obsessions. ..... Yes No

13. In the past month, did you do something repeatedly without being able to resist doing it? Examples: ○ washing or cleaning excessively, ○ counting or checking things over and over, ○ repeating, collecting, or arranging things, ○ other superstitious rituals. ..... Yes No

14. Have you ever experienced, witnessed, or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? Examples: ○ serious accidents, ○ sexual or physical assault, ○ terrorist attack, ○ being held hostage, ○ kidnapping, ○ fire, ○ discovering a body, ○ sudden death of someone close to you, ○ war, ○ natural disaster. ..... Yes No

15. Have you re-experienced the awful event in a distressing way in the past month? Examples: ○ dreams, ○ intense recollections, ○ flashbacks, ○ physical reactions. ..... Yes No

Section C – Please circle "yes" or "no" for each question.

16. Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? ..... Yes No

17. Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking? ..... Yes No

18. Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Or, have you ever felt that you were possessed? ..... Yes No

19. Have you ever believed that you were being sent special messages through the TV, radio, or newspaper? Did you believe that someone you did not personally know was particularly interested in you? ..... Yes No

20. Have your relatives or friends ever considered any of your beliefs strange or unusual? ..... Yes No

21. Have you ever heard things other people couldn't hear, such as voices? ..... Yes No

22. Have you ever had visions when you were awake or have you ever seen things other people couldn't see? ..... Yes No

Structured Clinical Interview for DSM-5 Personality Disorders

(SCID-5-PD)

Please answer True (T) or False (F) to the following statements as they might apply to you over the last 5 years. If you are unsure of an answer please select the one that is more likely to be correct.

1. I usually get fun and enjoyment out of life	T / F
2. I trust people I know	T / F
3. I'm not fussy about little details	T / F
4. I can't decide what kind of person I want to be	T / F
5. I show my feelings for everyone to see	T / F
6. I let others make my decisions for me	T / F
7. I get upset when I hear bad news about someone I know	T / F
8. Giving in to some of my urges gets me into trouble	T / F
9. Many people I know envy me	T / F
10. I give my general impression of things and don't bother with details	T / F
11. I've never been arrested	T / F
12. People think I'm cold and detached	T / F
13. I get into very intense relationships that don't last	T / F
14. Most people are fair and honest with me	T / F
15. People have a high opinion of me	T / F
16. I feel awkward or out of place in social situations	T / F
17. I'm too easily influenced by what goes on around me	T / F
18. I usually feel bad when I hurt or upset someone	T / F
19. I feel it very difficult to throw things out	T / F
20. At times I've refused to hold a job, even when I was expected to	T / F
21. When I'm praised or criticized I let others know how I feel	T / F
22. I use people to get what I want	T / F
23. I spend too much time trying to do things perfectly	T / F

24. People often make fun of me behind my back	T / F
25. I've never threatened suicide or injured myself on purpose	T / F
26. My feelings are like the weather, they're always changing	T / F
27. To avoid being criticized, I prefer to work alone	T / F
28. I like to dress so I stand out in a crowd	T / F
29. I will lie or con someone it if serves my purpose	T / F
30. I am more superstitious than most people	T / F
31. I have little or no desire to have sex with anyone	T / F
32. People think I'm to strict about rules and regulations	T / F
33. I usually feel uncomfortable or helpless when I'm alive	T / F
34. I wont get involved with people until I know that they like me	T / F
35. I would rather not be the centre of attention	T / F
36. I think my spouse (or lover) may be unfaithful to me	T / F
37. People think I have too high an opinion of myself	T / F
38. I am careful about what I tell others about myself	T / F
39. I worry a lot that people may not like me	T / F
40. I often feel "empty" inside	T / F
41. I work so hard I don't have time for anything else	T / F
42. I worry about being left alone and having to care for myself	T / F
43. I have tantrums or angry outbursts	T / F
44. I have a reputation for being a flirt	T / F
45. I feel very close to people I've just met	T / F
46. I prefer activities that I can do by myself	T / F
47. I lose my temper and get into physical fights	T / F
48. Some people think I'm tight or stingy with my money	T / F

49. I often seek advice or reassurance about everyday decisions T / F

50. I get people to like me. I help them with unpleasant jobs T / F

51. I'm afraid of making a fool of myself with people I'm close to T / F

52. I'm often mistake objects or shadows for people T / F

53. I'm very moody T / F

54. It's hard for me to get used to a new way of doing things T / F

55. I daydream about being famous T / F

56. I take chances and do reckless things T / F

57. Everyone needs a friend or two to be happy T / F

58. I discover hidden threats in what people tell me T / F

59. I usually try to get people to do things my way T / F

60. When I'm under stress, things around me don't seem real T / F

61. I get annoyed when people wont do what I ask T / F

62. When a close relationship ends, I can hardly wait to start a new one T / F

63. I avoid unfamiliar activities so I wont be embarrassed trying to do them T / F

64. People find it hard to get the point of what I'm saying T / F

65. I prefer to associate with talented people T / F

66. I've been the victim of unfair attacks on my character or reputation T / F

67. I don't show much emotion T / F

68. I do things to get people to admire me T / F

69. I'm usually able to start projects on my own T / F

70. People think I'm odd or eccentric T / F

71. I feel at ease in social situations T / F

72. I've held grudges against people for years T / F

73. I find it hard to disagree with people I depend on a lot T / F

74. It's hard for me to stay out of trouble T / F

75. I go to extremes to try to keep people from leaving me T / F

76. When I first meet someone. I don't say much T / F

77. I have close friends T / F

Yale-Brown Obsessive Compulsive Scale

- Home
- Tests
- About Us
- Get Help

This self-rating scale is designed to assess the severity and type of symptoms in patients with OCD. Before you begin the test, read the following definitions and examples of "obsessions" and "compuls

Obsessions

are unwelcome or distressing ideas, thoughts, images or impulses that repeatedly enter your m They may seem to occur against your will. They may be repugnant to you, are often senseless may not fit your actual personality at all (*for example, the recurrent thought or impulse to har your children, even though you never would*).

Compulsions

are behaviors or acts that you feel driven to perform, even though you may recognize them as senseless or excessive. At times, you may try to resist doing them, but this may prove difficult may experience anxiety that does not diminish until the behavior is completed.

Answer each question based on the **average occurrence** of each item over the **past week**. The first 5 questions relate to obsessive thoughts, the last 5 questions relate to compulsive behaviors.

1. How much of your time is occupied by obsessive thoughts?
   - ◯ None
   - ◯ Less than 1 hour per day
   - ◯ 1-3 hours per day
   - ◯ 3-8 hours per day
   - ◯ More than 8 hours per day
2. How much do your obsessive thoughts interfere with functioning in your social, work, or othe roles?
   - ◯ None
   - ◯ Slight interference, but no impairment
   - ◯ Definite interference, but managable
   - ◯ Substantial intereference
   - ◯ Extreme intereference, incapacitating
3. How much distress do your obsessive thoughts cause you?
   - ◯ None
   - ◯ Mild, not too disturbing
   - ◯ Moderate, disturbing, but still manageable
   - ◯ Severe, very disturbing
   - ◯ Extreme, near constant and disabling distress
4. How much of an effort do you make to resist the obsessive thoughts?
   - ◯ Always make an effort to resist, or don't even need to resist
   - ◯ Try to resist most of the time
   - ◯ Make some effort to resist
   - ◯ Reluctantly yield to all obsessive thoughts

- ○ Completely and willingly yield to all obsessions

5. How much control do you have over your obsessive thoughts?
   - ○ Complete control
   - ○ Much control, usually able to stop or divert obsessions with some effort and concentration
   - ○ Moderate control, sometimes able to stop or divert obsessions
   - ○ Little control, rarely successful in stopping or dismissing obsessions
   - ○ No control, rarely able to even momentarily alter obsessive thinking
6. How much time do you spend performing compulsive behaviors?
   - ○ None
   - ○ Less than 1 hour per day
   - ○ 1-3 hours per day
   - ○ 3-8 hours per day
   - ○ More than 8 hours per day
7. How much do your compulsive behaviors interfere with functioning in your social, work, or other roles?
   - ○ None
   - ○ Slight interference, but no impairment
   - ○ Definite interference, but managable
   - ○ Substantial intereference
   - ○ Extreme intereference, incapacitating
8. How anxious would you become if you were prevented from performing your compulsive behaviors?
   - ○ No anxiety
   - ○ Only slightly anxious
   - ○ Some anxiety, but managable
   - ○ Prominent and disturbing anxiety
   - ○ Extreme, incapacitating anxiety
9. How much of an effort do you make to resist the compulsions?
   - ○ Always make an effort to resist, or don't even need to resist
   - ○ Try to resist most of the time
   - ○ Make some effort to resist
   - ○ Reluctantly yield to all complusions
   - ○ Completely and willingly yield to all complusions
10. How much control do you have over the compulsions?
    - ○ Complete control
    - ○ Much control, usually able to stop or divert compulsive behavior with some effort and concentration
    - ○ Moderate control, sometimes able to stop or divert compulsive behavior
    - ○ Little control, rarely successful in stopping or dismissing compulsive behavior
    - ○ No control, rarely able to even momentarily alter compulsive behavior

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.

0	I am no more irritated by things than I ever was.
1	I am slightly more irritated now than usual.
2	I am quite annoyed or irritated a good deal of the time.
3	I feel irritated all the time.

12.

0	I have not lost interest in other people.
1	I am less interested in other people than I used to be.
2	I have lost most of my interest in other people.
3	I have lost all of my interest in other people.

13.

0	I make decisions about as well as I ever could.
1	I put off making decisions more than I used to.
2	I have greater difficulty in making decisions more than I used to.
3	I can't make decisions at all anymore.

14.

0	I don't feel that I look any worse than I used to.
1	I am worried that I am looking old or unattractive.
2	I feel there are permanent changes in my appearance that make me look unattractive
3	I believe that I look ugly.

15.

0	I can work about as well as before.
1	It takes an extra effort to get started at doing something.
2	I have to push myself very hard to do anything.
3	I can't do any work at all.

16.

0	I can sleep as well as usual.
1	I don't sleep as well as I used to.
2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3	I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0	I don't get more tired than usual.
1	I get tired more easily than I used to.
2	I get tired from doing almost anything.
3	I am too tired to do anything.

18.

0	My appetite is no worse than usual.
1	My appetite is not as good as it used to be.
2	My appetite is much worse now.
3	I have no appetite at all anymore.

19.

0	I haven't lost much weight, if any, lately.
1	I have lost more than five pounds.
2	I have lost more than ten pounds.
3	I have lost more than fifteen pounds.

20.

0	I am no more worried about my health than usual.
1	I am worried about physical problems like aches, pains, upset stomach, or constipation.
2	I am very worried about physical problems and it's hard to think of much else.
3	I am so worried about my physical problems that I cannot think of anything else.

21.

0	I have not noticed any recent change in my interest in sex.
1	I am less interested in sex than I used to be.
2	I have almost no interest in sex.
3	I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

HAI

Each question is this section consists of a group of four statements. Please read each group of statements carefully and then select the one which best describes your feelings, over the past six months (or other agreed time period). Identify the statement by ringing the letter next to it, i.e. if you think that statement *a.)* is correct, ring statement *a.)*. It may be that more than one statement applies, in which case, please ring any that are applicable.

1. *a.)* I do not worry about my health.

b.) I occasionally worry about my health.
c.) I spend much of my time worrying about my health.
d.) I spend most of my time worrying about my health.

2. *a.)* I notice aches/pains less than most other people (of my age).

b.) I notice aches/pains as much as most other people (of my age).
c.) I notice aches/pains more than most other people (of my age).
d.) I am aware of aches/pains in my body all the time.

3. *a.)* as a rule I am not aware of bodily sensations or changes.

b.) sometimes I am aware of bodily sensations or changes.
c.) I am often aware of bodily sensations or changes.
d.) I am constantly aware of bodily sensations or changes.

4. *a.)* resisting thoughts of illness is never a problem.

b.) most of the time I can resist thoughts of illness.
c.) I try to resist thoughts of illness but am often unable to do so.
d.) thoughts of illness are so strong that I no longer even try to resist them.

5. *a.)* as a rule I am not afraid that I have a serious illness.

b.) I am sometimes afraid that I have a serious illness.
c.) I am often afraid that I have a serious illness.
d.) I am always afraid that I have a serious illness.

6. *a.)* I do not have images (mental pictures) of myself being ill.

b.) I occasionally have images of myself being ill.
c.) I frequently have images of myself being ill.
d.) I constantly have images of myself being ill.

7. *a.)* I do not have any difficulty taking my mind off thoughts about my health.

b.) I sometimes have difficulty taking my mind off thoughts about my health.

c.) I often have difficulty in taking my mind off thoughts about my health.
d.) Nothing can take my mind off thoughts about my health.

8. *a.)* I am lastingly relieved if my doctor tells me there is nothing wrong.

b.) I am initially relieved but the worries sometimes return later.
c.) I am initially relieved but the worries always return later.
d.) I am not relieved if my doctor tells me there is nothing wrong.

9. *a.)* if I hear about an illness I never think I have it myself.

b.) if I hear about an illness I sometimes think I have it myself.
c.) if I hear about an illness I often think I have it myself.
d.) if I hear about an illness I always think I have it myself.

15. *a.)* if I have a bodily sensation or change I rarely wonder what it means.

b.) if I have a bodily sensation or change I often wonder what it means.
c.) if I have a bodily sensation or change I always wonder what it means.
d.) if I have a bodily sensation or change I must know what it means.

11. a.) I usually feel at very low risk for developing a serious illness.
b.) I usually feel at fairly low risk for developing a serious illness.
c.) I usually feel at moderate risk for developing a serious illness.
d.) I usually feel at high risk for developing a serious illness.

12. *a.)* I never think I have a serious illness.
b.) I sometimes think I have a serious illness.
c.) I often think I have a serious illness.
d.) I usually think that I am seriously ill.

13. *a.)* if I notice an unexplained bodily sensation I don't find it difficult to think about other things.
b.) if I notice an unexplained bodily sensation I sometimes find it difficult to think about other things.
c.) if I notice an unexplained bodily sensation I often find it difficult to think about other things.
d.) if I notice an unexplained bodily sensation I always find it difficult to think about other things.

14. *a.)* my family/friends would say I do not worry enough about my health.
b.) my family/friends would say I have a normal attitude to my health.
c.) my family/friends would say I worry too much about my health.
d.) my family/friends would say I am a hypochondriac.

For the following questions, please think about what it might be like if you had a serious illness of a type which particularly concerns you (e.g.

heart disease, cancer, multiple sclerosis & so on). Obviously you cannot know for definite what it would be like; please give your best estimate of what you *think* might happen, basing your estimate on what you know about yourself and serious illness in general.

15. *a.)* if I had a serious illness I would still be able to enjoy things in my life quite a lot.
b.) if I had a serious illness I would still be able to enjoy things in my life a little.
c.) if I had a serious illness I would be almost completely unable to enjoy things in my life.
d.) if I had a serious illness I would be completely unable to enjoy life at all.

16. *a.)* if I developed a serious illness there is a good chance that modern medicine would be able to cure me.
b.) if I developed a serious illness there is a moderate chance that modern medicine would be able to cure me.
c.) if I developed a serious illness there is a very small chance that modern medicine would be able to cure me.
d.) if I developed a serious illness there is no chance that modern medicine would be able to cure me.

17. *a.)* a serious illness would ruin some aspects of my life.
b.) a serious illness would ruin many aspects of my life.
c.) a serious illness would ruin almost every aspect of my life.
d.) a serious illness would ruin every aspect of my life.

18. *a.)* if I had a serious illness I would not feel that I had lost my dignity.
b.) if I had a serious illness I would feel that I had lost a little of my dignity.
c.) if I had a serious illness I would feel that I had lost quite a lot of my dignity.
d.) if I had a serious illness I would feel that I had totally lost my dignity.

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐

(j) Other reason(s), please describe

_____

_____

How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	Very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a Problem has it been for you to keep up Enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or roommate?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had…

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a)…loud snoring	☐	☐	☐	☐
(b)…long pauses between breaths while asleep	☐	☐	☐	☐
(c)…legs twitching or jerking while you sleep	☐	☐	☐	☐
(d)…episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e)...other restlessness while you sleep: please describe:	☐	☐	☐	☐

Sleep Disorders Questionnaire

This questionnaire is a screening tool for physicians to assist their clinical evaluation of insomnia. It can be used to screen for a sleep disorder. See page 2 for guide to interpreting the questionnaire.

The physician should perform a more detailed clinical evaluation and/or refer to specialist when appropriate.

Grade your answer by circling one number for each of the following questions:		Grading Scale				
		Never	Rarely	Occasionally	Most Nights/Days	Always
1	Do you have trouble falling asleep?	1	2	3	4	5
2	Do you have trouble staying asleep?	1	2	3	4	5
3	Do you take anything to help you sleep?	1	2	3	4	5
4	Do you use alcohol to help you sleep?	1	2	3	4	5
5	Do you have any medical conditions that disrupt your sleep?	1	2	3	4	5
6	Have you lost interest in hobbies or activities?	1	2	3	4	5
7	Do you feel sad, irritable, or hopeless?	1	2	3	4	5
8	Do you feel nervous or worried?	1	2	3	4	5
9	Do you think something is wrong with your body?	1	2	3	4	5
10	Are you a shift worker or is your sleep schedule irregular?	1	2	3	4	5
11	Are your legs restless and/or uncomfortable before bed?	1	2	3	4	5
12	Have you been told that you are restless or that you kick your legs in your sleep?	1	2	3	4	5
13	Do you have any unusual behaviours or movements during sleep?	1	2	3	4	5
14	Do you snore?	1	2	3	4	5
15	Has anyone said that you stop breathing, gasp, snort, or choke in your sleep?	1	2	3	4	5
16	Do you have difficulty staying awake during the day?	1	2	3	4	5

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

DO YOU SUFFER WITH PAIN DUE TO YOUR DYSTONIA?

YES

NO

If no, please skip to the SF-36 "Medical outcomes study Short-Form 36 Health Survey"

CHRONIC PAIN ACCEPTANCE QUESTIONNAIRE

Below you will find a list of statements. Please rate the truth of each statement as it applies to you. Use the following rating scale to make your choices. For instance, if you believe a statement is 'Always True,' you would write a 6 in the blank next to that statement.

0	1	2	3	4	5	6
Never true	Very rarely true	Seldom True	Sometimes true	Often true	Almost always true	Always true

_____ 1. I am getting on with the business of living no matter what my level of pain is.

_____ 2. My life is going well, even though I have chronic pain.

_____ 3. It's OK to experience pain.

_____ 4. I would gladly sacrifice important things in my life to control this pain better.

_____ 5. It's not necessary for me to control my pain in order to handle my life well.

_____ 6. Although things have changed, I am living a normal life despite my chronic pain.

_____ 7. I need to concentrate on getting ride of my pain.

_____ 8. There are many activities I do when I feel pain.

_____ 9. I lead a full life even though I have chronic pain.

_____ 10. Controlling my pain is less important than any other goals in my life.

_____ 11. My thoughts and feelings about pain must change before I can take important steps in my life.

_____ 12. Despite the pain, I am now sticking to a certain course in my life.

_____ 13. Keeping my pain level under control takes first priority whenever I'm doing something.

_____ 14. Before I can make any serious plans, I have to get some control over my pain.

_____ 15. When my pain increases, I can still take care of my responsibilities.

_____ 16. I will have better control over my life if I can control my negative thoughts about pain.

_____ 17. I avoid putting myself in situations where my pain might increase.

_____ 18. My worries and fears about what pain will do to me are true.

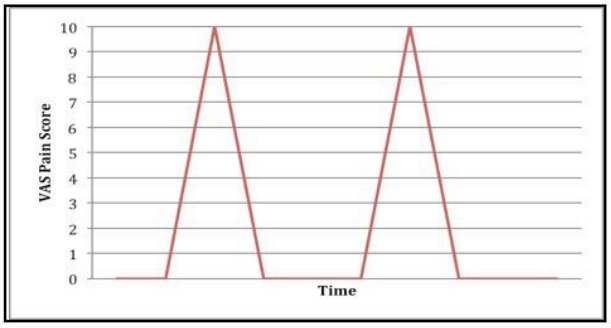
_____ 19. It's a great relief to realize that I don't have to change my pain to get on with life.

_____ 20. I have to struggle to do things when I have pain.

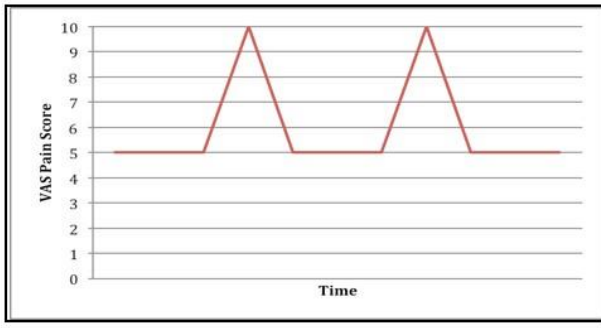
Pain time-course Images

Please select the image that best describes the time course of your pain.

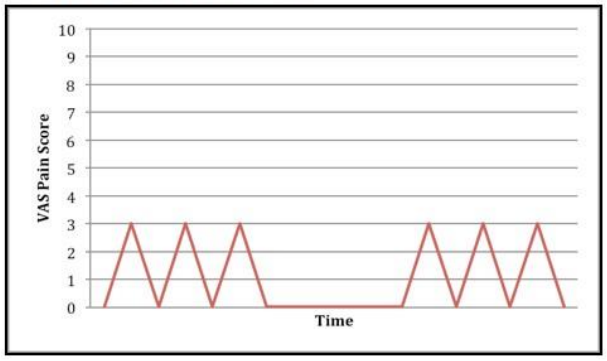
a) Pain episodes with no pain in between them



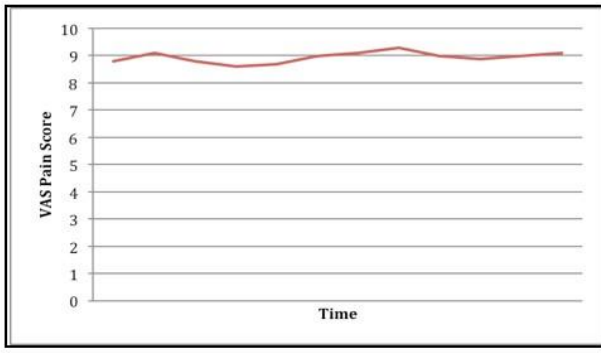
b) Pain episodes with pain in between the



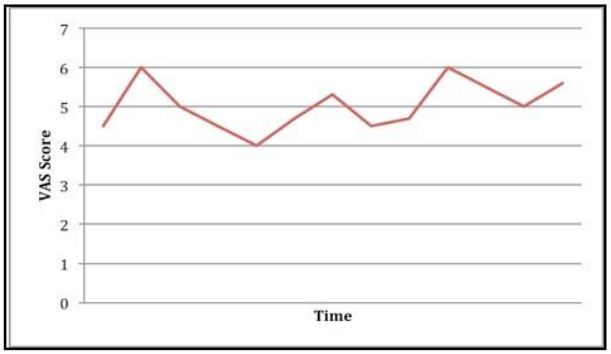
c) Intermittent clusters of pain with no pain in between them



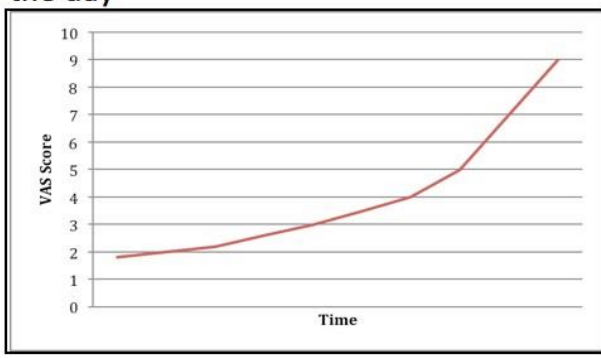
d) Constant pain



e) Continuous fluctuant pain



f) Continuous pain that increases through the day



Pain Catastrophising Scale (PCS)

Sullivan MJL, Bishop S, Pivik J. (1995)

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

Instructions:
We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

RATING	0	1	2	3	4
MEANING	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time

When I'm in pain …

Number	Statement	Rating
1	I worry all the time about whether the pain will end.	
2	I feel I can't go on.	
3	It's terrible and I think it's never going to get any better	
4	It's awful and I feel that it overwhelms me.	
5	I feel I can't stand it anymore	
6	I become afraid that the pain will get worse.	
7	I keep thinking of other painful events	
8	I anxiously want the pain to go away	
9	I can't seem to keep it our of my mind	
10	I keep thinking about how much it hurts.	
11	I keep thinking about how badly I want the pain to stop	
12	There's nothing I can do to reduce the intensity of the pain	
13	I wonder whether something serious may happen.	

Medical Outcomes Study Questionnaire Short Form 36 Health Survey

(SF-36 Questionnaire)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(Circle One Number on Each Line)

	Yes, Limited a Lot (1)	**Yes, Limited a Little (2)**	**No, Not limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Circle One Number on Each Line)

	Yes (1)	**No (2)**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?	
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. **(Circle One Number on Each Line)**

9. How much of the time during the **past 4 weeks** . . .

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Participant Satisfaction with Dystonia Survey Questionnaire

We would like to thank you for your taking time to complete these questionnaires. Your participation in our research project is much appreciated.

The following questions ask you about your overall satisfaction with this survey as a whole. We are asking these questions so that we can gain feedback about this survey and make any amendments to the survey according to your feedback.

15. **How long did it take you to complete this survey?**

    Less than an hour

    One and a half hours

    2 hours

    More than 2 hours

2. **How easy did you find it to complete the questionnaires on a scale of 0-10 (where 0 = Very hard; 10 = Very easy)?**

3. **Did you find the questionnaires too long?**

    Yes No

4. **How many times did you have to return to the survey to complete all of it?**

    None – I completed it in one attempt

    Once

    Twice

    Three times

    More than three times

15. **How would you rate your level of satisfaction of this survey on a scale of 0-10 (where 0 = Not at all satisfied; 10 = Extremely satisfied)?**

A. MAJOR DEPRESSIVE EPISODE

(Means: go to the diagnostic boxes, circle NO in all diagnostic boxes, and move to the next module)

A1	a	Have you ever been consistently depressed or down, most of the day, nearly every day, for at least two weeks?	NO	YES
	If A1a=YES:			
	b	Have you been consistently depressed or down, most of the day, nearly every day, for the past 2 weeks?	NO	YES
A2	a	Have you ever been much less interested in most things or much less able to enjoy the things you used to enjoy most f the time over at least two weeks?	NO	YES
	If A2a = YES:			
	b	In the past 2 weeks, have you been much less interested in most things or much less able to enjoy the thing you used to enjoy?	NO	YES
	Is **A1a** or **A2a** coded **YES**?		NO	YES

IF CURRENTLY DEPRESSED (**A1b** OR **A2b** = **YES**), EXPLORE THE CURRENT EPISODE AND THE MOST SYMPTOMATIC PAST EPISODE. OTHERWISE EXPLORE THE MOST SYMPTOMATIC PAST EPISODE.

A3 **Over the two-week period when you felt depressed or uninterested:**

		Current Episode		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally?	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES

	d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
	e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
		IF **A3e** = **YES**: ASK FOR AN EXAMPLE THE EXAPMPLE IS CONSISTENT WITH A DELUSIONAL IDEA.		NO	YES	
	f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
	g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES	NO	YES
A4		ARE **3** OR MORE **A3** ANSWERS CODED **YES** (OR **4 A3** ANSWERS, IF **A1**a OR **A2a** ARE CODED **NO** FOR PAST EPISODE OR IF **A1b** OR **A2b** ARE CODED NO FOR CURRENT EPISODE)? VERIFY IF THE POSITIVE SYMPTOMS OCCURRED DURING THE SAME 2 WEEK TIME FRAME IF **A4** IS CODED **NO** FOR CURRENT EPISODE THEN EXPLORE **A3a – A3g** FOR MOST SYMPTOMATIC EPISODE	NO	YES	NO	YES
A5		Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?			NO	YES
A6		Are the symptoms due entirely to the less of a loved one (bereavement) and are they similar in severity, level of impairment, and duration to what most others would suffer under similar circumstances? If so, this is uncomplicated bereavement. Has uncomplicated bereavement been ruled out?			NO	YES
A7	a	Where you taking any drugs or medicines just before these symptoms began? No Yes				
	b	Did you have any medical illness just before these symptoms began? No Yes IN THE CLINICIAN'S JUDGEMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S				

DEPRESSION? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.

A7 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES UNCERTAIN

A8 CODE YES IF **A7(summary)** = **YES** OR **UNCERTAIN**
SPECIFY IF THE PEISODE IS CURRENT AND/OR PAST AND/OR BOTH (RECURRENT)

NO	**YES**
Major Depressive Episode	
Current	☐
Past	☐

A9 CODE **YES** IF **A7b** = **YES** AND **A7(summary)** = **NO**
SPECIFY IF THE EPISODE IS CURRENT AND/OR PAST AND/OR BOTH (RECURRENT)

NO	**YES**
Mood Disorder Due to a General Medical Condition	
Current	☐
Past	☐

A10 CODE **YES** IF **A7a** = **YES** AND **A7(summary)** = **NO**
SPECIFY IF THE EPISODE IS CURRENT AND/OR PAST AND/OR BOTH (RECURRENT)

NO	**YES**
Substance Induced Mood Disorder	
Current	☐
Past	☐

CHRONOLOGY

A11 How old were you when you first began having symptoms of depression? ☐ Age

A12 During your lifetime, how many distinct times did you have these symptoms of depression (daily for at least 2 weeks)? ☐

A13 Is there any family history of bipolar disorder or any relative ever treated with a mood stabiliser? YES NO

B. DYSTHMIA

(Means: go to the diagnostic boxes, circle NO in all diagnostic boxes, and move to the next module)

If a patient's symptoms currently meet criteria for major depressive episode, do NOT explore current dysthymia, but do explore PAST dysthymia. Make sure that the past dysthymia explored is not one of the past major depressive episodes, and that it was separated from any prior major depressive episode by at least 2 months of full remission. [APPLY THIS RULE ONLY IF YOU ARE INTERESTED IN EXPLORING DOUBLE DEPRESSION.]

SPECIFY WHICH TIME FRAME IS EXPLORED: Current
Past

B1	a	Have you felt sad, low or depressed most of the time for the last two years? (Or if exploring past dysthymia: " In the past, did you ever feel sad, low or depressed for 2 year continuously?")	NO	YES
	b	Was this period interrupted by your feeling OK for two months or more?	NO	YES

B3		**During this period of feeling depressed most of the time:**		
	a	Did your appetite change significantly?	NO	YES
	b	Did you have trouble sleeping or sleep excessively?	NO	YES
	c	Did you feel tired or without energy?	NO	YES
	d	Did you lose your self-confidence?	NO	YES
	e	Did you have trouble concentrating or making decisions?	NO	YES
	f	Did you feel hopeless?	NO	YES
		ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	NO	YES
B4		Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	NO	YES

B5 Were you taking any drugs or medicines just before these symptoms began?
Did you have any medical illness just before these symptoms began?
IN THE CLINICIAN'S JDGEMENT: ARE EITHER OF THESE LIKELY RO BE DIRECT CAUSES OF THE PATIENT'S DEPRESSION?
HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES

IS **B5** CODED **YES**?

NO	**YES**
DYSTHYMIA	
Current	☐
Past	☐

CHRONOLOGY

B6 How old were you when you first began having symptoms of 2 years of continuous depression? ☐ Age

15. (HYPO)MANIC EPISODE

(Means: go to the diagnostic boxes, circle NO in all diagnostic boxes, and move to the next module)

D1	a	Have you ever had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated in drugs or alcohol.)	NO	YES
		IF **NO**, CODE **NO** TO **D1b**: IF **YES** ASK:		
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy? If patient is puzzled or unclear about what you mean by 'up' or 'high', clarify as follows: by 'up' or 'hyper' I mean: having elevated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behaviour.	NO	YES
D2	a	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified?	NO	YES
		IF **NO**, CODE **NO** TO **D2b**: IF **YES** ASK		
	b	Are you **currently** feeling persistently irritable?	NO	YES
		IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 If D1b or D2b = YES: explore current and most symptomatic past episode, otherwise IF D1b and D2b = NO: explore the most symptomatic past episode

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things other couldn't do, or that you were an especially important person? IF **YES** ASK FOR EXAMPLES.	NO	YES	NO	YES

THE EXAMPLES ARE CONSISTANT WITH A DELUSIONAL IDEA. ☐ No ☐ Yes

	b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
	c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
	d	Have racing thoughts?	NO	YES	NO	YES
	e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
	f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
	g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES
		D3(SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES**? (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS **NO** (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES 4 OF THE D3 SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE ASME TIME PERIOD.	NO	YES	☐ NO	YES

D4	a	Were you taking any drugs or medications just before these symptoms began?		NO	YES
	b	Did you have any medical illness just before these symptoms began?		NO	YES
		IN THE CLINICIAN'S JUDGEMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S (HYPO)MANIA? IF NECESSARY, ASK ADDITIONAL OPEN-ENDED QUESTIONS.		NO	YES
		D4(SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT?	NO	YES	UNCERTAIN

D5	b	Did these symptoms last at least a week and cause problems beyond your control at home, work, school, or were you hospitalized for these problems?	NO ↓	YES ↓	NO ↓	YES ↓
		IF **YES** TO ANY, CODE **YES**				

	Current Hypomanic Episode	*Current Manic Episode*	*Past Hypomanic Episode*	*Past Manic Episode*

IF **D5** IS CODED NO FOR CURRENT EPISODE, THEN EXPLORE **D3**, **D4** AND **D5** FOR THE MOST SYMPTOMATIC PAST EPISODE.

TYPICAL LENGTH OF (HYPO)MANIC PHASE _____

TYPICAL LENGTH OF DEPRESSED PHASE _____

ARE THE SWITCHES FROM (HYPO)MANIA TO DEPRESSION SUDDEN OR GRADUAL? _____

ARE THE SWITCHES FROM DEPRESSION TO (HYPO)MANIA SUDDEN OR GRADUAL? _____

D6 IF **D3(SUMMARY)** = **YES** AND **D4(SUMMARY)** = **YES** OR **UNCERTAIN** AND **D5** = **NO**, AND NO DELUSIONAL IDEA WAS DESCRIBED IN **D3a**, CODE **YES** FOR HYPOMANIC EPISODE

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST

NO	**YES**
HYPOMANIC EPISODE	
Current	☐
Past	☐

D7 IF **D3(SUMMARY)** = **YES** AND **D4**(**SUMMARY**)=**YES** OR **UNCERTAIN** AND EITHER **D5** = **YES** OR A DELUSIONAL IDEA WAS DESCRIBED IN **D3a**, CODE **YES** FOR MANIC EPISODE

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST

NO	**YES**
MAINC EPISODE	
Current	☐
Past	☐

D8 IF **D3**(**SUMMARY**) AND **D4b** AND **D5** = **YES** AND **D4**(**SUMMARY**) = **NO**, CODE **YES**

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST

NO	**YES**
(Hypo) Manic Episode Due to General Medical Condition	
Current	☐
Past	☐

D9 IF **D3**(**SUMMARY**) AND **D4a** AND **D5** = **YES** AND **D4**(**SUMMARY**) = **NO**, CODE **YES**

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST

NO	**YES**
Substance Induced (Hypo) Manic Episode	
Current	☐
Past	☐

IF D8 OR D9 = YES, GO TO THE NEXT MODULE

SUBTYPES

Rapid Cycling

Have you had four or more episodes of mood disturbance in 12 months?

NO YES

Rapid Cycling

Mixed Episode

PATIENT MEETS CRIETERA FOR BOTH MANIC EPISODE AND MAJOR DEPRESSIVE EPISODE NEARLY EVERY DAY DURING AT LEAST A ONE WEEK PERIOD

NO YES

Mixed Episode

Seasonal Pattern

THE ONSET AND REMISSIONS OR SWITCHES FROM DEPRESSION TO MANIA OR HYPOMANIA CONSISTENTLY OCCUR AT A PARTICULAR TIME OF YEAR

NO YES

Seasonal Pattern

With Full Inter-Episode Recovery

Between the two most recent mood episodes did you fully recover?

NO N/A YES

With Full Inter-episode Recovery

MOST RECENT EPISODE WAS MANIC/HYPOMANIC/MIXED/DEPRESSED (CIRCLE ONE)

CHRONOLOGY

D10 How old were you when you first began having symptoms manic/hypomanic episodes? ☐ Age

D11 Since the first onset how many distinct times did you have significant symptoms of mania/hypomania? ☐

D12 Is there any family history of bipolar disorder or any relative ever treated with a mood stabiliser? Yes No

E. PANIC DISORDER

(□ Means: go to E6 and E7 and E8 and E9 and E10, circle NO to all and move to the next module)

E1	a	Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable, or uneasy, even in situations where most people would not feel that way?	□ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	□ NO	YES
E2		At any time in the past, did any of these spells or attacks come on unexpectedly or spontaneously, or occur in an unpredictable or unprovoked manner?	□ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack or worries about the consequences of the attack? Or did you make a significant change in your behaviour because of the attacks (e.g. shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, it seeing your doctor more frequently because of the symptoms?	NO	YES
E4		During the worst spell can you remember:		
	a	Did you have a skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a chocking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhoea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached, or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES

	j	Did you feel that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have a tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
		E4(**SUMMARY**): ARE **4** OR MORE **E4** ANSWERS CODED **YES**?	NO	YES
E5	a	Were you taking any drugs or medicines just before these symptoms began?	NO	YES
	b	Did you have any medical illness just before these symptoms began?	NO	YES
		IN THE CLINICIAN'S JUDGEMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S PANIC DISORDER?		
		E5(**SUMMARY**): HAS AN ORGANIC CAUSE BEEN RULED OUT? If **E5**(**SUMMARY**) IS CODED **NO**, SKIP TO **E9**	NO	YES
E6		DOES **E3** AND **E4**(**SUMMARY**) AND **E5**(**SUMMARY**) = **YES**?	NO	YES ***Panic Disorder*** **Lifetime**
		IF **E6** = **YES**, SKIP TO **E8**		
E7		IF **E6** = **NO**, ARE ANY **E4** ANSWERS CODED **YES**?	NO	YES ***Limited Symptom attacks*** **Lifetime**
		THEN SKIP TO NEXT SECTION.		
E8		In the past month, did you have such attacks repeatedly (2 or more), followed by persistent concern about having another attack? (IF THIS IS DENIED BY THE PATIENT – CHALLENGE BY REVIEWING THE SYMPTOMS ENDRSED IN **E4**).	NO	YES ***Panic Disorder*** **Current**
E9		ARE **E3** AND **E4**(**SUMMARY**) AND **E5b** ALL CODED **YES** AND **E5**(**SUMMARY**) CODED **NO**?	**NO**	**YES** ***Anxiety Disorder with Panic Attacks Due to a General Medical Condition*** **CURRENT**

E10	ARE **E3** AND **E4**(**SUMMARY**) AND **E5a** ALL CODED **YES** AND **E5**(**SUMMARY**) CODED **NO**?	**NO** **YES** ***Substance Induced Anxiety Disorder with Panic Attacks*** **CURRENT**

CHRONOLOGY

E11	How old were you when you first began having symptoms of panic attacks?	☐ Age
E12	During the past year, for how many months did you have significant symptoms of panic attacks or worries about having an attack?	☐

F. AGORAPHOBIA

F1	Have you ever felt anxious or uneasy in places or situations where you might have a panic attack or the panic attack-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crown, standing in a line (queue), when you are alone away from home, or when crossing a bridge, travelling in a bus, train or car?	NO	YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2** AND **F3**.

F2 Have you ever feared these situations so much that you avoided them, or suffered through them, or needed a companion to face them?

NO **YES**

AGORAPHOBIA **LIFETIME**

Do you **NOW** fear or avoid these places or situations?

