Pharmacotherapeutic interventions in Parkinson's disease: investigating prescribing factors and health outcomes

This thesis is submitted for the degree of Doctor of Philosophy at Cardiff University

By

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Abstract

The current thesis is the first thorough exploration of the epidemiology and pharmacoepidemiology of Parkinson's disease (PD) in Wales. Several factors, including age, sex, and social deprivation status, were evaluated that could contribute to specific estimates of prevalence and incidence, and also to patterns of prescribing of Parkinson's medications in newly diagnosed People with Parkinson's disease (PwP). Furthermore, as cardiovascular episodes have been identified as a concern and potential risk factor associated with levodopa usage in PwP, cardiovascular outcomes in newly diagnosed PwP initiating levodopa therapy were estimated at population level.

After conducting a thorough systematic literature review, a retrospective study of PwP in Wales, aged 40 years or older, identified from the Secure Anonymised Information Linkage (SAIL) Databank between January 2000 and December 2016 was employed. During the study, 9,142 newly diagnosed PwP who had initiated PD therapy were identified. The analysis revealed that the incidence rate of PD did not differ significantly between the year 2000 and the majority of years of the study period (in 2016, the incidence rate ratio (IRR) was 1.05 95% CI 0.93–1.18). However, the overall prevalence rate increased between 2000 and 2016 (in 2016 the prevalence rate ratio (PRR) was 1.16 95% CI 1.11–1.21). Importantly, the incidence rate of PD was significantly lower in the most socially deprived areas compared to the least deprived areas (IRR = 0.82, 95% CI 0.77-0.87). Interestingly, social deprivation also impacted on medication, with PwP residing in the least deprived areas being 22.1% less likely to be prescribed levodopa compared to those from the most deprived areas (p-value = 0.007). From a safety perspective, although there were no statistically significant associations between levodopa monotherapy for up to one year after its initiation and increased risk of ischemic heart disease (p=0.561), other cardiovascular events (p=0.233), or all-cause mortality (p=0.334), the small sample size warrants further study with a larger population to detect clinically important differences in cardiovascular risk.

Overall the findings support those of other studies which indicate that PD incidence appears stable, but its prevalence is increasing, likely to be due to an ageing population. The association with lower prevalence in areas of lower socioeconomic status similarly reflected other findings but uniquely identified a change in medication regimens. In concert, these findings are consistent with the hypothesis that individuals with lower socioeconomic status may be diagnosed later in their disease (which may be due to multiple factors), at which point the prescriber may be more likely to initiate treatment with levodopa rather than a MAO-B inhibitor. Given their accessibility, pharmacists could play a role in identify early signs and symptoms of PD in socioeconomically deprived areas but other recommendations are also made for further exploration of this area. Further research exploring this unwarranted variation in care and how it may be addressed is needed.

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LIST OF ABBREVIATIONS

Abbreviation	Stands For
AAN	American Academy of Neurology
ADAGIO	Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) study
ADDE	Annual District Death Extract
ALF	Anonymised Linkage Field
APC	Admitted Patient Care
BNF	British National Formulary
CALM.PD	Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) trial
CI	Confidence Interval
COMT	Catechol-O-Methyl Transferase Inhibitor
COTE	Care of the Elderly
CPRD	Clinical Practice Research Datalink
DA	Dopamine Agonists
DBS	Deep Brain Stimulation
DDD	Defined Daily Doses
DID	Defined Daily Doses per 1000 inhabitants per day
DLB	Dementia with Lewy Bodies
DOMINION	Impulse Control Disorders in Parkinson's Disease Patients Treated With MIRAPEX® (Pramipexole) and Other Anti-Parkinson Agents trial
DRL	Deterministic Record Linkage
ELLDOPA	Long-Term Dopamine Transporter Imaging and Clinical Assessment of Parkinson's Disease Progression trial
EMR	Electronic Medical Records
FDA	Food and Drug Administration
GP	General Practitioner
HIRU	Health Information Research Unit
HIV	Human Immunodeficiency Virus
ICC	Intraclass Correlation Coefficient
ICD	International Statistical Classification of Diseases
ICDs	Impulse Control Disorders

IGRP	Information Governance Review Panel
IHD	Ischemic Heart Disease
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LEAP	Later Levodopa Therapy in Parkinson Disease (ELLDOPA) trial
LED	Levodopa Equivalent Dose
LEDD	Levodopa Equivalent Daily Dose
LID	Levodopa-Induced Dyskinesia
LSOA	Lower Super Output Area
MACRAL	Matching Algorithm for Consistent Results in Anonymous Linkage
MAO-B	Monoamine Oxidase B
MCCD	Medical Certificate of the Cause of Death
MDS	Movement Disorder Society
MSA	Multiple System Atrophy
MUR	Medicines Use Review
NA	Not Applicable
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NMDA	N-Methyl-D-Aspartate
NWIS	NHS Wales Informatics Service
OGL	Open Government Licence
ONS	Office of National Statistics
OPCS	Operation Classification System's
OR	Odds Ratio
OTC	Over the Counter
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PDNS	Parkinson's Disease Nurse Specialist
PDRG-UK	Parkinson's Disease Research Group of the United Kingdom trial
PEDW	Patient Episode Database for Wales
PH	Proportional Hazard
PIGD	Postural Instability and Gait Difficulty
PRL	Probabilistic Record Linkage
PROUD	Pramipexole On Underlying Disease study
PRR	Prevalence Risk Ratio
PSALF	Project-specific Anonymised Linkage Field

PSP	Progressive Supranuclear Palsy
PwP	People with Parkinson's disease
PYAR	Person Year at Risk
QOL	Quality of Life
RALF	Residential Anonymous Linking Field
RBD	Rapid Eye Movement Behaviour Disorder
RCT	Randomized Clinical Trials
ROC	Receiver Operating Characteristic
SAIL	Secure Anonymised Information Linkage
SD	Standard Deviation
SES	Socioeconomic Status
SPSS	Statistical Package for the Social Sciences
SQL	Structured Query Language
SSRI	Selective Serotonin Reuptake Inhibitors
STRIDE	Efficacy and Safety of Carbidopa/Levodopa/Entacapone in Patients With Parkinson's Disease Requiring Initiation of Levodopa Therapy
TCA	Tricyclic Antidepressants
TEMPO	A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study
THIN	The Health Improvement Network
TRUD	Technology Reference Data Update Distribution
TTP	Trusted Third Party
UKPDBB	UK Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale
VPN	Virtual Private Network
WDS	Welsh Demographic Service
WHO	World Health Organization
WIMD	Welsh Index of Multiple Deprivation
WLGP	Welsh Longitudinal General Practice Dataset

CHAPTER 1: General Introduction

1.1 General background about Parkinson's disease

1.1.1 Epidemiology

After Alzheimer's disease, Parkinson's disease (PD) is the most common neurodegenerative disease (1). PD is common in elderly people. While over 1% of the population over the age of 60 are expected to have PD, this percentage may reach 5% for those over the age of 85 (2). A recent meta-analysis that examined 47 PD prevalence studies worldwide found a strong positive association between PD prevalence and age (3). The prevalence of PD in patients aged 40-49 years was estimated to be 41 per 100,000 population, while in patients older than 80 years, the prevalence was 1,903 per 100,000 population (3). In the United Kingdom (UK), prevalence for all ages in 2015 was estimated to be 210.1 per 100,000 population, without significant variations between England and Wales (4) . In 2015, there were about 114,560 PwP in England, 7,275 in Wales, 11,522 in Scotland, and 3,460 in Northern Ireland (4). Due to the increase in population growth and population aging, a 23.2 % increase in the total number of PwP is anticipated in the UK by 2025 (4). Generally, PD prevalence tends to be more common in western countries (Europe, North America, and South America) compared to Asian countries, and it is more common in men compared to women (3-6). Several risk factors have been associated with an altered PD risk: exposure to pesticides (↑ 62%), living in a rural area (↑ 32%), consumption of dairy products (↑ 40%), and previous head injuries (↑ 55%) are associated with increase in risk, while smoking (↓ 36%), coffee consumption (↓ 33%), ibuprofen use (↓ 27%), and physical exercise (↓ 34%) are associated with a decreased risk (7, 8).

1.1.2 Economic burden

Since PD risk increases with age, and due to the increase in the life expectancy of the general population, it is suggested that there will be an increasing number of people with PD, which will in turn lead to a substantial increase in health care costs (9, 10). These costs include costs of PD medications and hospitalization episodes, and costs due to loss of productivity (11). In the United States of America (USA), the PD national economic burden was $14.4 billion in 2010, and it is estimated that this amount will increase substantially in the next decade (12). In the UK, one cross-sectional study has shown that the PD economic burden is roughly £450 million per year (13). Given that this amount is thought to be based on a very conservative calculation, it is estimated that when the current PD prevalence rate is considered, the suggested annual expenditure will be approximately £3.3 billion, and for every person with Parkinson's, the average annual cost of PD is £29,000 (14, 15). Compared to a person without PD with the same age, sex, and comorbidities, heath care costs for a person with PD are significantly greater. Weir et al. found that the mean difference in health care costs between PwP and non-PwP in the UK was £2,471 in the first year after PD diagnosis, and £4,004 ten years after PD diagnosis (16). The cost of PD is positively associated with the duration of the disease, a higher Hoehn and Yahr stage (a scale that used to assess the progression of PD), and care home placement (13, 16). Additionally, one major factor that substantially increases costs is hospitalization. In a recent study in the UK, it was found that over four years, from 2009 to 2013, the number of admissions for PwP was 324,055, which resulted in an expenditure of £907 million (9). Finally, many PwP who are cognitively impaired may require personalized one-to-one care, and that have the potential to increase the cost dramatically (17).

1.1.3 Pathology

PD is a progressive neurodegenerative disease involving continuous loss and degeneration of the dopaminergic neurons in the substantia nigra. The substantia nigra, the striatum, globus pallidus, and subthalamic nucleus constitute what is known as the “basal ganglia” (18). The development of motor-symptoms of PD (which will be discussed later) is clearly associated with dopaminergic neuron loss. Importantly from a symptom-based diagnostic perspective, the motor symptoms of PD are only observed when there is an 60% loss of dopaminergic neurons in the substantia nigra and with a respective 80% loss of dopamine striatum, respectively (19).

In addition to the loss of nigrostriatal dopaminergic pathways, there are abnormal aggregations of a protein in structures termed "Lewy bodies" in the nigral neurons and other parts of the brain in PwP, which can be visualised under the microscope (18). It was later found that a mutated protein, alpha-synuclein, is a major component of Lewy bodies (20). Importantly, PD is not the only disease that contains alpha-synuclein in its pathology: alpha-synuclein is present in a group of diseases known as synucleinopathies, such as dementia with Lewy bodies (DLB), pure autonomic failure, and multiple system atrophy (MSA) (21).

Although the loss of the nigrostriatal dopaminergic pathway could explain the progression of the motor symptoms of PD, the emergence of some non-motor symptoms of PD (depression, psychosis, and others) prior to the motor symptoms is best explained by the alpha-synuclein hypothesis (21). In 2003, Braak and colleagues (22) introduced a new hypothesis to explain why some non-motor symptoms, such as the loss of sense of smell (hyposmia) and constipation predate motor symptoms by identifying six pathological stages of the disease (22) (See Section 1.1.5). Although in-conclusive, more recent data

has supported and extended Braak's findings by showing that PD could originate outside of the central nervous system and especially in the gut region (23). Other contributors to PD pathogenesis include genetic mutations, oxidative stress, misfolded protein accumulation inside cells, and dysfunction in the ubiquitin-proteasome system (24, 25). Recently, a prion-like process has been proposed to explain the pathology of PD, which is based on the possible spreading of misfolded protein from cell to cell (26).

1.1.4 Diagnosis

A diagnosis of PD is based mainly on motor features which can look like other Parkinsonism-plus syndromes that have some similarities to PD diagnosis. For instance, rigidity and slowness of movement (bradykinesia) are two of the four cardinal motor symptoms of PD; however, they may also be present with diseases such as progressive supranuclear palsy (PSP) and MSA (25, 27). There is no biological marker that confirms a PD diagnosis during a patient's lifetime (25, 27); the only way to confirm a PD diagnosis is by finding Lewy bodies and degenerated dopaminergic neurons in the affected regions in the post-mortem brain (25, 28). Loss of dopamine can be determined with a DaTSCAN (approved by the National Health Service (NHS)), but there is no imaging technique that can detect alpha-synuclein/Lewy bodies (25, 28). A positive response to levodopa (L-dopa) is also a diagnostic feature, but other diseases in early stages, such as MSA, can also respond to L-dopa (25, 28).

Given the difficulties mentioned above, it is believed that, in practical terms, a PD diagnosis should be mainly based on clinical findings (29, 30). There are several clinical diagnostic criteria for PD, but the most widely used are those proposed in 1988 by the UK Parkinson's Disease Society Brain Bank (UKPDBB) (29). In these criteria, the diagnosis of PD is based on the presence of

bradykinesia with one of the following: rest tremor, muscle rigidity, or postural instability (Table 1-1) (29).

1.1.4.1 Motor symptoms

As mentioned in the UKPDBB Clinical Diagnostic Criteria for PD (31), there are four cardinal motor symptoms of PD. Some scientists have grouped them using the acronym TRAP: T for tremor, R for rigidity, A for Akinesia, and finally, P for postural instability. Other motor symptoms that may manifest in PD include freezing and gait deformities (1). Based on its most prominent symptom, PD can be classified into two subtypes: (1) tremor dominant PD and (2) postural instability and gait difficulty (PIGD) PD (32). The former is characterized by earlier age of onset and more prominent tremor, and the latter is characterized by more prominent bradykinesia, cognitive dysfunction, and a rapidly progressive disease course (32).