NO **YES**

AGORAPHOBIA **CURRENT**

CHECK ONLY IF YES

IS AGORAPHOBIA CODED YES? **F2** ☐ lifetime **F3** ☐ current

IS PANIC DISORDER CODED YES? **E6** ☐ lifetime **E8** ☐ current

F4 a IS PANIC DISORDER, CURRENT (**E8**), CODED **YES**,

AND

IS AGNORAPHOBIA, CURRENT (**F3**), CODED **NO**?

NO **YES**

Panic Disorder,* Current *without AGORAPHOBIA

b IS PANIC DISORDER, CURRENT (**E8**), CODED **YES**,

AND

IS AGORAPHOBIA, CURRENT (**F3**), CODED **YES**?

NO **YES**

Panic Disorder,* Current *with AGORAPHOBIA

c IS PANIC DISORDER, LIFETIME (**E6**), CODED **NO**,

AND

IS AGORAPHOBIA, CURRENT (**F3**), CODED **YES**?

NO	**YES**
AGORAPHOBIA, CURRENT without history of Panic Disorder	

d IS AGORAPHOBIA, CURRENT (**E3**), CODED **YES**,

AND PANIC DISORDER, CURRENT (**F8**), CODED **NO**

AND IS PANIC DISORDER, LIFETIME (**E6**) CODED **YES**?

NO	**YES**
AGORAPHOBIA,* Current *without CURRENT Panic Disorder but with a past history of Panic Disorder	

e IS AGORAPHOBIA, CURRENT (**E3**), CODED **YES**,

AND LIMITED SYMPTOM ATTACKS (**E7**), CODED **NO**?

NO	**YES**
AGORAPHOBIA,* Current *without history of Limited Symptom Attacks	

CHRONOLOGY

F5 How old were you when you first began to fear or avoid these situations (agoraphobia)? ☐ Age

F6 During the past year, for how many months did you have significant fear or avoidance of these situations (agoraphobia)? ☐

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(Means: go to the diagnostic boxes, circle NO, and move to the next module)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes situations like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	NO	YES
G2	If this social fear excessive or unreasonable?	NO	YES
G3	Do you fear these social situations so much that you avoid them or suffer through them?	NO	YES

G4 Do these social fears disrupt your normal work or social functioning or cause you significant distress?

SUBTYPES

Do you fear and avoid 4 or more social situations?

IF **YES** Generalised social phobia (social anxiety disorder)

IF **NO** Non-generalised social phobia (social anxiety disorder)

Note to interviewer: Please assess whether the subject's fears are restricted to non-generalised ("only 1 or several") social situations r extended to generalised ("most") social situations. "Most" social situations is usually operationalised to more 4 or more social situations, although the DSM-IV does not explicitly state this.
Examples of such social situation typically include initiating or maintaining a conversation, participating in small groups, dating, speaking to authority figures, attending parties, public speaking, eating in front of other, urinating in a public washroom, etc.

NO	**YES**

SOCIAL PHOBIA (Social Anxiety Disorder) CURRENT

GENERALISED ☐

NON-GENERALISED ☐

CHRONOLOGY

F5	How old were you when you first began to fear social situations?	☐ Age
F6	During the past year, for how many months did you have significant fear of social situations?	☐

H. SPECIFIC PHOBIA

(Means: go to the diagnostic boxes, circle NO, and move to the next module)

H1	In the past month, have you been excessively afraid of things like: flying, driving, heights, storms, animals, insects, or seeing blood or needles?	NO	YES
H2	If this fear excessive or unreasonable?	NO	YES
H3	Do you fear these situations so much that you avoid them or suffer through them?	NO	YES
H4	Does this fear disrupt your normal work or social functioning or cause you significant distress?	**NO**	**YES**

SPECIFIC PHOBIA
CURRENT

H5	How old were you when you first began to fear or avoid this situation?	☐ Age
H6	During the past year, how many times have you had significant fear of this situation?	☐

I. OBSESSIVE-COMPULSIVE DISORDER

(☐ Means: go to the diagnostic boxes, circle NO in all diagnostic boxes, and move to the next module)

I1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, OR fear of contaminating others, OR fear of harming someone even though you didn't want to, OR fearing you would act on some impulse, OR fear or superstitions that you would be responsible for things going wrong, OR obsessions with sexual thoughts, images or impulses, OR hoarding, collecting, OR religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIDE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIV PLEASURE FROM THE ACTIVITY AD MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO ☐ to 14	YES
I2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO ☐ to 14	YES
I3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO	YES **obsessions**
I4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over, or repeating, collecting, arranging things, or other superstitious rituals?	NO	YES **compulsions**
	IS I3 OR I4 CODED YES?	☐ NO	YES
I5	Did you recognise that either these obsessional thoughts or compulsive behaviours were excessive or unreasonable?	☐ NO	YES
I6	Did these obsessive thoughts and/or compulsive behaviours significantly interfere with your normal routine, your work or school, your usual social	NO	YES

activities, or relationships, or did they take more than one hour a day?

I7	a	Were you taking and drugs or medicines just before these symptoms began?	No	Yes
	b	Did you have any medical illness just before these symptoms began?	No	Yes

IN THE CLINICAN'S JUDGEMENT: AR EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S OBSESSIVE COMPULSIVE DISORDER?

I7(**SUMMARY**): HAS AN ORGANIC CAUSE BEEN RULED OUT?	NO	YES

ARE **I6** AND **I7**(**SUMMARY**) CODED **YES**?

NO	**YES**
	O.C.D CURRENT

I8 ARE **I6** AND **I7b** CODED **YES** AND **I7**(**SUMMARY**) CODED **NO**?

NO	**YES**
	O.C.D **CURRENT** Due to a General Medical Condition

I9 ARE **I6** AND **I7a** CODED **YES** AND **I7**(**SUMMARY**) CODED **NO**?

NO	**YES**
	Current Substance Induced ***O.C.D***

I10 How old were you when you first began having symptoms of OCD? ☐ Age

I11 During the past year, how many months did you have significant symptoms of OCD? ☐

15. ALCOHOL ABUSE AND DEPENDENCE

(□ Means: go to the diagnostic boxes, circle NO in BOTH and move to the next optional K module)

			□	
K1		**In the past 12 months,** have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES
K2		**In the past 12 months:**		
	a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
	b	When you cut down on drinking, did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF **YES** TO EITHER QUESTION, CODE **YES**.	NO	YES
	c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
	d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
	e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
	g	Have you continued to drink even though you knew that the drinking caused to health or mental problems?	NO	YES
		ARE **3** OR MORE **K2** ANSWERS CODED **YES**?	**NO**	**YES***
		*IF YES, SKIP K3 QUESTION, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.	***ALCOHOL DEPENDENCE*** **CURRENT**	
K3		**In the past 12 months:**		
	a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
	b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES

c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

NO	**N/A**	**YES**
ALCOHOL ABUSE **CURRENT**		

15. LIFETIME ALCOHOL ABUSE AND DEPENDENCE

(Means: go to the diagnostic boxes, circle NO in BOTH and move to the next module)

K4		Did you ever have 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES
K5		**In your lifetime:**		
	a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
	b	When you cut down on drinking, did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? If YES to either question, code YES.	NO	YES
	c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
	d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
	e	On the days that you drank, did you spend substantial time obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
	f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
	g	Have you continued to drink even though you knew that the drinking caused to health or mental problems?	NO	YES
		ARE **3** OR MORE **K5** ANSWERS CODED **YES**? *IF YES, SKIP **K6** QUESTION, CIRCLE **N/A** IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.	**NO**	**YES***
			ALCOHOL DEPENDENCE **LIFETIME**	
K3		**In your lifetime:**		
	a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES

b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Have you had any legal problems because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Have you continued to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **K6** ANSEWRS CODED **YES**?

NO	N/A	YES
ALCOHOL ABUSE **LIFETIME**		

M. PSYCHOTIC DISORDERS – Part 1

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CURRENTLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".
DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.
HALLUCINATIONS ARE SCORED "Bizarre" IF: A VOICE COMMENTS ON THE PERSON'S THOUHGTS OR BEHAVIOUR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.
ALL OF THE PATIENT'S RESPONSES TO THE QUESTIONS SHOULD BE CODED IN COLUMN A. USE THE CLINICIANS JUDGEMENT COLUMN (COLUMN B) ONLY IF THE CLINICIAM KNOWS FROM OTHER OUTSIDE EVIDENCE (FOR EXAMPLE FAMILY INPUT) THAT THE SYMPTOM IS PRESENT BUT IS BING DENIED BY THE PATIENT.

Now I am going to ask you about unusual experiences that some people have.

			COLUMN A Patient Response			COLUMN B Clinician Judgement (if necessary)	
					BIZARRE		BIZARRE
M1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you?	NO	YES	YES	YES	YES
	b	If **YES/YES BIZARRE**: Do you currently believe these things? NOTE: ASK FOR EXAMPLES, TO RULE OUT ACTUAL STALKING.	NO	YES	YES **↑M6**	YES	YES **↑M6**
M2	a	Have you ever believed that someone was reading your mind or could hear your thoughts or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES	YES	YES
	b	If **YES/YES BIZARRE**: Do you currently believe these things?	NO	YES	YES **↑M6**	YES	YES **↑M6**
M3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES	YES	YES
	b	If **YES/YES BIZARRE**: Do you currently believe these things?	NO	YES	YES **↑M6**	YES	YES **↑M6**

M4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES		YES	YES
	b	If **YES/YES BIZARRE**: Do you currently believe these things?	NO	YES	YES **↑M6**		YES	YES **↑M6**
M5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. CODE **YES** ONLY IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS (FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JELOUSY, GUILT, RUIN OR DESTITUTION OF OTHER NOT EXPLORED IN **M1** TO **M4**).	NO	YES	YES		YES	YES
	b	If **YES/YES BIZARRE:** Do they currently consider your beliefs strange?	NO	YES	YES		YES	YES
M6	a	Have you ever hear things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:	NO	YES	YES		YES	YES
		IF **YES** OR **YES BIZARRE**: Did you hear a voice commenting on your thoughts or behaviour, or did you hear two or more voices talking to each other?	NO		YES		NO	YES
	b	IF **YES**: Have you heard these things in the past month? SCORE AS "YES BIZARRE" IF PATIENT HEARD A VOICE COMMENTING ON THIE THOUGHTS OR BEHAVIOUR OR HEARD TWO OR MORE VOICES TALKING TO EACH OTHER.	NO	YES	YES **↑M8**		YES	YES **↑M8**
M7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES			YES	
	b	IF YES: Have you seen these things in the past month?	NO	YES			YES	
		CLINICIAN'S JUDGEMENT						
M8	b	Is the patient currently exhibiting incoherence, disorganised speech, or marked loosening of associations?					NO	YES

M9 b Is the patient currently exhibiting disorganised or catatonic behaviour? NO YES

M10 b Are negative symptoms of schizophrenia, for example, significant affective flattening, poverty of speech (alogia) or an inability to initiate or persist in goal-directed activities (avolition) prominent during the interview? NO YES

M11 a Is there at least one "**YES**" from **M1** to **M10b**? NO YES

M11 b

ARE THE ONLY SYMPTOMS PRESENT THOSE IDENTIFIED BY THE CLINICIAN FROM **M1** TO **M7**(COLUMN B) AND FROM **M8b** OR **M9b** OR **M10b**?
IF **YES**, SPECIFY IF THE LAST EPISODE IS CURRENT (AT LEAST ONE "**b**" QUESTION IS CODED "**YES**" FROM **M1** TO **M10b**) AND/OR LIFETIME (ANY QUESTION CODED YES FROM **M1** TO **M10b**) AND PASS TO THE NEXT DIAGNOSTIC SECTION.

IF **NO**, CONTINUE.

NO **YES**

PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED *

Current ☐
Lifetime ☐

***Provisional diagnosis due to insufficient information available at this time.**

WARNING: IF AT LEAST ONE "**b**" QUESTION IS CODED **YES**, CODE **M11c** AND **M11d**.
IF ALL "**b**" ARE CODED **NO**, CODE ONLY **M11d**

M11 c

FROM **M1** TO **M10b**: ARE ONE OR MORE "**b**" ITEMS CODED "YES **BIZARRE**"?

OR

ARE TWO OR MORE "**b**" ITEMS CODED "**YES**" BUT NOT "**YES BIZARRE**"?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO

Then Criterion "A" of Schizophrenia is not currently met

YES

Then Criterion "A" of "Schizophrenia" is currently met

M11 d FROM **M1** TO **M10b**: ARE ONE OR MORE "**a**" ITEMS CODED "**YES BIZARRE**"?

OR ARE TWO OR MORE "**a**" ITEMS CODED "**YES**" BUT NOT "**YES BIZARRE**"? (CHECK THAT AT LEAST 2 ITEMS OCCURRED DURING THE SAME 1 MONTH PERIOD.)

NO
Then Criterion "A" of Schizophrenia is not met Lifetime

OR IS **M11c** CODED "**YES**"

YES
Then Criterion "A" of Schizophrenia is met Lifetime

M12 a Were you taking and drugs or medicines just before these symptoms began? No Yes

b Did you have any medical illness just before these symptoms began? No Yes

c IN THE CLINICAN'S JUDGEMENT: AR EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S PSYCHOSIS? No Yes

d HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES UNCERTAIN

IF **M12d** = **NO**: SCORE **M13**(**a**, **b**) AND GO TO THE NEXT DISORDER
IF **M12d** = **YES**: CODE **NO** IN **M13** (**a**, **b**) AND GO TO **M14**
IF **M12d** = **UNCERTAIN**: CODE **UNCERTAIN** IN **M13** (**a**, **b**) AND GO TO **M14**

M13 a IS **M12d** CODED **NO** BECAUSE OF A GENERAL MEDICAL CONDITION?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE "**b**" QUESTION IS CODED **YES** FROM **M1** TO **M10b**)
AND/OR LIFETIME ("**a**" OR "**b**") QUESTION IS CODED YES FROM **M1** TO **M10b**

NO **YES**

PSYCHOTIC DISORDER Due to a General Medical Condition
Current ☐
Lifetime ☐
Uncertain, code later ☐

M13 b IS **M12d** CODED **NO** BECAUSE OF A DRUG?
IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE QUESTION "b**"** IS CODED **YES** FROM M1 TO **M10b**)
AND/OR/LIFETIME (ANY "**a**" OR "**b**" QUESTION CODED **YES** FROM **M1** TO **M10b**).

NO **YES**

Substance Induced PSYCHOTIC DISORDER
Current ☐
Lifetime ☐
Uncertain, code later ☐

M14 How long was the longest period during which you had those beliefs or experiences? _____
IF <1 DAY, GO TO THE NEXT SECTION

M15 a During or after a period when you had these beliefs or experiences, did you have difficulty working, or difficulty in your relationships with others, or in taking care of yourself? NO YES

b If **YES**, how long did these difficulties last?
IF ≥ 6 MONTHS, GO TO M16. _____

c Have you been treated with medications or were you hospitalised because of these beliefs or experiences, or the difficulties caused by these problems? NO YES

d If **YES**, what was the longest time you were treated with medication or were hospitalised for these problems? _____

M16 a THE PATIENT REPORTED DISABILITY (**M15a** CODED **YES**) OR WAS TREATED OR HOSPITALISED FOR PSYCHOSIS (**M15c** = **YES**). NO YES

b CLINICIAN'S JUDGEMENT: CONSIDERING YOUR EXPERIENCE, RATE THE PATIENT'S **LIFETIME** DISABILITY CAUSED BY THE PSYCHOSIS.

absent	☐	1
mild	☐	2
moderate	☐	3
severe	☐	4

M17 WHAT WAS THE TOTAL DURATION OF THE PSYCHOSIS, TAKING INTO ACCOUNT THE ACTIVE PHASE (**M14**) AND THE ASSOCIATED DIFFICULTIES (**M15b**) AND PSYCHIATRIC TREATMENT (**M15d**).

1□ ≥1 to <1 month
2□ ≥1 month to < 6 months
3□ ≥6 months

CHRONOLOGY

M17 a How old were you when you first began having these unusual beliefs or experiences? ☐ Age

M18 b Since the first onset how many distinct times did you have significant episodes of these unusual beliefs or experiences? ☐

P. GENERALISED ANXIETY DISORDER

(☐ Means: go to the diagnostic boxes, circle NO in all diagnostic boxes, and move to the next module)

			☐	
P1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO	YES
			☐	
	b	Are these worries present most days?	NO	YES
				☐
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES
			☐	
P2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO	YES
P3		FOR THE FOLLOWING, CODE NO, IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT. (E.G. PRIMARILY IN SOCIAL SITUATIONS, TRIGGERED PRIMARILY BY MEMORIES OF A TRAUMATIC EVENT OR PRIMARILY TO FEARS OF HAVING A PANIC ATTACK)		
		When you were anxious over the past 6 months, most of the time did you:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening, or sleeping excessively)?	NO	YES
			☐	
		SUMMARY OF **P3**: ARE **3** OR MORE **P3** ANSWERS CODED **YES**?	NO	YES
			☐	
P4		Did these symptoms of anxiety cause you significant distress or impair your ability to function at work, socially, or in some other important way?	NO	YES
P5	a	Were you taking any drugs or medicines just before these symptoms began?	No	Yes

b Did you have any medical illness just before these symptoms began? No Yes

IN THE CLINICIAN'S JUDGEMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S GENERALISED ANXIETY DISORDER?

P5(**SUMMARY**): HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES

IS **P5**(**SUMMARY**) CODED **YES**?

NO	**YES**
Generalised Anxiety Disorder **CURRENT**	

P6 IS **P5**(**SUMMARY**) CODED **NO** AND **P5b** CODED **YES**?

NO	**YES**
Current *Generalised Anxiety Disorder.* Due to a General Medical Condition	

P7 IS **P5**(**SUMMARY**) CODED **NO** AND **P5a** CODED **YES**?

NO	**YES**
Current Substance Induced *Generalised Anxiety Disorder*	

CHRONOLOGY

P8 a How old were you when you first began having symptoms of generalised anxiety? ☐ Age

P9 b During the past year, for how many months did you have significant symptoms of generalised anxiety? ☐

Q. ANTISOCIAL PERSONALITY DISORDER

(Means: go to the diagnostic box, circle NO, and move to the next module)

Q1 B**efore you were 15 years old, did you:**

a	repeatedly skip school or run away from home over night?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	ARE **2** OR MORE **Q1** ANSWERS CODED **YES**?	NO	YES

DO NOT CODE YES TO THE BEHAVIOURS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

Q2 **Since you were 15 years old, have you**:

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	No	Yes
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	No	Yes
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES
	ARE **3** OR MORE **Q2** QUESTIONS CODED **YES**?		

NO	**YES**
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

U. PAIN DISORDER

(□ Means: go to the diagnostic box, circle NO in all diagnostic boxes, and move to the next module)

U1	Currently, is pain your main problem?	□ NO	YES
U2	**Currently, is the pain severe enough to need medical attention?**	□ NO	YES
U3	Currently is the pain causing you significant distress, or interfering significantly with your ability to function at work, socially, or in some other important way?	NO	YES
U4	Did psychological factors or stress have an important role in the onset of the pain, or did they make it worse, or keep it going?	NO	YES
U5	Is the pain a pretense or intentionally produced or feigned? (As in a factitious disorder?)	NO	YES
U6	Did a medical condition have an important role in the onset of the pain, or did the medical condition make it worse, or keep it going?	NO	YES
U7	Has the pain been present for more than 6 months?	NO ↓ Acute	YES ↓ Chronic

U8 IS **U6** CODED **NO**?

NO	**YES**
	PAIN DISORDER **associated with psychological factors CURRENT**

U9 IS **U6** CODED **YES**?

IF **U8** OR **U9** ARE CODED YES
AND **U7** = **NO**, ADD: ACUTE T DIAGNOSIS TITLE
AND **U7** = **YES**, ADD: CHRONIC TO DIAGNOSIS TITLE

NO	**YES**
	PAIN DISORDER **associated with psychological factors and general medical condition CURRENT**

X. ADJUSTMENT DISORDERS

(→ Means: go to the diagnostic box, circle NO in all diagnostic boxes, and move to the next module)

EVEN IF A LIFE STRESS IS PRESENT OR A STRESS PRECIPITATED THE PATIENT'S DISORDER, DO NOT USE AN ADJUSTMENT DISORDER DIAGNOSIS IF ANY OTHER PSYCHIATRIC DISORDER IS PRESENT. SKIP THE ADJUSTMENT DISORDER SECTION IF THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOTHER SPECIFIC AXIS I DISORDER OR ARE MERELY AN EXACERBATION OF A PREEXISTING AXIS I OR II DISORDER.

ONLY ASK THESE QUESTION IF PATIENT CODES NO TO ALL OTHER DISORDERS.

X1		Are you having emotional or behavioural symptoms as a result of a life stress? [Examples include anxiety/depression/misbehaviour/physical complaints (examples of misbehaviour include fighting, driving recklessly, skipping school, vandalism, violating the rights of others, or doing illegal things)].	→ NO	YES
X2		Did these emotional/behavioural symptoms start within 3 months of the onset of the stressor?	→ NO	YES
X3	a	Are these emotional/behavioural symptoms causing marked distress beyond what would be expected?	→ NO	YES
	b	Are these emotional/behavioural symptoms causing significant impairment in your ability to function socially, at work, or at school?	→ NO	YES
X4		Are these emaotional/behavioural symptoms due entirely to the loss of a loved one (bereavement) and are they similar in severity, level of impairment and duration to what most other would suffer under similar circumstances? (Id so this is uncomplicated bereavement.)		
		HAS UNCOMPLICATED BEREAVEMENT BEEN RULED OUT?	→ NO	YES
X5		Have these emotional/behavioural symptoms continued for more than 6 months after the stress stopped?	→ NO	YES

WHICH OF THESE EMOTIONAL/BEHAVIOURAL SUBTYPES ARE PRESENT? MARK ALL THAT APPLY

A Depression, tearfulness or hopelessness ☐

B Anxiety, nervousness, jitteriness, worry ☐

☐

C Misbehaviour (for example fighting, driving recklessly, skipping school, vandalism, violating other's rights, doing illegal things). ☐

D Work problems, school problems, physical complaints or social withdrawal.

IF MARKED:

- A only, then code as Adjustment disorder **with depressed mood.**
- B only, then code as Adjustment disorder **with anxious mood.**
- C only, then code as Adjustment disorder **of conduct.**
- A and B only, then code as Adjustment disorder **with mixed anxiety and depressed mood.**
- C and (A or B), then code as Adjustment disorder of **emotions and conduct.**
- D only, then code as Adjustment Disorder **unspecified.**

IF **X5** IS CODED **NO**, THEN CODE DISORDER **YES** WITH SUBTYPE.

NO	**YES**
Adjustment Disorder with _____ (see above for subtypes)	

7 National Adult Reading Test (NART)

National Adult Reading Test (NART)
Word Card

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

8 CANTAB privacy policy

Privacy Policy for Cambridge Cognition's Web-Based Cognitive Testing Application ("the Application")

This privacy policy explains how the Application collects information about you and your responses to the cognitive tests which are run by the Application and how that information will be used ("the Privacy Policy").

15) About the Application

The Application is intended to help with the conduct of research studies by allowing participants to take some or all of the study assessments without having to visit the research centre or site in person. We hope that this makes it more convenient for participants to take part in research and therefore helps researchers carry out research studies.

The Application has been developed by Cambridge Cognition Limited ("Cambridge Cognition", "we", "us" or "our") and is being made available to you by, or on behalf of, the organisation(s) responsible for conducting the research studies ("the Researcher").

2) About this Privacy Policy

Cambridge Cognition takes your privacy seriously and asks that you read this Privacy Policy carefully as it contains important information about what to expect when the Application collects personal information about you and how that personal information will be used.

3) Information that the Application collects about you

The Application collects information and enables participants to conduct tests which help the Researcher conduct a research study ("Study") on a group of individuals ("Participants").

The Application may prompt you for Personal Information which the Researcher believes relevant to the Study. Examples of this could include asking you to provide your name, gender, age, nationality or to give some information regarding your education, work or medical history. The Application may request contact information from you, such as your e-mail address and other contact details. Your responses are recorded by the Application. Personal information is only collected if you choose to take part in the Study and volunteer the information requested by the Application.

The Study may require you to take a number of tests using the Application on a number of different occasions. Your responses to the tests are recorded by the Application.
The information that you provide may therefore be sufficient to allow you to be identified and may provide some details about your health. For these reasons, we and the Researcher need to be certain that you agree to our collecting, using and sharing the information you provide on the basis described in this Privacy Policy. In this privacy policy, we refer to the information you give to us and your responses to the tests carried out by the Application as "Personal Information".

4) Age and capacity to participate in the Study

The Application is intended for use by adults able to give free and informed consent to the processing of their Personal Information.

We do not intend to collect Personal Information regarding individuals under the age of 18 or, if higher, the age of legal majority in the country in which you live. We do not intend to collect Personal Information regarding individuals who do not have capacity to provide free and informed consent.

If you are not an adult who is able to give free and informed consent, you should not submit information into the Application.

If you are concerned that your child or relative has provided Personal Information in circumstances not in accordance with this paragraph, please contact us (see Section 13).

If we become aware that Personal Information has been provided to us that goes against these principles we shall use reasonable efforts to remove such Personal Information and cancel the registration to the Application.

5) How will the information you provide be used?

Your Personal Information will be processed by us, our Group, agents and sub-contractors to enable you to take part in the Study, to communicate with you on any matter relating to

your use of the Application and also to provide analysis and reports on the Study to the Researcher.

Your Personal Information may also be accessed by, and/or transferred to, the Researcher, its agents and sub-contractors to use for the purposes of the Study.

We, our Group, agents, and sub-contractors may use aggregate information and statistics for the purposes of monitoring the Application and to develop the Application and other current or future products and services. Where this takes place, the information will be de-identified so that the information cannot be used to identify you.

Your Personal Information will be processed by us for the duration of the Study and for the period of time afterwards that the Researcher needs to retain research records under applicable law or regulation after which we shall use reasonable efforts to de-identify it so that you can no longer be identified from it.

We do not use your Personal Information for marketing purposes without first seeking your approval.

We use the term "Group" in this paragraph and elsewhere in the Privacy Policy to refer to the family of companies that are under our control or (where applicable) under the control of the Researcher, such as subsidiary companies and parent companies. For example, our Group includes Cambridge Cognition Holdings plc, Cambridge Cognition, LLC and Cantab Corporate Health Limited.

6) Our use of cookies and other information-gathering technologies

The Application does not use cookies. It simply records the visits to the Application which are made from your computer or device.

7) How we protect the information

Personal Information will be collected, stored and accessed from our servers and the servers of our data processors.

We use reasonable efforts to safeguard your Personal Information, including the following measures:

we carefully select and audit our data processors to ensure that there are adequate technical and organisational procedures in place to protect personal data;
we enter into written contracts with them to create legally binding obligations with regard to compliance with applicable data protection laws and regulations;
we encrypt data when it is (a) stored locally on the electronic device used to collect your Personal Information; and (b) when the data is transmitted to or from our data processors.
Your data is stored in a HIPAA (Health Information Portability and Accountability Act) and GDPR (General Data Protection Regulation) compliant data centre which is HITRUST certified.

8) Overseas Transfers

Your Personal Information may be transferred to countries outside the country where you live.
These transfers are required to enable the Application to operate on an international basis because Participants, the Researcher, data processors and other persons able to access Personal Information in accordance with this Privacy Policy may be located in different countries.

Our data processors are currently located in the United States of America. We reserve the right to change our data processor and also to add or remove locations and countries where the Personal Information is processed.

If you are in the European Economic Area (being the European Union member states plus Norway, Iceland and Liechtenstein) ("EEA"), your information may be transferred to countries outside EEA, including the USA. In order to ensure the security of your information, we put in place written agreements with our data processors in countries outside the EEA. These agreements place obligations on the data processors to provide the same safeguards over your information as is required within the EEA.

By submitting your Personal Information you consent to these transfers for the purposes specified in this Privacy Policy.

9) Access to your information and updating and correcting your information

You have the right to request a copy of the Personal Information that we hold about you. If you would like a copy of some or all of your Personal Information, please send an email or letter to us at the address in see Section 13. We may make a small administrative charge for this service.

We want to ensure that your Personal Information is accurate and up to date. If any of the information that you have provided to us changes, for example if you change your email address, name or contact details, please let us know the correct details by sending an email or letter to us.

You may ask us, or we may ask you, to correct information you or we think is inaccurate, and you may also ask us to remove information which is inaccurate.

10) Transfer of the Study or Application

The Study may be run as a collaboration involving more than one Researcher or the Study may be transferred to another Researcher. If this happens, your Personal Information, may be shared with, or transferred to, those organisations collaborating in running the Study and they will be permitted to process the Personal Information as set out in accordance with the Privacy Policy.

If the Application is sold to another business, then the new owner of the Application would be permitted to process your Personal Information instead of Cambridge Cognition.

11) Your consent

By submitting your Personal Information to the Application you consent to the collection, use, transfer and other processing of your Personal Information as set out in this Privacy Policy.

If at any time you wish to withdraw your consent in respect of any further processing of your Personal Information, you may do so by sending a notice to us in writing by e-mail or letter at the email or postal address set out below.
If you do withdraw your consent, this will take effect 30 days after receipt by us of your notice and we shall de-identify all your Personal Information within the Application so that it can no longer be used to identify you unless we, or the Researcher, are required to retain a record of your Personal Information in order to comply with legal requirements.
If you do withdraw your consent, we, and the Researcher, may continue to use such de-identified Personal Information or other non-identifiable information provided to us through your use of the Application on the basis set out in this Privacy Policy.
12) Links to other applications or websites

The Application may contain links to other applications or websites. This privacy policy only applies to the Application so if you link to other applications or websites you should satisfy yourself as to the terms of their own privacy policies.

13) Contact Details

If you wish to contact us to have your data anonymised, amended or have questions on this privacy policy you must use the contact details below referencing “web-based testing”

Postal Address:

Cambridge Cognition Limited
Tunbridge Court
Tunbridge Lane
Bottisham
Cambridge
CB25 9TU
United Kingdom

14) Ownership and licensing of the Application

The Application is the proprietary software of Cambridge Cognition and is protected by copyright and/or other intellectual property rights and is licensed strictly for you to use in connection with the Study. CANTAB and CAMBRIDGE COGNITION are trade marks of Cambridge Cognition.

The Application is not to be copied except where such copying is incidental to its normal use or where it is necessary for the purpose of back-up or operational security.

15) Changes to the Privacy Policy

We keep the Privacy Policy under regular review. If we change the Privacy Policy we will make those changes available so that you may be aware of the information we collect and how we use it at all times. We may make the changes to the Privacy Policy available to you by any of the following ways:

posting to our website, currently at www.cambridgecognition.com; or

updating the policy within the Application, where you continue to access the service;

sending you an e-mail, where we have been provided with your e-mail address; or

requesting that the Researcher provides you with a copy.

Any changes to the Privacy Policy may take effect from the earliest date on which we notify you by any of the methods described above or such later date as specified in the new version of the Privacy Policy. However, we may make changes to the Privacy Policy which have retrospective effect but such changes shall not limit your ability to withdraw your consent to the further processing of Personal Information.

CAMBRIDGE COGNITION LIMITED Version 1.1

This Privacy Policy was last updated on 23rd January 2018

9 Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

10 Epworth Sleepiness Scale

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness. The test is a list of eight situations in which you rate your tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. When you finish the test, add up the values of your responses. Your total score is based on a scale of 0 to 24. The scale estimates whether you are experiencing excessive sleepiness that possibly requires medical attention.

How Sleepy Are You?

How likely are you to doze off or fall asleep in the following situations? You should rate your chances of dozing off, not just feeling tired. Even if you have not done some of these things recently try to determine how they would have affected you. For each situation, decide whether or not you would have:

- No chance of dozing =0
- Slight chance of dozing =1
- Moderate chance of dozing =2
- High chance of dozing =3

Write down the number corresponding to your choice in the right hand column. Total your score below.

Situation	Chance of Dozing
Sitting and reading	•
Watching TV	•
Sitting inactive in a public place (e.g., a theater or a meeting)	•
As a passenger in a car for an hour without a break	•
Lying down to rest in the afternoon when circumstances permit	•
Sitting and talking to someone	•
Sitting quietly after a lunch without alcohol	•
In a car, while stopped for a few minutes in traffic	•

11 Sleep diary

1) What time did you go to bed last night?
2) After settling down, how long (in minutes) did it take you to fall asleep? Please give us your best estimate
3) After falling asleep, did you wake up in the night at all? If yes, how many times?
4) If you did wake up, for how long were you awake in the night for in total? Please give us your best estimate
5) What time did you wake up this morning?
6) What time did you get up this morning?
7) How would you rate the quality of you sleep last night? 1(very poor) to 5 (very good)
8) During the first-half hour after you wake-up in the morning, how do you feel: Very refreshed, Fairly refreshed, Fairly tired or Very tired

12 Different combinations of Read codes to develop case ascertainment algorithm using Welsh Longitudinal General Practice dataset

Algorithm 1				Algorithm 2				Algorithm 3				Algorithm 4				Algorithm 5			
Read Code	**Description**	**Level**	**Sensitivity (n)**	**Read Code**	**Description**	**Level**	**Sensitivity (n)**	**Read Code**	**Description**	**Level**	**Sensitivity (n)**	**Read Code**	**Description**	**Level**	**Sensitivity (n)**	**Read Code**	**Description**	**Level**	**Sensitivity (n)**
16A3.	Torticollis - symptom	1	73.7% (59)	16A3.	Torticollis - symptom	1	73.7% (59)	16A3.	Torticollis - symptom	1	73.7% (59)	16A3.	Torticollis - symptom	1	73.7% (59)	16A3.	Torticollis - symptom	1	73.7% (59)
F136.	Idiopathic torsion dystonia			F136.	Idiopathic torsion dystonia			F136.	Idiopathic torsion dystonia			F136.	Idiopathic torsion dystonia			F136.	Idiopathic torsion dystonia		
F1360	Idiopathic familial dystonia			F1360	Idiopathic familial dystonia			F1360	Idiopathic familial dystonia			F1360	Idiopathic familial dystonia			F1360	Idiopathic familial dystonia		
F137.	Symptomatic torsion dystonia			F137.	Symptomatic torsion dystonia			F137.	Symptomatic torsion dystonia			F137.	Symptomatic torsion dystonia			F137.	Symptomatic torsion dystonia		
F1380	Blepharospasm			F1380	Blepharospasm			F1380	Blepharospasm			F1380	Blepharospasm			F1380	Blepharospasm		
F1382	Spasmodic torticollis			F1382	Spasmodic torticollis			F1382	Spasmodic torticollis			F1382	Spasmodic torticollis			F1382	Spasmodic torticollis		
F1383	Organic writers' cramp			F1383	Organic writers' cramp			F1383	Organic writers' cramp			F1383	Organic writers' cramp			F1383	Organic writers' cramp		

F138z	Torsion dystonia fragm. NOS	F138z	Torsion dystonia fragm. NOS	F138z	Torsion dystonia fragm. NOS	F138z	Torsion dystonia fragm. NOS	F138z	Torsion dystonia fragm. NOS
F13A.	Paroxysmal dystonia	F13A.	Paroxysmal dystonia	F13A.	Paroxysmal dystonia	F13A.	Paroxysmal dystonia	F13B.	Myoclonic dystonia
F13B.	Myoclonic dystonia	F13B.	Myoclonic dystonia	F13B.	Myoclonic dystonia	F13B.	Myoclonic dystonia	F13C.	Segawa syndrome
F13C.	Segawa syndrome	F13C.	Segawa syndrome	F13C.	Segawa syndrome	F13C.	Segawa syndrome	F13X.	Dystonia, unspecified
F13X.	Dystonia, unspecified	F13X.	Dystonia, unspecified	F13X.	Dystonia, unspecified	F13X.	Dystonia, unspecified	Fyu24	[X]Other dystonia
Fyu24	[X]Other dystonia	Fyu24	[X]Other dystonia	Fyu24	[X]Other dystonia	Fyu24	[X]Other dystonia	Fyu2A	[X]Dystonia, unspecified
Fyu2A	[X]Dystonia, unspecified	Fyu2A	[X]Dystonia, unspecified	Fyu2A	[X]Dystonia, unspecified	Fyu2A	[X]Dystonia, unspecified	N135.	Torticollis unspecified
N135.	Torticollis unspecified	N135.	Torticollis unspecified	N135.	Torticollis unspecified	N135.	Torticollis unspecified	N1350	Intermittent torticollis
N1350	Intermittent torticollis	N1350	Intermittent torticollis	N1350	Intermittent torticollis	N1350	Intermittent torticollis	N135z	Torticollis NOS

N135z	Tortico llis NOS			N135z	Tortico llis NOS			N135z	Tortico llis NOS			N135z	Tortico llis NOS			F137y	Sympt omat torsion dystoni a OS	2	82.5 (66)
F131.	Essent. +other specifie d tremor	2: medicat ion and diagnos is 2: diagnos is	83.75 (67) 83.75 (67)	F131.	Essent. +other specifie d tremor	2: diagnos is 2: diagnos is and medicat ion	82.5% (66) 82.5% (66)	F131.	Essent. +other specifie d tremor	2: diagnos is 2: diagnos is and medicat ion	82.5% (66) 82.5% (66)	F131.	Essent. +other specifie d tremor	2		F137z	Sympt omat torsion dystoni a NOS		
F1310	Benign essentia l tremor			F1310	Benign essentia l tremor			F1310	Benign essentia l tremor			F1310	Benign essentia l tremor			F138.	Fragm ents of torsion dystoni a		
F1372	Drug-induced dystoni a			F137y	Sympto mat torsion dystoni a OS			F137y	Sympto mat torsion dystoni a OS			F137y	Sympto mat torsion dystoni a OS			1B22.	Has a tremor		
F137y	Sympto mat torsion dystoni a OS			F137z	Sympto mat torsion dystoni a NOS			F137z	Sympto mat torsion dystoni a NOS			F137z	Sympto mat torsion dystoni a NOS						
F137z	Sympto mat torsion dystoni a NOS			F138.	Fragme nts of torsion dystoni a			F138.	Fragme nts of torsion dystoni a			F138.	Fragme nts of torsion dystoni a						
F138.	Fragme nts of torsion dystoni a			1B22.	Has a tremor			1B22.	Has a tremor			1B22.	Has a tremor						

1B22.	Has a tremor	F131z	Essential and other specified forms of tremor	F131z	Essential and other specified forms of tremor	F131z	Essential and other specified forms of tremor
1B25.	Has spasms	ds3..	CLOSTRIDIUM BOTULINUM A T-HC	ds3..	CLOSTRIDIUM BOTULINUM A T-HC		
F131z	Essential and other specified forms of tremor	ds31.	*BOTULINUM A D-HC 500units inj	ds31.	*BOTULINUM A D-HC 500units inj		
ds3..	CLOSTRIDIUM BOTULINUM A T-HC	ds32.	DYSPORT 500units injection	ds32.	DYSPORT 500units injection		
ds31.	*BOTULINUM A D-HC 500units inj	ds33.	BOTOX 100units inj powder	ds33.	BOTOX 100units inj powder		
ds32.	DYSPORT 500units injection	ds34.	*CLOSTRIDIUM BOTUL 100u inj	ds34.	*CLOSTRIDIUM BOTUL 100u inj		

ds33.	BOTOX 100units inj powder	ds36.	*CLOSTRIDIUM BOTUL 50u inj pdr	ds36.	*CLOSTRIDIUM BOTUL 50u inj pdr
ds34.	*CLOSTRIDIUM BOTUL 100u inj	ds37.	XEOMIN 100units pdr for inj	ds37.	XEOMIN 100units pdr for inj
ds36.	*CLOSTRIDIUM BOTUL 50u inj pdr	ds38.	BOTOX 50units pdr for inj	ds38.	BOTOX 50units pdr for inj
ds37.	XEOMIN 100units pdr for inj	ds3C.	XEOMIN 50units pdr for inj	ds3C.	XEOMIN 50units pdr for inj
ds38.	BOTOX 50units pdr for inj	T8531	Accid.pois.-anticholinesterase	7Q040	Torsion dystonias other involuntary movements drugs Band 1
ds3B.	DYSPORT 300units injection	T854.	Accid.pois.-anticholinergics		
ds3C.	XEOMIN 50units pdr for inj	T854z	Accid.pois.-anticholinerg. NOS		