In order to measure the motor symptoms of PD, different measurement scales have been introduced into practice. The Unified Parkinson's Disease Rating Scale (UPDRS) is widely accepted and is considered to be a valid and reliable measurement of the motor symptoms of PD (1, 33). The UPDRS scale focuses only on motor symptoms, daily life activities, and mood status, but ignores non-motor symptoms of PD. Therefore, the Movement Disorder Society (MDS) has included non-motor symptoms in its new modified scale (MDS-UPDRS) (34). The Hoehn and Yahr scale is another scale; it divides the severity of PD into five stages, ranging from the first, that is "no sign of PD", to the fifth stage, that is, "bedridden or wheelchair bound" (35). Some have argued that although the Hoehn and Yahr scale is simple and widely accepted, it does not capture all motor symptoms of PD, which is why a modified scale has been introduced to overcome some of the original scale's pitfalls; however, there are still doubts

about its reliability and validity (36, 37). The focus of this review will be limited to the four cardinal motor symptoms of PD, which are: bradykinesia, rigidity, tremor, and postural instability.

Table 1-1- UKPDBB Clinical Diagnostic Criteria of PD

Step 1. Diagnosis of a parkinsonian syndrome

Bradykinesia and at least one of the following:

- muscular rigidity
- rest tremor (4–6 Hz)
- postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.

Step 2. Exclusion criteria for PD

History of:

- repeated strokes with stepwise progression
- repeated head injury
- antipsychotic or dopamine-depleting drugs
- definite encephalitis and/or oculogyric crises on no drug treatment
- more than one affected relative
- sustained remission
- negative response to large doses of levodopa (if malabsorption excluded)
- strictly unilateral features after 3 years
- other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis
- exposure to known neurotoxin
- presence of cerebral tumour or communicating hydrocephalus on neuroimaging.

Step 3. Supportive criteria for PD

Three or more required for diagnosis of definite PD:

- unilateral onset
- rest tremor present
- progressive disorder
- persistent asymmetry affecting the side of onset most
- excellent response to levodopa
- severe levodopa-induced chorea
- levodopa response for over 5 years
- clinical course of over 10 years.

Adapted from NICE 2006 (31)

1.1.4.1.1 Bradykinesia

Bradykinesia or slowness of movement is the most important clinical sign that characterizes PD (1). It is strongly associated with dopamine loss in the basal ganglia (38, 39). Bradykinesia manifests in different forms, such as slowness in performing daily activities; slow reaction times; loss of gesturing skills; slowness in swallowing, which may lead to drooling; and loss of facial expression (1).

1.1.4.1.2 Rigidity

Muscle rigidity manifests as an increase in the resistance to muscles' passive movement (40). Usually, this resistance appears as "cogwheel" rigidity; however, it may also appear smooth and continuous. It occurs in both proximal and distal muscles. For example, rigidity could affect the shoulders, neck, and hip proximally, and it could also affect ankles and wrists distally (1).

1.1.4.1.3 Tremor

Tremor is an easily recognized symptom in PD (1). It manifests as an involuntary shaking of body parts. It is defined as a 4-6 HZ tremor that appears in the resting state (resting tremor) and usually disappears with movement. It is characterized in the hands as a "pill rolling" tremor, which starts on one side of the body and spreads later to the other side. Rest tremor can affect the hands, legs, jaw, lips, and chin (41). Tremor that affects the neck, head, and voice is not common in rest tremor, but it is common in other diseases like essential tremor (1).

1.1.4.1.4 Postural instability

The loss of postural reflexes, which causes postural instability, usually occurs after other cardinal motor symptoms in the advanced stage of the disease (42). Postural instability can be identified by conducting the pull test. In this test, the clinician quickly pulls the patient's shoulder backward or forward. If the patient takes more than two steps, this indicates instability in the postural reflexes (1). Postural instability may cause falls, which have been reported in 46% of patients in the advanced stage of the disease (43). Consequently, falling may lead to hip fracture, which is one of the main reasons for hospital admission in PwP (44). Furthermore, falling and fear of falling could dramatically affect PwP's quality of life (QoL) (45).

1.1.4.2 Non-motor symptoms

Although in 1817 James Parkinson discussed in his original work "An Essay on the Shaking Palsy" (46) the presence of some non-motor symptoms of PD, such as constipation, drooling, bladder dysfunction, and sleep problems, it was not until the 1990s that those symptoms attracted researchers' attention (47). Nowadays, it is accepted that neuropsychiatric, sensory, autonomic, and sleep-related symptoms are important and should be treated in PwP as they have a profound effect on QoL (48). Based on the accumulated evidence, at least four non-motor symptoms may predate the motor symptoms. Those symptoms include rapid eye movement behaviour disorder (RBD), hyposmia, constipation, and depression (Table 1-2) (49).

Consequently, several studies have been conducted to find the impact of those non-motor symptoms in both patients' and clinicians' practice. In PwP, it is evident that non-motor symptoms could reduce patients' QoL (50). Furthermore,

some studies have shown that non-motor symptoms impact negatively on PwP's QoL more than motor symptoms do (49). Additionally, the most dominant risk factor for care home placement in PwP is non-motor symptoms, specifically psychosis (48, 51). Nonetheless, it is suggested that treating neurologists tend to underestimate or under-recognize non-motor symptoms (52, 53). In this review, the focus was limited to three non-motor symptoms: depression, psychosis, and dementia, since they relate to the method used to identify the PD cohort in this thesis (See Sections 5.3.2, 6.3.3, and 6.3.4.4).

1.1.4.2.1 Depression

Depression is very common in PwP. Some recent reviews have estimated that 35% of PwP have depression (54, 55). This depression may occur as a result of PD motor symptoms; however, in most cases, it predates the motor symptoms of PD, which means that it is not only a consequence of feeling depressed due to struggling with motor symptoms, but rather, it has a major role in the disease progression (54, 56). The risk factors of depression in PD include a previous history of depression in the patient or patient's family and female sex (57). A positive correlation has been discovered between depression in PwP and the duration of the disease, the occurrence and severity of the PD motor symptoms, PD medications and dosages, and motor fluctuations that are caused by PD medications (54). Additionally, other non-motor symptoms of PD have been correlated with an increasing risk of depression in PwP. Those symptoms include cognition impairment, psychosis, sleep problems, autonomic dysfunction, and anxiety (58). Therefore, it seems obvious that depression has a negative impact on the QoL of PwP (59, 60).

1.1.4.2.2 Psychosis

Psychotic episodes in PD mostly include hallucinations and delusions. The new UK guidelines for PD (31) emphasise that it is better to classify hallucinations and delusions separately and not to combine them under the label of “psychosis”. Although new reports suggest an early emergence of minor hallucinations in PwP even before the occurrence of motor symptoms (25, 61), more significant hallucinations and delusions are not common in the first stages of PD; rather, in most patients, they develop in the advanced stages of PD (62, 63). It is estimated that visual hallucinations and delusions affect 40% of PwP (54). Psychotic episodes may occur as a result of the disease itself, or they may be caused by some PD medications, like dopamine agonists (DAs) (50). Some experts suggest that PD psychosis can be a part of the PD pathological pathway, but also, it can be modified or triggered by using DAs (57). Therefore, it is important when treating psychosis to manage the PD medications and doses first, and then consider antipsychotic medications (42). Given that episodes of hallucinations are more common in the late stages of PD, it is evident that they are the main predictor of nursing home placement in PwP (48).

1.1.4.2.3 Dementia

James Parkinson did not consider cognitive deterioration as a non-motor symptom; rather, he claimed that the intellect was uninjured (46). Nowadays, however, it is well known that cognitive impairment is common, occurring in almost 80% of PwP, especially in the late stages of the disease (54). Clinically, there are some other types of dementia that may overlap with PD dementia (PDD), such as DLB (64). In practical terms, if dementia develops within one year of the onset of PD motor symptoms, it is considered to be DLB, but if dementia develops after one year or more of PD motor symptoms, then it is considered to

be PDD (42). Although new diagnostic criteria of PD do not consider this one-year rule and accept a PD diagnosis irrespective of when the dementia starts (30, 65), some experts still support the one-year rule and suggest that further evaluation is needed before this rule is rejected (66). As dementia is common in the advanced stages of the disease, it is one of the key predictors of nursing home placement in PwP (67). Cognitive impairment is also common in non-demented PwP. A prevalence of 25% to 30% of mild cognitive impairment has been reported in PwP without dementia (57, 68).

Table 1-2-Non-Motor Symptoms of PD

Spectrum of non-motor symptoms in PD. Symptoms in italics indicate poorly understood or lesser known symptoms. MCI = minimal cognitive impairment

Neuropsychiatric symptoms
Depression
Anxiety
Apathy
Hallucinations, delusions, illusions
Delirium (may be drug-induced)
Cognitive impairment (Dementia, MCI)
Dopamine dysregulation syndrome (drug induced)
Impulse control disorders (drug induced)
Panic attacks

Sleep disorders and symptoms
REM sleep behavior disorder (possible pre-motor)
Excessive daytime somnolence, narcolepsy-type "sleep attack"
Restless legs syndrome, periodic leg movements
Insomnia
Sleep disordered breathing
Non-REM parasomnias

Fatigue
Central fatigue
Peripheral fatigue

Sensory symptoms
Pain
Olfactory disturbance
Visual disturbance (blurred vision, diplopia), impaired contrast-sensitivity

Autonomic dysfunction
Bladder urgency, frequency, nocturia
Sexual dysfunction (may be drug-induced)
Sweating abnormalities (Hyperhidrosis)
Orthostatic hypotension

Gastrointestinal symptoms
Dribbling of saliva
Dysphagia
Constipation
Nausea
Vomiting
Reflux
Fecal incontinence

Drug-induced NMS
Hallucinations, delusions
Dopamine dysregulation syndrome
Impulse control disorders (e.g., *compulsive gambling, hypersexuality, binge eating*)

Non-motor fluctuations
Dysautonomic
Cognitive/psychiatric
Sensory/pain

Other symptoms
Weight loss
Weight gain (may be drug-related)

Adapted from Chaudhuri et al. (49)

1.1.5 Early stages vs. advanced stage

By its very nature, PD is a progressive disorder, which means that loss of dopaminergic neurons will continue until the patient's death (69). Therefore, researchers in the PD field are working very hard to find a way to protect neurons from continuous degeneration (70). Based on this continuous neuronal degeneration, clinicians classify the disease stages into early and advanced stages (56). This classification may differ based on the pathological pattern of PD and the clinical symptoms.

Pathologically, Braak divided PD into six stages. The first and second stages represent the pre-motor symptoms, like hyposmia, which is when the brainstem and olfactory area are affected. The third and fourth stages represent the early motor symptoms, when the aggregation of Lewy bodies affects the substantia nigra. Finally, the fifth and sixth stages represent the advanced stages of PD, such as impaired cognition, when the cerebral cortex is involved in the PD processes (22).

Clinically, the early stages of PD also could be distinguished from the advanced stages by using clinical scales like the Hoehn and Yahr scale (36). Basically, stages 1 and 2, when there are no difficulties in walking, are considered early stages. Stages 4 and 5, when there are substantial difficulties in walking, are considered advanced stages, and stage 3, when there are minimum to moderate difficulties in walking, is in the middle (36). In addition to the Hoehn and Yahr scale, other scales may be used to measure PD severity, such as UPDRS, the Schwab and England Disability Scale, and others (42). There are some reports that suggest involving the prodromal signs and symptoms that predate PD motor-symptoms in early PD. For example, in 2014, the International Parkinson’s Disease and Movement Disorder Society (MDS) suggested classifying PD early stages into

three classes. The first is preclinical PD, which includes loss of dopaminergic neurons, but without any symptoms. The second is prodromal PD, which includes loss of dopaminergic neurons with some symptoms that are not severe enough to be classified as classical PD. Thirdly, clinical PD includes both loss of neurons and the traditional cardinal motor symptoms (65, 71). Later, and based on the suggested prodromal signs of PD, MDS created a tool that helps to calculate the probability of prodromal PD (72); however, both the validity and the reliability of this tool are under question, since it has shown low sensitivity and low predictive value in some reports (73-75). For clinical PD, the MDS task force classified the clinical PD diagnosis into probable and clinically established PD (30) with a diagnostic sensitivity of 94.5% and a specificity of 88.5% for probable PD (76). For the purpose of recruiting *de novo* and early PD patents in clinical trials that examine the neuroprotective properties of a candidate drug, the MDS published criteria called the "Clinically Established Early PD" criteria, which had a significantly higher specificity (95.4%) with a sensitivity of 69.8% (77). In clinical trials, test specificity is more important than sensitivity, since lower sensitivity can be addressed by increasing the sample size, and therefore does not alter the power of the study (78). In contrast, lower specificity can lead to an increase in the number of recruited patients who have false positive tests, which may expose those patients to unnecessary harm resulting from the drug being tested (79).

1.2 Treatment of Parkinson's disease (motor symptoms)

Until now, there has been no approved neuroprotective or disease modifying pharmacotherapeutic agent that could stop or slow the progression of alpha-synuclein pathology or substantia nigral neuronal loss in PwP (31). However, there are various approaches that help in treating the symptoms of PD. In addition to traditional pharmacological therapy, surgery, including deep brain stimulation (DBS), physiotherapy and occupational therapy have shown some

benefits in ameliorating motor and non-motor symptoms (25, 42). The focus of this introduction will be limited to the pharmacological therapies.

1.2.1 Medications

Despite the lack of neuroprotective evidence for all PD medications, they may improve QoL and increase life expectancy for many PwP (80). Therefore, it is essential to treat PD symptoms appropriately in order to help patients engage in their social activities and improve their QoL (69, 81). As the lack of dopamine is the main pathological problem in PD, most PD medications have been designed to increase dopamine levels in the brain by different pathways, as will be discussed in the following sections (82). (To see all PD medications in the UK market, see Table 1–3, Table 1–4, and Table 1–5 (83)).