T8531	Accid.pois.-anticholinesterase	TJ953	AR - tetrabenazine		
T854.	Accid.pois.-anticholinergics	TJB05	AR - anticholinesterase		
T854z	Accid.pois.-anticholinerg. NOS	7Q040	Torsion dystonias other involuntary movements drugs Band 1		
TJ953	AR - tetrabenazine	F1311	Familial tremor	3: diagnosis 3: diagnosis and medication	83.75% (67) 87.5% (70)
TJB05	AR - Anticholinesterase	H1y74	Laryngeal spasm		
7Q040	Torsion dystonias other involuntary movements drugs Band 1	R0102	[D]Spasms NOS		

F1311	Familial tremor	3: diagnosis 3: diagnosis and medication	85% (68) 88.75% (71)	dn41.	RIVOTRIL 500micrograms tablets
H1y74	Laryngeal spasm			dn42.	RIVOTRIL 2mg tablets
F132.	Myoclonus			dn4w.	CLONAZEPAM 0.5mg/5mL s/f soln
F132y	Myoclonus OS			dn4x.	CLONAZEPAM 2mg/5mL s/f soln
F132z	Myoclonus NOS			dn4y.	CLONAZEPAM 500mcg tablets
Fyu27	[X]O spcf extrpyr mdl+m vmnt dis			dn4z.	CLONAZEPAM 2mg tablets
Fyu28	[X]Extr pyrmdl +mvmt diso/dis CE			j82..	BACLOFEN

PE1..	Congenital sternomastoid torticollis	j821.	LIORESAL 10mg tablets
R0102	[D]Spasms NOS	j822.	LIORESAL 5mg/5mL sf liquid
dn41.	RIVOTRIL 500microgrms tablets	j823.	*BACLOSPAS 10mg tablets
dn42.	RIVOTRIL 2mg tablets	j827.	LYFLEX 5mg/5mL s/f oral soln
dn4w.	CLONAZEPAM 0.5mg/5mL s/f soln	j82t.	BACLOFEN 40mg/20mL soln inj
dn4x.	CLONAZEPAM 2mg/5mL s/f soln	j82v.	BACLOFEN 50mcg/1mL i-t inj
dn4y.	CLONAZEPAM 500mcg tablets	j82w.	BACLOFEN 10mg/5mL i-t inj

dn4z.	CLONAZEPAM 2mg tablets	j82w.	BACLOFEN 10mg/5mL i-t inj
j82..	BACLOFEN	j82x.	BACLOFEN 10mg/20mL i-t inj
j821.	LIORESAL 10mg tablets	j82y.	BACLOFEN 10mg tablets
j822.	LIORESAL 5mg/5mL sf liquid	j82z.	BACLOFEN 5mg/5mL sf liquid
j823.	*BACLOSPAS 10mg tablets	T8502	Accid.pois.-levodopa (L-dopa)
j827.	LYFLEX 5mg/5mL s/f oral soln	TJ641	AR - levodopa - L-dopa
j82t.	BACLOFEN 40mg/20mL soln inj		
j82v.	BACLOFEN 50mcg/1mL i-t inj		

j82w.	BACLOFEN 10mg/5mL i-t inj		
j82x.	BACLOFEN 10mg/20mL i-t inj		
j82y.	BACLOFEN 10mg tablets		
j82z.	BACLOFEN 5mg/5mL sf liquid		
T8502	Accid.pois.-levodopa (L-dopa)		
TJ641	AR - levodopa - L-dopa		
E2601	Psychogenic torticollis	4	88.75% (71)
Eu45y	Psychogenic torticollis - other somatoform disorders		

F312.	Clonic hemifacial spasm
N23y4	Spasm of muscle
N23yE	Spasm of back muscles

13 Read codes and ICD-10 codes used to identify psychiatric disorders

Psychiatric disorder	ICD-10 Code	Read Code	Description
ADHD			
		6A61.	ADHD annual review
		8BPT.	Drug therapy for ADHD
		8BPT0	Stimulant drug therapy ADHD
		8BPT1	Non-stimulnt drug therapy ADHD
		9Ngp.	On drug therapy ADHD
		9Ngp0	On stimulant drug therapy ADHD
		9Ngp1	On non-stimulnt drug ther ADHD
		9Ol8.	ADHD monitr invitatn 1st lettr
		9Ol9.	ADHD monitr invitatn 2nd lettr
		9OlA.	ADHD monitr invitatn 3rd lettr
		E2E..	Childhood hyperkinetic syndr.
		E2E0.	Child attention deficit disord
		E2E00	Attention deficit-not hyperact
		E2E01	Attention deficit +hyperactive
		E2E0z	Child attent.deficit dis.NOS
		E2E1.	Hyperkinesis+development delay
	F901	E2E2.	Hyperkinetic conduct disorder
		E2Ey.	Other hyperkinetic manifestat.
		E2Ez.	Hyperkinetic syndrome NOS
	F90	Eu90.	[X]Hyperkinetic disorders
	F900	Eu900	[X]Disturbance activity/attntn
		Eu901	[X]Hyperkinetic conduct disord
		Eu902	[X]Def atten motor cont percep
	F908	Eu90y	[X]Oth hyperkinetic disorders
	F909	Eu90z	[X]Hyperkinetic disorder, unsp
		Eu9y7	[X]Attention deficit disorder
Anxiety			

	2258.	O/E - anxious
	2259.	O/E - nervous
	1B12.	Nerves - nervousness
	1B13.	Anxiousness
	1B1V.	C/O - panic attack
	225J.	O/E - panic attack
	8G52.	Antiphobic therapy
	8G94.	Anxiety management training
	8HHp.	Ref guid self-help for anxiety
	E200.	Anxiety states
	E2000	Anxiety state unspecified
	E2001	Panic disorder
	E2002	Generalised anxiety disorder
	E2003	Anxiety with depression
	E2004	Chronic anxiety
	E2005	Recurrent anxiety
	E200z	Anxiety state NOS
F40	E202.	Phobic disorders
	E2020	Phobia unspecified
	E2021	Agoraphobia with panic attacks
	E2022	Agoraphobia - no panic attacks
	E2023	Social phobia-eating in public
	E2024	Social phobia-public speaking
	E2025	Social phobia-public washing
	E2026	Acrophobia
	E2027	Animal phobia
	E2028	Claustrophobia
	E2029	Fear of crowds
	E202A	Fear of flying
	E202B	Cancer phobia
	E202C	Dental phobia
	E202D	Fear of death

	E202E	Fear of pregnancy
	E202z	Phobic disorder NOS
	E203.	Obsessive-compulsive disorders
	E2030	Compulsive neurosis
	E2031	Obsessional neurosis
	E203z	Obsessive-compulsive dis NOS
	E28z.	Acute stress reaction NOS
	E2920	Separation anxiety disorder
	E2D0.	Anxiety/fear child/adoles.dis.
	E2D00	Child/adolesc.overanxious.dis.
	E2D01	Child/adolesc.fearfulness dis.
	E2D0z	Anxiety/fear child/adolesc.NOS
	Eu40.	[X]Phobic anxiety disorders
F400	Eu400	[X]Agoraphobia
F401	Eu401	[X]Social phobias
F402	Eu402	[X]Specific (isolated) phobia
	Eu403	[X]Needle phobia
F408	Eu40y	[X]Other phobic anxiety disord
F409	Eu40z	[X]Phobic anxiety disordr unsp
F41	Eu41.	[X]Other anxiety disorders
F410	Eu410	[X]Panic episodic paroxysm anx
F411	Eu411	[X]Generalized anxiety disord
F412	Eu412	[X]Mixed anxiety/depressve dis
F413	Eu413	[X]Other mixed anxiety disord
F418	Eu41y	[X]Other specif anxiety disord
F419	Eu41z	[X]Anxiety disord unspecified
F42	Eu42.	[X]Obsessive - compulsive dis
F420	Eu420	[X]Predom obsessional thoughts
F421	Eu421	[X]Predom compuls acts/ritual
F422	Eu422	[X]Mixed obsess thoughts/acts
F428	Eu42y	[X]Oth obsessve-compulsve dis
F429	Eu42z	[X]Obsessve-complsve dis unsp
F930	Eu930	[X]Separ anxiety dis childhood

	F931	Eu931	[X]Phobic anxiet dis childhood
	F932	Eu932	[X]Social anx dis childhood
		R2y2.	[D]Nervousness
Autism			
		1J9..	Suspected autism
		E140.	Infantile autism
		E1400	Infantile autism - active
		E1401	Infantile autism - residual
		E140z	Infantile autism NOS
		Eu84.	[X]Pervasive development dis
	F840	Eu840	[X]Childhood autism
	F841	Eu841	[X]Atypical autism
	F842	Eu842	[X]Rett's syndrome
	F843	Eu843	[X]Oth child disintegrat dis
	F844	Eu844	[X]Overact+retard+stereotyp mv
	F845	Eu845	[X]Asperger's syndrome
		Eu846	Pathological demand avoidance
	F848	Eu84y	[X]Oth pervasive develop dis
	F849	Eu84z	[X]Pervasve develop dis unsp
Conduct disorder			
		E2C..	Disturbance of conduct NEC
		E2C0.	Aggress.unsocial conduct dis.
		E2C0z	Aggressive unsocial disord.NOS
		E2C1.	Nonaggr.unsocial conduct dis.
		E2C10	Unsocial childhood truancy
		E2C1z	Nonaggr.unsocial cond.dis.NOS
		E2C2.	Socialised conduct disorder
		E2C20	Socialised childhood truancy
		E2C2z	Socialised conduct disord. NOS
		E2C4.	Mixed conduct/emotion disturb.
		E2C4z	Mixed conduct/emotion dist.NOS
		E2Cy.	Other conduct disturbances
		E2Cyz	Other conduct disturbances NOS

		E2Cz.	Disturbance of conduct unspec.
		E2Czz	Conduct disturbance NOS
		E2Dy0	Childhood oppositional disord.
		E2E2.	Hyperkinetic conduct disorder
	F901	Eu901	[X]Hyperkinetic conduct disord
	F91	Eu91.	[X]Conduct disorders
	F910	Eu910	[X]Conduct dis family context
	F911	Eu911	[X]Unsocialized conduct disord
	F912	Eu912	[X]Socialized conduct disorder
	F913	Eu913	[X]Oppositional defiant disord
	F918	Eu91y	[X]Other conduct disorders
	F919	Eu91z	[X]Conduct disorder, unspecif
	F92	Eu92.	[X]Mixed dis conduct/emotion
	F920	Eu920	[X]Depressive conduct disorder
	F928	Eu92y	[X]Oth mix disord conduct/emot
	F929	Eu92z	[X]Mixed dis conduct/emot unsp
Depression			
		2257.	O/E - depressed
		1B17.	Depressed
		1B1U.	Symptoms of depression
		1BP..	Loss of interest
		1BP0.	Loss of inter prev enjoy activ
		1BQ..	Loss of capacity for enjoyment
		1BT..	Depressed mood
		1BU..	Loss of hope for the future
		E112.	Single major depressive episod
		E1120	Single major depression-unspec
		E1121	Single major depression-mild
		E1122	Single major depress.-moderate
		E1123	Single major depression-severe
		E1125	Single maj.depres.-part remiss
		E1126	Single maj.depres.-full remiss
		E112z	Single major depression NOS

	E113.	Recurrent major depressive epi
	E1130	Recurr.major depression-unspec
	E1131	Recurr.major depression-mild
	E1132	Recurr.major depress.-moderate
	E1133	Recurr.major depression-severe
	E1135	Recurr.maj.depres.-part remiss
	E1136	Recurr.maj.depres.-full remiss
	E1137	Recurrent depression
	E113z	Recurr. major depression NOS
	E118.	Seasonal affective disorder
	E135.	Agitated depression
	E2003	Anxiety with depression
	E204.	Neurotic (reactive) depression
	E291.	Prolonged depressive reaction
	E2B..	Depressive disorder NEC
	E2B0.	Postviral depression
	E2B1.	Chronic depression
F32	Eu32.	[X]Depressive episode
F320	Eu320	[X]Mild depressive episode
F321	Eu321	[X]Moderate depressve episode
F322	Eu322	[X]Severe depressiv no psychot
F328	Eu324	[X]Mild depression
F329	Eu325	[X]Major depression, mild
F33	Eu326	[X]Major depression, moder sev
F330	Eu327	[X]Maj dep, sev wthout psy sym
F331	Eu32B	[X]Antenatal depression
F332	Eu32y	[X]Other depressive episodes
F334	Eu32z	[X]Depressive episode, unspecf
F338	Eu33.	[X]Recurrent depressive disord
F339	Eu330	[X]Recurr depress current mild
F341	Eu331	[X]Recurr depress current mod
F412	Eu332	[X]Recurr dep now sever no psy
F32	Eu334	[X]Recurr depress in remission

F320	Eu33y	[X]Oth recurr depressve disord
F321	Eu33z	[X]Recurrent depress dis unsp
F322	Eu341	[X]Dysthymia
F328	Eu412	[X]Mixed anxiety/depressve dis
Eating disorder		
	1467.	H/O: anorexia nervosa
	1612.	Appetite loss - anorexia
	1FF..	Binge eating
	8HTN.	Refer eating disorders clinic
	9Nk9.	Seen in eating disorder clinic
	E271.	Anorexia nervosa
	E275.	Other non-organic eating dis.
	E2750	Non-organic eating dis.unspec.
	E2751	Bulimia (non-org. overeating)
	E275y	Non-organic eating disord. OS
	E275z	Non-organic eating disord. NOS
F50	Eu50.	[X]Eating disorders
F500	Eu500	[X]Anorexia nervosa
F501	Eu501	[X]Atypical anorexia nervosa
F502	Eu502	[X]Bulimia nervosa
F503	Eu503	[X]Atypical bulimia nervosa
	Eu504	[X]Overeat + oth psychol dist
	Eu50y	[X]Other eating disorders
F509	Eu50z	[X]Eating disorder unspecified
	R030.	[D]Anorexia
	R030z	[D]Anorexia NOS
	R0360	[D]Excessive eating
F982		Feeding disorder of infancy and childhood

Learning difficulties			
		2B5..	O/E - symbolic dysfunction
		2B55.	O/E - dyslexia
		8E23.	Dyslexia training
		E2F02	Developmental dyslexia
	F80	Eu80.	[X]Spec develop dis speech/lan
	F800	Eu800	[X]Specif speech articulat dis
	F801	Eu801	[X]Expressive language disordr
	F809	Eu80z	[X]Dev disord speech/lang unsp
	F81	Eu81.	[X]Specif scholastic devel dis
	F810	Eu810	[X]Specific reading disorder
	F811	Eu811	[X]Specific spelling disorder
	F812	Eu812	[X]Specific disord arithmetic
	F813	Eu813	[X]Mixed scholastic skill dis
	F818	Eu81y	[X]Oth dis scholastic skills
	F819	Eu81z	[X]Dev dis scholas skills unsp
	F82	Eu82.	[X]Spec devel disor motor func
	F83	Eu83.	[X]Mix specific develop disord
		R046.	[D]Other symbolic dysfunction
		R0463	[D]Dyslexia
	R48		Dyslexia and other symbolic dysfunctions, not elsewhere classified
	R480		Dyslexia and alexia
Severe mental illness			
		1464.	H/O: schizophrenia
		146D.	H/O: manic depressive disorder
		146H.	H/O: psychosis

8HHs.	Ref psychosis early inter ser
9H8..	On severe mental illnes regist
E10..	Schizophrenic disorders
E100.	Simple schizophrenia
E1000	Schizophrenia - unspecified
E1001	Schizophrenia - subchronic
E1002	Schizophrenia - chronic type
E1003	Schizophrenia-subchr.+acute ex
E1004	Schizophrenia-chr.+acute exac.
E1005	Schizophrenia in remission
E100z	Simple schizophrenia NOS
E101.	Hebephrenic schizophrenia
E1010	Hebephrenia - unspecified
E1011	Hebephrenia - subchronic
E1012	Hebephrenia - chronic
E1013	Hebephrenia-subchr.+acute exac
E1014	Hebephrenia-chronic+acute exac
E1015	Hebephrenia - in remission
E101z	Hebephrenic schizophrenia NOS
E102.	Catatonic schizophrenia
E1020	Catatonia - unspecified
E1021	Catatonia - subchronic
E1022	Catatonia - chronic
E1023	Catatonia-subchr.+acute exac.
E1024	Catatonia-chronic+acute exacer
E1025	Catatonia - in remission
E102z	Catatonic schizophrenia NOS
E103.	Paranoid schizophrenia
E1030	Paranoid schizo.- unspecified

	E1031	Paranoid schizo.- subchronic
	E1032	Paranoid schizo.- chronic
	E1033	Paranoid schizo.-subchr.+ac ex
	E1034	Paranoid schizo.-chr.+acute ex
	E1035	Paranoid schizo.-in remission
	E103z	Paranoid schizophrenia NOS
	E104.	Acute schizophrenic episode
	E105.	Latent schizophrenia
	E1050	Latent schizo.- unspecified
	E1051	Latent schizo.- subchronic
	E1052	Latent schizo.- chronic
	E1053	Latent schizo.-subchr.+ac.exac
	E1054	Latent schizo.-chr.+acute exac
	E1055	Latent schizo.- in remission
	E105z	Latent schizophrenia NOS
	E106.	Residual schizophrenia
	E107.	Schizo-affective schizophrenia
	E1070	Schizo-affective - unspecified
	E1071	Schizo-affective - subchronic
	E1072	Schizo-affective - chronic
	E1073	Schizo-affective-subchr.+ac ex
	E1074	Schizo-affective-chr.+acute ex
	E1075	Schizo-affective-in remission
	E107z	Schizo-affective schizophr.NOS
	E10y.	Other schizophrenia
	E10y0	Atypical schizophrenia
	E10y1	Coenesthopathic schizophrenia
	E10yz	Other schizophrenia NOS
	E10z.	Schizophrenia NOS

	E11..	Affective psychoses
	E110.	Manic disorder, single episode
	E1100	Single manic episode-unspecif
	E1101	Single manic episode-mild
	E1102	Single manic episode-moderate
	E1103	Single manic episode-severe
	E1104	Single manic epis.-severe+psyc
	E1105	Single manic epis-part remiss.
	E1106	Single manic epis-full remiss.
	E110z	Manic disorder-single epis.NOS
	E111.	Recurrent manic episodes
	E1110	Recurrent manic episode-unspec
	E1111	Recurrent manic episode-mild
	E1112	Recurrent manic epis.-moderate
	E1113	Recurrent manic epis.-severe
	E1114	Recurr.manic epis.-severe+psyc
	E1115	Recur.manic epis.-part remiss.
	E1116	Recur.manic epis.-full remiss.
	E111z	Recurrent manic episode NOS
	E1124	Single maj.depress.severe+psyc
	E1134	Recurr.maj.depres.-severe+psyc
	E114.	Bipolar affective - now manic
	E1140	Manic bipolar affective-unspec
	E1141	Manic bipolar affective-mild
	E1142	Manic bipolar affect.-moderate
	E1143	Manic bipolar affect.-severe
	E1144	Manic bipol.affect.severe+psyc
	E1145	Manic bipol.affect.part remiss
	E1146	Manic bipol.affect.full remiss

E114z	Manic bipolar affective NOS
E115.	Bipolar affective - now depres
E1150	Depressed bipolar affect.-unsp
E1151	Depress.bipolar affect.-mild
E1152	Depr.bipolar affect.-moderate
E1153	Depr.bipolar affect.-severe
E1154	Depr.bipol.affect.-severe+psyc
E1155	Depr.bipol.affect.-part remiss
E1156	Depr.bipol.affect.-full remiss
E115z	Depressed bipolar affect. NOS
E116.	Mixed bipolar affective disord
E1160	Mixed bipolar affective-unspec
E1161	Mixed bipolar affective-mild
E1162	Mixed bipolar affect.-moderate
E1163	Mixed bipolar affect.-severe
E1164	Mixed bipol.affect.severe+psyc
E1165	Mixed bipol.affect.part remiss
E1166	Mixed bipol.affect.full remiss
E116z	Mixed bipolar affective NOS
E117.	Unspec bipolar affect disord
E1170	Unspecified bipolar affective
E1171	Unsp.bipolar affective-mild
E1172	Unsp.bipolar affect.-moderate
E1173	Unsp.bipolar affect.-severe
E1174	Unsp.bipol.affect.-severe+psyc
E1175	Unsp.bipol.affect.-part remiss
E1176	Unsp.bipol.affect.-full remiss
E117z	Unspecif.bipolar affective NOS
E11y.	Other manic-depressive psychos

E11y0	Unspec manic-depressive psycho
E11y1	Atypical manic disorder
E11y2	Atypical depressive disorder
E11y3	Other mixed manic-depres psych
E11yz	Other manic-depress.psych.NOS
E11z.	Other/unsp.affective psychoses
E11z0	Unspecif.affective psych.NOS
E11zz	Other affective psychosis NOS
E12..	Paranoid states
E120.	Simple paranoid state
E121.	Chronic paranoid psychosis
E122.	Paraphrenia
E123.	Shared paranoid disorder
E12y.	Other paranoid states
E12y0	Paranoia querulans
E12yz	Other paranoid states NOS
E12z.	Paranoid psychosis NOS
E13..	Other nonorganic psychoses
E130.	Reactive depressive psychosis
E131.	Acute hysterical psychosis
E132.	Reactive confusion
E133.	Acute paranoid reaction
E134.	Psychogenic paranoid psychosis
E13y.	Other reactive psychoses
E13y0	Psychogenic stupor
E13y1	Brief reactive psychosis
E13yz	Other reactive psychoses NOS
E13z.	Nonorganic psychosis NOS
E1y..	Non-organic psychoses OS

	E1z..	Non-organic psychosis NOS
	E2122	Schizotypal personality
	Eu2..	[X]Schizoph,schizotyp,delusion
F20	Eu20.	[X]Schizophrenia
F200	Eu200	[X]Paranoid schizophrenia
F201	Eu201	[X]Hebephrenic schizophrenia
F202	Eu202	[X]Catatonic schizophrenia
F203	Eu203	[X]Undifferentiated schizophrn
F204	Eu204	[X]Post-schizophrenic depressn
F205	Eu205	[X]Residual schizophrenia
F206	Eu206	[X]Simple schizophrenia
F208	Eu20y	[X]Other schizophrenia
F209	Eu20z	[X]Schizophrenia, unspecified
F21, F21X	Eu21.	[X]Schizotypal disorder
F22	Eu22.	[X]Persistent delusional dis
F220	Eu220	[X]Delusional disorder
	Eu221	[X]Delusion misidentificat syn
	Eu222	[X]Cotard syndrome
	Eu223	[X]Paranoid state in remission
F228	Eu22y	[X]Oth persistent delusion dis
F229	Eu22z	[X]Persist delusion dis, unsp
F23	Eu23.	[X]Acute/transient psychot dis
F230	Eu230	[X]Ac polymorph psych,no schiz
F231	Eu231	[X]Ac polymorph psych + schiz
F232	Eu232	[X]Ac schizoph-like psych dis
F233	Eu233	[X]Oth ac predom delus psy dis
F238	Eu23y	[X]Oth ac and trans psych dis
F239	Eu23z	[X]Ac and trans psych dis unsp
F24, F24X	Eu24.	[X]Induced delusional disorder

F25	Eu25.	[X]Schizoaffective disorders
F250	Eu250	[X]Schizaffect dis manic type
F251	Eu251	[X]Schzaffctve dis depres type
F252	Eu252	[X]Schizaffctve dis mixed type
F258	Eu25y	[X]Ot schizoaffective disorder
F259	Eu25z	[X]Schizoaffective disord unsp
	Eu26.	[X]Nonorgan psychos in remiss
F28, F28X	Eu2y.	[X]Ot nonorganic psychotic dis
F29, F29X	Eu2z.	[X]Unspec nonorganic psychosis
F30	Eu30.	[X]Manic episode
F300	Eu300	[X]Hypomania
F301	Eu301	[X]Mania without psychotic sym
F302	Eu302	[X]Mania with psychotic sympts
F308	Eu30y	[X]Other manic episodes
F309	Eu30z	[X]Manic episode, unspecified
F31	Eu31.	[X]Bipolar affective disorder
F310	Eu310	[X]Bipol affec current hypoman
F311	Eu311	[X]Bipol aff, manic no psychos
F312	Eu312	[X]Bipol affect manic+psychos
F313	Eu313	[X]Bipol aff mild/mod depress
F314	Eu314	[X]Bipol AD,cur sev dep,no psy
F315	Eu315	[X]Bipol aff sev depress/psych
F316	Eu316	[X]Bipol affective dis, mixed
F317	Eu317	[X]Bipol affect dis remission
	Eu318	[X]Bipol affect disord type I
	Eu319	[X]Bipol affect disord type II
F318	Eu31y	[X]Oth bipolar affectve disord
F319	Eu31z	[X]Bipolar affectve dis unsp
F323	Eu323	[X]Severe depressive + psychot

	Eu328	[X]Maj dep, sev with psyc symp
	Eu329	[X]Sin ma dep ep sev ps ps rem
	Eu32A	[X]Rec ma dep ep sev ps ps rem
F333	Eu333	[X]Recurr dep now sever+psych
	ZV110	[V]PH - Schizophrenia
F38		Other mood [affective] disorders
F380		Other single mood [affective] disorders
F381		Other recurrent mood [affective] disorders
F388		Other specified mood [affective] disorders
F39, F39X		Unspecified mood [affective] disorder
Substance use disorder		
	E01..	Alcoholic psychoses
	E010.	Alcohol withdrawal delirium
	E011.	Alcohol amnestic syndrome
	E0110	Korsakovs alcoholic psychosis
	E0111	Korsakov + peripheral neuritis
	E0112	Wernicke-Korsakov syndrome
	E011z	Alcohol amnestic syndrome NOS
	E012.	Other alcoholic dementia
	E0120	Chronic alcoholic brain syndr.
	E013.	Alcohol withdrawal hallucinos.
	E014.	Pathological alcohol intoxic.
	E015.	Alcoholic paranoia
	E01y.	Other alcoholic psychosis
	E01y0	Alcohol withdrawal syndrome
	E01yz	Other alcoholic psychosis NOS
	E01z.	Alcoholic psychosis NOS
	E02..	Drug psychoses

	E020.	Drug withdrawal syndrome
	E021.	Drug-induced paranoia/hallucin
	E0210	Drug-induced paranoid state
	E0211	Drug-induced hallucinosis
	E021z	Drug-induc.paranoia/halluc NOS
	E022.	Pathological drug intoxication
	E02y.	Other drug psychoses
	E02y0	Drug-induced delirium
	E02y1	Drug-induced dementia
	E02y2	Drug-induced amnestic syndrome
	E02y3	Drug-induced depressive state
	E02y4	Drug-induced personality dis.
	E02yz	Other drug psychoses NOS
	E02z.	Drug psychosis NOS
	Eu1..	[X]Mental dis, psychoact subst
F10, F100-109	Eu10.	[X]Mental dis due to alcohol
	Eu100	[X]Acute alcohol intoxication
	Eu101	[X]Harmful use of alcohol
	Eu102	[X]Alcohol dependence syndrome
	Eu103	[X]Alcohol withdrawal state
	Eu104	[X]Alcohol withdrawal delirium
	Eu105	[X]Psychot dis due to alcohol
	Eu106	[X]Amnesic synd due to alcohol
	Eu107	[X]Resid psychotic due alcohol
	Eu108	[X]Alcohol withdraw-induc seiz
	Eu10y	[X]Ot ment/beh dis due alcohol
	Eu10z	[X]Uns ment/beh dis due alcohl
F11, F110-F119	Eu11.	[X]Mental dis due to opioids
	Eu110	[X]Acute opioid intoxication

	Eu111	[X]Harmful use of opioids
	Eu112	[X]Opioid dependence syndrome
	Eu113	[X]Opioid withthdrawal state
	Eu114	[X]Opioid withdrawal delirium
	Eu115	[X]Psychot dis due to opioids
	Eu116	[X]Amnesic synd due to opioids
	Eu117	[X]Resid psychotic due opioid
	Eu11y	[X]Oth ment/beh dis due opioid
	Eu11z	[X]Uns ment/beh dis due opioid
F12, F120-F129	Eu12.	[X]Mental dis due cannabinoids
	Eu120	[X]Acute cannabis intoxication
	Eu121	[X]Harmful use of cannabis
	Eu122	[X]Cannabis dependence syndrom
	Eu123	[X]Cannabis withdrawal state
	Eu124	[X]Cannabis withdrawl delirium
	Eu125	[X]Psychot dis due to cannabis
	Eu126	[X]Amnesic synd due cannabis
	Eu127	[X]Resid psychot due cannabis
	Eu12y	[X]Oth ment/beh dis cannabinds
	Eu12z	[X]Unsp mnt/beh dis cannabinds
F13, F130-F139	Eu13.	[X]Mental dis due sedat/hypnot
	Eu130	[X]Acute sedat/hypnotic intox
	Eu131	[X]Harmful use sedat/hypnotic
	Eu132	[X]Sedat/hypnotic depend syndr
	Eu133	[X]Sedat/hypnot withdraw state
	Eu134	[X]Sed/hypn withdraw delirium
	Eu135	[X]Psychot dis due sedat/hypn
	Eu136	[X]Amnesic synd due sedat/hypn
	Eu137	[X]Resid psychot due sed/hypn

	Eu13y	[X]Oth ment/beh dis sed/hypnot
	Eu13z	[X]Uns ment/beh dis sed/hypnot
F14, F140-F149	Eu14.	[X]Mental dis due use cocaine
	Eu140	[X]Acute cocaine intoxication
	Eu141	[X]Harmful use of cocaine
	Eu142	[X]Cocaine dependence syndrome
	Eu143	[X]Cocaine withdrawal state
	Eu144	[X]Cocaine withdrawal delirium
	Eu145	[X]Psychot dis due to cocaine
	Eu146	[X]Amnesic synd due to cocaine
	Eu147	[X]Resid psychot due cocaine
	Eu14y	[X]Ot ment/beh dis due cocaine
	Eu14z	[X]Uns ment/bh dis due cocaine
F15, F150-F159	Eu15.	[X]Ment dis oth stimul/caffein
	Eu150	[X]Acute intoxic oth stimulant
	Eu151	[X]Harmful use other stimulant
	Eu152	[X]Oth stimulant dependen synd
	Eu153	[X]Oth stimulant withdr state
	Eu154	[X]Oth stimulant withdr delir
	Eu155	[X]Psychotic dis oth stimulant
	Eu156	[X]Amnesic syndr oth stimulant
	Eu157	[X]Resid psychot oth stimulant
	Eu15y	[X]Oth ment/beh dis stimulant
	Eu15z	[X]Uns ment/beh dis stimulant
F16, F160-F169	Eu16.	[X]Mental disord hallucinogens
	Eu160	[X]Acute hallucinogen intoxic
	Eu161	[X]Harmful use hallucinogens
	Eu162	[X]Hallucinogen depend synd
	Eu163	[X]Hallucinogen withdraw state

	Eu164	[X]Hallucin withdraw delirium
	Eu165	[X]Psychotic due hallucinogen
	Eu166	[X]Amnesic synd due hallucinog
	Eu167	[X]Resid psychot hallucinogen
	Eu16y	[X]Oth ment/beh dis hallucinog
	Eu16z	[X]Uns ment/beh dis hallucinog
F18, F180-F189	Eu18.	[X]Ment dis volatile solvents
	Eu180	[X]Acute solvent intoxication
	Eu181	[X]Harmful use of solvents
	Eu182	[X]Solvent dependence syndrome
	Eu183	[X]Solvent withdrawal state
	Eu184	[X]Solvent withdrawal delirium
	Eu185	[X]Psychotic dis due solvent
	Eu186	[X]Amnesic syndr due solvent
	Eu187	[X]Resid psychotic due solvent
	Eu18y	[X]Ot ment/beh dis due solvent
	Eu18z	[X]Uns ment/beh due solvent
F19, F190-F199	Eu19.	[X]Ment disord multi drug use
	Eu190	[X]Acute intox multi drug use
	Eu191	[X]Harmful use multiple drugs
	Eu192	[X]Multiple drug dependence
	Eu193	[X]Multiple drug withdrawal
	Eu194	[X]Multi drug withdr delirium
	Eu195	[X]Psychotic due multi drugs
	Eu196	[X]Amnesic syn due multi drugs
	Eu197	[X]Resid psychotic multi drugs
	Eu19y	[X]Ot ment/beh due multi drugs
	Eu19z	[X]Un ment/beh due multi drugs
	Eu1A.	[X]Men behav dis due crack coc

Eu1A0	[X]Acute crack cocaine intoxic
Eu1A1	[X]Harmful use crack cocaine
Eu1A2	[X]Crack cocaine depend synd
Eu1A3	[X]Crack cocaine withdraw stat
Eu1A4	[X]Crack coc withdraw stat del
Eu1A5	[X]Crack cocaine psychotic dis
Eu1A6	[X]Crack cocaine amnesic synd
Eu1A7	[X]Cra coc res late-on psy dis
Eu1Ay	[X]Crac coc other ment beh dis
Eu1Az	[X]Crack coc unsp men beh dis
1365.	Heavy drinker - 7-9u/day
1366.	Very heavy drinker - >9u/day
1462.	H/O: alcoholism
1463.	H/O: drug dependency
136c.	Higher risk drinking
136P.	Heavy drinker
136Q.	Very heavy drinker
136R.	Binge drinker
136S.	Hazardous alcohol use
136T.	Harmful alcohol use
136W.	Alcohol misuse
136Y.	Drink in a.m. to rid hangover
13c..	Drug user
13c0.	Injecting drug user
13c1.	Intravenous drug user
13c2.	Never injecting drug user
13c3.	Intramuscular drug user
13c4.	Intranasal drug user
13c5.	Substance misuse increased

13c6.	Substance misuse decreased
13c7.	Current drug user
13c8.	Reduced drugs misuse
13c9.	Subcutaneous drug user
13cA.	Smokes drugs
13cB.	Misuses drugs orally
13cC.	Continuous use of drugs
13cD.	Episodic use of drugs
13cE.	Prolong high dose use cannabis
13cF.	Preoccup with substance misuse
13cG.	Drug tolerance
13cG0	Opioid tolerant
13cG1	Opioid naive
13cH.	Persistent substance misuse
13cJ.	Previously injecting drug user
13cK.	Current non recreat drug user
13cL.	Has never injected drugs
13cM.	Substance misuse
13cM0	Novl psychactve sbstnce misuse
13cM1	Opioid analgesic dependence
13cN.	Has nvr shrd drg injctn equipt
13cQ.	Behavioural tolerance to drug
13cR.	Physical tolerance to drug
13cS.	Psychological drug tolerance
13cT.	Reverse tolerance to drug
13Y8.	Alcoholics anonymous
146C.	Failed heroin detoxification
146E.	H/O: recreational drug use
146F.	H/O: drug abuse

1B1c.	Alcohol induced hallucinations
1P30.	Compul uncontrollable drug tak
1P31.	Compulsive drug taking
1T...	History of substance misuse
1T0..	H/O heroin misuse
1T00.	H/O daily heroin misuse
1T01.	H/O weekly heroin misuse
1T02.	Prev history of heroin misuse
1T03.	H/O infrequent heroin misuse
1T1..	H/O methadone misuse
1T10.	H/O daily methadone misuse
1T11.	H/O weekly methadone misuse
1T12.	H/O infrequent methadone misus
1T13.	Prev history methadone misuse
1T2..	H/O ecstasy misuse
1T20.	H/O daily ecstasy misuse
1T21.	H/O weekly ecstasy misuse
1T22.	H/O infrequent ecstasy misuse
1T23.	Prev history of ecstasy misuse
1T3..	H/O benzodiazepine misuse
1T30.	H/O daily benzodiazepin misuse
1T31.	H/O weekly benzodiazep misuse
1T32.	H/O infreq benzodiazep misuse
1T33.	Prev H/O benzodiazepine misuse
1T4..	H/O amphetamine misuse
1T40.	H/O daily amphetamine misuse
1T41.	H/O weekly amphetamine misuse
1T42.	H/O infrequent amphetam misuse
1T43.	Prev H/O amphetamine misuse

1T5..	H/O cocaine misuse
1T50.	H/O daily cocaine misuse
1T51.	H/O weekly cocaine misuse
1T52.	H/O infrequent cocaine misuse
1T53.	Prev H/O cocaine misuse
1T6..	H/O crack cocaine misuse
1T60.	H/O daily crack cocaine misuse
1T61.	H/O weekly crack cocain misuse
1T62.	H/O infrequ crack cocain misus
1T63.	Prev H/O crack cocaine misuse
1T7..	H/O hallucinogen misuse
1T70.	H/O daily hallucinogen misuse
1T71.	H/O weekly hallucinogen misuse
1T72.	H/O infrequ hallucinog misuse
1T73.	Prev H/O hallucinogen misuse
1T8..	H/O cannabis misuse
1T80.	H/O daily cannabis misuse
1T81.	H/O weekly cannabis misuse
1T82.	H/O infrequent cannabis misuse
1T83.	Prev H/O cannabis misuse
1T9..	H/O solvent misuse
1T90.	H/O daily solvent misuse
1T91.	H/O weekly solvent misuse
1T92.	H/O infrequent solvent misuse
1T93.	Prev history of solvent misuse
1TA..	H/O barbiturate misuse
1TA0.	H/O daily barbiturate misuse
1TA1.	H/O weekly barbiturate misuse
1TA2.	H/O infrequ barbiturate misuse

1TA3.	Prev H/O barbiturate misuse
1TB..	H/O major tranquilliser misuse
1TB0.	H/O daily maj tranquilli misus
1TB1.	H/O weekl maj tranquilli misus
1TB2.	H/O infreq maj trnquillis miss
1TB3.	Prev H/O major tranq misuse
1TC..	H/O anti-depressant misuse
1TC0.	H/O daily anti-depress misuse
1TC1.	H/O weekly anti-depress misuse
1TC2.	H/O infreq anti-depress misuse
1TC3.	Prev H/O anti-depressnt misuse
1TD..	H/O opiate misuse
1TD0.	H/O daily opiate misuse
1TD1.	H/O weekly opiate misuse
1TD2.	H/O infrequent opiate misuse
1TD3.	Prev history of opiate misuse
1TE..	Uses heroin on top subst ther
1TF..	Dsnt use heroin top subst ther
1TG..	H/O nov psychoact subst misuse
1V...	Drug misuse behaviour
1V0..	Misuses drugs
1V00.	Occasional drug user
1V01.	Long-term drug misuser
1V02.	Poly-drug misuser
1V03.	Misuses drugs sublingually
1V04.	Misuses drugs rectally
1V05.	Misuses drugs vaginally
1V06.	Uses drug paraphernalia
1V07.	Notified addict

	1V08.	Smokes drugs in cigarette form
	1V09.	Smokes drugs through a pipe
	1V0A.	Chases the dragon
	1V0B.	Sniffs drugs
	1V0C.	Drug addict
	1V0D.	Am spent per day on drug habit
	1V0E.	Health prob sec to drug misuse
	1V1..	Time devotd drug rel activties
	1V10.	Time spent obtaining drugs
	1V11.	Time spent taking drugs
	1V12.	Time spent recover from drugs
	1V2..	Frequency of drug misuse
	1V22.	Age at starting drug misuse
	1V23.	Time since stopped drug misuse
	1V24.	Total time drugs misused
	1V26.	Misused drugs in past
	1V3..	Drug injection behaviour
	1V30.	Injects drugs subcutaneously
	1V31.	Injects drugs intramuscularly
	1V32.	Neck injector
	1V33.	Groin injector
	1V34.	Does not inject drugs
	1V35.	Shares drug equipment
	1V36.	Frontloading
	1V37.	Drug inject equipment hygiene
	1V38.	Sharing drug inject equipment
	1V3A.	Not share drug inject equipmen
	1V3B.	Shares syringes
	1V3C.	Shares needles

1V3D.	Cleaning of needles
1V3E.	Cleans own needles
1V3F.	Cleans needles with bleach
1V3G.	Does not clean needles
1V3H.	Obtains clean needles
1V3J.	Uses needle exchange scheme
1V3K.	Obtains clean syringes
1V3L.	Needle syringe exch scheme use
1V3M.	Needle + syringe exch not used
1V3N.	Needle and syringe exch used
1V4..	Priority of drug activity
1V40.	No priority to drug activities
1V41.	Priority to drug activities
1V42.	Drug priority ov social obligs
1V43.	Drug priority over family
1V44.	Drug priority ov finance oblig
1V5..	Routine drug-related activity
1V50.	No routine of drug activities
1V51.	Has routine of drug activities
1V52.	Same drug routine every day
1V53.	Drug-related rituals
1V54.	Follows drug-related rituals
1V55.	Not follow drug-relate rituals
1V6..	Drug-relat offending behaviour
1V64.	Illicit drug use
1V65.	Heroin misuse
1V66.	Ecstasy misuse
38Dz.	Sever alcoh depend questionn
66e..	Alcohol disorder monitoring

66e0.	Alcohol abuse monitoring
677T.	Subst misuse structurd counsel
7P220	Delivery rehab drug addiction
7P221	Del rehab alcohol addiction
8AA..	Drug abuse monitoring
8B23.	Drug addiction therapy
8B230	Drug add maint ther naltrexone
8B231	Drug add maint ther lofexidine
8B2M.	Buprenorphine maintenance ther
8B2N.	Drug add detox ther methadone
8B2P.	Drug add maint ther methadone
8B2Q.	Drug add maint ther buprenorph
8B2R.	Drug add detox ther buprenorph
8B2S.	Opioid agonist substitut thera
8B2T.	Opioid antagonist therapy
8BA8.	Alcohol detoxification
8BA9.	Detoxification dependence drug
8BAc.	Subs mis mgt stop - self withd
8BAd.	Opiate dependence detoxificatn
8BAs.	Alcohol relapse prevention
8BAt.	Drug relapse prevention
8BAu.	Alcohol harm reduction prog
8BAv.	Drug harm reduction programme
8BAw.	Alcohol twelve step programme
8BAW.	Drug depen self detoxification
8BAX.	Drug depen home detoxification
8BAx.	Drug twelve step programme
8BE..	Maintenance therapy
8BE0.	Reinduct methadone maint thera

	8BE1.	Reinduct buprenorph maint ther
	8CAv.	Adv cont prim care alcoh workr
	8CR9.	Benzodiazepi clinical mgt plan
Z503	8FB..	Drug rehabilitation
	8FB0.	Drug detox programme completed
	8G32.	Aversion therapy - alcoholism
	8H35.	Admit to alcohol detox centre
	8H7p.	Refer community alcohol team
	8H7x.	Refer to drug abuse counsellor
	8Hh1.	Self refer substanc misus serv
	8HHd.	Referral to drug treatment cen
	8HHe.	Referral to com drug alco team
	8HHL.	Ref to comm drug dependen team
	8HkF.	Refer substance misuse service
	8HkG.	Ref to special alco treat serv
	8HkJ.	Ref alchl brief intervntin ser
	8Hl5.	Referral to drugs therapist
	8Hl6.	Referral to drugs worker
	8Hq..	Admsn substnc misuse detox cnt
	8I2N.	Drug depend home detox contra
	8IAF.	Brief intervent ex alc declind
	8IAJ.	Decld ref spec alco treat serv
	8IAt.	Ext inter exc alco consump dec
	8IE7.	Substance misuse assess declin
	8IEA.	Ref comm alcohol team declined
	9G2..	Drug addiction notification
	9G21.	Drug addict notific to CMO
	9G22.	Drug addict re-notific due
	9G23.	Drug addict re-notif to CMO

	9G2Z.	Drug addiction notif NOS
	9HC..	Substance misuse monitoring
	9HC0.	Initial substance misuse asses
	9HC1.	Follow up substa misuse assess
	9HC2.	Subst mis clin man plan agreed
	9HC3.	Subst mis clin man plan review
	9HC4.	Sub misuse treatment withdrawn
	9HC5.	Sub misus treat prog completed
	9HC6.	Substance misuse treatm declin
	9HC7.	Subst misuse treat not availbl
	9HC8.	Decl to give subst misuse hist
	9HC9.	Snc mse tmnt gvn othr hcr prdr
	9HCA.	Sbstnce misuse mntr 6 mnth rvw
	9HCB.	Substance misuse mntr annl rvw
	9HCC.	On substance misuse programme
	9k1..	Alcohol misuse - enh ser admin
	9k10.	Comm detoxification registered
	9k11.	Alcohol consumption counsellin
	9k12.	Alco misuse - enh serv complet
	9k14.	Alco counsel by other agencies
	9k19.	Alco asses dclnd - enh ser adm
	9k1A.	Brief intervent ex alc complet
	9k1B.	Extend intervent ex alc complt
	9k5..	Drug misuse - enhan serv admin
	9k50.	Drug misuse - enh serv complet
	9k51.	Share care drug misu trt - ESA
	9k52.	Drug misus trt prim care - ESA
	9k53.	Phrmcy attend drug misus - ESA
	9kS..	Drug mis asse decl - enha serv

	9N0Z.	Seen in drug rehab centre
	9N1yJ	Seen in drug misuse clinic
	9N6a.	Refer by drug statutor service
	9N6b.	Ref by drug non-statutory serv
	9N6g.	Refer by syringe excha service
	9NdN.	Declnd consnt notif drug misus
	9NgzH	Withdrawn alcohol detox progra
	9NJz.	In-house alcohol detoxificatin
	9NN1.	Under care community drug team
	9NN2.	Under care comm alcohol team
	9No5.	Seen in substance misuse clinc
	9NX2.	In-house subs misuse treatment
	9Nz9.	Emrgcy dept attn alcohl consum
	9NzA.	Hospital attend alcohl consump
E244	C1505	Alchl-indc pseud-Cushings syn
E512	C253.	Wernickes encephalopathy
	dj36.	SUBUTEX 400micrograms s/l tabs
	dj37.	SUBUTEX 2mg sublingual tablets
	dj38.	SUBUTEX 8mg sublingual tablets
	dj3c.	PREFIBIN 400mcg sublingual tab
	dj3d.	PREFIBIN 2mg sublingual tabs
	dj3D.	BUPRNRPHNE+NALOXN 2/0.5mg tabs
	dj3E.	SUBOXONE 2mg/0.5mg s/l tabs
	dj3e.	PREFIBIN 8mg sublingual tabs
	dj3F.	BUPRNRPHNE+NALOXN 8mg/2mg tabs
	dj3G.	SUBOXONE 8mg/2mg s/l tabs
	dj3K.	NATZON 400micrograms s/l tabs
	dj3L.	NATZON 2mg sublingual tablets
	dj3M.	NATZON 8mg sublingual tablets

dj3N.	GABUP 400micrograms s/l tabs
dj3O.	GABUP 1mg sublingual tablets
dj3P.	GABUP 2mg sublingual tablets
dj3Q.	GABUP 4mg sublingual tablets
dj3R.	GABUP 6mg sublingual tablets
dj3S.	GABUP 8mg sublingual tablets
dj3T.	BUPRENORPHINE 1mg s/l tabs
dj3U.	BUPRENORPHINE 4mg s/l tabs
dj3u.	BUPRENORPHINE 2mg s/l tabs
dj3V.	BUPRENORPHINE 6mg s/l tabs
dj3v.	BUPRENORPHINE 8mg s/l tabs
djc..	METHADONE HCL [ANALGESIC]
djc1.	PHYSEPTONE 5mg tablets
djc2.	PHYSEPTONE 10mg/1mL injection
djc3.	METHADONE 1mg/1mL mixture
djc4.	METHADONE HCL 50mg/5mL s/f liq
djc5.	MARTINDALE METHADONE DTF mixt
djc6.	METHODEX 1mg/1mL mixture
djc7.	METHADOSE 10mg/mL s/f liq
djc8.	METHADONE HCL 20mg/mL s/f liq
djc9.	METHADOSE 20mg/mL s/f liq
djcA.	METHADONE DILUENT liquid
djcB.	METHADOSE DILUENT liquid
djcC.	METHADONE 1mg/1mL s/f mixt
djcD.	METHAROSE 1mg/1mL s/f soln
djcE.	*PINADONE 1mg/1mL mixture
djcF.	*PINADONE 1mg/1mL s/f mixt
djcG.	PHYSEPTONE 20mg/2mL injection
djcH.	PHYSEPTONE 35mg/3.5mL inj

djcJ.	PHYSEPTONE 50mg/5mL injection
djcK.	PHYSEPTONE 1mg/1mL s/f mixture
djcL.	PHYSEPTONE 1mg/1mL mixture
djcM.	SYNASTONE 10mg/1mL injection
djcN.	SYNASTONE 20mg/2mL injection
djco.	METHADONE 20mg/20mL oral soln
djcO.	SYNASTONE 35mg/3.5mL injection
djcP.	SYNASTONE 50mg/5mL injection
djcp.	METHADONE 40mg/40mL oral soln
djcQ.	SYNASTONE 50mg/2mL injection
djcq.	METHADONE 60mg/60mL oral soln
djcR.	SYNASTONE 50mg/1mL injection
djcr.	METHADONE 100mg/20mL oral soln
djcS.	PHYSEPTONE 50mg/2mL injection
djcs.	METHADONE 5mg/mL oral solution
djct.	METHADONE HCL 50mg/2mL inj
djcT.	PHYSEPTONE 50mg/1mL injection
djcu.	METHADONE HCL 50mg/1mL inj
djcU.	EPTADONE 1mg/mL oral solution
djcV.	EPTADONE 5mg/mL oral solution
djcv.	METHADONE HCL 20mg/2mL inj
djcW.	EPTADONE 20mg/20mL oral soln
djcw.	METHADONE HCL 35mg/3.5mL inj
djcx.	METHADONE HCL 50mg/5mL inj
djcX.	EPTADONE 40mg/40mL oral soln
djcY.	EPTADONE 60mg/60mL oral soln
djcy.	METHADONE HCL 5mg tablets
djcz.	METHADONE HCL 10mg/1mL inj
djcZ.	EPTADONE 100mg/20mL oral soln

du1..	DISULFIRAM
du11.	DISULFIRAM 200mg tablets
du12.	ANTABUSE 200mg tablets
du2..	NALTREXONE HYDROCHLORIDE
du21.	NALTREXONE HCL 50mg tablets
du22.	NALOREX 50mg tablets
du23.	OPIZONE 50mg tablets
du24.	ADEPEND 50mg tablets
du4..	LOFEXIDINE HYDROCHLORIDE
du41.	BRITLOFEX 200mcg tablets
du42.	LOFEXIDINE HCL 200mcg tablets
du5..	ACAMPROSATE CALCIUM
du51.	ACAMPROSATE CAL 333mg e/c tabs
du52.	CAMPRAL EC 333mg e/c tablets
E23..	Alcohol dependence syndrome
E230.	Acute alcoholic intoxication
E2300	Acute alcoholic intoxic. unsp.
E2301	Acute alcoh.intox.-continuous
E2302	Acute alcoh.intox.-episodic
E2303	Acute alcoh.intox.in remission
E230z	Acute alcoholic intoxic. NOS
E231.	Chronic alcoholism
E2310	Chronic alcoholism unspecified
E2311	Chronic alcoholism-continuous
E2312	Chronic alcoholism-episodic
E2313	Chronic alcohol.- in remission
E231z	Chronic alcoholism NOS
E23z.	Alcohol dependence syndr. NOS
E24..	Drug dependence

E240.	Opioid type drug dependence
E2400	Opioid dependence-unspecified
E2401	Opioid dependence-continuous
E2402	Opioid dependence - episodic
E2403	Opioid dependence-in remission
E240z	Opioid drug dependence NOS
E241.	Hypnotic/anxiolytic dependence
E2410	Hypnotic/anxiol.depend.-unspec
E2411	Hypnot/anxiol.dep.-continuous
E2412	Hypnot/anxiol.dep.-episodic
E2413	Hypnot/anxiol.dep-in remission
E241z	Hypnotic/anxiolytic depend.NOS
E242.	Cocaine type drug dependence
E2420	Cocaine dependence-unspecified
E2421	Cocaine dependence-continuous
E2422	Cocaine dependence-episodic
E2423	Cocaine depend. - in remission
E242z	Cocaine drug dependence NOS
E243.	Cannabis type drug dependence
E2430	Cannabis dependence-unspecif.
E2431	Cannabis dependence-continuous
E2432	Cannabis dependence-episodic
E2433	Cannabis depend.- in remission
E243z	Cannabis drug dependence NOS
E244.	Amphetamine/psychostim.depend.
E2440	Amphetamine depend.-unspecif.
E2441	Amphetamine depend.-continuous
E2442	Amphetamine depend.-episodic
E2443	Amphetamine dep.-in remission

E244z	Amphetamine dependence NOS
E245.	Hallucinogen dependence
E2450	Hallucinogen depend.-unspecif.
E2451	Hallucinogen depend-continuous
E2452	Hallucinogen depend.-episodic
E2453	Hallucinogen dep.-in remission
E245z	Hallucinogen dependence NOS
E246.	Glue sniffing dependence
E2460	Glue sniffing - unspecified
E2461	Glue sniffing - continuous
E2462	Glue sniffing - episodic
E2463	Glue sniffing - in remission
E246z	Glue sniffing dependence NOS
E247.	Other specified drug dependen.
E2470	Other drug dependence unspecif
E2471	Other drug depend.-continuous
E2472	Other drug depend.-episodic
E2473	Other drug dep.-in remission
E247z	Other drug dependence NOS
E248.	Combined opioid+other drug dep
E2480	Opioid+other drug dep. unspec.
E2481	Continuous opioid+other depen.
E2482	Episodic opioid+other depend.
E2483	In remission-opioid+other dep.
E248z	Opioid+other drug depend. NOS
E249.	Combined drug dep. excl.opioid
E2490	Comb.drug dep ex opioid-unspec
E2491	Comb.drug dep ex opioid-contin
E2492	Comb.drug dep ex opioid-episod

E2493	Comb.drug dep ex opioid-in rem
E249z	Comb.drug dep ex opioid NOS
E24A.	Ecstasy type drug dependence
E24z.	Drug dependence NOS
E25..	Nondependent abuse of drugs
E250.	Alcohol abuse - nondependent
E2500	Alcohol abuse - unspecified
E2501	Alcohol abuse - continuous
E2502	Alcohol abuse - episodic
E2503	Alcohol abuse - in remission
E250z	Nondependent alcohol abuse NOS
E252.	Nondependent cannabis abuse
E2520	Nondep cannabis abuse - unspec
E2521	Nondep cannabis abuse - contin
E2522	Nondep cannabis abuse - episod
E2523	Nondep cannabis abuse in remis
E252z	Nondep cannabis abuse NOS
E253.	Nondependen hallucinogen abuse
E2530	Nondep hallucinogen abuse-unsp
E2531	Nondep hallucinogen abuse-cont
E2532	Nondep hallucinogen abuse-epis
E2533	Nondep hallucin abuse-in remis
E253z	Nondep hallucinogen abuse NOS
E254.	Nondep hypnot/anxiolytic abuse
E2540	Nondep hypnot/anxio.abuse-unsp
E2541	Nondep hypnot/anxio.abuse-cont
E2542	Nondep hypnot/anxio.abuse-epis
E2543	Nondep hypn/anxio.abuse-in rem
E254z	Nondep hypnot/anxiol abuse NOS

E255.	Nondependent opioid abuse
E2550	Nondep opioid abuse - unspecif
E2551	Nondep opioid abuse - continuo
E2552	Nondep opioid abuse - episodic
E2553	Nondep opioid abuse - in remis
E255z	Nondependent opioid abuse NOS
E256.	Nondependent cocaine abuse
E2560	Nondep cocaine abuse - unspec.
E2561	Nondep cocaine abuse - contin.
E2562	Nondep cocaine abuse - episod.
E2563	Nondep cocaine abuse -in remis
E256z	Nondependent cocaine abuse NOS
E257.	Nondep amphetamine type abuse
E2570	Nondep amphet type abuse -unsp
E2571	Nondep amphet type abuse -cont
E2572	Nondep amphet type abuse -epis
E2573	Nondep amph. type abuse-in rem
E257z	Nondep amphet. type abuse NOS
E258.	Nondep antidepress type abuse
E2580	Nondep antidep type abuse-unsp
E2581	Nondep antidep type abuse-cont
E2582	Nondep antidep type abuse-epis
E2583	Nondep antidep tp abuse-in rem
E258z	Nondep antidep type abuse NOS
E259.	Nondependent mixed drug abuse
E2590	Nondep mixed drug abuse-unspec
E2591	Nondep mixed drug abuse-contin
E2592	Nondep mixed drug abuse-episod
E2593	Nondep mixed drug abuse-in rem

	E2594	Misuse of prescription drugs
	E259z	Nondep mixed drug abuse NOS
	E25y.	Nondependent other drug abuse
	E25y0	Nondep other drug abuse-unspec
	E25y1	Nondep other drug abuse-contin
	E25y2	Nondep other drug abuse-episod
	E25y3	Nondep other drug abuse-in rem
	E25yz	Nondep other drug abuse NOS
	E25z.	Misuse of drugs NOS
G312		Degeneration of nervous system due to alcohol
	F11x0	Cerebral degenerat.-alcoholism
	F1440	Cerebellar ataxia-alcoholism
	F25B.	Alcohol-induced epilepsy
G621	F375.	Alcoholic polyneuropathy
G721	F3941	Alcoholic myopathy
I426	G555.	Alcoholic cardiomyopathy
	G8523	Oes varic alcohol cirr liver
K292	J153.	Alcoholic gastritis
K70		Alcoholic liver disease
K700	J610.	Alcoholic fatty liver
	J611.	Acute alcoholic hepatitis
K703	J612.	Alcoholic cirrhosis of liver
K702	J6120	Alcoholic fibrosis and scleros
	J613.	Alcoholic liver damage unspec.
K704	J6130	Alcoholic hepatic failure
K701	J617.	Alcoholic hepatitis
	J6170	Chronic alcoholic hepatitis
K709		Alcoholic liver disease, unspecified
K852	J6708	Alcohol-induced acute panc

K860	J6710	Alcohol-ind chron pancreatitis
	L183.	Pregnancy+drug dependence
	L1830	Preg.+drug dependence unspecif
	L1831	Preg.+drug dependence-deliver.
	L1832	Preg.+drug depend-del+p/n comp
	L1833	Preg.+drug depend-not deliver.
	L1834	Preg.+drug depend.+p/n complic
	L183z	Preg.+drug dependence NOS
	L255.	Fetus+drug damage
	L2550	Fetus+drug damage unspecified
	L2551	Fetus+drug damage-delivered
	L2552	Fetus+drug damage+a/n problem
O354	L2553	Mat care,susp dam fet from alc
O355		Mat care susp dam fet by drugs
	L255z	Fetus+drug damage NOS
	R103.	[D]Alcohol blood level excess.
R782	R10B0	[D]Finding of cocain in blood
R783	R10B1	[D]Find hallucinogen in blood
	R10B2	[D]Find psychotrop drug blood
R781	R10B4	[D]Finding, opiate drug in bld
R785	Ryu86	[X]Find ot drg addic poten,bld
	SL50.	Opiate/narcotic poisoning
	SL500	Unspecified opium poisoning
T401	SL501	Heroin poisoning
T403	SL502	Methadone poisoning
	SL50z	Opiate/narcotic poisoning NOS
T405	SL850	Cocaine poisoning
	SL96.	Hallucinogen poisoning
T407	SL960	Cannabis poisoning

T408	SL961	Lysergide (LSD) poisoning
	SL963	Mescaline poisoning
	SL964	Psilocybin poisoning
	SL96z	Hallucinogen poisoning NOS
	SL97.	Psychostimulant poisoning
	SL970	Amfetamine poisoning
	SL972	Ecstasy poisoning
	SL97z	Psychostimulant poisoning NOS
T436		Psychostimulants with abust potential
	SLH3.	Alcohol deterrent poisoning
T51	SM0..	Alcohol - toxic effect
	SM00.	Ethyl alcohol - toxic effect
T510	SM000	Ethanol - toxic effect
	SM001	Denatured alcohol-toxic effect
	SM002	Grain alcohol - toxic effect
	SM00z	Ethyl alcohol-toxic effect NOS
	SM01.	Methyl alcohol - toxic effect
T511	SM010	Methanol - toxic effect
	SM011	Wood alcohol - toxic effect
	SM01z	Methyl alcohol-toxic eff.NOS
T512	SM02.	Isopropyl alcohol-toxic effect
	SM020	Dimethyl carbinol-toxic effect
	SM021	Isopropanol - toxic effect
	SM022	Rubbing alcohol - toxic effect
	SM02z	Isopropyl alcohol-tox.eff.NOS
T513	SM03.	Fusel oil - toxic effect
	SM030	Amyl alcohol - toxic effect
	SM031	Butyl alcohol - toxic effect
	SM032	Propyl alcohol - toxic effect

	SM03z	Fusel oil - toxic effect NOS
T518	SM0y.	Other alcohol - toxic effect
	SM0z.	Alcohol - toxic effect NOS
T402	SyuFB	[X]Poisoning by other opioids
T404	SyuFC	[X]Poisoning by oth synth narc
T406	SyuFD	[X]Poisoning by oth/unsp narc
T409	SyuFE	[X]Pois,oth/un psychodysl/hall
T519	SyuG0	[X]Toxic eff of oth alcohols
	T800.	Accid.pois.- heroin
	T801.	Accid.pois.- methadone
	T8023	Accid.pois.- opium
	T841.	Accid.pois.- hallucinogens
	T8410	Accid.pois.- cannabis derivat.
	T8413	Accid.pois.- mescaline
	T8414	Accid.pois.- psilocin
	T8415	Accid.pois.- psilocybin
	T842.	Accid.pois.- psychostimulants
	T8420	Accid.pois.- amphetamine
	T8520	Accid.pois.- cocaine
	T900.	Accid.pois.- alcoholic drinks
	T9010	Accid.pois.- denatured alcohol
	T9011	Accid.pois.- methylated spirit
	T902.	Accid.pois.- methyl alcohol
	T903.	Accid.pois.- isopropyl alcohol
	T9032	Accid.pois.- rubbing alc.subst
	T904.	Accid.pois.- fusel oil
X42,X420-X429	U1A5.	[X]Accident poisoning narcotic
	U1A50	[X]Acc poison narcotic home
	U1A51	[X]Ac pois narcotic res ins

	U1A52	[X]Ac pois narcotic pub ins
	U1A53	[X]Ac pois narcotic sport ar
	U1A54	[X]Ac pois narcotic on hway
	U1A55	[X]Ac pois narcotic trade ar
	U1A56	[X]Ac pois narcotic indus ar
	U1A57	[X]Ac pois narcotic on farm
	U1A5y	[X]Ac pois narcotic OS place
	U1A5z	[X]Ac pois narcotic unsp pl
	U1A6.	[X]Acc poisoning hallucinogens
	U1A60	[X]Acc poison hallucinog home
	U1A61	[X]Ac pois hallucinog res ins
	U1A62	[X]Ac pois hallucinog pub ins
	U1A63	[X]Ac pois hallucinog sport ar
	U1A64	[X]Ac pois hallucinog on hway
	U1A65	[X]Ac pois hallucinog trade ar
	U1A66	[X]Ac pois hallucinog indus ar
	U1A67	[X]Ac pois hallucinog on farm
	U1A6y	[X]Ac pois hallucinog OS place
	U1A6z	[X]Ac pois hallucinog unsp pl
X45,X450-X459	U1A9.	[X]Accid poisoning by alcohol
	U1A90	[X]Acc poison alcohol home
	U1A91	[X]Ac pois alcohol res instit
	U1A92	[X]Ac pois alcohol pub instit
	U1A93	[X]Ac pois alcohol sport area
	U1A94	[X]Ac pois alcohol on highway
	U1A95	[X]Ac pois alcohol trade area
	U1A96	[X]Ac pois alcohol indust area
	U1A97	[X]Ac pois alcohol on farm
	U1A9y	[X]Ac pois alcohol OS place

	U1A9z	[X]Ac pois alcohol unsp place
X62,X620-X629	U205.	[X]Intent self poison narcotic
	U2050	[X]Self pois narcotic home
	U2051	[X]S/pois narcotic res ins
	U2052	[X]S/pois narcotic pub ins
	U2053	[X]S/pois narcotic sport ar
	U2054	[X]S/pois narcotic on hway
	U2055	[X]S/pois narcotic trade ar
	U2056	[X]S/pois narcotic indus ar
	U2057	[X]S/pois narcotic on farm
	U205y	[X]S/pois narcotic OS place
	U205z	[X]S/pois narcotic unsp pl
	U206.	[X]Int s/poising hallucinogens
	U2060	[X]Self pois hallucinog home
	U2061	[X]S/pois hallucinog res ins
	U2062	[X]S/pois hallucinog pub ins
	U2063	[X]S/pois hallucinog sport ar
	U2064	[X]S/pois hallucinog on hway
	U2065	[X]S/pois hallucinog trade ar
	U2066	[X]S/pois hallucinog indus ar
	U2067	[X]S/pois hallucinog on farm
	U206y	[X]S/pois hallucinog OS place
	U206z	[X]S/pois hallucinog unsp pl
X65, X650-X659		Int s/poisoning by alcohol
	U209.	[X]Self poisoning by alcohol
	U2090	[X]Self pois alcohol home
	U2091	[X]S/pois alcohol res instit
	U2092	[X]S/pois alcohol pub instit
	U2093	[X]S/pois alcohol sport area

	U2094	[X]S/pois alcohol on highway
	U2095	[X]S/pois alcohol trade area
	U2096	[X]S/pois alcohol indust area
	U2097	[X]S/pois alcohol on farm
	U209y	[X]S/pois alcohol OS place
	U209z	[X]S/pois alcohol unsp place
Y12, Y120-Y129		Poisoning by exposure to narcotic and psychodysleptics, NEC, ?intent
	U405.	[X]Poisoning ?intent narcotic
	U4050	[X]Pois ?intent narcotic home
	U4051	[X]Pois ?int narcotic resid
	U4052	[X]Pois ?int narcotic pub ins
	U4053	[X]Pois ?int narcotic sport ar
	U4054	[X]Pois ?int narcotic on hway
	U4055	[X]Pois ?int narcotic trade ar
	U4056	[X]Pois ?int narcotic indus ar
	U4057	[X]Pois ?int narcotic on farm
	U405y	[X]Pois ?int narcotic OS place
	U405z	[X]Pois ?int narcotic unsp pl
	U406.	[X]Poison ?intent hallucinogen
	U4060	[X]Pois ?intent hallucin home
	U4061	[X]Pois ?int hallucinog resid
	U4062	[X]Pois ?int hallucin pub ins
	U4063	[X]Pois ?int hallucin sport ar
	U4064	[X]Pois ?int hallucin on hway
	U4065	[X]Pois ?int hallucin trade ar
	U4066	[X]Pois ?int hallucin indus ar
	U4067	[X]Pois ?int hallucin on farm
	U406y	[X]Pois ?int hallucin OS place
	U406z	[X]Pois ?int hallucin unsp pl

Y15, Y151-Y159	U409.	[X]Poisoning ?intent alcohol
	U4090	[X]Poison ?intent alcohol home
	U4091	[X]Pois ?int alcohol res ins
	U4092	[X]Pois ?int alcohol pub inst
	U4093	[X]Pois ?int alcohol sport ar
	U4094	[X]Pois ?int alcohol on hway
	U4095	[X]Pois ?int alcohol trade ar
	U4096	[X]Pois ?int alcohol indust ar
	U4097	[X]Pois ?intent alcoh on farm
	U409y	[X]Pois ?int alcohol OS place
	U409z	[X]Pois ?int alcohol unsp plc
Y573	U60H3	[X]Alcohol deterrents adv eff
Y904	U804.	[X]Evid alc inv,80-99mg/100ml
Y905	U805.	[X]Ev alc inv,100-119mg/100ml
Y906	U806.	[X]Ev alc inv,120-199mg/100ml
Y907	U807.	[X]Ev alc inv,200-239mg/100ml
Y908	U808.	[X]Evid alc inv,240mg/100ml+
Y912	U812.	[X]Evid alc inv,severe intoxic
Y913	U813.	[X]Evid alc inv,very sev intox
	ZV113	[V]PH - Alcoholism
	ZV114	[V]Pers hist subst abuse
Z722	ZV4K1	[V]Drug use
Z721		Alcohol use
Z502	ZV57A	[V]Alcohol rehabilitation
Z714	ZV6D6	[V]Alcohl abus counsel+surveil
Z715	ZV6D7	[V]Drug abuse counsel+surveiln

14 Medication codes used to identify prescription of antidepressants, anxiolytics and hypnotics (packet/bottle level)

Drug	Read Code	Description
Antidepressants		
	d71..	Amitriptyline hydrochloride
	d72..	Butriptyline - discontinued
	d73..	Clomipramine hydrochloride
	d74..	Desipramine hydrochloride
	d75..	Dosulepin Hydrochloride
	d76..	Doxepin
	d77..	Imipramine hydrochloride
	d78..	Iprindole
	d79..	Lofepramine
	d7a..	Maprotiline hydrochloride
	d7b..	Mianserin hydrochloride
	d7c..	Nortriptyline
	d7d..	Protriptyline hydrochloride
	d7e..	Trazadone hydrochloride
	d7f..	Trimipramine
	d7g..	Viloxazine hydrochloride
	d7h..	Amoxapine
	d81..	Phenelzine
	d83..	Isocarboxazid
	d84..	Tranylcypromine
	d85..	Moclobemide
	d91..	Compound Antidepressants A-Z
	da1..	Flupentixol [Antidepressant]
	da2..	Tryptophan
	da3..	Fluvoxamine Maleate
	da4..	Fluoxetine hydrochloride
	da5..	Sertraline hydrochloride
	da6..	Paroxetine hydrochloride

	da7..	Venlafaxine
	da9..	Citalopram
	daA..	Reboxetine
	daB..	Mirtazapine
	daC..	Escitalopram
	daD..	Agomelatine
	gde..	Duloxetine
Hypnotics		
	d11..	Chloral hydrate
	d12..	Clomethiazole edisylate (hypnotic)
	d13..	Dichloralphenazone - discontinued
	d14..	Flumtrazepam - discontinued
	d15..	Flurazepam
	d16..	Loprazolam
	d17..	Lormetazepam
	d18..	Nitrazepam
	d1a..	Temazepam (hynotic)
	d1b..	Triazolam - discontinued
	d1c..	Triclofos sodium
	d1d..	Zopiclone
	d1f..	Zolpidem
	d1g..	Zaleplon
	d1h..	Melatonin
	d1i..	Dexmedetomidine
Anxiolytics		
	d21..	Diazepam
	d22..	Alprazolam
	d23..	Bromazepam
	d24..	Chlordiazepoxide
	d25..	Chlormezanone
	d26..	Clobazam
	d27..	Clorazepate dipotassium

	d28..	Hydroxyzine hcl (anxiolytic)
	d29..	Ketazolam - discontinued
	d2a..	Lorazepam (anxiolytic)
	d2b..	Medazepam - discontinued
	d2c..	Meprobamate
	d2d..	Oxazepam
	d2f..	Buspirone hydrocholoride
	d2g..	Flumazenil
Antipsychotics		
	d4…	ANTIPSYCHOTIC DRUGS
	d4f..	SULPIRIDE
	d4f1.	DOLMATIL 200mg tablets
	d4f2.	*SULPITIL 200mg tablets x28CP
	d4f3.	*SULPITIL 200mg tablets x112CP
	d4f4.	*SULPAREX 200mg tablets
	d4f5.	DOLMATIL 400mg tablets
	d4f6.	SULPOR 200mg/5mL oral solution
	d4fw.	SULPIRIDE 200mg/5mL oral solution
	d4fx.	SULPIRIDE 400mg tablets
	d4fy.	SULPIRIDE 200mg/5mL sugar free solution
	d4fz.	SULPIRIDE 200mg tablets
	d41..	CHLORPROMAZINE HYDROCHLORIDE
	d411.	CHLORPROMAZINE 10mg tablets
	d412.	CHLORPROMAZINE 25mg tablets
	d413.	CHLORPROMAZINE 50mg tablets
	d414.	CHLORPROMAZINE 100mg tablets
	d415.	CHLORPROMAZINE 25mg/5mL syrup
	d416.	CHLORACTIL 25mg tablets
	d417.	CHLORACTIL 50mg tablets
	d418.	CHLORACTIL 100mg tablets

	d419.	*DOZINE 25mg/5mL syrup
	d41A.	CHLORPROMAZINE 25mg/5mL sugar free solution
	d41B.	CHLORPROMAZINE 100mg/5mL sugar free solution
	d41a.	*LARGACTIL 10mg tablets
	d41b.	*LARGACTIL 25mg tablets
	d41c.	*LARGACTIL 50mg tablets
	d41d.	*LARGACTIL 100mg tablets
	d41e.	*LARGACTIL 25mg/5mL syrup
	d41f.	LARGACTIL FORTE 100mg/5mL syrup
	d41g.	*LARGACTIL 25mg/mL injection
	d41h.	LARGACTIL [CNS] 50mg/2mL injection
	d41i.	*LARGACTIL 100mg suppositories
	d41j.	CHLORPROMAZINE 100mg/5mL sugar free suspension
	d41k.	CHLORPROMAZINE 100mg suppositories
	d41l.	CHLORPROMAZINE 25mg/1mL injection
	d41m.	CHLORPROMAZINE 50mg/2mL injection
	d41o.	CHLORPROMAZINE 100mg/5mL syrup
	d42..	BENPERIDOL
	d421.	ANQUIL 250micrograms tablets
	d422.	*BENQUIL 250micrograms tablets
	d42z.	BENPERIDOL 250microgram tablets
	d43..	*CHLORPROTHIXENE
	d431.	*TARACTAN 15mg tablets
	d432.	*TARACTAN 50mg tablets
	d43y.	*CHLORPROTHIXENE 15mg tablets
	d43z.	*CHLORPROTHIXENE 50mg tablets
	d44..	DROPERIDOL [CENTRAL NERVOUS SYSTEM USE]
	d441.	*DROLEPTAN 10mg tablets
	d442.	*DROLEPTAN 1mg/mL oral liquid

	d443.	*DROLEPTAN 10mg/2mL injection
	d444.	XOMOLIX 2.5mg/1mL solution for injection
	d44w.	DROPERIDOL 2.5mg/1mL solution for injection
	d44x.	*DROPERIDOL 10mg tablets
	d44y.	*DROPERIDOL 1mg/mL oral liquid
	d44z.	*DROPERIDOL 10mg/2mL injection
	d45..	FLUPENTIXOL [ANTIPSYCHOTIC]
	d451.	DEPIXOL 3mg tablets
	d45z.	FLUPENTIXOL 3mg tablets
	d46..	FLUPHENAZINE HYDROCHLORIDE
	d461.	*MODITEN 1mg tablets
	d462.	*MODITEN 2.5mg tablets
	d463.	*MODITEN 5mg tablets
	d46x.	FLUPHENAZINE HYDROCHLORIDE 1mg tablets
	d46y.	FLUPHENAZINE HYDROCHLORIDE 2.5mg tablets
	d46z.	FLUPHENAZINE HYDROCHLORIDE 5mg tablets
	d47..	HALOPERIDOL [ANTIPSYCHOTIC]
	d471.	HALOPERIDOL 1.5mg tablets
	d472.	HALOPERIDOL 5mg tablets
	d473.	HALOPERIDOL 10mg tablets
	d474.	HALOPERIDOL 20mg tablets
	d475.	HALOPERIDOL 2mg/mL liquid
	d476.	DOZIC 1mg/mL liquid
	d477.	*DOZIC 2mg/mL liquid
	d478.	FORTUNAN 500micrograms tablets
	d479.	*FORTUNAN 1.5mg tablets
	d47A.	HALOPERIDOL 2mg/5mL sugar free solution
	d47B.	HALOPERIDOL 1mg/5mL sugar free solution
	d47C.	KENTACE 1.5mg tablets

	d47D.	KENTACE 5mg tablets
	d47E.	KENTACE 10mg tablets
	d47F.	KENTACE 20mg tablets
	d47a.	*FORTUNAN 5mg tablets
	d47b.	*FORTUNAN 10mg tablets
	d47c.	*FORTUNAN 20mg tablets
	d47d.	HALDOL 5mg tablets
	d47e.	HALDOL 10mg tablets
	d47f.	HALDOL 2mg/mL liquid
	d47g.	*HALDOL 10mg/mL liquid
	d47h.	HALDOL 5mg/1mL injection
	d47i.	*HALDOL 10mg/2mL injection
	d47j.	SERENACE 500micrograms capsules
	d47k.	SERENACE 1.5mg tablets
	d47l.	SERENACE 5mg tablets
	d47m.	SERENACE 10mg tablets
	d47n.	SERENACE 20mg tablets
	d47o.	SERENACE 2mg/mL liquid 100mL
	d47p.	SERENACE 5mg/1mL injection
	d47q.	SERENACE 20mg/2mL injection
	d47r.	HALOPERIDOL 500microgram capsules
	d47s.	SERENACE 2mg/mL liquid 500mL
	d47t.	HALOPERIDOL 1mg/mL liquid
	d47u.	HALOPERIDOL 500micrograms tablets
	d47v.	HALOPERIDOL 5mg/1mL injection
	d47w.	HALOPERIDOL 10mg/2mL injection
	d47x.	HALOPERIDOL 20mg/2mL injection

	d47y.	HALOPERIDOL 10mg/mL oral solution
	d48..	LEVOMEPROMAZINE
	d481.	NOZINAN 25mg/1mL injection
	d482.	*VERACTIL 25mg tablets
	d483.	NOZINAN 25mg tablets
	d48y.	LEVOMEPROMAZINE 25mg/1mL injection
	d48z.	LEVOMEPROMAZINE 25mg tablets
	d49..	OXYPERTINE
	d491.	*INTEGRIN 10mg capsules
	d492.	*INTEGRIN 40mg tablets
	d49y.	*OXYPERTINE 10mg capsules
	d49z.	*OXYPERTINE 40mg tablets
	d4a..	PERICYAZINE
	d4a1.	*NEULACTIL 2.5mg tablets
	d4a2.	*NEULACTIL 10mg tablets
	d4a3.	*NEULACTIL 25mg tablets
	d4a4.	*NEULACTIL FORTE 10mg/5mL syrp
	d4aw.	PERICYAZINE 2.5mg tablets
	d4ax.	PERICYAZINE 10mg tablets
	d4ay.	*PERICYAZINE 25mg tablets
	d4az.	PERICYAZINE 10mg/5mL syrup
	d4b..	PERPHENAZINE [CENTRAL NERVOUS SYSTEM USE]
	d4b1.	FENTAZIN 2mg tablets
	d4b2.	FENTAZIN 4mg tablets
	d4b3.	*FENTAZIN 8mg tablets
	d4b4.	*FENTAZIN 5mg/1mL injection
	d4b5.	PERPHENAZINE 2mg/5mL sugar free solution

	d4b6.	PERPHENAZINE 4mg/5mL sugar free solution
	d4bx.	PERPHENAZINE 2mg tablets
	d4by.	PERPHENAZINE 4mg tablets
	d4bz.	*PERPHENAZINE 8mg tablets
	d4c..	PIMOZIDE
	d4c1.	*ORAP 2mg tablets
	d4c2.	ORAP 4mg tablets
	d4c3.	*ORAP 10mg tablets
	d4cx.	*PIMOZIDE 2mg tablets
	d4cy.	PIMOZIDE 4mg tablets
	d4cz.	*PIMOZIDE 10mg tablets
	d4d..	PROCHLORPERAZINE [antipsych] [see dhe..]
	d4e..	PROMAZINE HYDROCHLORIDE
	d4e1.	*SPARINE 50mg/5mL suspension
	d4e2.	*SPARINE 50mg/1mL injection
	d4e3.	*SPARINE 100mg/2mL injection
	d4e4.	PROMAZINE 25mg tablets
	d4e5.	PROMAZINE 50mg tablets
	d4ev.	PROMAZINE 25mg/5mL syrup
	d4ew.	PROMAZINE 50mg/5mL syrup
	d4ex.	*PROMAZINE 50mg/5mL suspension
	d4ey.	PROMAZINE 50mg/1mL injection
	d4ez.	*PROMAZINE 100mg/2mL injection
	d4g..	THIORIDAZINE
	d4g1.	*MELLERIL 10mg tablets