1.2.1.1 L-dopa

Although L-dopa was first used in PD treatment more than fifty years ago, it continues to be the mainstay therapy in managing PD motor symptoms (84, 85). Pharmacologically, L-dopa is the precursor of dopamine, and upon administration, it increases the dopamine level in the substantia nigra, relieves the motor symptoms of PD, and improves QoL (80). Dopa decarboxylase inhibitors (carbidopa or benserazide) are taken along with L-dopa in order to inhibit its peripheral side effects, such as nausea and vomiting, and increase its central action on the brain (86). Since its discovery, L-dopa has been used widely, but in the 1990s, several experiments on animal models explored the possible neurotoxicity of L-dopa and found that neurons could not survive exposure to L-dopa (87). However, a human ELLDOPA trial found that L-dopa was not neurotoxic and slowed the progression of PD (88). Later, a LEAP study also found that L-dopa was not neurotoxic, but no disease-modifying effect was

observed (89). The difference between the disease-modifying outcomes in the two trials could be attributed to their design and duration of follow-up. In contrast to the ELLDOPA trial, which had a follow-up of 40 weeks and a 4-week washout period, the LEAP study had a follow-up of 80 weeks with two phases (40 weeks each) and a delayed-start that theoretically enabled distinction between the disease-modifying effect and symptomatic effect of L-dopa. In the first 40 weeks of the LEAP study, PwP were randomly assigned to L-dopa or placebo groups, and in the second 40 weeks, all PwP groups received L-dopa. By the end of 80 weeks, the motor symptoms (the UPDRS scores) were similar in both groups, which appeared to confirm that L-dopa had no disease-modifying effect (89). However, although these results have led some experts to claim that the LEAP study provided "the final nail in the coffin of disease modification for dopaminergic therapies" (90), there are still opportunities for future trials that could prove the disease-modifying effect of L-dopa, especially if the understanding of disease pathogenesis develops and if clinical trials take the clinical, pathological, and genetic phenotypes of PD into consideration during the study design phase (91).

L-dopa has very beneficial and observable effects in ameliorating motor symptoms without significant side effects in the early stages of PD. However, after five years of treatment, dyskinesia (involuntary muscle movement) may develop. Patients with troublesome dyskinesia (that causes functional disability and/or meaningful discomfort) may require modifications to be made to their treatment plan, such as decreasing the L-dopa dosage or/and adding other medications such as catechol-O-methyl transferase (COMT) inhibitors, amantadine, and monoamine oxidase-B (MAO-B) inhibitors (86, 92). It is a matter of debate whether non-troublesome dyskinesia requires treatment and if PwP should accept it instead of being under-medicated, slow, and rigid (93, 94). There should not be a 'one size fits all' strategy for dealing with dyskinesia, and

every patient should be examined and treated individually based on the troublesomeness of their dyskinesia and its impact on their QOL and other PD symptoms (94). In the early stages of PD, L-dopa response is typically of quite long duration, and most PwP respond very well, to the extent that they may skip some doses without noticing any worsening or fluctuations in their symptoms (95). However, this long response to L-dopa does not persist; after a few years, a 'wearing off' or 'short response' to L-dopa develops in most patients (84). In this case, patients feel better for an hour or less after they have taken L-dopa, and they may experience peak-dose dyskinesia and then a return of their motor symptoms until the next dose of L-dopa and so on, leading to more frequent dosing (96).

In order to maximize the effects of L-dopa and decrease the wearing-off phenomenon, different methods have been introduced. First, it is important to take L-dopa on an empty stomach (one hour before or two hours after food), since the concurrent protein intake may delay the oral absorption of L-dopa (97). The second method is adding entacapone (a COMT inhibitor) to the L-dopa/carbidopa combination in a fixed dose formulation (Stalevo®) (98) (See Section 1.2.1.5). Finally, a dosage form that allows continuous L-dopa infusion is achieved by inserting a tube into the gastric system (the levodopa-carbidopa intestinal gel Duodopa®) (99). Duodopa is only used as a surgical intervention in later stages when the disease is not well managed with traditional pharmacotherapy but is still responsive to L-dopa therapy.

In practice, most PwP do not receive L-dopa until the appearance of significant motor symptoms, which in turn, have a significant negative impact on QoL. Some studies have shown that initiating L-dopa at the time of PD diagnosis is associated with more improvement in QoL compared to the later initiation of L-dopa (96, 100) and compared to the early initiation of dopamine agonists (DAs)

and monoamine oxidase inhibitors B (MAO-B inhibitors) (101). Nonetheless, there continues to be a strong debate about the best therapy to start with in the early stages of PD, and this issue will be discussed later (see Section 2.1).

1.2.1.2 Dopamine agonists (DAs)

DAs exhibit their action in PD by stimulating post-synaptic dopaminergic receptors without the need for a special transport system or an enzymatic conversion to help them cross the blood–brain barrier (102). There are five types of dopamine receptors: D_1-D_5; however, D_1 and D_2 receptors are the main receptors that, once activated by DAs, lead to improved PD motor symptoms (103). The activation of D_3 receptors can also improve PD symptoms, but D_3 receptors are located in the limbic system, which may explain the behavioural side effects of DAs such as impulse control disorders (ICDs) (103). Different DAs have different affinity profiles across the range of dopamine receptors, which contributes to the side-effect profiles of each drug. For example, it is evident that ICDs are more common in PwP using pramipexole and ropinirole compared to rotigotine users (104, 105). Moreover, studies have demonstrated that the affinity of pramipexole and ropinirole to D_3 receptors is 100 times greater than to D_2 receptors, whereas the affinity of transdermal rotigotine to D_3 receptors is only 20 times greater than to D_2 receptors (104, 105).

DAs were originally derivations of the ergot plant based compounds whilst the newer generation of drugs are non-ergot derivatives. Oral ergot DAs were the first to be used in practice; however, they are rarely used nowadays due to the risk of cardiac valvular fibrosis related to their serotonergic effects (106). In contrast to L-dopa, all DAs have a longer half-life and allow for less complex medication regimens in the early stages of PD (104, 107). However, DAs are less effective for treating PD motor symptoms than L-dopa (102). The Comparison of

the Agonist Pramipexole versus L-dopa on Motor Complications of Parkinson's Disease (CALM-PD) trial found that after 48 months of initial therapy, L-dopa resulted in significantly improved motor symptoms (assessed by the UPDRS score) compared to pramipexole ($p = 0.003$) (108).

Common side effects of all DAs include hallucinations, oedema, and cognitive decline (109). Therefore, it is common practice to avoid using DAs in the very elderly, who may suffer from cognitive problems (109, 110). Behavioural side effects such as ICDs, characterised by failure to resist the urge for sexual intercourse, gambling, eating, etc.) could also occur explicitly in the non-ergot derived DA agonists (104). One longitudinal study found that the five-year cumulative incidence of ICDs in PwP was 46%, which was associated with increasing the dose and duration of DAs (111). Additionally, recent reports have suggested a strong correlation between DAs and the incidence of heart failure (112).

Regarding DAs' place in a PD treatment plan, DAs could be initiated as a monotherapy in the early stages; however, after 2-5 years, the addition of L-dopa is required in the majority of patients (113). Although it has been argued that starting with L-dopa monotherapy is sufficient in the early stages of PD, a combination of L-dopa and DAs was found to be superior to L-dopa monotherapy in a large meta-analysis of 15 clinical trials (114).