	d4g2.	*MELLERIL 25mg tablets
	d4g3.	*MELLERIL 50mg tablets
	d4g4.	*MELLERIL 100mg tablets
	d4g5.	*MELLERIL 25mg/5mL suspension
	d4g6.	MELLERIL 100mg/5mL oral suspension
	d4g7.	MELLERIL 25mg/5mL orange syrup
	d4gp.	THIORIDAZINE 10mg/5mL syrup
	d4gq.	THIORIDAZINE 25mg/5mL sugar free solution
	d4gr.	THIORIDAZINE 50mg/5mL sugar free solution
	d4gs.	THIORIDAZINE 100mg/5mL sugar free solution
	d4gt.	*THIORIDAZINE 10mg tablets
	d4gu.	THIORIDAZINE 25mg tablets
	d4gv.	THIORIDAZINE 50mg tablets
	d4gw.	THIORIDAZINE 100mg tablets
	d4gx.	THIORIDAZINE 25mg/5mL suspension
	d4gy.	THIORIDAZINE 100mg/5mL oral suspension
	d4gz.	*THIORIDAZINE 25mg/5mL syrup
	d4h..	TRIFLUOPERAZINE [ANTIPSYCHOTIC]
	d4h1.	STELAZINE 1mg tablets
	d4h2.	STELAZINE 5mg tablets
	d4h3.	*STELAZINE 2mg m/r capsules
	d4h4.	*STELAZINE 10mg m/r capsules
	d4h5.	*STELAZINE 15mg m/r capsules
	d4h6.	STELAZINE 1mg/5mL syrup
	d4h7.	STELAZINE CONCENTRATE 10mg/mL liquid
	d4h8.	*STELAZINE 1mg/1mL injection

	d4h9.	TRIFLUOPERAZINE 5mg/5mL sugar free syrup
	d4hA.	STELAZINE FORTE 5mg/5mL sugar free oral suspension
	d4hr.	TRIFLUOPERAZINE 5mg/5mL sugar free oral suspension
	d4hs.	TRIFLUOPERAZINE 1mg tablets
	d4ht.	TRIFLUOPERAZINE 5mg tablets
	d4hu.	*TRIFLUOPERAZINE 2mg m/r caps
	d4hv.	*TRIFLUOPERAZINE 10mg m/r caps
	d4hw.	*TRIFLUOPERAZINE 15mg m/r caps
	d4hx.	TRIFLUOPERAZINE 1mg/5mL syrup
	d4hy.	TRIFLUOPERAZINE 10mg/mL liquid
	d4hz.	TRIFLUOPERAZINE 1mg/1mL injection
	d4i1.	TRIFLUPERIDOL
	d4i2.	TRIPERIDOL 500micrograms tablets
	d4iy.	*TRIPERIDOL 1mg tablets
	d4iz.	TRIFLUPERIDOL 500microgram tablets
	d4l..	*TRIFLUPERIDOL 1mg tablets
	d4j..	ZUCLOPENTHIXOL DIHYDROCHLORIDE
	d4j1.	CLOPIXOL 2mg tablets
	d4j2.	CLOPIXOL 10mg tablets
	d4j3.	CLOPIXOL 25mg tablets
	d4jx.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 2mg tablets
	d4jy.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 10mg tablets
	d4jz.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 25mg tablets
	d4k..	LOXAPINE SUCCINATE
	d4k1.	*LOXAPINE 10mg capsules

	d4k2.	*LOXAPINE 25mg capsules
	d4k3.	*LOXAPINE 50mg capsules
	d4k4.	*LOXAPAC 10mg capsules
	d4k5.	*LOXAPAC 25mg capsules
	d4k6.	*LOXAPAC 50mg capsules
	d4n..	ZUCLOPENTHIXOL ACETATE
	d4n1.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)
	d4n2.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)
	d4n3.	ZUCLOPENTHIXOL ACETATE 50mg/1mL injection (oily)
	d4n4.	ZUCLOPENTHIXOL ACETATE 100mg/2mL injection (oily)
	d5...	ANTIPSYCHOTIC DEPOT INJECTIONS
	d51..	FLUPENTIXOL DECANOATE
	d511.	DEPIXOL 20mg/1mL injection
	d512.	*DEPIXOL 20mg/1mL syringe
	d513.	DEPIXOL 40mg/2mL injection
	d514.	*DEPIXOL 40mg/2mL syringe
	d515.	*DEPIXOL 200mg/10mL injection
	d516.	DEPIXOL CONC. 100mg/1mL injection
	d517.	DEPIXOL CONC. 500mg/5mL injection
	d518.	DEPIXOL CONC. 50mg/0.5mL injection
	d519.	FLUPENTIXOL 50mg/0.5mL injection
	d51a.	DEPIXOL LOW VOLUME 200mg/1mL intramuscular injection
	d51s.	FLUPENTHIXOL DECANOATE 20mg/1mL prefilled syringe
	d51t.	FLUPENTHIXOL DECANOATE 40mg/2mL prefilled syringe
	d51u.	FLUPENTIXOL DECANOATE 200mg/1mL intramuscular injection
	d51v.	FLUPENTIXOL DECANOATE 20mg/1mL injection

	d51w.	FLUPENTIXOL DECANOATE 40mg/2mL injection
	d51x.	FLUPENTHIXOL DECANOATE 200mg/10mL injection
	d51y.	FLUPENTIXOL DECANOATE 100mg/1mL injection
	d51z.	FLUPENTHIXOL DECANOATE 500mg/5mL injection
	d52..	FLUPHENAZINE DECANOATE
	d521.	MODECATE 12.5mg/0.5mL injection
	d522.	MODECATE 25mg/1mL injection
	d523.	*MODECATE 25mg/1mL syringe
	d524.	MODECATE 50mg/2mL injection
	d525.	*MODECATE 50mg/2mL syringe
	d526.	*MODECATE 250mg/10mL injection
	d527.	MODECATE CONCENTRATE 50mg/0.5mL injection
	d528.	MODECATE CONCENTRATE 100mg/1mL injection
	d529.	FLUPHENAZINE DECANOATE 50mg/0.5mL injection
	d52A.	*DECAZATE 25mg/1mL injection
	d52B.	*DECAZATE 50mg/0.5mL injection
	d52C.	*DECAZATE 100mg/1mL injection
	d52a.	FLUPHENAZINE DECANOATE 100mg/1mL injection
	d52s.	FLUPHENAZINE DECANOATE 25mg/1mL prefilled syringe
	d52t.	FLUPHENAZINE DECANOATE 50mg/2mL prefilled syringe
	d52u.	FLUPHENAZINE DECANOATE 12.5mg/0.5mL injection
	d52v.	FLUPHENAZINE DECANOATE 25mg/1mL injection
	d52w.	FLUPHENAZINE DECANOATE 50mg/2mL injection
	d52x.	FLUPHENAZINE DECANOATE 250mg/10mL injection
	d53..	*FLUPHENAZINE ENANTHATE
	d531.	MODITEN ENANTHATE 25mg/1mL injection
	d532.	FLUPHENAZINE ENANTHATE 25mg/1mL injection

	d54..	FLUSPIRILENE
	d541.	*REDEPTIN 2mg/1mL injection
	d542.	*REDEPTIN 6mg/3mL injection
	d543.	*REDEPTIN 12mg/6mL injection
	d544.	FLUSPIRILENE 2mg/1mL injection
	d545.	FLUSPIRILENE 6mg/3mL injection
	d546.	FLUSPIRILENE 12mg/6mL injection
	d55..	HALOPERIDOL DECANOATE
	d551.	HALDOL DECANOATE 50mg/1mL injection
	d552.	HALDOL DECANOATE 100mg/1mL injection
	d553.	HALOPERIDOL 50mg/1mL injection
	d554.	HALOPERIDOL 100mg/1mL injection
	d56..	PIPOTIAZINE PALMITATE
	d561.	PIPORTIL DEPOT 50mg/1mL injection
	d562.	PIPORTIL DEPOT 100mg/2mL injection
	d563.	PIPOTIAZINE 50mg/1mL injection
	d564.	PIPOTIAZINE 100mg/2mL injection
	d57..	ZUCLOPENTHIXOL DECANOATE
	d571.	CLOPIXOL 200mg/1mL injection
	d572.	*CLOPIXOL 2g/10mL injection
	d573.	CLOPIXOL CONC. 500mg/1mL injection
	d574.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)
	d575.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)
	d576.	ZUCLOPENTHIXOL DECANOATE 200mg/1mL injection
	d577.	ZUCLOPENTHIXOL DECANOATE 50mg/1mL injection
	d578.	ZUCLOPENTHIXOL DECANOATE 100mg/2mL injection

	d57y.	ZUCLOPENTHIXOL DECANOATE 2g/10mL injection
	d57z.	ZUCLOPENTHIXOL DECANOATE 500mg/1mL injection
	d4l..	CLOZAPINE
	d4l1.	CLOZAPINE 25mg tablets
	d4l2.	CLOZAPINE 100mg tablets
	d4l3.	CLOZARIL 25mg tablets x84CP
	d4l4.	CLOZARIL 100mg tablets x84CP
	d4l5.	CLOZARIL COMMUNITY PACK 25mg tablets x28CP
	d4l6.	CLOZARIL COMMUNITY PACK 100mg tablets x28CP
	d4l7.	DENZAPINE 25mg tablets
	d4l8.	DENZAPINE 100mg tablets
	d4l9.	ZAPONEX 25mg tablets
	d4lA.	ZAPONEX 100mg tablets
	d4lB.	DENZAPINE 50mg/mL oral suspension 100mL
	d4lC.	CLOZAPINE 50mg/mL oral suspension
	d4lD.	DENZAPINE 50mg tablets
	d4lE.	CLOZAPINE 50mg tablets
	d4lF.	DENZAPINE 200mg tablets
	d4lG.	CLOZAPINE 200mg tablets
	d4m..	REMOXIPRIDE
	d4m1.	REMOXIPRIDE 150mg m/r capsules
	d4m2.	REMOXIPRIDE 300mg m/r capsules
	d4m3.	*ROXIAM 150mg m/r capsules
	d4m4.	*ROXIAM 300mg m/r capsules
	d4p..	RISPERIDONE
	d4p1.	RISPERIDONE 1mg tablets
	d4p2.	RISPERIDONE 2mg tablets

	d4p3.	RISPERIDONE 3mg tablets
	d4p4.	RISPERIDONE 4mg tablets
	d4p5.	RISPERDAL 1mg tablets
	d4p6.	RISPERDAL 2mg tablets
	d4p7.	RISPERDAL 3mg tablets
	d4p8.	RISPERDAL 4mg tablets
	d4p9.	RISPERIDONE 1mg/mL liquid
	d4pA.	RISPERDAL 1mg/mL liquid
	d4pB.	RISPERIDONE 6mg tablets
	d4pC.	RISPERDAL 6mg tablets
	d4pD.	RISPERDAL 0.5mg tablets
	d4pE.	RISPERDAL CONSTA 25mg powder+solvent for suspension for injection
	d4pF.	RISPERDAL CONSTA 37.5mg powder+solvent for suspension for injection
	d4pG.	RISPERDAL CONSTA 50mg powder+solvent for suspension for injection
	d4pH.	RISPERIDONE 1mg oro-dispersible tablets
	d4pJ.	RISPERIDONE 2mg oro-dispersible tablets
	d4pK.	RISPERDAL QUICKLET 1mg oro-dispersible tablets
	d4pL.	RISPERDAL QUICKLET 2mg oro-dispersible tablets
	d4pM.	RISPERIDONE 0.5mg oro-dispersible tablets
	d4pN.	RISPERDAL QUICKLET 0.5mg oro-dispersible tablets
	d4pO.	RISPERDAL QUICKLET 3mg oro-dispersible tablets
	d4pP.	RISPERDAL QUICKLET 4mg oro-dispersible tablets
	d4pQ.	RISPERIDONE 3mg oro-dispersible tablets
	d4pR.	RISPERIDONE 4mg oro-dispersible tablets
	d4pw.	RISPERIDONE 50mg powder+solvent for suspension for injection
	d4px.	RISPERIDONE 37.5mg powder+solvent for suspension for injection

	d4py.	RISPERIDONE 25mg powder+solvent for suspension for injection
	d4pz.	RISPERIDONE 0.5mg tablets
	d4q..	SERTINDOLE
	d4q1.	SERTINDOLE 4mg tablets
	d4q2.	SERTINDOLE 12mg tablets
	d4q3.	SERTINDOLE 16mg tablets
	d4q4.	SERTINDOLE 20mg tablets
	d4q5.	SERDOLECT 4mg tablets
	d4q6.	SERDOLECT 12mg tablets
	d4q7.	SERDOLECT 16mg tablets
	d4q8.	SERDOLECT 20mg tablets
	d4r..	OLANZAPINE
	d4r1.	OLANZAPINE 5mg tablets
	d4r2.	OLANZAPINE 7.5mg tablets
	d4r3.	OLANZAPINE 10mg tablets
	d4r4.	ZYPREXA 5mg tablets
	d4r5.	ZYPREXA 7.5mg tablets
	d4r6.	ZYPREXA 10mg tablets
	d4r7.	OLANZAPINE 2.5mg tablets
	d4r8.	ZYPREXA 2.5mg tablets
	d4r9.	ZYPREXA VELOTAB 5mg dispersible tablets
	d4rA.	ZYPREXA VELOTAB 10mg dispersible tablets
	d4rB.	ZYPREXA 15mg tablets
	d4rC.	ZYPREXA VELOTAB 15mg dispersible tablets
	d4rD.	ZYPREXA 10mg injection (pdr for recon)
	d4rE.	ZYPREXA VELOTAB 20mg dispersible tablets

	d4rF.	ZYPREXA 20mg tablets
	d4rG.	ZALASTA 2.5mg tablets
	d4rH.	ZALASTA 5mg tablets
	d4rI.	ZALASTA 7.5mg tablets
	d4rJ.	ZALASTA 15mg tablets
	d4rK.	ZALASTA 20mg tablets
	d4rL.	ZALASTA 5mg dispersible tablets
	d4rM.	ZALASTA 10mg dispersible tablets
	d4rN.	ZALASTA 15mg dispersible tablets
	d4rO.	ZALASTA 20mg dispersible tablets
	d4rP.	ZALASTA 10mg tablets
	d4rt.	OLANZAPINE 20mg tablets
	d4ru.	OLANZAPINE 20mg dispersible tablets
	d4rv.	OLANZAPINE 10mg injection (pdr for recon)
	d4rw.	OLANZAPINE 15mg dispersible tablets
	d4rx.	OLANZAPINE 15mg tablets
	d4ry.	OLANZAPINE 5mg dispersible tablets
	d4rz.	OLANZAPINE 10mg dispersible tablets
	d4s..	QUETIAPINE
	d4s1.	QUETIAPINE 25mg tablets
	d4s2.	QUETIAPINE 100mg tablets
	d4s3.	QUETIAPINE 200mg tablets
	d4s4.	QUETIAPINE 25mg+100mg tablets starter pack
	d4s5.	SEROQUEL 25mg tablets
	d4s6.	SEROQUEL 100mg tablets

	d4s7.	SEROQUEL 200mg tablets
	d4s8.	SEROQUEL 25mg+100mg tablets starter pack
	d4s9.	SEROQUEL 150mg tablets
	d4sA.	SEROQUEL 25mg+100mg+150mg tablets starter pack
	d4sB.	SEROQUEL 300mg tablets
	d4sC.	SEROQUEL XL 50mg m/r tablets
	d4sD.	SEROQUEL XL 200mg m/r tablets
	d4sE.	SEROQUEL XL 300mg m/r tablets
	d4sF.	SEROQUEL XL 400mg m/r tablets
	d4sG.	SEROQUEL XL 150mg m/r tablets
	d4ss.	QUETIAPINE 150mg m/r tablets
	d4st.	QUETIAPINE 400mg m/r tablets
	d4su.	QUETIAPINE 300mg m/r tablets
	d4sv.	QUETIAPINE 200mg m/r tablets
	d4sw.	QUETIAPINE 50mg m/r tablets
	d4sx.	QUETIAPINE 300mg tablets
	d4sy.	QUETIAPINE 25mg+100mg+150mg tablets starter pack
	d4sz.	QUETIAPINE 150mg tablets
	d4t..	AMISULPRIDE
	d4t1.	AMISULPRIDE 50mg tablets
	d4t2.	AMISULPRIDE 200mg tablets
	d4t3.	SOLIAN 50mg tablets
	d4t4.	SOLIAN 200mg tablets
	d4t5.	SOLIAN 400mg tablets
	d4t6.	SOLIAN 100mg/mL sugar free oral solution
	d4t7.	SOLIAN 100mg tablets

	d4tx.	AMISULPRIDE 100mg tablets
	d4ty.	AMISULPRIDE 100mg/mL sugar free oral solution
	d4tz.	AMISULPRIDE 400mg tablets
	d4u..	ZOTEPINE
	d4u1.	*ZOTEPINE 25mg tablets
	d4u2.	*ZOTEPINE 50mg tablets
	d4u3.	*ZOTEPINE 100mg tablets
	d4u4.	*ZOLEPTIL 25mg tablets
	d4u5.	*ZOLEPTIL 50mg tablets
	d4u6.	*ZOLEPTIL 100mg tablets
	d4v..	ARIPIPRAZOLE
	d4v1.	ABILIFY 10mg tablets
	d4v2.	ABILIFY 15mg tablets
	d4v3.	ABILIFY 30mg tablets
	d4v4.	ABILIFY 5mg tablets
	d4v5.	ABILIFY 10mg oro-dispersible tablets
	d4v6.	ABILIFY 15mg oro-dispersible tablets
	d4v7.	ABILIFY 1mg/mL oral solution
	d4v8.	ABILIFY 9.75mg/1.3mL solution for injection
	d4vs.	ARIPIPRAZOLE 9.75mg/1.3mL solution for injection
	d4vt.	ARIPIPRAZOLE 1mg/mL oral solution
	d4vu.	ARIPIPRAZOLE 10mg oro-dispersible tablets
	d4vv.	ARIPIPRAZOLE 15mg oro-dispersible tablets
	d4vw.	ARIPIPRAZOLE 5mg tablets
	d4vx.	ARIPIPRAZOLE 30mg tablets
	d4vy.	ARIPIPRAZOLE 15mg tablets
	d4vz.	ARIPIPRAZOLE 10mg tablets
	d4w..	PALIPERIDONE

	d4w1.	INVEGA 3mg m/r tablets
	d4w2.	INVEGA 6mg m/r tablets
	d4w3.	INVEGA 9mg m/r tablets
	d4w4.	*INVEGA 12mg m/r tablets
	d4w5.	XEPLION 50mg suspension for injection prefilled syringe
	d4w6.	XEPLION 75mg suspension for injection prefilled syringe
	d4w7.	XEPLION 100mg suspension for injection prefilled syringe
	d4w8.	XEPLION 150mg suspension for injection prefilled syringe
	d4ws.	PALIPERIDONE 150mg suspension for injection pfs
	d4wt.	PALIPERIDONE 100mg suspension for injection pfs
	d4wu.	PALIPERIDONE 75mg suspension for injection prefilled syringe
	d4wv.	PALIPERIDONE 50mg suspension for injection prefilled syringe
	d4ww.	*PALIPERIDONE 12mg m/r tablets
	d4wx.	PALIPERIDONE 9mg m/r tablets
	d4wy.	PALIPERIDONE 6mg m/r tablets
	d4wz.	PALIPERIDONE 3mg m/r tablets
	d4x..	ASENAPINE
	d4x1.	SYCREST 5mg sublingual tablets
	d4x2.	ASENAPINE 5mg sublingual tablets
	d4x3.	SYCREST 10mg sublingual tablets
	d4x4.	ASENAPINE 10mg sublingual tablets
	d58..	OLANZAPINE PAMOATE
	d581.	ZYPADHERA 210mg powder+solvent for suspension for injection
	d582.	ZYPADHERA 300mg powder+solvent for suspension for injection
	d583.	ZYPADHERA 405mg powder+solvent for suspension for injection
	d58x.	OLANZAPINE 405mg powder+solvent for suspension for injection

	d58y.	OLANZAPINE 300mg powder+solvent for suspension for injection
	d58z.	OLANZAPINE 210mg powder+solvent for suspension for injection
	d4gv.	THIORIDAZINE 50mg tablets
	d4gw.	THIORIDAZINE 100mg tablets
	d4gx.	THIORIDAZINE 25mg/5mL suspension
	d4gy.	THIORIDAZINE 100mg/5mL oral suspension
	d4gz.	*THIORIDAZINE 25mg/5mL syrup
	d4h..	TRIFLUOPERAZINE [ANTIPSYCHOTIC]
	d4h1.	STELAZINE 1mg tablets
	d4h2.	STELAZINE 5mg tablets
	d4h3.	*STELAZINE 2mg m/r capsules
	d4h4.	*STELAZINE 10mg m/r capsules
	d4h5.	*STELAZINE 15mg m/r capsules
	d4h6.	STELAZINE 1mg/5mL syrup
	d4h7.	STELAZINE CONCENTRATE 10mg/mL liquid
	d4h8.	*STELAZINE 1mg/1mL injection
	d4h9.	TRIFLUOPERAZINE 5mg/5mL sugar free syrup
	d4hA.	STELAZINE FORTE 5mg/5mL sugar free oral suspension
	d4hr.	TRIFLUOPERAZINE 5mg/5mL sugar free oral suspension
	d4hs.	TRIFLUOPERAZINE 1mg tablets
	d4ht.	TRIFLUOPERAZINE 5mg tablets
	d4hu.	*TRIFLUOPERAZINE 2mg m/r caps
	d4hv.	*TRIFLUOPERAZINE 10mg m/r caps
	d4hw.	*TRIFLUOPERAZINE 15mg m/r caps
	d4hx.	TRIFLUOPERAZINE 1mg/5mL syrup
	d4hy.	TRIFLUOPERAZINE 10mg/mL liquid

	d4hz.	TRIFLUOPERAZINE 1mg/1mL injection
	d4i1.	TRIFLUPERIDOL
	d4i2.	TRIPERIDOL 500micrograms tablets
	d4iy.	*TRIPERIDOL 1mg tablets
	d4iz.	TRIFLUPERIDOL 500microgram tablets
	d4l..	*TRIFLUPERIDOL 1mg tablets
	d4j..	ZUCLOPENTHIXOL DIHYDROCHLORIDE
	d4j1.	CLOPIXOL 2mg tablets
	d4j2.	CLOPIXOL 10mg tablets
	d4j3.	CLOPIXOL 25mg tablets
	d4jx.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 2mg tablets
	d4jy.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 10mg tablets
	d4jz.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 25mg tablets
	d4k..	LOXAPINE SUCCINATE
	d4k1.	*LOXAPINE 10mg capsules
	d4k2.	*LOXAPINE 25mg capsules
	d4k3.	*LOXAPINE 50mg capsules
	d4k4.	*LOXAPAC 10mg capsules
	d4k5.	*LOXAPAC 25mg capsules
	d4k6.	*LOXAPAC 50mg capsules
	d4n..	ZUCLOPENTHIXOL ACETATE
	d4n1.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)
	d4n2.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)
	d4n3.	ZUCLOPENTHIXOL ACETATE 50mg/1mL injection (oily)
	d4n4.	ZUCLOPENTHIXOL ACETATE 100mg/2mL injection (oily)
	d5...	ANTIPSYCHOTIC DEPOT INJECTIONS

	d51..	FLUPENTIXOL DECANOATE
	d511.	DEPIXOL 20mg/1mL injection
	d512.	*DEPIXOL 20mg/1mL syringe
	d513.	DEPIXOL 40mg/2mL injection
	d514.	*DEPIXOL 40mg/2mL syringe
	d515.	*DEPIXOL 200mg/10mL injection
	d516.	DEPIXOL CONC. 100mg/1mL injection
	d517.	DEPIXOL CONC. 500mg/5mL injection
	d518.	DEPIXOL CONC. 50mg/0.5mL injection
	d519.	FLUPENTIXOL 50mg/0.5mL injection
	d51a.	DEPIXOL LOW VOLUME 200mg/1mL intramuscular injection
	d51s.	FLUPENTHIXOL DECANOATE 20mg/1mL prefilled syringe
	d51t.	FLUPENTHIXOL DECANOATE 40mg/2mL prefilled syringe
	d51u.	FLUPENTIXOL DECANOATE 200mg/1mL intramuscular injection
	d51v.	FLUPENTIXOL DECANOATE 20mg/1mL injection
	d51w.	FLUPENTIXOL DECANOATE 40mg/2mL injection
	d51x.	FLUPENTHIXOL DECANOATE 200mg/10mL injection
	d51y.	FLUPENTIXOL DECANOATE 100mg/1mL injection
	d51z.	FLUPENTHIXOL DECANOATE 500mg/5mL injection
	d52..	FLUPHENAZINE DECANOATE
	d521.	MODECATE 12.5mg/0.5mL injection
	d522.	MODECATE 25mg/1mL injection
	d523.	*MODECATE 25mg/1mL syringe
	d524.	MODECATE 50mg/2mL injection
	d525.	*MODECATE 50mg/2mL syringe

	d526.	*MODECATE 250mg/10mL injection
	d527.	MODECATE CONCENTRATE 50mg/0.5mL injection
	d528.	MODECATE CONCENTRATE 100mg/1mL injection
	d529.	FLUPHENAZINE DECANOATE 50mg/0.5mL injection
	d52A.	*DECAZATE 25mg/1mL injection
	d52B.	*DECAZATE 50mg/0.5mL injection
	d52C.	*DECAZATE 100mg/1mL injection
	d52a.	FLUPHENAZINE DECANOATE 100mg/1mL injection
	d52s.	FLUPHENAZINE DECANOATE 25mg/1mL prefilled syringe
	d52t.	FLUPHENAZINE DECANOATE 50mg/2mL prefilled syringe
	d52u.	FLUPHENAZINE DECANOATE 12.5mg/0.5mL injection
	d52v.	FLUPHENAZINE DECANOATE 25mg/1mL injection
	d52w.	FLUPHENAZINE DECANOATE 50mg/2mL injection
	d52x.	FLUPHENAZINE DECANOATE 250mg/10mL injection
	d53..	*FLUPHENAZINE ENANTHATE
	d531.	MODITEN ENANTHATE 25mg/1mL injection
	d532.	FLUPHENAZINE ENANTHATE 25mg/1mL injection
	d54..	FLUSPIRILENE
	d541.	*REDEPTIN 2mg/1mL injection
	d542.	*REDEPTIN 6mg/3mL injection
	d543.	*REDEPTIN 12mg/6mL injection
	d544.	FLUSPIRILENE 2mg/1mL injection
	d545.	FLUSPIRILENE 6mg/3mL injection
	d546.	FLUSPIRILENE 12mg/6mL injection
	d55..	HALOPERIDOL DECANOATE
	d551.	HALDOL DECANOATE 50mg/1mL injection
	d552.	HALDOL DECANOATE 100mg/1mL injection

	d553.	HALOPERIDOL 50mg/1mL injection
	d554.	HALOPERIDOL 100mg/1mL injection
	d56..	PIPOTIAZINE PALMITATE
	d561.	PIPORTIL DEPOT 50mg/1mL injection
	d562.	PIPORTIL DEPOT 100mg/2mL injection
	d563.	PIPOTIAZINE 50mg/1mL injection
	d564.	PIPOTIAZINE 100mg/2mL injection
	d57..	ZUCLOPENTHIXOL DECANOATE
	d571.	CLOPIXOL 200mg/1mL injection
	d572.	*CLOPIXOL 2g/10mL injection
	d573.	CLOPIXOL CONC. 500mg/1mL injection
	d574.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)
	d575.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)
	d576.	ZUCLOPENTHIXOL DECANOATE 200mg/1mL injection
	d577.	ZUCLOPENTHIXOL DECANOATE 50mg/1mL injection
	d578.	ZUCLOPENTHIXOL DECANOATE 100mg/2mL injection
	d57y.	ZUCLOPENTHIXOL DECANOATE 2g/10mL injection
	d57z.	ZUCLOPENTHIXOL DECANOATE 500mg/1mL injection
	d4l..	CLOZAPINE
	d4l1.	CLOZAPINE 25mg tablets
	d4l2.	CLOZAPINE 100mg tablets
	d4l3.	CLOZARIL 25mg tablets x84CP
	d4l4.	CLOZARIL 100mg tablets x84CP
	d4l5.	CLOZARIL COMMUNITY PACK 25mg tablets x28CP
	d4l6.	CLOZARIL COMMUNITY PACK 100mg tablets x28CP
	d4l7.	DENZAPINE 25mg tablets

	d4l8.	DENZAPINE 100mg tablets
	d4l9.	ZAPONEX 25mg tablets
	d4lA.	ZAPONEX 100mg tablets
	d4lB.	DENZAPINE 50mg/mL oral suspension 100mL
	d4lC.	CLOZAPINE 50mg/mL oral suspension
	d4lD.	DENZAPINE 50mg tablets
	d4lE.	CLOZAPINE 50mg tablets
	d4lF.	DENZAPINE 200mg tablets
	d4lG.	CLOZAPINE 200mg tablets
	d4m..	REMOXIPRIDE
	d4m1.	REMOXIPRIDE 150mg m/r capsules
	d4m2.	REMOXIPRIDE 300mg m/r capsules
	d4m3.	*ROXIAM 150mg m/r capsules
	d4m4.	*ROXIAM 300mg m/r capsules
	d4p..	RISPERIDONE
	d4p1.	RISPERIDONE 1mg tablets
	d4p2.	RISPERIDONE 2mg tablets
	d4p3.	RISPERIDONE 3mg tablets
	d4p4.	RISPERIDONE 4mg tablets
	d4p5.	RISPERDAL 1mg tablets
	d4p6.	RISPERDAL 2mg tablets
	d4p7.	RISPERDAL 3mg tablets
	d4p8.	RISPERDAL 4mg tablets
	d4p9.	RISPERIDONE 1mg/mL liquid
	d4pA.	RISPERDAL 1mg/mL liquid

	d4pB.	RISPERIDONE 6mg tablets
	d4pC.	RISPERDAL 6mg tablets
	d4pD.	RISPERDAL 0.5mg tablets
	d4pE.	RISPERDAL CONSTA 25mg powder+solvent for suspension for injection
	d4pF.	RISPERDAL CONSTA 37.5mg powder+solvent for suspension for injection
	d4pG.	RISPERDAL CONSTA 50mg powder+solvent for suspension for injection
	d4pH.	RISPERIDONE 1mg oro-dispersible tablets
	d4pJ.	RISPERIDONE 2mg oro-dispersible tablets
	d4pK.	RISPERDAL QUICKLET 1mg oro-dispersible tablets
	d4pL.	RISPERDAL QUICKLET 2mg oro-dispersible tablets
	d4pM.	RISPERIDONE 0.5mg oro-dispersible tablets
	d4pN.	RISPERDAL QUICKLET 0.5mg oro-dispersible tablets
	d4pO.	RISPERDAL QUICKLET 3mg oro-dispersible tablets
	d4pP.	RISPERDAL QUICKLET 4mg oro-dispersible tablets
	d4pQ.	RISPERIDONE 3mg oro-dispersible tablets
	d4pR.	RISPERIDONE 4mg oro-dispersible tablets
	d4pw.	RISPERIDONE 50mg powder+solvent for suspension for injection
	d4px.	RISPERIDONE 37.5mg powder+solvent for suspension for injection
	d4py.	RISPERIDONE 25mg powder+solvent for suspension for injection
	d4pz.	RISPERIDONE 0.5mg tablets
	d4q..	SERTINDOLE
	d4q1.	SERTINDOLE 4mg tablets
	d4q2.	SERTINDOLE 12mg tablets
	d4q3.	SERTINDOLE 16mg tablets
	d4q4.	SERTINDOLE 20mg tablets

	d4q5.	SERDOLECT 4mg tablets
	d4q6.	SERDOLECT 12mg tablets
	d4q7.	SERDOLECT 16mg tablets
	d4q8.	SERDOLECT 20mg tablets
	d4r..	OLANZAPINE
	d4r1.	OLANZAPINE 5mg tablets
	d4r2.	OLANZAPINE 7.5mg tablets
	d4r3.	OLANZAPINE 10mg tablets
	d4r4.	ZYPREXA 5mg tablets
	d4r5.	ZYPREXA 7.5mg tablets
	d4r6.	ZYPREXA 10mg tablets
	d4r7.	OLANZAPINE 2.5mg tablets
	d4r8.	ZYPREXA 2.5mg tablets
	d4r9.	ZYPREXA VELOTAB 5mg dispersible tablets
	d4rA.	ZYPREXA VELOTAB 10mg dispersible tablets
	d4rB.	ZYPREXA 15mg tablets
	d4rC.	ZYPREXA VELOTAB 15mg dispersible tablets
	d4rD.	ZYPREXA 10mg injection (pdr for recon)
	d4rE.	ZYPREXA VELOTAB 20mg dispersible tablets
	d4rF.	ZYPREXA 20mg tablets
	d4rG.	ZALASTA 2.5mg tablets
	d4rH.	ZALASTA 5mg tablets
	d4rI.	ZALASTA 7.5mg tablets
	d4rJ.	ZALASTA 15mg tablets
	d4rK.	ZALASTA 20mg tablets

	d4rL.	ZALASTA 5mg dispersible tablets
	d4rM.	ZALASTA 10mg dispersible tablets
	d4rN.	ZALASTA 15mg dispersible tablets
	d4rO.	ZALASTA 20mg dispersible tablets
	d4rP.	ZALASTA 10mg tablets
	d4rt.	OLANZAPINE 20mg tablets
	d4ru.	OLANZAPINE 20mg dispersible tablets
	d4rv.	OLANZAPINE 10mg injection (pdr for recon)
	d4rw.	OLANZAPINE 15mg dispersible tablets
	d4rx.	OLANZAPINE 15mg tablets
	d4ry.	OLANZAPINE 5mg dispersible tablets
	d4rz.	OLANZAPINE 10mg dispersible tablets
	d4s..	QUETIAPINE
	d4s1.	QUETIAPINE 25mg tablets
	d4s2.	QUETIAPINE 100mg tablets
	d4s3.	QUETIAPINE 200mg tablets
	d4s4.	QUETIAPINE 25mg+100mg tablets starter pack
	d4s5.	SEROQUEL 25mg tablets
	d4s6.	SEROQUEL 100mg tablets
	d4s7.	SEROQUEL 200mg tablets
	d4s8.	SEROQUEL 25mg+100mg tablets starter pack
	d4s9.	SEROQUEL 150mg tablets
	d4sA.	SEROQUEL 25mg+100mg+150mg tablets starter pack
	d4sB.	SEROQUEL 300mg tablets
	d4sC.	SEROQUEL XL 50mg m/r tablets
	d4sD.	SEROQUEL XL 200mg m/r tablets

	d4sE.	SEROQUEL XL 300mg m/r tablets
	d4sF.	SEROQUEL XL 400mg m/r tablets
	d4sG.	SEROQUEL XL 150mg m/r tablets
	d4ss.	QUETIAPINE 150mg m/r tablets
	d4st.	QUETIAPINE 400mg m/r tablets
	d4su.	QUETIAPINE 300mg m/r tablets
	d4sv.	QUETIAPINE 200mg m/r tablets
	d4sw.	QUETIAPINE 50mg m/r tablets
	d4sx.	QUETIAPINE 300mg tablets
	d4sy.	QUETIAPINE 25mg+100mg+150mg tablets starter pack
	d4sz.	QUETIAPINE 150mg tablets
	d4t..	AMISULPRIDE
	d4t1.	AMISULPRIDE 50mg tablets
	d4t2.	AMISULPRIDE 200mg tablets
	d4t3.	SOLIAN 50mg tablets
	d4t4.	SOLIAN 200mg tablets
	d4t5.	SOLIAN 400mg tablets
	d4t6.	SOLIAN 100mg/mL sugar free oral solution
	d4t7.	SOLIAN 100mg tablets
	d4tx.	AMISULPRIDE 100mg tablets
	d4ty.	AMISULPRIDE 100mg/mL sugar free oral solution
	d4tz.	AMISULPRIDE 400mg tablets
	d4u..	ZOTEPINE
	d4u1.	*ZOTEPINE 25mg tablets
	d4u2.	*ZOTEPINE 50mg tablets
	d4u3.	*ZOTEPINE 100mg tablets

	d4u4.	*ZOLEPTIL 25mg tablets
	d4u5.	*ZOLEPTIL 50mg tablets
	d4u6.	*ZOLEPTIL 100mg tablets
	d4v..	ARIPIPRAZOLE
	d4v1.	ABILIFY 10mg tablets
	d4v2.	ABILIFY 15mg tablets
	d4v3.	ABILIFY 30mg tablets
	d4v4.	ABILIFY 5mg tablets
	d4v5.	ABILIFY 10mg oro-dispersible tablets
	d4v6.	ABILIFY 15mg oro-dispersible tablets
	d4v7.	ABILIFY 1mg/mL oral solution
	d4v8.	ABILIFY 9.75mg/1.3mL solution for injection
	d4vs.	ARIPIPRAZOLE 9.75mg/1.3mL solution for injection
	d4vt.	ARIPIPRAZOLE 1mg/mL oral solution
	d4vu.	ARIPIPRAZOLE 10mg oro-dispersible tablets
	d4vv.	ARIPIPRAZOLE 15mg oro-dispersible tablets
	d4vw.	ARIPIPRAZOLE 5mg tablets
	d4vx.	ARIPIPRAZOLE 30mg tablets
	d4vy.	ARIPIPRAZOLE 15mg tablets
	d4vz.	ARIPIPRAZOLE 10mg tablets
	d4w..	PALIPERIDONE
	d4w1.	INVEGA 3mg m/r tablets
	d4w2.	INVEGA 6mg m/r tablets
	d4w3.	INVEGA 9mg m/r tablets
	d4w4.	*INVEGA 12mg m/r tablets
	d4w5.	XEPLION 50mg suspension for injection prefilled syringe
	d4w6.	XEPLION 75mg suspension for injection prefilled syringe

	d4w7.	XEPLION 100mg suspension for injection prefilled syringe
	d4w8.	XEPLION 150mg suspension for injection prefilled syringe
	d4ws.	PALIPERIDONE 150mg suspension for injection pfs
	d4wt.	PALIPERIDONE 100mg suspension for injection pfs
	d4wu.	PALIPERIDONE 75mg suspension for injection prefilled syringe
	d4wv.	PALIPERIDONE 50mg suspension for injection prefilled syringe
	d4ww.	*PALIPERIDONE 12mg m/r tablets
	d4wx.	PALIPERIDONE 9mg m/r tablets
	d4wy.	PALIPERIDONE 6mg m/r tablets
	d4wz.	PALIPERIDONE 3mg m/r tablets
	d4x..	ASENAPINE
	d4x1.	SYCREST 5mg sublingual tablets
	d4x2.	ASENAPINE 5mg sublingual tablets
	d4x3.	SYCREST 10mg sublingual tablets
	d4x4.	ASENAPINE 10mg sublingual tablets
	d58..	OLANZAPINE PAMOATE
	d581.	ZYPADHERA 210mg powder+solvent for suspension for injection
	d582.	ZYPADHERA 300mg powder+solvent for suspension for injection
	d583.	ZYPADHERA 405mg powder+solvent for suspension for injection
	d58x.	OLANZAPINE 405mg powder+solvent for suspension for injection
	d58y.	OLANZAPINE 300mg powder+solvent for suspension for injection
	d58z.	OLANZAPINE 210mg powder+solvent for suspension for injection
	d4lE.	CLOZAPINE 50mg tablets
	d4lF.	DENZAPINE 200mg tablets
	d4lG.	CLOZAPINE 200mg tablets
	d4m..	REMOXIPRIDE

	d4m1.	REMOXIPRIDE 150mg m/r capsules
	d4m2.	REMOXIPRIDE 300mg m/r capsules
	d4m3.	*ROXIAM 150mg m/r capsules
	d4m4.	*ROXIAM 300mg m/r capsules
	d4p..	RISPERIDONE
	d4p1.	RISPERIDONE 1mg tablets
	d4p2.	RISPERIDONE 2mg tablets
	d4p3.	RISPERIDONE 3mg tablets
	d4p4.	RISPERIDONE 4mg tablets
	d4p5.	RISPERDAL 1mg tablets
	d4p6.	RISPERDAL 2mg tablets
	d4p7.	RISPERDAL 3mg tablets
	d4p8.	RISPERDAL 4mg tablets
	d4p9.	RISPERIDONE 1mg/mL liquid
	d4pA.	RISPERDAL 1mg/mL liquid
	d4pB.	RISPERIDONE 6mg tablets
	d4pC.	RISPERDAL 6mg tablets
	d4pD.	RISPERDAL 0.5mg tablets
	d4pE.	RISPERDAL CONSTA 25mg powder+solvent for suspension for injection
	d4pF.	RISPERDAL CONSTA 37.5mg powder+solvent for suspension for injection
	d4pG.	RISPERDAL CONSTA 50mg powder+solvent for suspension for injection
	d4pH.	RISPERIDONE 1mg oro-dispersible tablets
	d4pJ.	RISPERIDONE 2mg oro-dispersible tablets
	d4pK.	RISPERDAL QUICKLET 1mg oro-dispersible tablets
	d4pL.	RISPERDAL QUICKLET 2mg oro-dispersible tablets

	d4pM.	RISPERIDONE 0.5mg oro-dispersible tablets
	d4pN.	RISPERDAL QUICKLET 0.5mg oro-dispersible tablets
	d4pO.	RISPERDAL QUICKLET 3mg oro-dispersible tablets
	d4pP.	RISPERDAL QUICKLET 4mg oro-dispersible tablets
	d4pQ.	RISPERIDONE 3mg oro-dispersible tablets
	d4pR.	RISPERIDONE 4mg oro-dispersible tablets
	d4pw.	RISPERIDONE 50mg powder+solvent for suspension for injection
	d4px.	RISPERIDONE 37.5mg powder+solvent for suspension for injection
	d4py.	RISPERIDONE 25mg powder+solvent for suspension for injection
	d4pz.	RISPERIDONE 0.5mg tablets
	d4q..	SERTINDOLE
	d4q1.	SERTINDOLE 4mg tablets
	d4q2.	SERTINDOLE 12mg tablets
	d4q3.	SERTINDOLE 16mg tablets
	d4q4.	SERTINDOLE 20mg tablets
	d4q5.	SERDOLECT 4mg tablets
	d4q6.	SERDOLECT 12mg tablets
	d4q7.	SERDOLECT 16mg tablets
	d4q8.	SERDOLECT 20mg tablets
	d4r..	OLANZAPINE
	d4r1.	OLANZAPINE 5mg tablets
	d4r2.	OLANZAPINE 7.5mg tablets
	d4r3.	OLANZAPINE 10mg tablets
	d4r4.	ZYPREXA 5mg tablets
	d4r5.	ZYPREXA 7.5mg tablets
	d4r6.	ZYPREXA 10mg tablets

	d4r7.	OLANZAPINE 2.5mg tablets
	d4r8.	ZYPREXA 2.5mg tablets
	d4r9.	ZYPREXA VELOTAB 5mg dispersible tablets
	d4rA.	ZYPREXA VELOTAB 10mg dispersible tablets
	d4rB.	ZYPREXA 15mg tablets
	d4rC.	ZYPREXA VELOTAB 15mg dispersible tablets
	d4rD.	ZYPREXA 10mg injection (pdr for recon)
	d4rE.	ZYPREXA VELOTAB 20mg dispersible tablets
	d4rF.	ZYPREXA 20mg tablets
	d4rG.	ZALASTA 2.5mg tablets
	d4rH.	ZALASTA 5mg tablets
	d4rI.	ZALASTA 7.5mg tablets
	d4rJ.	ZALASTA 15mg tablets
	d4rK.	ZALASTA 20mg tablets
	d4rL.	ZALASTA 5mg dispersible tablets
	d4rM.	ZALASTA 10mg dispersible tablets
	d4rN.	ZALASTA 15mg dispersible tablets
	d4rO.	ZALASTA 20mg dispersible tablets
	d4rP.	ZALASTA 10mg tablets
	d4rt.	OLANZAPINE 20mg tablets
	d4ru.	OLANZAPINE 20mg dispersible tablets
	d4rv.	OLANZAPINE 10mg injection (pdr for recon)
	d4rw.	OLANZAPINE 15mg dispersible tablets
	d4rx.	OLANZAPINE 15mg tablets
	d4ry.	OLANZAPINE 5mg dispersible tablets
	d4rz.	OLANZAPINE 10mg dispersible tablets

	d4s..	QUETIAPINE
	d4s1.	QUETIAPINE 25mg tablets
	d4s2.	QUETIAPINE 100mg tablets
	d4s3.	QUETIAPINE 200mg tablets
	d4s4.	QUETIAPINE 25mg+100mg tablets starter pack
	d4s5.	SEROQUEL 25mg tablets
	d4s6.	SEROQUEL 100mg tablets
	d4s7.	SEROQUEL 200mg tablets
	d4s8.	SEROQUEL 25mg+100mg tablets starter pack
	d4s9.	SEROQUEL 150mg tablets
	d4sA.	SEROQUEL 25mg+100mg+150mg tablets starter pack
	d4sB.	SEROQUEL 300mg tablets
	d4sC.	SEROQUEL XL 50mg m/r tablets
	d4sD.	SEROQUEL XL 200mg m/r tablets
	d4sE.	SEROQUEL XL 300mg m/r tablets
	d4sF.	SEROQUEL XL 400mg m/r tablets
	d4sG.	SEROQUEL XL 150mg m/r tablets
	d4ss.	QUETIAPINE 150mg m/r tablets
	d4st.	QUETIAPINE 400mg m/r tablets
	d4su.	QUETIAPINE 300mg m/r tablets
	d4sv.	QUETIAPINE 200mg m/r tablets
	d4sw.	QUETIAPINE 50mg m/r tablets
	d4sx.	QUETIAPINE 300mg tablets
	d4sy.	QUETIAPINE 25mg+100mg+150mg tablets starter pack
	d4sz.	QUETIAPINE 150mg tablets
	d4t..	AMISULPRIDE
	d4t1.	AMISULPRIDE 50mg tablets

	d4t2.	AMISULPRIDE 200mg tablets
	d4t3.	SOLIAN 50mg tablets
	d4t4.	SOLIAN 200mg tablets
	d4t5.	SOLIAN 400mg tablets
	d4t6.	SOLIAN 100mg/mL sugar free oral solution
	d4t7.	SOLIAN 100mg tablets
	d4tx.	AMISULPRIDE 100mg tablets
	d4ty.	AMISULPRIDE 100mg/mL sugar free oral solution
	d4tz.	AMISULPRIDE 400mg tablets
	d4u..	ZOTEPINE
	d4u1.	*ZOTEPINE 25mg tablets
	d4u2.	*ZOTEPINE 50mg tablets
	d4u3.	*ZOTEPINE 100mg tablets
	d4u4.	*ZOLEPTIL 25mg tablets
	d4u5.	*ZOLEPTIL 50mg tablets
	d4u6.	*ZOLEPTIL 100mg tablets
	d4v..	ARIPIPRAZOLE
	d4v1.	ABILIFY 10mg tablets
	d4v2.	ABILIFY 15mg tablets
	d4v3.	ABILIFY 30mg tablets
	d4v4.	ABILIFY 5mg tablets
	d4v5.	ABILIFY 10mg oro-dispersible tablets
	d4v6.	ABILIFY 15mg oro-dispersible tablets
	d4v7.	ABILIFY 1mg/mL oral solution
	d4v8.	ABILIFY 9.75mg/1.3mL solution for injection
	d4vs.	ARIPIPRAZOLE 9.75mg/1.3mL solution for injection

	d4vt.	ARIPIPRAZOLE 1mg/mL oral solution
	d4vu.	ARIPIPRAZOLE 10mg oro-dispersible tablets
	d4vv.	ARIPIPRAZOLE 15mg oro-dispersible tablets
	d4vw.	ARIPIPRAZOLE 5mg tablets
	d4vx.	ARIPIPRAZOLE 30mg tablets
	d4vy.	ARIPIPRAZOLE 15mg tablets
	d4vz.	ARIPIPRAZOLE 10mg tablets
	d4w..	PALIPERIDONE
	d4w1.	INVEGA 3mg m/r tablets
	d4w2.	INVEGA 6mg m/r tablets
	d4w3.	INVEGA 9mg m/r tablets
	d4w4.	*INVEGA 12mg m/r tablets
	d4w5.	XEPLION 50mg suspension for injection prefilled syringe
	d4w6.	XEPLION 75mg suspension for injection prefilled syringe
	d4w7.	XEPLION 100mg suspension for injection prefilled syringe
	d4w8.	XEPLION 150mg suspension for injection prefilled syringe
	d4ws.	PALIPERIDONE 150mg suspension for injection pfs
	d4wt.	PALIPERIDONE 100mg suspension for injection pfs
	d4wu.	PALIPERIDONE 75mg suspension for injection prefilled syringe
	d4wv.	PALIPERIDONE 50mg suspension for injection prefilled syringe
	d4ww.	*PALIPERIDONE 12mg m/r tablets
	d4wx.	PALIPERIDONE 9mg m/r tablets
	d4wy.	PALIPERIDONE 6mg m/r tablets
	d4wz.	PALIPERIDONE 3mg m/r tablets
	d4x..	ASENAPINE
	d4x1.	SYCREST 5mg sublingual tablets

	d4x2.	ASENAPINE 5mg sublingual tablets
	d4x3.	SYCREST 10mg sublingual tablets
	d4x4.	ASENAPINE 10mg sublingual tablets
	d58..	OLANZAPINE PAMOATE
	d581.	ZYPADHERA 210mg powder+solvent for suspension for injection
	d582.	ZYPADHERA 300mg powder+solvent for suspension for injection
	d583.	ZYPADHERA 405mg powder+solvent for suspension for injection
	d58x.	OLANZAPINE 405mg powder+solvent for suspension for injection
	d58y.	OLANZAPINE 300mg powder+solvent for suspension for injection
	d58z.	OLANZAPINE 210mg powder+solvent for suspension for injection

15 Case report studies examining sleep in movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Parkinsonism	Tracik et al.[788]	2001	PD (1)	48 hours of continuous PSG, MSLT	PLMS and MSLT were normal, patient presented with irresistible sleep onset and 'sleep attacks' marked with K-complexes
Parkinsonism	Cormican et al.[789]	2004	MSA (1)	Thoracic and abdominal strain-gauge impedance plethysmogram	Presence of CSA
Parkinsonism	Suzuki et al.[790]	2010	MSA (1)	Overnight PSG	Complex SBD, central apnea emerged. No RBD or RLS
Parkinsonism	Tachibana et al.[791]	2004	MSAS (1)	One night of PSG longitudinally over three years	Abnormal movements were observed during RWA. Sleep architecture including NREM/REM cycle was intact, although sleep spindles became scarcer in the third PSG. The percentage of REM sleep (including RWA) in total sleep time remained almost the same (11.9, 21.2, 16.3%), but the ratio of RWA to the whole of REM sleep increased (75.8, 84.7, 100%)
Parkinsonism	Garcia-Sanchez et al.[792]	2016	MSA (1)	PSG, ESS	Reduced REM sleep and sleep efficiency, normal ESS, presence of CSA
Parkinsonism	Moccia et al.[793]	2015	PSP (1)	IRLSSG, PSQI, ESS	RLS diagnosis was fulfilled, impaired sleep quality (10) and EDS (13)
Parkinsonism	Tateno et al.[794]	2011	PSP (1)	EMG	Presented with OSA
Parkinsonism	Lee[795]	1991	PSP (1)	PSG	PSG revealed fragmented sleep architecture, very little SWS and REM sleep and central apnea
Huntington's Disease	Evers et al.[796]	2003	HD (1)	PSG with PLMS index	RLS was found in a family with HD. Family reports revealed some members had RLS and not HD. Patient had a PLMS index of 10
Huntington's Disease	Savva et al.[797]	2009	HD (1)	PSG, IRSLLG	Complaints of daytime sleepiness. PSG confirmed presence of PLMS and suggested that RLS may be an early feature in some HD patients
Huntington's Disease	Banno et al.[798]	2005	HD (1)	Overnight PSG, ESS	OSA during REM sleep – AHI was 6.6 per hour. ESS score was 8
SCA	Shindo et al.[799]	2019	SCA 31 (1)	Overnight PSG	RWA determined by PSG and husband reported patient talking loudly during sleep
SCA	Ghorayeb et al.[800]	2005	SCA3 (1)	Overnight PSG	Abnormal movements occurred during NREM postulated as a parasomnia. PLM were not disclosed by PSG.
SCA	Fukutake et al.[801]	2002	SCA3 (1)	Overnight PSG	Patient reported severe insomnia. PSG showed decreased rates of sleep time and REM stage
SCA	Kapoor et al.[802]	2015	SCA 13 (1)	Overnight PSG	Significantly elevated PLMI, mild OSA and absence of REM sleep, diagnosis of insomnia
Wilson's Disease	Firneisz et al.[662]	2000	WD (1)	PSG	Hypersomnia was confirmed by PSG
Wilson's Disease	Amann et al.[803]	2015	WD (1)	PSG, MSLT, ESS	Patient had an ESS of 13. PSG did not show any abnormalities. The MSLT confirmed diagnosis of hypersomnolence
NBIA	Gore et al.[804]	2016	MPAN (1)	Clinical evaluation	Sleeping 14 hours a day and developed RBD
NBIA	Long et al.[805]	2015	BPAN (1)	Clinical evaluation	Described as a restless sleeper but sleep evaluation was normal
NBIA	Ohba et al.[806]	2014	BPAN (1)	Clinical evaluation	Sleep disturbances were unobserved

NBIA	Endo et al.[807]	2017	BPAN (1)	Clinical evaluation	Showed symptoms of sleep problems
NBIA	Paudel et al.[808]	2015	BPAN (1)	Clinical review	Patient presented with disturbed sleep with early morning awakening
NBIA	Yoganathan et al.[809]	2016	BPAN (1)	EEG, clinical evaluation	Circadian rhythm sleep disorder with fragmented sleep
NBIA	Hoffjan et al.[810]	2016	BPAN (1)	EEG, clinical evaluation	Sleep pattern appeared not to be disturbed
NBIA	Guk et al.[811]	2019	PKAN (1)	PSG	Patient presented with symptoms of OSA, AHI of 16.2/h. AHI was markedly higher during REM sleep (31.4/h). Patient had no PLMS or parasomnia
Tic Disorders	Trajanovic et al.[812]	2004	TS (1)	Longitudinal case report 4yrs, PSG (1999 + 2002)	Report of REM and non-REM parasomnia and PLMS in this patient

Abbreviations: AHI: Apnea Hypopnea Index, BPAN: Beta-propeller protein-associated neurodegeneration, CSA: Central Sleep Apnea, EDS: Excessive daytime sleepiness, EEG: Electroencephalogram, EMG: Electromyography, ESS: Epworth Sleepiness Scale, HD: Huntington's Disease, IRLSSG: International Restless Legs Syndrome Study Group, MPAN: Mitochondrial membrane protein-associated neurodegeneration, MSA: Multiple System Atrophy, MSLT: Multiple Sleep Latency Test, NBIA: Brain Iron Accumulation Disorders, OSA: Obstructive Sleep Apnea, PD: Parkinson's Disease, PKAN: Pantothenate kinase-associated neurodegeneration, PLMS: Periodic Limb Movements during Sleep, PSG: Polysomnography, PSP: Progressive Supranuclear Palsy, PSQI: Pittsburgh Sleep Quality Index, RBD: REM sleep behaviour disorder, REM: Rapid Eye Movement Sleep, RLS: Restless Leg Syndrome, RWA: REM sleep without atonia, SBD: Sleep Breathing Disorders, SCA: Spinocerebellar Ataxia, TS: Tourette's Syndrome, WD: Wilson's Disease.

16 Smaller case studies (≤5) identifying sleep disturbances in movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Parkinsonism	Tison et al.[813]	1995	MSA (2)	PSG	RBD preceded other symptoms and signs of disease. PSG showed little N1 and N2 in one patient
Parkinsonism	Vetrugno et al.[814]	2009	MSA (2)	One night of PSG	Documented status dissociatus. During disease progression RBD diminished but sleep became more abnormal, suggesting the potential progression of RBD into SD
Parkinsonism	Vetrugno et al.[815]	2007	MSA (3)	One night of PSG	All patients had paradoxical breathing during sleep, increased WASO, reduced sleep efficiency and RBD. One patient had RLS with PLMS
Parkinsonism	Hamada et al.[816]	2015	MSA (2)	PSG	Both diagnosed with OSA
Spinocerebellar Ataxia	Dang et al.[817]	2010	SCA1 (2)	PSG, MSLT, ESS	PSG showed moderate OSA in Case 1. Case 2 presented with EDS and a mean sleep latency of 5 minutes on the MSLT
Spinocerebellar Ataxia	Boesch et al.[818]	2006	SCA6 (5) from 3 families	IRLSSG, two nights of PSG	40% reached the criteria for RLS. Increased PLMS index in 80% of patients.
Spinocerebellar Ataxia	Hsu et al.[819]	2016	SCA2 (3) from one family	PSG, ESS, clinical interview to determine insomnia	All cases had snoring and EDS. RLS and RBD detected in one case. Insomnia and EDS significantly improved with use of antidepressants
DRPLA	Licht et al.[820]	2002	DRPLA (3)	Clinical examinations	Severe OSA was reported in two cousins
DRPLA	Kim et al.[821]	2018	DRPLA (5)	PSG	PSG evaluation showed that the patient and his daughters presented with RWA and to various degrees RBD, reduced sleep efficiency and increased PLMS. They had no respiratory related sleep problems
DRPLA	Miyamoto et al.[822]	1996	DRPLA (2)	PSG	PSG revealed an increased percentage of slow wave sleep in both patients (30.2% and 70.4%), with sleep spindles occurring in N3. Sleep apnea was not observed
Wilson's Disease	Tribl et al.[661]	2014	WD (4)	v-PSG RBDQ-HK, RBDSQ, MSQ, PSQI, ESS, BDI	RBD presented as an initial symptom in three of the four cases
Neuroacanthocytosis	Hori et al.[823]	1985	NA (2)	PSG	PSG recordings were characterised by high voltage slow activity during REM, with increased number of awakenings and decreased slow wave sleep. One patient had an average of 40 episodes of predominantly central apnea per night
Neuroacanthocytosis	Dolenc-Grošelj et al.[824]	2005	ChAc (2)	PSG	Sleep apnea, RLS or PLMS were not detected. Increased latency was detected in one patient. Arousals were frequent and sleep efficiency was low. REM sleep was decreased with a prolonged latency in both patients
Neuroacanthocytosis	Weaver et al.[825]	2019	MLS (5)	PSG	A retrospective review, which found that three cases had severe OSA confirmed by PSG.
Neuroacanthocytosis	Ghorayeb et al.[826]	2008	ChAc (3) MLS (2)	PSG, ESS	Mean total sleep time was globally reduced, but mean sleep latency was within normal range. WASO was relatively high and median sleep efficacy was reduced. V-PSG revealed reduction of abnormal movements during sleep, RBD was not observed. Only one patient had abnormal ESS score and MSLT, and OSA
NBIA	Illingworth et al.[827]	2014	PLAN (5)	Clinical reviews, respiratory sleep study	When lights were on at night, patients presented with CSA
NBIA	Blake et al.[828]	2016	PLAN (2)	Clinical review	A sleep study showed one patient had central and OSA

NBIA	Bohlega et al.[829]	2016	PLAN (4); two families (early onset parkinsonism)	Clinical evaluation	One presented with RBD, and all four had unspecified sleep disorders and three had sleep fragmentation
NBIA	Chard et al.[830]	2019	BPAN (3)	Clinical evaluation	One patient had difficulty with sleep and frequent night-time awakenings. A second case had difficulty sleep and wakes frequently throughout the night
NBIA	Verhoeven et al.[831]	2014	BPAN (3)	EEG, clinical evaluation	One patient showed sleep disturbances and nightly incontinence
NBIA	Fantini et al.[832]	2010	PKAN (3)	v-PSG	Reduced total sleep time was seen in two patients with low sleep efficiency. Percentage of N3 was normal to elevated in two patients and absent from one patient. None had apnea (AHI <5). One patient showed mild PLMS, exclusively to NREM. No EMG activity was observed in NREM
Tic Disorders	Müller et al.[833]	1994	TS+RLS (1) RLS (2)	PSG	Mother and son both showing RLS with son also having TS

Key: AHI: Apnea Hypopnea Index, BDI: Beck's Depression Inventory, BPAN: Beta-propeller protein-associated neurodegeneration, ChAc: Chorea-Acanthocytosis, CSA: Central Sleep Apnea, DRPLA: Dentatorubral-pallidoluysian atrophy, EDS: Excessive Daytime Sleepiness, EEG: Electroencephalogram, EMG: Electromyography, ESS: Epworth Sleepiness Scale, IRLSSG: International Restless Legs Syndrome Study Group, MLS: McLeod's Syndrome, MSA: Multiple System Atrophy, MSLT: Mean Sleep Latency Test, MSQ: Mayo Sleep Questionnaire, N3: Non-Rapid Eye Movement Sleep stage 3, NA: Neuroacanthocytosis, NBIA: Brain Iron Accumulation Disorders, NREM: Non-Rapid Eye Movement Sleep, OSA: Obstructive Sleep Apnea, PD: Parkinson's Disease, PLAN: PLA2G6-associated neurodegeneration, PLMS: Periodic Leg Movements during Sleep, PKAN: Pantothenate kinase-associated neurodegeneration, PSG: Polysomnography, PSP: Progressive Supranuclear Palsy, PSQI: Pittsburgh Sleep Questionnaire Index, RBD: REM-sleep Behaviour Disorder, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, RBDQ-HK: REM Sleep Behavior Disorder Screening Questionnaire Hong Kong version, RLS: Restless Leg Syndrome, RWA: REM-sleep Without Atonia, SCA: Spinocerebellar Ataxia, TS: Tourette's Syndrome, v-PSG: Video Polysomnography, WASO: Wake After Sleep Onset, WD: Wilson's Disease.

17 Large case series (>5) identifying sleep disturbances in movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Parkinsonism	Gjerstad et al.[834]	2007	PD (142); follow up of patients from Tandberg et al., (1999)	Stavanger sleepiness questionnaire (self-constructed)	Insomnia was present in 54-60% of patients at three study visits but varied in individuals over time. 83% experienced insomnia at one or more visits over 8 years
Parkinsonism	Yoritaka et al.[835]	2009	PD (150)	Clinical interviews – abnormal sleep movements, urge to move legs and sleep attacks, RBD according to ICSD	54% of PD patients met RBD criteria with 44% reporting it preceded parkinsonism
Parkinsonism	Scaglione et al.[836]	2005	PD (195)	Interviewed for RBD using semi-structured questionnaire, ICSD criteria	33% patients met the criteria for RBD, 27% had RBD onset before PD
Parkinsonism	Poryazova et al.[837]	2013	PD (417)	Questionnaire including items on sleep quality, sleep disorders, RBDSQ, ESS	43% of patients with PD reported RBD and was associated with longer disease duration. 23% reported falling asleep whilst driving. 20% reported RLS
Parkinsonism	Gjerstad et al.[838]	2002	PD (142); follow up of patients from Tandberg et al., (1999)	ESS	30 patients had developed EDS after a four year follow up. Those with EDS had a more rapid decline on the UPDRS score
Parkinsonism	Azmin et al.[839]	2013	PD (113)	IRLSSG criteria	RLS occurred in 10% of PD patients and was associated with younger onset of PD and less advanced disease stage
Parkinsonism	Verbaan et al.[840]	2010	PD (269)	IRLSSG criteria	RLS was present in 11% of patients. RLS severity correlated positively with daytime sleepiness, depressive symptoms, PD severity and motor fluctuations
Parkinsonism	Lee et al.[841]	2009	PD (447)	IRLSSG criteria	16% were diagnosed with RLS, those with RLS had longer duration of PD symptoms and more severe PD
Parkinsonism	Tan et al.[842]	2002	PD (125)	IRLSSG criteria	15% of patients had motor restlessness but none fulfilled the criteria of RLS compared to published control data (0.6%) this was non-significant
Parkinsonism	Peralta et al.[843]	2009	PD (113)	IRLSSG criteria	24% of patients met the RLS criteria, those who did had an earlier onset of PD and were younger
Parkinsonism	Höglund et al.[844]	2019	PD (30)	ESS	A prospective study that investigated EDS overtime. EDS remained stable over 10 years
Parkinsonism	Porter et al.[845]	2008	PD (161)	PDSS, HAM-D	22% had marked sleep disorders, with sleep fragmentation and nocturia being most commonly reported. Disturbances worsened with Parkinson's symptoms
Parkinsonism	Oberholzer et al.[846]	2011	PD (417)	Questionnaire including: ESS, RBDSQ, and items on sleep duration,	9% of PD patients reported sleep walking, 47 out of 417 had ESS ≥10, 57% reported sleep problems. Those who slept walked had higher ESS, longer disease duration and reported more hallucinations and nightmares

				insomnia, sleep latency, snoring, RLS	
Parkinsonism	Pandey et al.[847]	2016	PD (100)	PSQI, ESS, PDQ-39, HAM-A, IDS-SR	50% had poor sleep quality. EDS was only present in 9%. Higher disease severity scores correlated with poorer sleep quality. Patients with poor sleep quality had worse quality of life
Parkinsonism	Gómez-Esteban et al.[848]	2006	PD (70)	PDSS	No increase in EDS, lowest scores were on sleep fragmentation and nocturia. There was a weak correlation between PDSS and disease severity
Parkinsonism	Estrada-Bellmann et al.[849]	2016	PD (52)	NMSS, PDQ-8	76% of PD patients reported sleep disturbances and fatigue, this was the most common NMS. Sleep was associated with worse PDQ-8 scores
Parkinsonism	Zhu et al.[850]	2017	PD (519)	NMSQuest, PDSS, HAM-D	PDSS score was correlated to disease stage. Poor sleep was a predictor of depression. Mean PDSS scores were 117.88 ± 20.53. 65% reported sleep disturbances on the HAM-D
Parkinsonism	Braga-Neto et al.[851]	2004	PD (86)	ESS	53% of patients had insomnia, 50% had RLS, 55% vivid dreams. 72% snoring and 32% had EDS. RLS was more frequent with longer duration of illness
Parkinsonism	Maiga et al.[852]	2016	PD (35)	PDSS, PSQI, ESS	74% of patients had abnormally high PSQI, pains or cramps frequently interrupted sleep, PDSS score increased with disease stage
Parkinsonism	Phattanarudee et al.[853]	2019	PD (160)	ESS, PDSS, subjective information about the presence of sleep attack	Night-time sleep disturbance was prevalent in 47% of patients. Patients with EDS and sleep attacks were most affected by nocturnal disturbances
Parkinsonism	Yu et al.[854]	2013	PD (211)	PSQI, HAM-D24, HAM-A14, FS-14, IRLSSG, The Scale For Outcomes in PD For Autonomic Symptoms for autonomic dysfunction, NMSQuest	65% of PD patients had sleep disturbances. The highest scoring on the PSQI was daytime dysfunction. Depression, restless leg syndrome, autonomic symptoms and fatigue contributed 68.6% of the variance of PSQI score
Parkinsonism	Arnaldi et al.[855]	2016	PD (123)	ESS, PDSS-2, HAM-D	46% of patients had poor sleep based on PDSS-2 score and correlated to PD duration, motor severity, disease stage and ESS scores
Parkinsonism	Palmeri et al.[856]	2019	PD (48)	PDQ-39, ESS, PSQI, BDI, HAM-A	Sleep problems and excessive daytime sleepiness are frequent problems in PD that has a strong influence on cognition and health-related quality of life
Parkinsonism	Zhang et al.[857]	2016	PD (1119)	ESS, PSQI, RLS scale, RBDSQ, FSS, NMS-Quest, HAM-D, HAM-A, PDQ-39	14% reported daytime sleepiness, 65% reported sleep disorders on the PSQI, 23% had clinical RBD, 21% had moderate RLS and 15% had severe RLS
Parkinsonism	Lin et al.[858]	2017	PD (225)	ESS, PSQI, PDSS, PDQ-39	54% were poor sleepers, 26% had EDS which correlated to disease stage
Parkinsonism	Svensson et al.[859]	2012	PD (176)	PDSS, ESS, FQ, SF-36, IRLSSG criteria	Over 1/3 of the cohort reported poor quality sleep. Sleep problems were common. 17% of PD patients had an abnormal PDSS score. 27% had RLS.
Parkinsonism	Hobson et al.[627]	2002	PD (638)	ESS and ISCS	ESS was present in 51% of patients. ESS and ISCS score correlated with disease duration.
Parkinonism	Ondo et al.[860]	2001	PD (320)	ESS, modified NSF, assessed the presence of RLS	ESS score was abnormally high in 50% of patients and correlated with more advanced and longer duration of PD

Parkinsonism	Yliksoki et al.[861]	2015	PD (1447)	Questionnaire based on the BNSQ (including a question on presence of OSA), including ESS, RBDSQ, UNS, ICD-10 for insomnia, IRLSSG	Narcolepsy was suspected in 9% of subjects, RBD in 39%, hallucinations in the evening occurred in 6%, cataplexy symptoms in PD patients
Parkinsonism	Yliksoki et al.[862]	2017	PD (1447)	Questionnaire based on the BNSQ (including a question on presence of OSA), BQ, including ESS, RBDSQ, BDI-SF	33% of patients had short sleep, 21% poor sleep, 34% sleep deprivation, 47% had disrupted sleep, 12% had difficulties falling asleep .44% self-rated poor quality of life and health
Parkinsonism	Melka et al.[863]	2019	PD (155)	PDSS-2 and ESS	All patients reported some sleep problem. Over 43.9% had a PDSS score >18. Median score of ESS was 9, with 77 having possible EDS.
Parkinsonism	Valko et al.[598]	2010	PD (88)	FSS, ESS, BDI	PD patients had 59% fatigue and 48% had EDS. Fatigue patients had higher motor scores, BDI scores and disease stages
Parkinsonism	Sixel-Döring et al.[864]	2011	PD (457)	At least one night of PSG	RBD was found in 46% of patients. Patients with RBD had longer disease duration and advanced disease stages. Presence of RBD related to higher REM sleep and more PLMS
Parkinsonism	Eisensehr et al.[865]	2001	PD (19) Other sleep disorders (273)	Reviewed PSGs from the last three years with at least two nights of PSG, sleep interview: medication and dream content	47% of PD patients had RBD compared to occurring in 4 patients without PD
Parkinsonism	Louter et al.[866]	2014	PD (45)	One night of v-PSG, 8 nights of Actigraphy, ICSD-2 and clinical interview	PSG allowed for a diagnosis of 7 patients with RBD, actigraphy proved a reliable diagnostic tool for RBD in those with a clinical suspicion of RBD. Disease severity was higher in patients with RBD with longer disease duration and more advanced disease stages. 2 patients had OSA, 2 had RLS, 3 had increased PLMS
Parkinsonism	Trotti et al.[589]	2010	PD (55)	Three nights of PSG, ESS, questions about typical night of sleep and daytime symptoms related to sleep	PD patients had similar rates of OSA to published control data
Parkinsonism	Roth et al.[867]	2003	PD with abnormal ESS (24)	Two nights of PSG, MSLT	42% had pathological sleepiness. Patients with sleep episodes had no difference between total sleep time, sleep efficiency, sleep architecture or RLS presence compared to those who did not have episodes
Parkinsonism	Kamble et al.[868]	2019	PD+RBD (31) PD-RBD (25)	PSG, RBDSQ, MSQ	RBDSQ was used to screen and determine whether patients had RBD. PSG was recorded on those with probable RBD, with PSG confirming 25/31 had RBD. PD+RBD had worse MSQ scores than PD patients without RBD.
Parkinsonism	Martinez-Ramirez et al.[869]	2015	PD (55)	One night of PSG	56.6% of patients had OSA, 49.1% had RBD, 24.5% had PLMS, and one had RLS. PSG also confirmed reduced REM sleep and sleep efficiency

Parkinsonism	Joy et al.[870]	2014	PD drug-naïve (30)	Overnight PSG, FSS, ESS, PSQI, NCSDQ, HAM-A	10 patients had impaired PSQI scores, 3 patients had EDS, PSG revealed poor SE in 87% and slow wave sleep was shortened. Respiration was impaired, with 43% having AHI ≥ 5 (predominantly OSA)
Parkinsonism	Norlinah et al.[871]	2009	PD (46)	Overnight PSG, PDSS	36/44 had PSG sleep disorders, 52% had sleep fragmentation, 55% had SRBD and 32% had PLMS. EDS was present in 9% and insomnia reported in 32%
Parkinsonism	Mansour et al.[872]	2013	PD (36)	One night of v-PSG, ESS, PSQI, MSQ, HAM-D	36% of patients were found to have RBD confirmed by PSG. PSG showed longer REM latency and higher PLMI and RDI
Parkinsonism	Stevens et al.[873]	2004	PD (20)	Overnight PSG, MSLT, MWT	MSLT revealed 47% of patients were sleepy, only 26% had abnormal MWT scores. Daytime sleepiness was related to poor sleep quality
Parkinsonism	Di Fabio et al.[874]	2013	PD (30)	One night of v-PSG, RBDSQ, ESS, Sleep Walking Questionnaire, BDI, BAI	RBD was confirmed in 18/30 PD patients, and 5 patients with no history of RBD or sleep walking had RWA
Parkinsonism	Shafazand et al.[875]	2017	PD (66)	Overnight PSG, PSQI, PDSS, AIS, BQ, ESS, PDQ-39, BDI, BAI	46% of patients reported insomnia symptoms, OSA was noted in 47%. Fairly bad to very bad sleep quality was reported by 21% of participants. Sleep quality was a significant determinant of overall health-related quality of life
Parkinsonism	Sobreira-Neto et al.[876]	2017	PD (88)	Overnight PSG, ESS, PSQI, RLS criteria, PDQ-39	97% had sleep disorders. 63% had RBD, 63% OSA, 56% insomnia and 28% had RLS. QoL correlated to PSQI and ESS
Parkinsonism	Sobreira-Neto et al.[877]	2019	PD (88)	v-PSG, PSQI, ESS, IRLSSSG, clinical interviews	OSA occurred in 62.5% of PD patients, those with OSA had less insomnia. PD and OSA patients had a lower percentage of N3 sleep in relation to those without OSA.
Parkinsonism	Monaca et al.[878]	2006	PD (222)	One night of PSG (on 36 patients), MSLT, questionnaire including the ESS, treatment, subjective sleep parameters	43% of patients had ESS scores ≥10 and 7% reported unintended sleep episodes. PSG and MSLT results showed correlation between sleep latency and ESS score
Parkinsonism	Young et al.[879]	2002	PD+EDS (18)	Overnight PSG, ESS, BDI	Mild and severe PD patients slept poorly compared to published control data. They also had decreased sleep efficiency and REM sleep, and increased sleep latency. PSG showed no difference between mild and severe PD
Parkinsonism	Shen et al.[880]	2020	PD+OSA (66) PD-OSA (173)	One night of v-PSG, ESS, FSS, PSQI, HAM-A, HAM-D	239 PD patients were recruited, 66 had OSA (AHI >5) and 173 had no OSA. PD+OSA had increased N1 sleep, wake after sleep onset, ESS scores and decreased cases of RBD.
Parkinsonism	Neikrug et al.[881]	2014	PD (86)	Overnight PSG, ESS, RBDSQ, NMSQuest, MFSI-SF, PDSS, PDQ-39, BDI	36 patients were diagnosed with RBD (based on objective and subjective measures) and 24 had probable RBD. RBD groups reported more depression and fatigue
Parkinsonism	Arnulf et al.[882]	2002	PD (54)	Overnight PSG, MSLT, ESS, interview about sleep disorders	Sleep latency was normal, ESS mean score was abnormal, PLMS were rare (15%) but OSA were frequent (20%)

Parkinsonism	Covassin et al.[883]	2012	PD (45)	One night of PSG, PDSS, ESS, RBDSQ, IRLSSG criteria, PDQ-39	PLMS was observed in PD and compared to published data was higher than healthy elderly. Patients with and without RLMS reported EDS. PLMS was related to PD severity. PLMS was associated with increased subjective measures compared to PLMS absence, objective measures found no difference
Parkinsonism	Chung et al.[884]	2013	PD (128)	PSG and MSLT (38 PD patients), ESS, ISI, FSS, BDI, PDQ-39	OSA was frequently observed in PD patients and was predicted by objective daytime sleepiness. Non-motor symptoms were associated with subjective insomnia. Fatigue was associated with subjective daytime sleepiness
Parkinsonism	Alatriste-Booth et al.[885]	2015	PD (120)	One night of PSG, SCOPA-Sleep Scale, PSQI, ESS, PDSS	From PSG: 61 fulfilled criteria for sleep apnea-hypopnea syndrome, PLMS in 39, RBD in 48 and RWA in 7.
Parkinsonism	Plomhause et al.[886]	2013	PD (57): newly diagnosed treatment naive	Two nights of PSG, MSLT, ESS, RBD according to ICSD	30% met the criteria for RBD. Non-RBD patients had shorter daytime sleep latency than RBD patients. ESS was normal
Parkinsonism	Neikrug et al.[887]	2013	PD (86)	Overnight PSG, RBDSQ, ICSD-2, IRLSSG criteria, ESS, MFSI-SF, PDSS, BDI, NMSQuest, PDQ-39	55% were diagnosed with OSA, 42% with RBD, and 22% with RLS. PLMI were also considered high – only 2 patients were diagnosed with PLMS
Parkinsonism	Zhang et al.[888]	2017	MSA (172)	NMSS, PDQ-39, HAM-D24, HAM-A	NMSS sleep/fatigue was second most determinant of poor quality of life. 87% reported sleep/fatigue symptoms in MSA
Parkinsonism	Vetrugno et al.[889]	2004	MSA (19) OSA (10)	One night of PSG	Increased NREM 1 and 2 sleep and decreased NREM 3 and 4, sleep efficiency was reduced. 42% of MSA had stridor. All MSA patients had RBD and 88% had PLMS
Parkinsonism	Vetrugno et al.[890]	2007	MSA (10) RLS (10)	Two nights of PSG	MSA patients had fragmented sleep, with lower total sleep time, sleep efficiency, percentages of NREM 3 and 4 and REM sleep, and higher REM sleep latency. 6 MSA patients had SBD, and all had PLMS
Parkinsonism	Manni et al.[891]	1993	MSA (10)	PSG	Patients showed fragmented sleep, with reduced REM sleep, 6 patients had SBD, with 3 having OSA and 4 having laryngeal stridor
Parkinsonism	Alfonsi et al.[892]	2016	MSA (17)	Full night of PSG	Nocturnal stridor was detected at PSG, EMG findings showed the severity of breathing abnormalities related to the presence of stridor
Parkinsonism	Silber et al.[893]	2000	MSA (42)	Overnight PSG (29)	Stridor PSG during night: 24/29 had index of >5 PLMS, muscle tone was increased in REM in 20/28 and 17 of these had history of RBD, with 20 patients having an index of >5 per hour on AHI mean 22.4 per hour
Parkinsonism	Flabeau et al.[894]	2017	MSA (30)	Overnight PSG	PSG from 28 patients found 11 had sleep apnea. Sleep apnea was associated with mortality in MSA
Parkinsonism	Plazzi et al.[895]	1997	MSA (39)	At least one night of PSG	27 reported nocturnal paroxysmal episodes, PSG showed 35 had RBD, 6 had OSA, laryngeal stridor in 8 and PLMS in 10.
Parkinsonism	Cochen De Cock et al.[646]	2011	MSA (49)	PSG	RBD was observed in 88% of MSA patients. 31/43 bed partners indicated 81% of patients showed improvement of parkinsonism during RBD
Parkinsonism	Sadaoka et al.[896]	1996	MSA (8) PBVFP (3)	PSG and nasendoscopic PSG	Of the 8 MSA patients 5 had glottic snoring and two were suspected of glottic snoring