1.2.1.3 Apomorphine

Apomorphine is a dopamine agonist, and in PD treatment, it is available either as a subcutaneous injection or as a continuous infusion (86). It differs from other DAs in its catechol moiety, which allows for stronger binding to D_1 receptors whilst most other DAs have negligible D_1 affinity (115). It is considered as a

"rescue therapy" that helps reduce "off" time (the time when PD medication does not work well) in the advanced stages of PD (116). It is characterized by a rapid onset (4-12 minutes) and a short duration of action that does not interfere with other PD medication regimens (45-60 minutes) (117). One major problem with its use is that it may cause significant nausea and vomiting, which may require the use of an antiemetic like domperidone or trimethobenzamide at least two days before the apomorphine dose (118). The more complex formulation and administration requires support from specially trained PD nurse specialists (PDNS).

1.2.1.4 Monoamine Oxidase B (MAO-B) inhibitors

MAO-B is an enzyme that metabolizes dopamine in dopaminergic synapses in the brain, and when this enzyme is inhibited by MAO-B inhibitors (selegiline, rasagiline and the recently released safinamide), the striatal dopamine level increases accordingly (119). Vertigo, nausea, and headaches are common side effects of these medications; however, some have their own specific side effects. For instance, selegiline may cause insomnia, since it is metabolized to methamphetamine, which is not the case with rasagiline (120).

In practice, MAO-B inhibitor could be used as an add-on therapy to L-dopa in PwP with motor fluctuations (121, 122). While different clinical trials (TEMPO, ADAGIO) have suggested the possible neuroprotective properties of MAO-B inhibitors, the American Food and Drug Administration (FDA) voted against the neuroprotective indication of rasagiline, and several guidelines did not support this claim (31, 123-126). Nevertheless, with its symptomatic effects, it is still can be used as a monotherapy in early PD (102).

1.2.1.5 Catechol-O-Methyl Transferase (COMT) inhibitors

Although the prevention of dopa-decarboxylase blocks L-dopa conversion to dopamine in the periphery, COMT enzyme is still able to metabolize L-dopa to dopamine in the periphery. Therefore, COMT inhibitors could maximize dopamine concentration in the brain, and they can work in PD only as an add-on therapy to L-dopa (127, 128).

Three different medications from this class have been approved in PD: tolcapone, entacapone, and the 3rd generation opicapone. Tolcapone is black listed in the UK and not commonly used nowadays due the risk of hepatic failure (129), even though one study found that for selected patients with the appropriate monitoring of liver enzymes, tolcapone can be used safely (130). Tolcapone is more potent and has a longer half-life than entacapone; however, most neurologists prefer to use entacapone and sacrifice the benefits of tolcapone due to its hepatotoxicity unless patients struggle to tolerate the fixed dose STALEVO® (42).

Even though COMT inhibitors theoretically should increase the "on" time (the time when PD medication works well) in those who are on L-dopa therapy without increasing dyskinesia, many studies have found an increase in L-dopa-induced dyskinesia, which leads to a more than 25% decrease in the daily dose of L-dopa in patients taking COMT inhibitors (42, 84).The STRIDE-PD study found that adding entacapone to L-dopa/carbidopa in the early stages of PD led to a higher risk of L-dopa-induced dyskinesia compared to L-dopa/carbidopa alone (131). Therefore, initiation of COMT inhibitors should be delayed until the manifestation of motor fluctuations (i.e., the wearing-off phenomenon caused by L-dopa) (31).

1.2.1.6 N-Methyl-D-Aspartate (NMDA) antagonists

The pharmacological action of NMDA antagonists in PD treatment is complex (132), but it is evident that amantadine (NMDA antagonist and antiviral) could improve L-dopa-induced dyskinesia (133). Recent guidelines recommend not using amantadine to reduce dyskinesia unless DAs, MAO-B inhibitors, and COMT inhibitors have been tried first (31)

1.2.1.7 Anticholinergics

Anticholinergics were routinely used in the treatment of PD before the discovery of L-dopa; however, due to their troublesome side effects, their use nowadays is limited to managing severe tremor in younger patients who do not suffer from any cognitive problems (86). In the recent National Institute for Health and Care Excellence (NICE) guidelines, the use of anticholinergics in treating dyskinesia or motor fluctuations is not recommended (31).

1.2.1.8 L-dopa equivalent daily dose (LEDD)

As there are different PD medications which have multiple doses and intensities that complicate the therapy, a simple and reliable number that estimates the overall burden of treatment is needed. The L-dopa equivalent dose (LED) of any PD medication is the dose that results in the same symptomatic effect as 100 mg of L-dopa (immediate release formula) (134). The total LEDs that the patients take in one day is called the "L-dopa equivalent daily dose", which in turn, could be used to compare the overall burden of PD treatment in PwP (134). To see the LEDs for all PD medications, see Table 1-6.

Table 1-3- L-dopa Products

Medication / Feature	CO-BENELDOPA Levodopa and Benserazide			CO-CARELDOPA Levodopa and Carbidopa			Levodopa/Carbidopa/Entacapone
Dosage form	Dispersible tablet	Modified release capsule	Capsule	Modified release tablet	Tablet	Gel	Tablet
Strength	Madopar® 50/12.5 Madopar® 100/25	Madopar® CR 100/25	Co-beneldopa 50/12.5 Co-beneldopa 100/25 Co-beneldopa 200/50 Madopar® 50/12.5 Madopar® 100/25 Madopar® 200/50	Caramet® CR 100/25 Caramet® CR 200/50 Co-careldopa 100/25 Co-careldopa 200/50 Half sinemet® CR 100/25 Sinemet® CR 200/50 Lecado® 100/25 Lecado® 200/50 Apodespan® PR 200/50 Prolonged-release Tablets	Co-careldopa 50/12.5 Co-careldopa 100/10 Co-careldopa 100/25 Co-careldopa 200/25 Sinemet® 50/12.5 Sinemet® 100/10 Sinemet® 100/25 Sinemet® 250/25	Duodopa® intestinal gel 100 ml Levodopa 20 mg / 1ml Carbidopa 5 mg /1 ml	Three brands (Sastravi®, Stalevo®, Stanek®) 50/12.5/200 75/18.75/200 100/25/200 125/31.25/200 150/37.5/200 175/43.75/200 200/50/200