Parkinsonism	Shimohata et al.[897]	2007	MSA (21)	PSG, daytime blood gas analysis, pulmonary function tests and fiberopic laryngoscopy	29% of patients experienced daytime sleepiness. 65% fulfilled the criteria of SAS. Sleep architecture revealed decreased slow wave sleep percentage, decreased REM sleep, and sleep efficiency.
Parkinsonism	Tachibana et al.[898]	1997	MSA (21)	Overnight PSG, family interview on sleep history	6 patients self-reported EDS. Total REM sleep time was increased. 19 patients had various movements during REM, 6 patients had OSA and hypopnoea
Parkinsonism	Iranzo et al.[899]	2000	MSA (20)	Overnight PSG, clinical sleep questionnaire	15% had RLS, reduced total sleep time was shown in all patients, with 25% having nocturnal stridor, 40% had OSA, PLMS in 50% and RBD in 90%
Parkinsonism	Stanzani-Maserati et al.[900]	2014	MSA (10)	Overnight PSG, ESS, Interview, BDI	80% of patients complained of sleep fragmentation, 2 patients had abnormal AHI, ESS was normal, sleep efficiency was reduced, and REM latency increased. 9 patients had PLMS
Parkinsonism	Martinez-Rodriguez et al.[901]	2007	MSA (15)	Overnight PSG, MSLT, ESS	ESS scores were normal. MSLT showed normal sleep latency in 4 of 5 patients.
Parkinsonism	Muntean et al.,[902]	2013	MSA-C (11) MSA-P (28)	One night of PSG, PDSS-2	Sleep efficiency decreased in both groups and PLMS and PLMW were high in both groups. RBD was found in 73% of MSA-C and 76% in MSA-P. Almost one-third of the MSA patients of both groups presented features of RLS on v-PSG. No significant difference in the overall subjective quality of night-time sleep was found between the two subgroups
Parkinsonism	Ghorayeb et al.[903]	2005	MSA (22)	PSG and a second PSG if stridor and elevated AHI was present, ESS	15 patients presented with stridor alone or accompanied with apneas, all patients presented with sleep fragmentation, reduced total sleep and sleep efficiency. PLMs in 73% and RBD in 64%
Parkinsonism	Palma et al.[904]	2015	MSA (42)	PSG, Innsbruck RBD inventory, RBD1Q	Sleep questionnaires found 76% reported symptoms suggesting RBD. PSG confirmed 81% patients had signs of RBD
Parkinsonism	Ohshima et al.[905]	2017	MSA (24)	Overnight PSG, ESS	Patients with a worsening of apnea/hypopnea index with time compared to patients with stable results had a shorter disease duration when first recorded suggesting that patients with MSA who develop sleep disordered breathing in the early stages will experience continuous deterioration/progression of the breathing disorders
Parkinsonism	Wang et al.[906]	2019	MSA+RBD (18) MA-RBD (37)	v-PSG, PSQI, ESS, FSS, RBDSQ, HAM-D, HAM-A	None of the sleep parameters significantly differed between MSA patients with or without RBD
Parkinsonism	Ghorayeb et al.[907]	2014	MSA (30)	One night of PSG, ESS, PSQI, IRLSSG, BDI	27% met RLS criteria. Pittsburgh Sleep Quality Index scores were significantly higher in patients with restless legs syndrome than those without (9.3 ± 3.7 vs. 4.8 ± 2.9, $p = 0.00165$). Periodic limb movements were found in 75 % of patients with restless legs syndrome. Restless legs syndrome is more prevalent in multiple system atrophy as compared to the acknowledged prevalence in the general population.
Parkinsonism	Shimohata et al.[908]	2012	MSA (25)	PSG, ESS	Normal ESS score 6.2 ± 0.9, 24% patients presented with EDS. PSG found that sleep efficiency was reduced, reduced NREM3 compared to published normal values. 24 MSA patients fulfilled SDB criteria. Abnormal PLMS in 44%, RLS in 18%
Parkinsonism	Chaithra et al.[909]	2020	PSP (66)	PDSS, HAM-D	One of the most prevalent non-motor symptoms was in the sleep/fatigue domain.
Parkinsonism	Aldrich et al.[910]	1989	PSP (10)	Three nights of PSG	Two subjects had sleep apnea (1 OSA and 1 CSA) and PLMS. Sleep spindles poor or absent in 5 patients. Sleep latency and time awake was longer, sleep efficiency was reduced, N3 and N4 was reduced compared to published norms. Suggestive of insomnia

Parkinsonism	Diederich et al.[911]	2008	PSP (30) CBD (14)	Questionnaire investigating hallucinations and RBD and an interview with six caregivers, one patient and one pair	20% of PSP patients and 7% of CBD patients acted out dreams. RBD symptoms were not linked to disease duration
Parkinsonism	Cooper et al.[912]	2009	PSP (10) CBD (11)	Questioned patients on the presence of photophobia, visual hallucinations and RBD	PSP absent of RBD, one CBD patient had RBD
Parkinsonism	Ghorayeb et al.[913]	2002	MSA (57) PD (62); age-, gender- and disease duration-matched	Structured interview assessing sleep problems	MSA had a higher percentage of patients with sleep disorders; stridor, RBD and sleep complaints. Those with complaints in PD and MSA had longer disease duration, higher mean motor scores and more disabled
Parkinsonism	Munhoz et al.[914]	2014	PD (100) PSP (87) MSA (72) DLB (50) CBD (18); all groups age-, gender- and disease stage-matched	Probable RBD was established by IRLSSG criteria	Probable RBD was found in 58% of PD patients, 82% with MSA, 74% with DLB, 37% with PSP and 5.5% with CBD
Parkinsonism	Matsubara et al.[915]	2018	PD (63) MSA (17) PSP (11)	RLS assessed on IRLSSG criteria, sleep questionnaires, PDSS-2, ESS, NMSS, BDI	RLS criteria met in 12.7% (PD), 5.9% (MSA), 0% (PSP)
Parkinsonism	Olson et al.[916]	2000	PD (25) Dementia without Parkinsonism (7) MSA (14) Narcolepsy (4) Encephalitis (2) PSP (1) Brainstem infarction (1)	Overnight PSG (68) and half nasal positive airway pressure (25)	RBD developed before parkinsonism in 52% of PD patients. One patient with idiopathic RBD developed PD later. RBD preceded onset of MSA in 5 patients.
Parkinsonism	Nomura et al.[917]	2011	PD (49) MSA (16)	Overnight PSG	27% of patients with PD and 69% with MSA had RWA. PLMI scores higher in MSA (68.2 ± 105.4) than those in PD (10.0 ± 25.9)

Parkinsonism	Nomura et al.[918]	2012	PSP (20) PD (93)	Overnight PSG and clinical interview regarding sleep problems: abnormal motor behaviours and dream enactment	PSP had lower TST and sleep efficiency on PSG compared to PD. PSP had lower number of patients with RWA than PD (20% vs 60%). No PSP patients experienced RBD whereas 30 PD patients did
Parkinsonism	Iranzo et al.[919]	2005	MSA (26) PD (45) iRBD (39)	One overnight PSG, clinical interview	MSA compared to PD had higher RWA, PMLI and reduced total sleep time. RBD symptoms was similar across the groups
Parkinsonism	Sixel-Döring et al.[650]	2009	PSP (20) PD (20); age- and cognition-matched	Two nights of PSG, PDSS	PSP patients had lower sleep efficiency compared to PD patients. Seventeen PSP patients and 19 PD patients had RWA. 7 PSP and 13 PD patients had clinical RBD. 11 PSP and 11 PD patients were diagnosed with SDB
Parkinsonism	Baumann et al.[920]	2005	PD (10) DLB (3) MSA (1)	PSG, MSLT, ESS, Actigraphy	PLMS were documented in six patents, abnormal AHI in 7, 2 patients had no REM sleep, MSLT mean sleep latency was 3.5 minutes, abnormal ESS score
Parkinsonism	Ratti et al.[921]	2015	PD (10) DLB (8) MSA (12)	Retrospective PSG analysis, ESS	12 excluded of the remaining 18, 4 had parasomnias (2PD, 2MSA) all had EDS and SRBD. Both MSA patients had high PLMI and one had RLS
Huntington's Disease	Taylor et al.[922]	1997	HD (518)	Postal survey questionnaire	292 responded. 88% reported sleep problems, 62% rated them as 'very' or 'moderately' important contributors to problems
Huntington's Disease	Moser et al.[923]	2017	Juvenile HD (42)	Web-based survey evaluating sleep symptoms	Out of the 33 remaining, sleep problems were the most prevalent reported at 87%, with 48% reporting 'severe' and 40% 'moderate' with most complaints around falling asleep or maintaining sleep
Huntington's Disease	Baker et al.[924]	2016	Pre-HD (35) HD (32)	BDI to evaluate sleep problems (item-16)	Increased sleep disturbances related to worse neuropsychiatric symptom
Huntington's Disease	Videnovic et al.[925]	2009	HD (30)	PSQI, ESS, interviewed for RBD, BDI	77% had abnormal sleep, median global PSQI score was 6. EDS was present in 50% of patients
Huntington's Disease	Antczak et al.[926]	2013	HD (13)	PSQI, ESS, Embletta screening for nocturnal respiration	Abnormal AHI was found in three subjects. PSQI and ESS revealed poor sleep quality and EDS in six and five patients respectively
Huntington's Disease	Piano et al.[927]	2017	HD (30)	Overnight v-PSG PSQI, HDSQ, ESS, BQ, IRLSSG, RBDQ, Bologna questionnaire, ZARS (item 54), BDI	Sleep questionnaires did not correlate to PSG data. EDS in 6 patients, BQ detected "high risk" sleepiness in 7 cases. PSQI above score in 18 subjects, HDSQ found 10 poor sleepers
SCA	Brusse et al.[928]	2011	SCA4 (44) ADCA (31) SCA6 (26) SCA14 (7) SCA1 (5)	PSQI, ESS, FSS, BDI, SF-36	Severe fatigue was present in 69% of all SCA subgroups, 47% had poor sleep quality

			SCA2 (4) SCA7 (3) SCA13 (2) SCA17 (1)		
SCA	Jacobi et al.[929]	2013	SCA1 (82) SCA2 (109) SCA3 (46) SCA6 (27) From 178 families	PSQI, RLS: four diagnostic questions	Median scores on PSQI were normal except in SCA6 non-carriers. No SCA6 patients had RLS, 3 in SCA1, 3 in SCA2 and 3 in SCA3.
SCA	Schöls et al.[930]	1998	SCA1 (6) SCA2 (11) SCA3 (51) SCA6 (21)	Overnight PSG (7 SCA3), standardized questionnaire and IRLSSG criteria	RLS was present in 45% of SCA3 patients, none with SCA1 and 18% of SCA6 patients. PSG revealed prolonged sleep onset latency, reduced N3 and N3 REM sleep and PLMS
SCA	Folha Santos et al.[660]	2018	SCA3 (47)	Overnight PSG, ESS	34% had OSA and 43% had EDS. ESS did not correlate to AHI
SCA	Tuin et al.[931]	2006	SCA2 (8) from five families	Three nights of v-PSG, BDI, PSQI, ESS, interview regarding sleep quality,	Interviews revealed "good" subjective sleep quality, except for one depressed patient. PSQI scores were normal except in depressed patient. PSG revealed long WASO and low sleep efficiency, REM sleep was abnormal in all patients. 3 patients had reduced NREM and increased SWS
SCA	Seshagiri et al.[932]	2018	SCA1 (12) SCA2 (13) SCA3 (9)	Overnight v-PSG, PSQI, ESS	Absent REM sleep states in 69% SCA2, 44% SCA and 8% in SCA1. REM reduction correlated with disease severity. Sleep efficiency was normal. PSQI and ESS mean score was normal
Niemann-Pick Type C	Maubert et al.[933]	2016	NPC (22)	Questionnaires sent to relatives/doctors based on hospital records	27% had sleep disorders
Niemann-Pick Type C	Rangel et al.[934]	2019	NPC (8)	PSG, MSLT, use of ICSD-3, ESS, PSQI, IRLSSG, MEQ, RBDSQ-BR	Four patients had a PSQI indicating poor sleep quality. One patient had sleepwalking and hypersomnia when NPC symptoms started. Four patients showed clinical signs of OSA but only one underwent PSG. One patient had high scores on IRLSSG and one had a mild score. All patients showed reduced or disorganised sleep: lower total sleep time, sleep efficiency and REM. Three had high N3 sleep, and two had reduced REM latency. MSLT was only abnormal in one patient
Neuroacanthocytosis	Danek et al.[935]	2001	MLS (22)	PSG, review of clinical phenotypes	Three patients had sleep apnea, with a PSG describing central and peripheral components of the breathing disorder. One patient had developed insomnia before death
NBIA	Hogarth et al.[936]	2013	MPAN (23)	Medical record review	One patient had RBD
NBIA	Hayflick et al.[937]	2013	BPAN (23)	Medical record review	Sleep abnormalities were noted in six subjects, including abnormal MSLT with shorted sleep latency, abnormal REM sleep, hypersomnolence, and movements during the onset of sleep
NBIA	Nishioka et al.[938]	2015	BPAN (7)	EEG, clinical evaluation	Sleep problems were not prominent, but two patients presented with unspecified problems
Dystonia	Klingelhoefer et al.[431]	2014	CD (102)	Adapted version of NMSQuest for	"yes" difficulties were 60% of falling or staying asleep

				Parkinson's - "yes" or "no" response	
Dystonia	López-Laso et al.[939]	2011	Segawa's disease (14): 7 adult, 7 paediatric from two families	PSQI, BDI	Sleep disturbances were found in four patients; one insomnia, two chronic sleep insufficiency, and one insufficient rest. Two children presented with sleepwalking
Dystonia	Weiss et al.[940]	2017	CD (159)	PSQI, BDI	CD patients showed an improvement in sleep quality and depressive symptoms following botulinum toxin injections
Dystonia	Wagle Shukla et al.[693]	2016	Generalised dystonia (9) Segmental dystonia (18) CD (39) Cranial dystonia (21) Other (4)	FSS, ESS, MFI, PDSS, BDI	Moderate to severe fatigue was presented in 43% of the cohort, 7% had EDS and other sleep disturbances 26% (PDSS). FSS and MFSI correlated significantly with health-related quality of life and had a negative impact even when controlled for comorbid depression
Dystonia	Sforza et al.[336]	1991	BSP and Meige's syndrome (10)	PSG over three nights	Number of spasms per hour decreased during the night, then gradually increased, particularly before waking. A reduction in REM sleep and sleep efficiency and an increase in number of awakenings was present. Patients with a high index of spasm in awake state exhibited a greater number of awakenings, poorest sleep efficiency and amount of stage REM
Dystonia	Silvestri et al.[334]	1990	BSP (1) Meige's syndrome (6)	PSG for at least two nights	Abnormal movements were still present in patients with blepharospasm, but decreased in frequency and amplitude in all sleep stages, especially REM
Dystonia	Van Hove et al.[680]	2006	Segawa's disease (22), from three families	PSG, MSLT, PSQI, ESS, structured interview	EDS, difficulty in sleep onset and maintenance, frequent nightmares were present in 55% of patients. All patients had pathological PSQI scores
Essential Tremor	Huang et al.[941]	2020	ET (280)	Medical records	121 patients were reclassified as having ET-plus, those with ET-plus showed significantly probable RBD
Essential Tremor	Lacerte et al.[942]	2014	ET (46)	RBDSQ	43.5% of ET patients possibly suffered from RBD, compared to estimates of 0.5% in the general population
Essential Tremor	Barbosa et al.[943]	2017	ET (92)	RBDSQ	14 ET patients had RBD. Those with RBD had higher automatic symptoms scores
Essential Tremor	Rohl et al.[682]	2016	ET (96)	PSQI, ESS	PSQI scores did not differ between ET patients classified with normal cognition, mild cognitive impairment or dementia. ESS scores were highest in ET patients with mild cognitive impairment, followed by dementia and lastly ET and normal cognitive impairment
Essential Tremor	Ondo et al.[944]	2006	ET (100) RLS (68)	IRLSSG	RLS was diagnosed in 33 ET patients
Essential Tremor	Salsone et al.[945]	2019	ET (55)	PSG, RBD1Q	Ten ET patients had PSG-confirmed RBD

Benign Hereditary Chorea	Iodice et al.[946]	2019	*NKX2* (7)	PSQI, ESS (adult and paediatric), a single RLS question (adult and paediatric), BQ, SDSC, clinical evaluation for sleep quality and sleep disorders	Two children and one adult (43%) displayed possible RLS symptoms consistent with diagnosis, no other sleep disorders were identified. Chorea tended to improve gradually with age
Tic Disorders	Teive et al.[947]	2001	TS (33) Chronic tics (10) Transitionary (1)	Retrospective analysis of hospital records	18 patients had sleep disorders (unspecified)
Tic Disorders	Freeman et al.[948]	2007	TS (3500)	Clinical reports	Sleep problems were twice as common in comorbid TS than in TS only. About 25% of children reported sleep problems, increasing to 65% with comorbid ADHD
Tic Disorders	Lipinski et al.[949]	1997	TS (32)	Semi structured interview to evaluate sleep patterns and RLS	A frequency of 59% of RLS was found
Tic Disorders	Barabas et al.[950]	1984	TS (57) Seizure disorders (57)	Questionnaire	TS had higher rates of somnambulism (17.5%) compared to children with learning difficulties (3.5%) and children with seizure disorders (1.7%)
Tic Disorders	Lespérance et al.[951]	2004	TS (144)	IRLSSG	RLS was present in 10% of TS
Tic Disorders	Wand et al.[952]	1993	TS (446)	Self-reported questionnaire	In ages 6-17: Problems getting to sleep – often 29.7%, sometimes 36.7% Problems staying asleep – often 9.3%, sometimes 22.0% Sleep walking – often 4.7%, sometimes 18.8%
Tic Disorders	Mol Debes et al.[953]	2008	TS (314)	CBCL (sleep items)	17% of the children had a score of more than 6 on the items on the Child Behaviour Checklist that deal with sleep disturbances
Tic Disorder	Groth et al.[954]	2017	TS (314)	Sleep items from CBCL on two occasions 6 years apart	Sleep disturbance increased significantly with age
Tic Disorder	Storch et al.[955]	2009	TS/CTD (56)	CBCL (6 items), MASC (1 item)	80.4% experiencing at least one SRP and 19.7% experiencing four or more. Children with a comorbid anxiety disorder experienced significantly more sleep related problems ($p<0.001$)
Tic Disorders	Ghosh et al.[956]	2014	TS (48) TS+ADHD (75)	Standardised questionnaire during interview	65% had sleep disorders (coded for by Diagnostic and Statistical Manual of Mental Disorders 5th Edition) irrespective of comorbid ADHD. Trouble initiating and maintaining sleep. Ritualistic behaviours before sleep, periodic limb movements, sleepwalking, sleep talking, and vivid nightmares. Significant difficulty waking up, feeling unrefreshed after sleep, and excessive daytime sleepiness
Tic Disorders	Jankovic et al.[957]	1987	TS (112)	PSG (34)	18 patients had reduced REM sleep and 23 had motor tics in all stages

Mixed	Ghika et al.[958]	2015	ET (121) PD (54); developed after ET	Self-reports assessing RBD and RLS	ET patients had significantly more cases of RLS (34.8%) and significantly fewer cases of RBD compared to PD patients
Mixed	Walter et al.[959]	2003	ET (56) PD (85) TS (118)	IRLSSG	1.7% of TS had RLS, ET patients had the highest percentage of RLS with 5.4% and 4.7% of PD patients had RLS. All patients compared to the normal population
Mixed	Puschmann et al.[960]	2011	ET (16) PD (8) RLS (13) all from one family	IRLSSG	A prominent overlap of RLS, PD or ET was seen across 5 generations of a family
Mixed	Miller et al.[961]	2007	ET (53) PD (354) Dystonia (83)	BDI	The highest symptoms were insomnia (57.4%) and fatigability (79.4%). 56.6% of ET patients reported insomnia and 77.4% fatigability
Mixed	Giorelli et al.[962]	2014	ET (21) PD (31)	NMSQuest	PD patients had an increased number of patients who experienced vivid dreams and acting out during dreams compared to ET patients
Mixed	Giorelli et al.[963]	2014	ET (20) PD (31)	NMSQuest	After a one-year follow up PD non-motor symptoms complaints decreased: insomnia and RLS, whereas complaints of daytime sleepiness increased. ET patients reported reduction in RLS. PD patients exhibited higher symptoms of RBD (10/31) than ET (1/21)
Mixed	Kwon et al.[964]	2015	ET (28) PD (24)	RBD symptoms queried with partner, NMSS	PD patients had significantly more RBD-like symptoms than ET patients. None of the ET patients had RLS, but 4 patients with ET+PD did
Mixed	Louis et al.[965]	2016	ET+PD (27) PD (35) ET (109)	ESS, PSQI	Patients with ET+PD had significantly higher ESS scores than ET and PD alone
Mixed	Silvestri et al.[966]	1995	HD (6) TS (9) NA (6)	Two nights of PSG	HD patients had reduced total sleep time, and very low sleep efficiency and a very high WASO. REM was absent in two patients and reduced in four (mean 14.9%) with reduced REM density. NA patients had decreased frequency, amplitude and duration of abnormal movements. Decreased total sleep time and increased WASO was noted. N1 was increased in all patients, and N2 was globally reduced. REM latency was reduced in two patients

Key: ADHD: Attention deficit hyperactivity disorder, AHI: Apnea Hypopnea Index, AIS: Athens Insomnia Scale, BDI(SF): Beck's Depression Inventory (Short Form), BNSQ: Basic Nordic Sleep Questionnaire, BPAN: Beta-propeller protein-associated neurodegeneration, BSP: Blepharospasm, BQ: Berlin Questionnaire, CBCL: Child Behaviour Checklist, CBD: Corticobasal Degeneration, CD: Cervical Dystonia, ChAc: Chorea-Acanthocytosis, CSA: Central Sleep Apnea, CTD: Chronic Tic Disorder, DLB: Dementia with Lewy Bodies, EDS: Excessive Daytime Sleepiness, EEG: Electroencephalogram, EMG: Electromyography, ESS: Epworth Sleepiness Scale, ET: Essential Tremor, FS-14: Fatigue Scale 14 items, FSS: Fatigue Severity Scale, FQ: Fatigue Questionnaire, GQS: General Questionnaire for Sleep, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HD: Huntington's Disease, HDSQ: Huntington's Disease Sleep Questionnaire, ICSD: International Classification of Sleep Disorders, IDS-SR: Inventory of Depression Symptomatology Self-Report, iRBD: Idiopathic REM-sleep Behaviour Disorder, IRLSSG: International Restless Legs Syndrome Study Group, ISI: Insomnia Severity Index, ISCS: Inappropriate Sleep Composite Score, MASC: Multidimensional Anxiety Scale for Children, MEQ: Morningness–eveningness Questionnaire, MFI: Multidimensional Fatigue Inventory, MFSI-SF: Multidimensional Fatigue Symptom Inventory Short Form, MLS: McLeod's Syndrome, MPAN: Mitochondrial membrane protein-associated neurodegeneration, MSA: Multiple System Atrophy, MSA-C: Multiple System Atrophy Cerebellar Type, MSA-P: Multiple System Atrophy Parkinsonian Type, MSLT: Mean Sleep Latency Test, MSQ: Mayo Sleep Questionnaire, MWT: Maintenance of Wakefulness Test, N3: Non-Rapid Eye Movement Sleep stage 3, NA: Neuroacanthocytosis, NBIA: Brain Iron Accumulation Disorders, NCSDQ: NIMHANS comprehensive sleep disorder questionnaire, NMSQuest: Non-Motor Symptoms Questionnaire, NMSS: Non-Motor Symptoms Scale, NPC: Niemann-Pick Type C, NREM: Non-Rapid Eye Movement Sleep, NSF: National Sleep Foundation Sleep Survey, OSA: Obstructive Sleep Apnea, PD: Parkinson's Disease, PDSS: Parkinson's Disease Sleep Scale, PDQ-8/39: Parkinson's Disease Questionnaire, PLAN: PLA2G6-associated neurodegeneration, PLMI: Periodic Leg Movements Index, PLMS: Periodic Leg Movements during Sleep, PKAN: Pantothenate kinase-associated neurodegeneration, PSG: Polysomnography, PSP: Progressive Supranuclear Palsy, PSQI: Pittsburgh Sleep Questionnaire Index, RBD1Q: REM-sleep Behaviour Disorder Single-Question Screen,

RBD: REM-sleep Behaviour Disorder, RBDSQ: REM Sleep Behaviour Disorder Screening Questionnaire, RBDSQ-BR: REM-sleep Behaviour Disorder Screening Questionnaire Brazilian Portuguese version, RBDQ-HK: REM-sleep Behaviour Disorder Screening Questionnaire Hong Kong version, RDI: Respiratory Disturbance Index, RLS: Restless Leg Syndrome, RWA: REM-sleep Without Atonia, SCA: Spinocerebellar Ataxia, SCOPA-Sleep: Scales for Outcomes in Parkinson's Disease in Sleep, SDSC: Sleep Disturbance Scale for Children, SRBD: Sleep Related Breathing Disorders, TS: Tourette's Syndrome, UNS: Ullanlinna Narcolepsy Scale, v-PSG: Video Polysomnography, WASO: Wake After Sleep Onset, ZARS: Zung Self-Rating Anxiety Scale, ZDRS: Zung Self-Rating Depression Scale.

18 Case control studies identifying sleep disturbances in movement disorders

Disorder	Author	Year	Cohort	Assessment	Outcome
Parkinsonism	Factor et al.[967]	1990	PD (78) HC (43): elderly	Questionnaire regarding sleep initiation, sleep maintenance parasomnias and daytime somnolence, and the effect of sleep on motor symptoms	67% of PD patients experienced difficult with sleep initiation compared to 54% of elderly controls. Those with PD had increased awakenings than controls
Parkinsonism	Smith et al.[968]	1997	PD-spouse pairs (153) HC (103)	Self-ratings of sleep disturbance	Mean ratings of 'poor sleep' were higher in PD-spouse than controls
Parkinsonism	Tandberg et al.[969]	1999	PD (245) Patients with diabetes mellitus (100) HC (100): elderly	Interviewed, questionnaire to assess daytime somnolence, use of sleep medication and nocturnal sleep problems	16% of PD patients had EDS which was significantly higher than patients with diabetes and HC
Parkinsonism	Pal et al.[970]	2004	PD (40) Care givers (30)	PSQI, GQS (self-designed), ZDRS, ZARS	Only 9% of care givers complained of sleep disturbances. PSQI showed 84% of PD patients were poor sleepers, predominant complaints were sleep disturbances and sleep quality and efficiency. 100% of patients complained of sleep disturbances
Parkinsonism	Calzetti et al.[971]	2009	PD (118) HC (110); age- and gender-matched	IRLSSG criteria	13% of PD patients compared to 6% of controls reported previously suffering RLS, however, this reach statistical significance
Parkinsonism	Krishnan et al.[972]	2003	PD (126) HC (128); age- and gender-matched controls	Predesigned questionnaire, interviewed for RLS using IRLSSG criteria, ESS, JHRLS	RLS present in 8% of PD cases vs 0.8% of controls. Those with RLS had higher prevalence of depression. Only 2/10 patients had abnormal ESS. 90% of patients with RLS showed delayed sleep onset
Parkinsonism	Hagell et al.[973]	2016	PD (149) HC (53); age-matched	SCOPA-SLEEP	Daytime sleepiness is less severe and common in HC compared to PD
Parkinsonism	Högl et al.[974]	2003	PD (99)	ESS	ESS revealed significantly increased daytime sleepiness compared to controls. 33% of PD patients had scores ≥10 and 11% of controls.

			HC (44); age-matched		
Parkinsonism	Brodsky et al.[975]	2003	PD (101) HC (100); age-matched	ESS	EDS was reported in 76% of patients compared to 47% of controls, 41% had scores ≥10 compared to 19% of controls
Parkinsonism	Rana et al.[976]	2018	PD (100) HC (100); age- and gender-matched	PSQI, IRLSSG criteria	PD patients had higher global scores compared to HC on PSQI and significantly more patients with RLS (27%) in PD than controls (6%). Poor sleep was related to greater pain severity and interfering pain
Parkinsonism	van Hilten et al.[977]	1993	PD (90) HC (71); age-matched	ESS	ESS was similar in both groups. 81% of PD patients and 92% of controls reported sleep disturbances
Parkinsonism	Suzuki et al.[978]	2012	PD (93) HC (93); age- and gender-matched	PDSS-2, BDI-2, PSQI, ESS, PFS, PDQ-39	PD patients had impaired PDSS-2, ESS, BDI-2 and PFS scores compared to HC. RLS presence was not different between groups
Parkinsonism	Abe et al.[979]	2005	PD (64) HC (60); age- and sex-matched	PDSS	PDSS scores in PD groups were significantly different from controls, suggesting more sleep disturbances in PD
Parkinsonism	Kumar et al.[980]	2002	PD (149) HC (115); age-matched	Questionnaire on experiences of night-time sleep and items taken from: ESS, the Case Western Reserve Health Sleep Study Questionnaire	42% of PD patients compared to 12% of controls reported sleep problems. Insomnia (32%), nightmares (32%) and EDS (15%) were seen more in PD compared to 5%, 5% and 6% respectively in controls. EDS correlated with disease stage
Parkinsonism	Kay et al.[981]	2018	PD (50) HC (48); age-, race-, gender- and education-matched	PSQI, ISI, BDI-2	PD patients had poorer sleep quality on the PSQI, higher rates of sleep disturbances and were more likely to report sleeping more than usual on the BDI-2, they also had higher ISI total scores. ISI scores and sleeping less than usual were associated with depression
Parkinsonism	Telarovic et al.[982]	2015	PD (110) HC (110)	PSQI, ESS, PDSS, PDQ-8/39	Median PSQI scores was three times higher than control group. The most common sleep disturbance was fragmented sleep (38%) and nocturia (38%). Sleep significantly affected QoL
Parkinsonism	Fabbrini et al.[983]	2002	De novo PD (25) Treated PD (50)	ESS, PSQI	ESS and PSQI scores were not different between de novo PD and controls, but higher in treated PD. ESS scores may be explained by treatment effect

			HC (25); age- and gender-matched		
Parkinsonism	Videnovic et al.[595]	2014	PD (20) HC (15) age-matched	ESS, PSQI, BDI	PSQI was the same in both groups (n.s.). ESS scores were higher in PD group than controls
Parkinsonism	Gjerstad et al.[984]	2011	De novo PD (200) HC (173); age- and gender-matched	PDSS, IRLSSG criteria, semi-structure interview	13% of PD patients vs 7% of controls met the criteria for RLS
Parkinsonism	Sanjiv et al.[985]	2001	PD (160) HC (40)	ESS	ESS scores were significantly lower in the control group compared to four groups of PD based on medication
Parkinsonism	Verbaan et al.[986]	2008	PD (420) HC (150); age- and gender-matched	SCOPA-Sleep, BDI	PD patients had significantly more EDS 43 vs 10% and excessive night-time sleep problems 27 vs 9% or used sleep medication 17 vs 12%
Parkinsonism	Goulart et al.[987]	2009	PD (50) HC (50); geriatric	FSS, ESS	Fatigue was reported by 70% of patients compared to 22% of controls, with 20 of the 35 PD patients having fatigue and depression. ESS scores did not differ between groups
Parkinsonism	Suzuki et al.[988]	2007	PD (188) HC (144)	PDSS-2, ZDRS	PD patients had more severe sleep disorders than controls according to PDSS scores. Differences in PDSS scores were observed between disease stages
Parkinsonism	Ferreira et al.[989]	2006	PD (176) HC (174)	ESS, PSQI	27% of PD patients reported sleep attacks compared to 32% of controls. They occurred more frequently and required more attention in PD patients. More patients had abnormal ESS and poor sleep quality
Parkinsonism	Chotinaiwattarakul et al.[990]	2011	PD (134) HC (94)	BQ, ESS, PDSS	49% of PD patients were at high risk for a SRBD compared to 35% of controls
Parkinsonism	Nomura et al.[991]	2006	PD (165) HC (131); age- and gender-matched	PSQI and RLS diagnosis via clinical interview (IRLSSG criteria)	PSQI scores did not differ. 2.3% of controls met the diagnosis criteria for RLS compared to.12% of PD patients. Those with RLS showed significantly higher PSQI scores than PD patients without RLS
Parkinsonism	Kataoka et al.[992]	2020	PD (157) HC (1101)	Two+ consecutive nights of Actigraphy	Sleep efficiency, wake after sleep onset and sleep fragmentation was significantly lower in patients in late stage PD compared to controls. Total sleep time and sleep onset latency were significantly shorter in patients with late- and early-stage PD compared to controls.
Parkinsonism	Stavitsky et al.[499]	2010	PD (30) HC (14)	Actigraphy, ESS, PDSS, sleep diary	Actigraphy data showed sleep efficiency and total sleep time was reduced, and increased sleep fragmentation in PD compared to HC. PD group had higher ESS scores than HC. Some subjective measures correlated to actigraphy data
Parkinsonism	Giganti et al.[993]	2013	De novo PD (18) HC (18); age-matched	Actigraphy for three consecutive days, MEQ	PD patients had higher sleepiness than controls at awakening and in the early afternoon

Parkinsonism	Prudon et al.[994]	2014	PD (106); early stages of disease HC (99); age-matched	ESS, PSQI, MSQ, NMSQuest, home monitoring sleep respiration (Embletta), three nights of Actigraphy, sleep diaries	Sleep questionnaire scores were the same between participants. Based on diaries PD patients had more daytime naps. PLMS were increased in PD. Otherwise; subjective and objective sleep disturbances were minimal between groups
Parkinsonism	Maria et al.[995]	2003	PD (15) HC (15)	Full night of PSG	9 PD patients met the criteria for OSA and 1 for CSA – all had reduced REM percentage sleep.
Parkinsonism	Sixel-Döring et al.[996]	2016	PD (113) HC (102)	PSG	De novo baseline compared to a two year follow up showed patients with PD had increased RBD from 25% to 43%, whereas, HC had an increased from 2% to 4%, although this did not reach statistical significance
Parkinsonism	Ferri et al.[997]	2012	PD (27) HC (19)	PSG	Patients had a reduced total sleep time and sleep efficiency, increased WASO, reduced N2 percentage, and increased RWA compared to controls
Parkinsonism	Christensen et al.[998]	2014	PD+RBD (15) PD-RBD (15) iRBD (15) HC (15)	At least one night of PSG	Sleep spindles in PD+RBD were significantly lower than control groups in N2, N3
Parkinsonism	Christensen et al.[999]	2015	PD (15) HC (15); age- and gender-matched	PSG	PD patients showed significantly different sleep spindles from controls, in terms of duration, amplitude, density and frequency
Parkinsonism	Bunner et al.[1000]	2002	de novo PD (9) HC (10)	PSG	There were no significant differences in the conventional sleep parameters between de novo patients with PD and controls. After medication was started N1 sleep and the number of awakenings increased significantly
Parkinsonism	Cai et al.[1001]	2019	PD (27) HC (20)	PSG	REM sleep latency, percentage REM, sleep efficiency, total sleep time and N3 was reduced in PD patients compared to controls
Parkinsonism	Apps et al.[1002]	1985	PD (12) HC (12)	PSG	Patients had more frequent wakes than controls and spent a longer time awake, this was associated with a shorter duration of REM sleep in PD. Six patients had REM sleep for less than one minute. Respiratory rate was greater in the control group during REM sleep
Parkinsonism	Cesari et al.[1003]	2018	PD-RBD (25) PD+RBD (29) HC (27) iRBD (29) PLMD (36)	PSG	PD+RBD had higher PLMS/h than controls. Both PD groups had significantly reduced sleep efficiency and increased REM sleep latency, reduced percentage N2 sleep, PD-RBD had increased N3 percentage and PD+RBD had reduced N3 sleep compared to controls
Parkinsonism	Palma et al.[1004]	2013	PD (33) HC (29); age- and gender-matched	One night of PSG	No differences in sleep parameters were noted between the two groups, there was also no differences in AHI and PLMS
Parkinsonism	Puligheddu et al.[1005]	2014	PD (44)	PSG	PD patients having drug therapy had reduced N2 sleep compared to controls, and PD patients taking therapy had reduced N3 sleep compared to PD patients without treatment

			HC (18); age-matched		
Parkinsonism	González-Naranjo et al.[1006]	2019	PD (77) HC (20)	PSG	Patients showed reduced N2, N3 and REM sleep stages compared to controls, and increased sleep wakefulness
Parkinsonism	Happe et al.[1007]	2004	PD (12) HC (10)	One night of PSG	There was no difference in sleep spindles in PD and controls
Parkinsonism	Wailke et al.[1008]	2011	PD (32) HC (16); age-matched	PSG	Compared to controls, patients with PD had decreased total sleep time, REM sleep and N3
Parkinsonism	Priano et al.[1009]	2019	PD (31) HC (34); age-matched	Two nights of PSG	PD patients showed significant increase in sleep onset latency, wake after sleep onset, increase N2 sleep, and a decrease in sleep efficiency and N3 sleep. PLM index was increased compared to controls
Parkinsonism	Wetter et al.[1010]	2001	de novo PD (17) HC (10)	PSG	There was no difference in sleep architecture and PLM between both groups
Parkinsonism	Amato et al.[1011]	2018	PD (36) HC (7); age-matched	One night of PSG and 7 nights of Actigraphy	6 PD patients had RBD/RWA. Sleep architecture correlated with disease duration, including total sleep time, sleep efficiency and slow wave sleep
Parkinsonism	Bolitho et al.[1012]	2014	PD (29); 13 unmedicated and 16 medicated HC (27); age-matched	Overnight PSG, 14 nights of Actigraphy	Sleep onset latency was lower in unmedicated PD compared to medicated and controls
Parkinsonism	Zhang et al.[1013]	2019	PD+RBD (12) iRBD (15) HC (23); age-, gender- and education-matched	Overnight v-PSG, SCOPA-Sleep	PD+RBD patients had an increased in N1, decreased N2 and N3 percentage and higher PLMI than healthy controls
Parkinsonism	Wienecke et al.[1014]	2012	Advanced PD (10) Early/drug naïve (5) HC (10); age-matched	PSG, ESS, questions relating to RBD and sleep paralysis	Advanced patients were significantly sleepier than controls and early PD patients on MSLT, sleep apnea and PLMS was not significantly different
Parkinsonism	Mariotti et al.[1015]	2015	PD+RBD (49) PD-RBD (36) HC (3)	Two consecutive nights of v-PSG, dream content was analysed, PSQI, ESS	No differences were seen in PSG scores, with the exception of atonia index which was elevated in PD+RBD

Parkinsonism	Rye et al.[1016]	2000	PD (27) HC (13)	One night of PSG, MSLT	PD patients as a group were not sleepier than controls, MLST on the first day were non-significant. But patients had considerable MSLT variability and sleepiness was common (30% ≤ min)
Parkinsonism	Placidi et al.[1017]	2008	de novo PD (12) HC (12); age- and gender-matched	Two nights of PSG, ESS	PD patients had lower sleep efficiency, increased WASO compared to controls, but no other sleep macrostructure differences at baseline. After the introduction of medication, patients had a reduction in N3 sleep
Parkinsonism	Imbach et al.[1018]	2016	PD (70) HC (64); age- and gender-matched	v-PSG, ESS	On PSG only arousal index was increased, ESS was also increased
Parkinsonism	Schroeder et al.[1019]	2016	PD (81) HC (31)	PSG, PDSS, ESS, NMSQuest,	Only REM density was decreased in comparison to controls. No other PSG parameters were
Parkinsonism	Margis et al.[1020]	2015	PD drug-naïve (8) HC (9)	PSG, PSQI, ESS, BDI	No differences in PSG sleep parameters, but elevated PSQI scores in PD patients compared to controls
Parkinsonism	Diederich et al.[593]	2005	PD (49) HC (49); age-, gender-, and AHI-matched	Retrospective one of night PSG analysis	43% of PD patients had SAS with 7 having severe SAS. PD patients had more deep sleep and nocturnal awakenings than controls
Parkinsonism	Gagnon et al.[1021]	2002	PD (33) HC (16); age- and sex-matched controls	One night of PSG, structured clinical interview – presence of motor events during sleep and information from bed partner	PSG increased the sensitivity diagnosis of RBD. 33% of patients met the criteria of RBD and none of the controls met criteria. Patients with PD (58%) had more RWA than controls (6%) and nearly 2/3 of patients had EMG activity during at least 20% of total REM sleep
Parkinsonism	Sixel-Döring et al.[1022]	2014	PD (158) – newly diagnosed and medication naïve HC (110); age-, gender- and education-matched controls	Two nights of PSG, RBD defined by ICSD-2, RBDSQ	RBE was detected in 51% of PD patients and 15% of HC. RBD in 25% of all patients and 2% of controls
Parkinsonism	Gagnon et al.[1023]	2004	PD+RBD (7) PD-RBD (8) HC (15)	PSG, ESS	No difference between groups were found in PSG variables

Parkinsonism	Arnaldi et al.[1024]	2016	PD+RBD (10) PD-RBD (10) iRBD (10) HC (10)	PSG, ESS	Both PD groups had worsened sleep efficiency and decreased total sleep time compared to controls. PD+RBD patients had lower percentage N3 than controls and higher sleepiness scores than controls. No difference in AHI, N1 and REM sleep were observed between groups
Parkinsonism	Zhong et al.[1025]	2013	PD (12) HC (11)	Two nights of PSG, RBDSQ	No differences in PSG sleep parameters compared to controls. Five patients had self-reported RBD compared to no controls, four of these demonstrated RWA on PSG
Parkinsonism	Happe et al.[1026]	2005	PD (17) HC (62); age-matched	Two nights of PSG, PSQI, two weeks of a sleep log, SSA	PD patients showed reduced subjective sleep, quality of time awake, decreased sleep duration and reduced sleep efficiency compared to controls. Objective and subjective ratings were impaired in PD patients
Parkinsonism	El-Senousy et al.[1027]	2012	PD (24) HC (10)	Overnight PSG, PDSS	Sleep disturbances correlated to disease duration and severity. PD patients had increased AHI, worse PDSS scores, increased sleep latency, reduced sleep efficiency, reduced REM sleep compared to controls
Parkinsonism	Diederich et al.[1028]	2013	PD (33); early stages of disease HC (37); age-matched	One night of PSG, PDSS	Total sleep time, sleep efficiency, awakenings, PLM, arousal and apnea/hypopnea were similar in both groups. PD patients had reduced REM sleep. PDSS scores were lower in PD than control group
Parkinsonism	Yong et al.[590]	2011	PD (56) HC (68); age-matched	Overnight PSG, MSLT, ESS	PD patients had shorter total sleep time, lower sleep efficiency and increased REM sleep latency compared to controls. ESS scores were higher in PD patients
Parkinsonism	Dhawan et al.[1029]	2006	PD drug naïve (25) PD advanced (34) HC (131)	Overnight PSG (in those with abnormal ESS: 9), PDSS, ESS	Controls reported higher PDSS scores than both groups of patients. PSG revealed OSA in 7, PLMS in 5, RBD in 1
Parkinsonism	Buskova et al.[1030]	2011	PD drug-naïve (20) HC (15); age- and gender-matched	Three nights of PSG, MSLT, ESS, PSQI, PDSS	PSQI scores were higher in PD compared to control. ESS did not differ between groups. ESS was abnormally high in one patient, short MSLT was found in 3 patients. PSG showed higher RWA percentage in patients (28%) compared to controls (3%)
Parkinsonism	Ferreira et al.[1031]	2014	PD drug-naïve (23) HC (31); age- and gender-matched	PSG, PDSS, ESS	Drug naïve patients had lower PDSS scores than controls. Reduced N3 and REM sleep, and increased sleep latency and WASO were seen. Medication improved sleep efficiency and reduced sleep latency
Parkinsonism	Cochen De Cock et al.[1032]	2010	PD (100 – 50 referred for sleepiness) HC (50); age-, gender- and BMI-matched	One night of PSG, ESS	Sleep apnea was frequent in PD patients (27%) vs in-hospital controls (40%). PD patients had reduced total sleep time and increased WASO

Parkinsonism	Shpirer et al.[1033]	2006	PD (46) HC (30); age-matched	One night of PSG, MSLT, ESS, HAM-D	PD patients were sleepier than controls (higher ESS – 50% >10 score), had a shorter total sleep time and REM sleep, sleep efficiency was lower, and N2 was longer compared to controls. 26% vs 0% of PD patients vs controls had RBD
Parkinsonism	Loo et al.[1034]	2008	PD (200) HC (200)	PSG in four PD patients with RLS, PSQI	RLS present in 0.5% of controls and 3% of PD patients (non-significant). PD patients had higher PSQI scores on all components than controls
Parkinsonism	Breen et al.[596]	2014	PD (30) HC (15)	Two nights of PSG, 14 nights of Actigraphy, ESS, PSQI, PDQ-39, PDSS, RBDQ-HK	Subjective complaints were present in almost half of newly diagnosed patients. PD patients had increased sleep latency, reduced sleep efficiency and reduced REM sleep
Parkinsonism	Cao et al.[1035]	2018	MSA (40) HC (40)	PSG, PDQ-39, ESS, HAM-D, HAM-A	MSA had longer SOL, reduced TST and REM time, increased arousal and reduced sleep efficiency compared to controls. SBD was found in 65% of MSA patients compared to 20% in HC. Patients with SBD had more frequent occurrences of ESS, hypopneas, OSA, higher HAM-D scores compared to those without SBD
Parkinsonism	Guo et al.[1036]	2013	MSA (30) HC (20); age- and gender-matched	PSG	PSG revealed that 29 patients had altered sleep architecture alteration. Longer N1, shorter REM, decreased sleep efficiency and total sleep time. 21 had OSA. Total sleep time was negatively correlated to motor disability
Parkinsonism	De Bruin et al.[1037]	1996	PSP (11) HC (8); age- and gender-matched	Structured sleep questionnaire and interview, spirometry and inspiratory and expiratory pressures were assessed, BDI	PSP reported fatigue, frequent nocturnal awakenings, immobility in bed more frequently than controls. All patients had regular breathing patterns
Parkinsonism	Montplaisir et al.[1038]	1997	PSP (6) HC (6); age- and gender-matched	Overnight PSG, MSLT on 3 patients	Patients with PSP had shorter total sleep time, lower REM percentage, and lower sleep efficiency compared to controls. Sleep spindles were nearly absent in PSP patients. MSLT showed high inter-subject variability
Parkinsonism	Walsh et al.[1039]	2017	PSP (20) HC (16)	Overnight PSG, MSLT, SSS	PSP took longer to fall asleep and more WASO, reduced N2, N3 and REM sleep compared to controls. During MSLT PSP took longer to fall asleep and subjectively reported sleepier on SSS
Parkinsonism	Moreno-López et al.[1040]	2011	MSA (86) PD (86); matched for age, gender and disease stage HC (86); age- and gender-matched	Modified ESS, PSQI, TSS, Sudden Onset of Sleep Scale, presence of RLS, presence of stridor	MSA and PD scores were comparable but higher than HC. 28% of MSA and 29% of PD had EDS compared to 2% of HC. Significant differences in RLS: 27% of MSA, 14% of PD patients and 7% of HC had RLS

Parkinsonism	Gama et al.[1041]	2010	PD (16) MSA (13) PSP (13) HC (12)	ESS, PSQI, IRLSSG, BQ	Poor sleep quality, risk of OSA and RLS were detected in all groups. MSA showed highest risk of OSA. PSP showed frequent risk (57%) of RLS and related reduced sleep duration and efficiency
Parkinsonism	Bhalsing et al.[1042]	2013	PD (134) PSP (27) MSA (21) DLB (5) HC (172)	IRLSSG, PSQI, ESS, PDSS	RLS was higher in patients than controls, and highest in PD (12%). RLS was only present in one patient with PSP and MSA and none with DLB. PSQI and ESS scores were higher in patients than controls
Parkinsonism	Wetter et al.[1043]	2000	PD (10) MSA (10) HC (10)	Two nights of PSG	Lower total sleep time, sleep efficiency, and sleep period time in PD and MSA compared to controls. PLMS were higher in PD but not MSA. 5 PD and 7 MSA patients had abnormal REM features compared to no HC
Parkinsonism	Li et al.[1044]	2017	iRBD (22) MSA (21) PD (22) HC (21)	One night of PSG	MSA and PD patients had shorter total sleep time, worse sleep efficiency, longer REM latencies, more PLMS and spent less time in N2. MSA patients also had lower percentage of sleep N2, and greater AHI. Loss of RWA was found in all MSA patients. The duration of RBD was positively correlated with PLM in the MSA patient group
Parkinsonism	Rekik et al.[647]	2018	PD (45) MSA (45) HC (45); age- and gender-matched	Overnight PSG	Higher PLMI and RBD behaviour was more frequent in MSA patients compared to PD and HC. 62% of MSA patients had SBD
Parkinsonism	Arnulf et al.[1045]	2005	PSP (15) PD (15) HC (15); age- and gender-matched	Overnight PSG, MSLT, sleep interview	RWA and RBD were frequent in PSP and PD. PSP had longer WASO and twice as much sleep fragmentation and percentage of N1 sleep than PD and HC. Similar AHI, PLMI and mean daytime sleep latencies in PSP and HC
Huntington's Disease	Goodman et al.[1046]	2010	HD (66) Two age and gender-matched HC groups: Carers (38) Non-carers (60)	Questionnaire modelled on Parkinson's sleep questionnaires – 45 questions focusing on issues such as duration, quality of sleep abnormal nocturnal behaviour and QoL, BDI	HD patients reported greater difficulty in falling asleep, maintaining sleep, taking more than an hour to get to sleep, needing 'more sleep', being awake at night and asleep during the day, and waking up early and not being able to go back to sleep compared to non-carer controls. More patients reported abnormal nocturnal behaviour and nocturnal painful muscle cramps
Huntington's Disease	Hametner et al.[1047]	2012	HD (26) HC (39); age- and gender-matched	PSQI	27% patients compared to 8% of HC complained of poor sleep quality

Huntington's Disease	Aziz et al.[600]	2010	HD (63) Premanifest mutation carriers (21) HC (84)	ESS, PSQI, SCOPA-Sleep, BDI	Sleep impairment was more prevalent in HD compared to controls; daytime sleepiness was normal in HD. SOL was delayed in HD compared to controls. Sleep disorders were associated with depression
Huntington's Disease	Bellosta Diago et al.[1048]	2017	HD (38) HC (38)	PSQI, ESS	HD had more impaired sleep quality and more EDS than controls, these scores correlated to variability in circadian blood pressure
Huntington's Disease	Bellosta Diago et al.[658]	2018	HD (38): early stage and premanifest carriers HC (38); age- and gender-matched	PSQI, ESS, HAM-D	HD patients had worse sleep quality compared to controls – they had increased sleep onset latency and later wake-up time. This was associated with depressive and anxiety symptoms
Huntington's Disease	Morton et al.[657]	2005	HD (8) HC (8)	ESS, HDSS, sleep diaries, Actiwatch-Neurologica to measure locomotor activity	HD spent longer in bed than controls. Patients had an increase in nocturnal activity vs control
Huntington's Disease	Hurelbrink et al.[1049]	2005	HD (8) HC (8); age- and gender-matched controls	ESS, HDSS, sleep diary, Actiwatch-Neurologica to measure locomotor activity	HD patients showed more activity and spent more time making acceleration movements than controls. No significant difference between ESS and HDSS scores
Huntington's Disease	Wiegand et al.[602]	1991	HD (12) HC (12); age- and gender-matched	Two nights of PSG	Patients had an increased sleep onset latency, reduced sleep efficiency, increased number of awakenings and reduced slow wave sleep compared to controls
Huntington's Disease	Wiegand et al.[603]	1991	HD (16) HC (16); age- and gender-matched	Two nights of PSG	HD patients had reduced sleep efficiency, increased sleep onset latency, reduced slow wave sleep and more time spent awake
Huntington's Disease	Neutel et al.[604]	2015	HD (29) HC (29); age- and gender-matched	v-PSG	Patients had longer total sleep and REM sleep onset latency. 2 patients had RWA. 7 patients had giant sleep spindles and one control
Huntington's Disease	Emser et al.[605]	1988	HD (10) HC (12); 7 volunteers, 2 patients with Menière's disease, and 3 patients with a	Two nights of PSG	HD and HC had no differences except for two patients who had a distinct reduction in slow wave sleep. Sleep spindle was also increased during N2 which correlated to duration of disease

			peripheral nerve lesion		
Huntington's Disease	Lazar et al.[606]	2015	HD (38): premanifest gene carriers HC (36): age- and gender-matched controls	Two nights of PSG and MSLT, two weeks of Actigraphy	Gene carriers had more disrupted sleep, characterised by fragmented sleep profile: a decrease in REM sleep
Huntington's Disease	Cuturic et al.[607]	2009	HD (12) HC (12): unaffected relatives, age-gender- and race-matched	One night of PSG, ESS	ESS score had no significant difference between groups. Sleep latency was significantly longer in patients. Nocturnal SRBD were absent
Huntington's Disease	Arnulf et al.[608]	2008	HD (25) Narcolepsy (25) HC (25); age- and gender-matched	Overnight PSG, MSLT, ESS, clinical interview	HD patients had insomnia, earlier sleep onset, lower sleep efficiency, increased PLMS and shortened REM sleep, ESS was normal. 12% exhibited RBD
Huntington's Disease	Goodman et al. [609]	2011	HD (9) HC (10); age-, gender-, race- and BMI-matched	Three nights of v-PSG, MSLT, ESS, 14 nights of Actigraphy, FOSQ, MOS, BDI-2	FOSQ, ESS and MOS scores didn't differ from controls. Sleep architecture (lower percentage of REM sleep) and sleep efficiency differed compared to controls
Huntington's Disease	Piano et al.[610]	2015	HD (30) HC (30); age- and gender-matched	One night of v-PSG, ESS, IRLSSG, BQ, RBDSQ	Two patients reported RLS, 8 had scores ≥ 9.8 patients had high risk of OSA. 2 had pathological RBD. PSG showed no RWA and RBD. Disease duration correlated with ESS
SCA	Abele et al.[1050]	2001	SCA1 (13) SCA2 (22) SCA3 (23) HC (40); age- and gender-matched	IRLSSG	RLS present in 23% of SCA1, 27% of SCA2, 30% of SCA3 and 10% of controls. 105% vs 28% in all SCA patients
SCA	Friedman et al.[1051]	2003	SCA3 (22) At risk (12) HC (17)	ESS and two questions concerning RBD	SCA3 had higher ESS scores than AR and HC. 56% of SCA3 endorsed both RBD questions and 16% of those at risk and 18% of HC
SCA	Yang et al.[1052]	2020	SCA3 (91) HC (85); age- and gender-matched	FS-14, PSQI, ESS, BDI	SCA patients had significantly higher PSQI, BDI, ESS and FS-14 scores

SCA	Howell et al.[1053]	2006	SCA6 (25) HC (25); age- and gender-matched	ESS, PSQI	ESS and PSQI was higher in SCA6 patients than controls
SCA	Martins et al.[1054]	2015	SCA1 (12) HC (15); age- and gender-matched	ESS, MFIS, BDI	MFIS mean and sub scores were higher in SCA1 patients than controls. 100% vs 26.6% met the criteria for fatigue. Patients also had higher ESS scores, although only 3 patients presented with EDS
SCA	Moro et al.[1055]	2017	SCA 10 (28) SCA 3 (28) HC (28)	MFIS, ESS, RBDSQ, IRLSSG, BDI, HAM-A	RLS and RBD were uncommon in SCA10. ESS in SCA10 and SCA3 were higher than controls. Fatigue scores were higher in SCA10 and SCA3 compared to HC
SCA	Pedroso et al.[1056]	2011	SCA3 (40) HC (38); age- and gender-matched	RBDSQ, IRLSSG, ESS, HAM-A, BDI	RBD and RLS frequency was higher in SCA than controls. No difference in EDS. Depression and anxiety correlated with RDB
SCA	Pedroso et al.[1057]	2017	SCA2 (33) from 9 families HC (26)	ESS, RBDSQ, BDI, HAM-A, structured interview	SCA2 had high frequency of RBD (48%) and EDS (42%) but ESS scores did not differ from HC. RLS was present in 18% but did not differ from HC (4%)
SCA	D'Abreu et al.[1058]	2009	SCA (53) HC (106)	ESS, NCS/EMG, questionnaire including items regarding RLS, cramps, RBD, SRBD	ESS score was not different from controls. 45% of SCA3 patients had scores >10 compared to 29% in controls. Sleep complaints were higher in patients, particularly insomnia with suggestive evidence of higher OSA and RLS
SCA	Seshagiri et al.[611]	2018	SCA1 (6) SCA2 (5) SCA3 (7) HC (6)	Overnight PSG	Sleep spindle density significantly decreased in SCA
SCA	Rodríguez-Labrada et al.[612]	2019	SCA2 (20) SCA2 preclinical carriers (20) HC (20)	One whole night of PSG	Compared to controls sleep spindle density was significantly reduced in SCA2 and preclinical patients. Reduced spindle activity correlated with reduced N3 sleep in SCA2 patients
SCA	Rueda et al.[613]	2016	SCA 6 (12) HC (12); age-, gender- and BMI-matched	Overnight PSG	SCA6 had higher frequency of snoring, respiratory disorders and slow wave sleep compared to controls
SCA	Zanatta et al.[614]	2019	SCA 2 (17) HC (17); age-, BMI- and gender-matched	One night of v-PSG	Increased REM sleep in 70%, increased REM latency in 52%, increased OSA in 82% and absent REM density in 76%. Compared to controls SCA2 had reduced total sleep time, sleep efficiency, sleep latency, sleep N3 latency, REM quantity, N2 and N3 quantity. Disease progression correlated with a reduction in REM density and decreased sleep efficiency

SCA	Iranzo et al.[615]	2003	SCA3 (9) HC (9); age- and gender-matched	Overnight PSG, sleep questionnaire	55% of patients has RBD compared to no controls. SCA3 patients had reduced total sleep time, sleep efficiency, REM sleep percentage, increased WASO and PLMI compared to controls
SCA	Pedroso et al.[616]	2013	SCA3 (22) from 15 families HC (20)	Overnight PSG, RBDSQ, IRLSSG	SCA3 patients; 54% had RLS, 77% had PLMS, 73% had RWA and 59% had RBD
SCA	Velázquez-Pérez et al.[617]	2011	SCA2 (32) HC (32); age- and gender-matched	Two nights of v-PSG, ESS, sleep interviews – subjective sleep quality and dream recall, snoring, somniloquy and motor complaints during sleep	Reduced REM sleep percentage and REM density, an increase in RWA, PLMS in 37.5% of patients. 21.8% complained of insomnia vs 3% in HC and RLS diagnosed in 25% of patients compared to 3% in HC. No difference in ESS scores
SCA	Silva et al.[618]	2016	SCA3 (47) HC (47); age- and gender-matched	Overnight PSG, IRLSSG, RBDSQ, non-validated parasomnia questionnaire	SCA3 had higher frequency of arousals from slow wave sleep, parasomnia complaints, RWA, PLMI, percentage of N1 and N3 sleep
SCA	Chi et al.[619]	2013	SCA 3 (15) HC (16)	Overnight PSG, ESS	SCA3 patients had reduced sleep efficiency and percentage of REM sleep which negatively correlated with severity of ataxia. ESS was normal to controls
SCA	Reimold et al.[620]	2006	SCA1 (10) SCA2 (4) SCA3 (2) HC (9); age-matched – in PET only	Overnight PSG, ESS	RLS present in 25% of SCA1 and SCA2 patients, 100% of SCA3 patients. All RLS patients had abnormal PLMS score. One RLS had OSA. 1 SCA2 and SCA3 patient had EDS
SCA	London et al.[621]	2018	SCA 10 (23) HC (23)	One night of PSG, ESS	SCA10 patients had longer REM sleep and more REM arousal than controls. REM sleep onset correlated with disease duration
Wilson's Disease	Grandis et al.[1059]	2017	WD (463) HC (14,742,438)	North American Medical Databases	Those with WD exhibited a higher risk for OSA by 29%
Wilson's Disease	Portala et al.[1060]	2002	WD (24) HC (24); age- and gender-matched	USI, qualitative questions about sleep patterns and sleep medication	WD patients had a significant difference in the number of nocturnal awakenings, with 59% reportedly frequently being awake for more than 30 minutes during the night, Sleep paralysis and cataplexy occurred more in patients, and they complained significantly more of daytime fatigue and taking more naps
Wilson's Disease	Netto et al.[1061]	2011	WD (25) HC (24)	PSQI, ESS	On the PSQI 15 patients had an abnormal PSQI score, significantly more than controls. ESS was abnormal in three patients, with two controls meeting EDS criteria. Sleep assessments detected abnormalities in 16 WD patients compared to 8 controls
Wilson's Disease	Netto et al.[1062]	2010	WD (25) HC (25)	PSG	Patients had reduced total sleep time, sleep efficiency, percentage of N3 sleep, and REM sleep, prolonged sleep-onset latency and latency to N2

Wilson's Disease	Trindade et al.[622]	2017	WD (42) HC (42); age- and gender-matched	v-PSG, IRLSSG, ESS, PSQI, BDI	Sleep quality was worse compared to HC. WD patients showed lower sleep efficiency, less N2 sleep and more WASO and arousal compared to HC. WD with RLS showed significantly more PLM, more N1 sleep and a longer REM sleep latency
Wilson's Disease	Tribl et al.[623]	2015	WD (41) HC (41); age- and gender-matched	v-PSG, RBDSQ, PSQI, ESS, MSQ, clinical and sleep interviews	5 WD patients fulfilled the RBD criteria and had significantly higher values in RWA. RWA in WD patients without RBD was still significantly increased compared to controls
Wilson's Disease	Nevsimalova et al.[624]	2011	WD (55) HC (55); age- and gender-matched	PSG (24 WD and HC), ESS, RBDSQ, questionnaire concerning sleeping habits	13 WD patients fulfilled RLS criteria. WD patients were more prone to daytime napping accompanied by EDS and poor nocturnal sleep. Mean ESS as well as RBDSQ was higher than controls. TST was lower, with decreased sleep efficiency and increased wakefulness. WD had lower latency of N1 and N2 sleep. 14% had MSLT <8 minutes
Niemann-Pick Type C	Vankova et al.[625]	2003	Juvenile NPC (5) HC (12)	At least one night of PSG, MSLT	In all patients, sleep was fragmented and disorganised. Total sleep time and sleep efficiency was lower, shorter sleep latency and increased WASO
Essential Tremor	Benito-León et al.[1063]	2013	ET (76) HC (3227)	Self-reported sleep duration	Those with ET had significantly shorter sleep duration than those without ET
Essential Tremor	Chen et al.[1064]	2018	ET (100) HC (201)	Interview and revised IRLSSG	Two ET patients fulfilled the diagnosis of RLS, increased risk associated with the MAP2K5/SKOR1 gene
Essential Tremor	Peng et al.[1065]	2020	ET (199) HC (132)	NMSS	ET was sub-grouped with and without head tremor, both groups showed high scores and prevalence (>50%) in difficulty falling asleep. Daytime sleepiness was significantly higher in patient subgroups than in the controls
Essential Tremor	Acar et al.[1066]	2019	ET (40) HC (38)	PSQI	PSQI scores were significantly higher in patients than the control group
Essential Tremor	Chandran et al.[1067]	2012	ET (50) HC (50)	PSQI, ESS, PFS	ET patients had a higher prevalence and higher mean scores of sleep disturbances and fatigue
Essential Tremor	Sengul et al.[1068]	2015	ET (45) HC (35); age-, gender-, education-matched	ESS, PSQI, FSS	Poor sleep quality and fatigue were common. EDS had a negative effect on physical and mental health
Essential Tremor	Wu et al.[1069]	2016	ET (58) HC (123); age- and gender-matched	RBDSQ, NMSQuest	ET patients had a significant increase in RLS. One of 60 ET patients screened positive for RBD, when compared to controls there was no significant difference
Essential Tremor	Shalash et al.[1070]	2019	ET (30) HC (30)	NMSS, PSQI	ET patients showed worse sleep and NMSS domains compared to controls that negatively affected quality of life

Dystonia	Timmers et al.[284]	2017	DRD (28), from ten families HC (28): age- and gender-matched	PSQI, FSS, ESS, BDI, BAI	Patients scored higher on ESS than controls. Health related quality of life was associated with worse quality of sleep. Patients did not significantly report more sleeping problems than controls
Dystonia	Avanzino et al.[331]	2010	BSP (52) CD (46) HC (56): age- and gender-matched	PSQI, ESS, BDI	Reduced sleep quality (75% in BSP and 72% in CD); excessive daytime sleepiness. Dystonia severity and duration uncorrelated with PSQI in BSP. In CD, no correlation with PSQI when adjusted for BDI. BDI score accounted for poorer sleep quality in only CD
Dystonia	Yang et al.[351]	2017	BSP (60) CD (60) HC (60): age-, gender-, and education-matched	PSQI, ESS, HAM-D, HAM-A	Reduced sleep quality (CD 71%, BSP 55%) vs controls. ESS not significantly different between patient and controls (CD 20%, BSP 25%)
Dystonia	Smit et al.[694]	2017	CD (44) HC (43): age- and gender-matched	FSS, ESS, PSQI, BDI, BAI	Snoring was more prevalent in patients than controls. Patients scored worse on ESS, FSS and PSQI
Dystonia	Paus et al.[333]	2011	CD (111) BSP (110) HC (93): age-matched to CD patients	PSQI, ESS, examined for sleep bruxism, "Do you have problems with sleep?", RLS, BDI	PSQI showed disturbed sleep quality higher than controls (BSP 46% and 44% in CD) and mean score higher. ESS was normal (BSP 7%, CD5%). Increased % of those with RLS (BSP 20%, CD 18%). BDI significantly lower in controls. Pain significantly more common in CD vs BL (87 vs 34%). 100% of CD patients attributed the pain to their dystonia vs 62% of BSP patients with pain
Dystonia	Trotti et al.[330]	2009	CD (43) HC (49): age- and gender-matched Other focal movement disorders (19)	ESS	EDS were excessive in patients compared to controls
Dystonia	Eichenseer et al.[332]	2014	CD (54) HC (55): age- and gender-matched	PSQI, ESS, BDI, HAM-A	Impaired sleep quality was twice as common in CD patients compared to matched controls and sleep disturbances did not improve despite improvement in CD motor symptoms
Dystonia	Ferrazzano et al.[281]	2019	BSP (60) HC (40) age-matched	PSQI, HAM-A, HAM-D	BSP had more sleep disorders, higher PSQI scores than controls
Dystonia	Novaretti et al.[286]	2019	CD (28) BSP (28) WC (24)	PSQI, ESS, BDI, BAI	Patients reported worse quality of sleep. ESS was normal. All three patients had body movements during REM sleep, significantly more than controls

			HC (80) age-, gender-, education matched		
Dystonia	Gadoth et al.[667]	1989	HPD (3) HC (11)	PSG over two nights (two patients, and one night in one patient and HC)	Sleep structure appeared to be normal in all subjects
Dystonia	Jankel et al.,[668]	1983	DMD (4) HC (4): age- and gender-matched	PSG over three nights	PSG showed increased sleep latency, reduced sleep efficiency, and unusually high voltage of sleep spindles (>100μV) sleep spindles during N2
Dystonia	Jankel et al.[669]	1984	DMD (9) HC (9): age- and gender-matched	PSG over three nights	All patients slept poorly, patients with advance stages of dystonia all displayed high-amplitude (>150μV) spindles during N2 and N3, increased sleep latency, less REM sleep, increased number of awakenings and poor sleep efficiency
Dystonia	Fish et al.[339]	1990	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10)	PSG over two nights	Four patients (taking benzodiazepines) with TD had increased sleep spindles more than both control groups. All patients with severe disease had abnormal sleep spindles
Dystonia	Fish et al.[670]	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39) HC (10) Same sample as Fish et al., 1990	PSG over two nights	All patients and controls showed reduced EMG activity during REM sleep compared to wakefulness. Patients with secondary TD had fewer bursts of activity than normal subjects. RBD was absent in all groups
Dystonia	Fish et al.[671]	1991	Primary TD (14) Secondary TD (10) Other neurological disorders (39)	PSG over two nights	Movements were most frequent during awakening, proceeded by N1, with very few movements during N2 and REM sleep. Sleep-related movements in primary and secondary TD emerged after brief awakenings

			HC (10) Same sample as Fish et al., 1990		
Dystonia	Lobbezoo et al.[335]	1996	CD (9) HC (9) age- and gender-matched	PSG over two nights	PSG in CD patient were normal. Sleep was associated with an improvement of symptoms in CD, with abnormal cervical muscle activity decreasing immediately when lying down and then being abolished when transitioning to light NREM sleep
Dystonia	Antelmi et al.[337]	2017	CD (20) HC (22): age- and gender-matched	One full night of PSG, RLS, PSQI, ESS, BDI	PSQI showed significant reduction in sleep quality, and correlation with higher scores of BDI. ESS scores were normal. Difficulties in sleep efficiency and increased sleep latency and increased REM sleep latency. Patients had lower muscle amplitude contraction over the dystonic muscles compared to HC in slow wave sleep and REM sleep
Dystonia	Brüggemann et al.[338]	2014	DRD (23) HC (26): age-matched	PSG over one night, PSQI, ESS, SSS, FEPS-2, BDI, self-administered comorbidity questionnaire	Sleep quality, SSS and ESS was similar across groups. 6 patients underwent PSG, 2 had reduced sleep efficiency, 2 increased sleep latency, 5 increased REM latency, 4 had initiation problems and 4 had increased in numbers of arousal
Tic Disorders	Lee et al.[1071]	2017	TS (1124) HC (3372)	National database review	Incidence rate of sleep disorders was 7.2% in children with TS compared to 3.5% in controls. Anxiety disorder was associated with highest risk for sleep disorders
Tic Disorders	Ricketts et al.[1072]	2018	TS (298) History of TS (122) HC (254)	Data taken from NSCH survey, parent interview	Controls shown to have 1.5 times more nights of sufficient sleep compared to both tic disorder groups. Older adolescent males with mild tic disorder had significantly fewer nights of sufficient sleep than children and early adolescents. Female early adolescents with moderate/severe tic disorder had fewer nights of sufficient sleep relative to males
Tic Disorders	Comings & Comings[1073]	1987	TS (247) ADD (17) HC (47)	Questionnaire examining sleep history and sleep problems (parent/patient)	TS increased frequency of sleepwalking, night terrors, trouble getting to sleep, early awakening, and inability to take afternoon naps as a young child
Tic Disorders	Saccomani et al.[1074]	2005	TS (48) CTD (48) HC (30); age-matched	Interview for sleep problems (parent and child)	Sleep problems present in 27.1% TS and 16.7% CTD
Tic Disorders	Modafferi et al.[1075]	2016	TS (28) CTD (8) HC (266); age- and gender-matched	SDQ-45 (parent)	Sleep was significantly more disturbed in patients with tic disorders than in controls. Difficulties in initiating sleep and increased motor activity during sleep were the most frequent sleep disturbances. Higher anxiety symptoms associated with increased motor activity during sleep
Tic Disorders	Allen et al.[1076]	1992	TS (57) TS+ADHD (89) HC (146); age-matched	Modified version of MSPSQ (parent)	Increased sleep difficulties related to additional presence of ADHD. The complaint of poor sleep occurred in 26% with TS-only, 48% with ADHD-only, and 41% with TS+ADHD; all were significantly different from 10% found in controls

Tic Disorders	Rickett et al.[1077]	2018	TS (39) HC (18)	Actigraphy, children's sleep habit questionnaire (parent), sleep self-report (child)	TS had increased sleep onset-latency, reduced sleep efficiency, increased WASO, and increased number of awakenings compared to controls. There were no differences in questionnaire reports
Tic Disorders	Moeller and Krieg[1078]	1992	TS (2); adults HC (14)	Sleep EEG	Decreased percentage of slow wave sleep
Tic Disorders	Hashimoto et al.[672]	1981	TS (9) HC (9)	PSG	At all stages of sleep, body movements during sleep were more frequent in cases of TS. Twitch movements in REM sleep were significantly increased in TS. TS patients had increased total sleep time, REM sleep and NREM sleep
Tic Disorders	Stephens et al.[673]	2013	TS (20) TS+ADHD (21) HC (16) ADHD (33)	Two nights of PSG, respiration belt	Total number of leg movements higher in TS+ADHD group compared to TS only. Children with TS and ADHD had a significant higher number of arousals from slow wave sleep and total arousals
Tic Disorders	Kirov et al.[674]	2007	TS (18) TS+ADHD (18) ADHD (18) HC (18)	Two nights of PSG	TS patients had lower sleep efficiency and elevated arousal index in sleep. TS+ADHD patients had reduced sleep efficiency, elevated arousal index and increase in REM sleep
Tic Disorders	Kirov et al.[675]	2007	TS+ADHD (19) HC (19)	Two nights of PSG	Shorter REM sleep latency and increased REM sleep duration in patients with TS+ADHD
Tic Disorders	Kirov et al.[676]	2017	TS (21) ADHD/TS (21) ADHD (24) HC (22); age- and gender-matched	Two nights of PSG	Increased REM sleep and shorted REM latency in children with psychiatric disorders than controls
Tic Disorders	Voderholzer et al.[677]	1997	TS (7) HC (7); age- and gender-matched	Two nights of PSG	5/7 showed frequent PLMS in NREM and total sleep time significantly lower in TS group ($p<0.05$)
Tic Disorders	Cohrs et al.[678]	2001	TS (25); adults HC (11)	v-PSG over two consecutive nights	Patients with TS showed reduced sleep efficiency, total sleep time/time in bed, and percentage of slow wave sleep, as well as significantly prolonged sleep latency, significantly increased percentage of N1, percentage of time awake, and increased number of awakenings and sleep stage changes/hour sleep period time
Tic Disorders	Kostanecka-Endress et al.[679]	2003	TS (17); children HC (16); age-, gender-, IQ-matched	Two nights of PSG, CBCL sleep items (parent), semi structured interview with parents and patients	Children with TS demonstrated changes in sleep parameters, including longer sleep period time, longer sleep latency, reduced sleep efficiency, and prolonged wakefulness after sleep onset. Short arousal-related movements were increased in TS. Periodic limb movements during sleep were only seen in one TS patient
Mixed	Adler et al.[1079]	2011	PD (49/60) RLS (30/39)	ESS, MSQ, IRLSSG, "Have	Probable RBD was more frequent in PD than in RLS, ET and controls. PD patients with ESS ≥ 10 was higher in (48%), than RLS (31%), ET (13%) and controls (11%)

			ET (53/93) HC (175/296)	you even been told that you act out your dreams?" as a marker for RBD	
Mixed	Lee et al.[1080]	2015	ET (60) PD (30) HC (22)	PSQI, ESS	ET patients had significant excessive daytime somnolence compared to controls
Mixed	Gerbin et al.[1081]	2012	ET (120) PD (40) HC (120)	PSQI, ESS	ESS scores were significantly higher in ET patients compared to controls. The global PSQI was not significantly different
Mixed	Aldaz et al.[1082]	2019	HD (53) PD (45) HC (25); age-matched to HD patients	NMSQuest	HD patients scored higher than PD on delusions, nightmare, and higher than controls on acting out dreams, insomnia, intense vivid dreams
Mixed	Barut et al.[1083]	2015	PD (21) ET (16) HC (14)	PSG, PSQI, ESS, FSS, interview to screen RBD	PD patients were more likely than ET to have a history of RBD and EDS.

Abbreviation: ADD: Attention Deficit Disorder, ADHD: Attention Deficit Hyperactive Disorder, AHI: Apnea-Hypopnea Index, BAI: Beck's Anxiety Inventory, BDI/-2: Beck's Depression Inventory, BQ: Berlin Questionnaire, BSP: Blepharospasm, CSA: Central Sleep Apnea, CD: Cervical Dystonia, CTD: Chronic Tic Disorder, DLB: Dementia with Lewy Bodies, DMD: Dystonia Musculorum Deformans, DRD: Dopamine-responsive dystonia, EDS: Excessive Daytime Sleepiness, EMG: Electromyography, ESS: Epworth Sleepiness Scale, ET: Essential Tremor, FEPS-2: Sleep-related Personality Traits Questionnaire, FOSQ: Functional Outcomes of Sleep Questionnaire, FS-14: Fatigue Scale, FSS: Fatigue Severity Scale, HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, HC: Healthy control, HD: Huntington's Disease, HDSS: Hungtinton's Disease Sleepiness Scale, HPD: Hereditary Progressive Dystonia, iRBD: idiopathic Rapid Eye Movement sleep Behaviour Disorder, IRLSSG: International Restless Leg Syndrome Study Group, ICSD-2: International Classification of Sleep Disorders, ISI: Insomnia Severity Index, JHRLS: John Hopkins Restless Leg Syndrome Severity Scale, MEQ: Morningness–Eveningness Questionnaire, MFIS: Modified Fatigue Impact Scale, MOS: Medical Outcomes Study Scale, MSA: Multiple System Atrophy, MSLT: Multiple Sleep Latency Test, MSPSQ: Modified Simonds and Parraga Sleep Questionnaire, MSQ: Mayo Sleep Questionnaire, NREM1/2/3: Non-Rapid Eye Movement Sleep stages, NCS: Nerve Conduction Study, NMSQuest: Non-Motor Symptoms Questionnaire, NMSS: Non-Motor Symptoms Scale, OSA: Obstructive Sleep Apnea, PD: Parkinson's Disease, PDSS/-2: Parkinson's Disease Sleep Scale, PDQ-8/39: Parkinson's Disease Quality of Life, PFS: Parkinson's Fatigue Scale, PLMD: Periodic Limb Movement Disorder, PLMI: Periodic Limb Movement Index, PLMS: Periodic Limb Movement during Sleep, PFS: Parkinson's Fatigue Scale, PSG: Polysomnography, PSP: Progressive Supranuclear Palsy, PSQI: Pittsburgh Sleep Quality Index, RBD: Rapid Eye Movement sleep Behaviour Disorder, RBDSQ: Rapid Eye Movement sleep Behaviour Disorder Screening Questionnaire, REM: Rapid Eye Movement sleep, RLS: Restless Leg Syndrome, RWA: Rapid Eye Movement sleep Without Atonia, SAS: Sleep Apnea Syndrome, SCA: Spinocerebellar Ataxia, SCOPA-Sleep: Scales for Outcomes in Parkinson's Disease in Sleep, SDQ-45: Sleep Disorder Questionnaire, SRBD: Sleep-related Breathing Disorder, SSA: Self-rated Sleep Scale, SSS: Stanford Sleepiness Scale, TD: Torsion Dystonia, TS: Tourette's Syndrome, TSS: Tandberg Sleepiness Scale, USI: Uppsala Sleep Inventory, v-PSG: Video Polysomnography, WASO: Wake After Sleep Onset, WC: Writer's Cramp, WD: Wilson's Disease, ZARS: Zung's Self-Rating Anxiety Scale, ZDRS: Zung's Self-Rating Depression Scale.