Table 1-4- Dopamine Agonists

Medication / Feature	Pramipexole Non-ergot		Ropinirole Non-ergot		Rotigotine Non-ergot	Cabergoline Ergot	Pergolide Ergot	Bromocriptine Ergot		Apomorphine	
Dosage form	Modified release tablet	Tablet	Modified release tablet	Tablet	Transdermal patch	Tablet	Tablet	Tablet	Capsule	Solution for injection	Solution for infusion
Strength	(Mirapexin®, Oprymea®, Pipexus®, pramipexole) 0.26 mg & 0.52 mg &1.05 mg &1.57 mg & 2.1 mg & 2.62 mg & 3.15 mg	(Mirapexin®, Oprymea®) 0.088 mg & 0.18 mg & 0.35 mg & 0.7 mg Pramipexole 88 mcg & 180 mcg & 350 mcg & 700 mcg	(Ipinnia® XL, Ralnea® XL, Raponer® XL, Requip® XL, Repinex® XL, Ropilynz® XL, Spiroco® XL) 2 mg & 4 mg & 8 mg Ipinnia® XL 3 mg & 6 mg	(Adartrel®, Requip®, Ropinirole) 250 mcg & 2 mg (Adartrel®, Ropinirole) 500 mcg (Requip®, Ropinirole) 1 mg & 5 mg	Neupro® 1mg/24 hours &2mg/24 hours & 3mg/24 hours &4mg/24 hours &6mg/24 hours &8mg/24 hours	(Cabergoline, Dostinex®) 500 mcg (Cabergoline, Cabaser®) 1 mg & 2 mg	Pergolide 50 mcg & 250 mcg & 1 mg	Bromocriptine 1 mg & 2.5 mg	Parlodel® 5 mg & 10 mg	Apogo® 500 mg / 5 ml Apogo® PEN 30 mg/ 3 ml	Apogo® PFS 50mg / 10ml

Table 1-5- Other PD Medications

Medication / Features	MAO-B inhibitors Rasagiline (Azilect®) Selegiline (Eldepryl®, Zelapar®) Safinamide (Xadago®)		COMT inhibitors Entacapone (Comtess®) Tolcapone (Tasmar®) Opicapone (Ongentys®) Levodopa/Carbidopa/Entacapone (Sastravi®, Stalevo®, Stanek®)		Anticholinergics Orphenadrine Procyclidine (Kemadrin®) Trihexyphenidyl			Amantadine	
Dosage form	Oral Lyophilisate	Tablet	Capsule	Tablet	Tablet	Oral solution	Solution for injection	Capsule	Oral solution
Strength	Zelapar® 1.25 mg	Azilect® 1 mg Rasagiline 1 mg Eldepryl® 5 mg & 10 mg Selegiline 5 mg & 10 mg Xadago® 50 mg & 100 mg	Ongentys® 50 mg	Comtess® 200 mg Entacapone 200 mg Tasmar® 100 mg Three brands (Sastravi®, Stalevo®, Stanek®) 50/12.5/200 75/18.75/200 100/25/200 125/31.25/200 150/37.5/200 175/43.75/200 200/50/200	Orphenadrine 50 mg Kemadrin® 5 mg Procyclidine 5 mg Trihexyphenidyl 2 mg & 5 mg	Orphenadrine 50 mg / 5 ml Procyclidine 2.5 mg/ 5 ml & 5 mg/ 5 ml Trihexyphenidyl 5 mg/ 5 ml	Procyclidine 10 mg / 2 ml	Amantadine 100 mg	Amantadine 50 mg/ 5 ml

Table 1-6- LEDs of PD Medications

Drug*	Total L-dopa equivalent dose (LED) mg/ 100 mg L-dopa
L-Dopa	100
Controlled release L-dopa	133
Duodopa	90
Entacapone	L-dopa * 0.33
Tolcapone	L-dopa * 0.5
Pramipexole	1 mg salt
Ropinirole	5
Rotigotine	3.3
Piribedil	100
Lisuride	1
Bromocriptine	10
Pergolide	1
Cabergoline	1.5
Selegiline 10 mg (oral)	10
Selegiline 1.25 mg (sublingual)	1.25
Rasagiline	1
Amantadine	100
Apomorphine (infusion or intermittent injections)	10

* “To calculate the total LED for COMT inhibitors, the total amount of L-dopa (including CR L-dopa if a COMT inhibitor is given simultaneously) should be calculated and then multiplied by the appropriate value. For Stalevo, the L-dopa and COMT inhibitor should be split and calculated separately. The British National Formulary states that selegiline 10 mg oral is equivalent 1.25 mg sublingual”. Adapted and quoted from Tomlinson et al (134).

1.3 Treatment of Parkinson's disease (non-motor symptoms)

1.3.1 Depression

Depression treatment in PwP is not very different from the traditional treatment of depression (42, 135). The recent NICE guidelines did not provide any recommendation for depression management in PwP (31). However, the recommendation of the previous NICE guidelines (NICE 2006) was to offer selective serotonin reuptake inhibitors (SSRI) to patients with moderate to severe depression (136). Although several meta-analyses and systematic reviews have tried to provide clear guidance (57, 137, 138), there is still some uncertainty regarding the evidence favouring some medications over others, and clinical experience plays a major role in such management (80). Some PD medications show promise in depression management, such as pramipexole (139), but most of the time, additional antidepressant therapy is required (57, 140). Regarding traditional antidepressants, tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) are the most common medications in managing depression in PD (84). Despite the clinical trials that have shown the superiority of TCA, like desipramine over SSRI, in managing depression in PwP, in practice, SSRI are more commonly used, and a new systemic review found that SSRI are the first line therapy despite their weak evidence (141).

1.3.2 Psychosis

Psychosis can be caused by PD itself and by PD medications like DAs, so, before starting antipsychotics, it is essential to reduce dopaminergic doses to a level that does not affect motor symptoms negatively (42, 140). If psychotic symptoms are not controlled with the previous strategy, atypical antipsychotics that include clozapine or quetiapine can be used (31). Although its efficacy has not been established in big randomized clinical trials, different experts, including

NICE 2017 (31, 140), have suggested that off-label prescribing of quetiapine should be the first-line therapy in PD psychosis. Clozapine has an approved indication for treating psychosis in PwP; however, it is considered to be a second line treatment after quetiapine due its risk of agranulocytosis and its requirement for continuous blood monitoring (31, 140). A cholinesterase inhibitor (rivastigmine) shows some evidence of hallucination reduction and improved behavioural symptoms in PwP, although it has a slower response compared to atypical antipsychotics (142). Recent NICE guidelines (2017) did not recommend rivastigmine as part of therapy; however, they recommended further research to compare rivastigmine with atypical antipsychotics in managing psychosis in PwP (31).

1.3.3 Dementia

Cholinesterase inhibitors and NMDA antagonists have shown efficacy in dementia management in PwP (84, 143). A recent Cochrane review revealed that there is an association between cholinesterase inhibitors and improvements in cognitive functions, behavioural symptoms, and daily life activities in PDD patients (142). An NMDA antagonist (Memantine) showed positive results in PDD; however, the evidence is still weak (140). Rivastigmine capsules are the only form of cholinesterase inhibitors approved in the UK to treat PDD; however, new NICE guidelines did not specify rivastigmine as a first line in PDD treatment. Rather, they considered the whole group of cholinesterase inhibitors as a first line in both PDD and DLB. According to NICE guidelines, memantine may be considered only if cholinesterase inhibitors are contraindicated or are not tolerated (31).

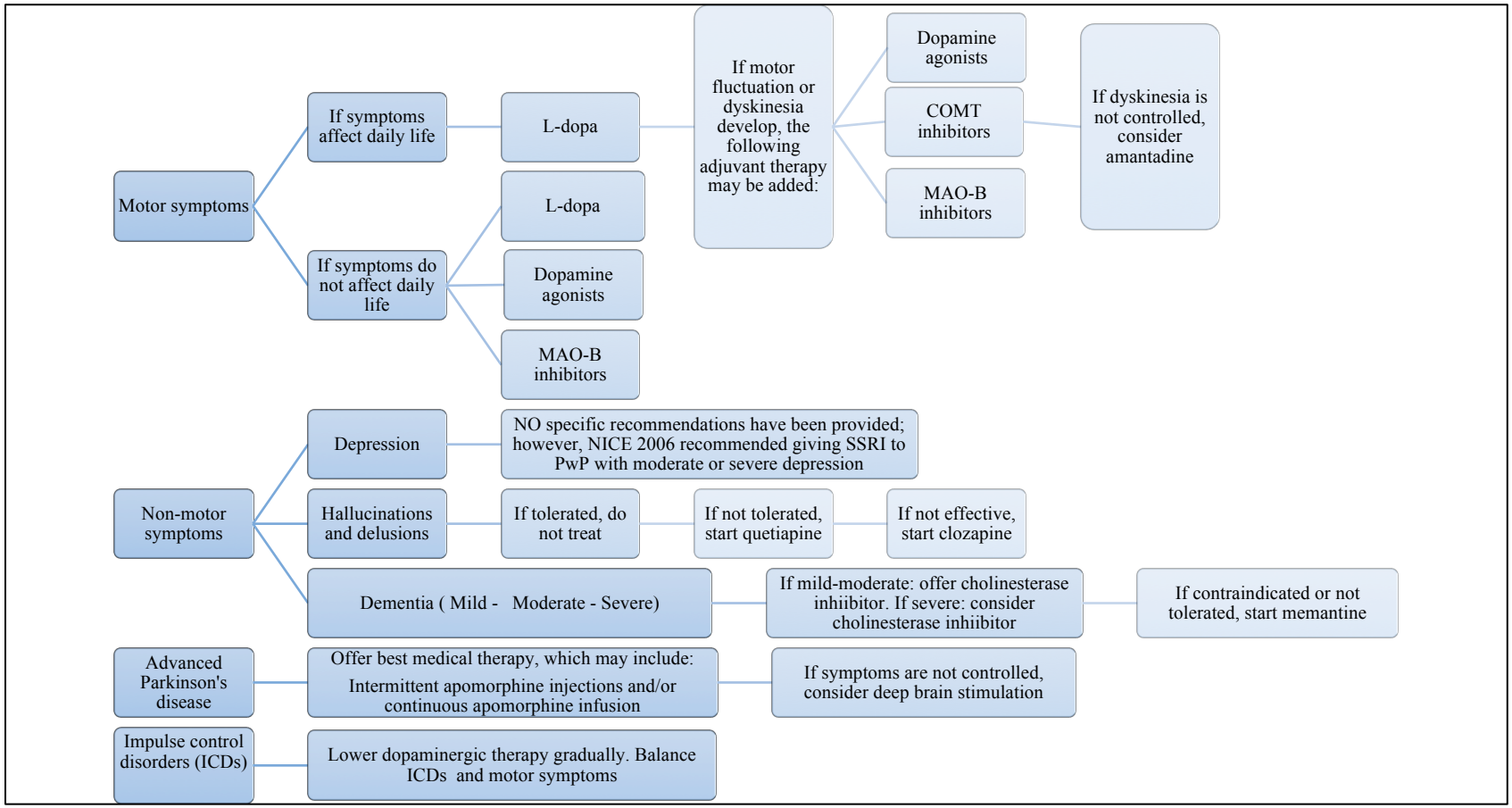
1.4 The National Institute for Health and Care Excellence (NICE) guidelines 2017

NICE published its updated Parkinson's guidelines in July 2017. There are no major changes in the pharmacological management of PD compared to NICE 2006; however, NICE 2017 emphasised the ICDs associated with DAs and provided some recommendations on recognition and management of ICDs. In contrast to NICE 2006, NICE 2017 did not recommend the use of ergot DAs in the early stages of PD, putting instead a "Do not offer" statement due to cardiac valvular problems. Additionally, in accordance with NICE 2006, NICE 2017 did not support neuroprotective indications for any PD medications. Finally, no specific recommendations have been provided for Duodopa® use and no clear recommendations for depression management in PwP have been provided (31, 136). A brief summary of NICE 2017 guidelines is shown in Figure 1-1.

1.5 Physicians compliance with prescribing national guidelines and prescribing factors

Physician adherence to national prescribing guidelines could be evaluated by measuring prescribing patterns, and doing so would help determine the factors that affect prescribing, such as sex, age, socioeconomic status, education, drug pricing, and other disparities (144). In PD, the national guidelines are not always implemented in practice; instead, research has identified some barriers to such implementation. For example, a cross-sectional survey performed on 213 neurologists in Germany sought to examine the main barriers to the implementation of PD guidelines. The barriers reported by the neurologists included lack of time, failure to reconcile patients' preferences with national guidelines, and neurologists' lack of awareness (145). Chapter 2 reviews in detail and at a global scale the studies that have examined both the extent to which guidelines are adhered to and other factors that may affect prescribing for PD.

Figure 1-1- A brief summary of NICE 2017 guidelines



1.6 Theoretical framework

1.6.1 Introduction

The theoretical framework underpinning the research and discussions in this thesis is based on the idea of linking pharmacoepidemiology as a broad umbrella for drug research to the concept of improving “population health”.

The thesis’s theoretical framework will merge the definition of pharmacoepidemiology and drug utilization research with two well-known frameworks, namely the Eisenberg Framework of Clinical Decision-Making and Judgment and the Integrated Framework for Risk Management and Population Health (146, 147). The rationale behind using the Eisenberg Framework is that it explains the factors that affect the prescribing decisions of physicians, which, in turn, have a big impact on drug utilization research (146, 148). Although the Eisenberg Framework explains clinical decision factors in detail, it does not mention the consequences of these factors on the population’s health (146). Additionally, it does not provide a measurement tool to identify the criteria of a good clinical decision (146). Therefore, the Integrated Framework for Risk Management and Population Health is used to link health determinants (the prescribing factors) to health risk science (the consequences of clinical decision factors on the population’s health) (147). Furthermore, prescriber adherence to national guidelines and literature recommendations is used in this thesis as a measurement tool for good prescribing (144) .

In this chapter, the concept of pharmacoepidemiology and drug utilization research will be defined. Then, the two theoretical frameworks used in this thesis will be discussed, followed by the presentation of a figure that combines the thesis framework with the concepts of both pharmacoepidemiology and drug utilization research.

1.6.2 Relationship between Pharmacoepidemiology and Drug Utilization Research

1.6.2.1 Pharmacoepidemiology

Pharmacoepidemiology can be defined as the study of the effects and use of medication in large populations (149, 150). It encompasses elements of both clinical pharmacology and epidemiology (149). It aims to examine the general use of medications in the population, including the pattern of use, efficacy and safety (150). Research in this field was started in the 1960s, employing very simple descriptive methods that were applied to relatively small samples of people or prescription drugs (150). However, the implementation of electronic health records that covered very large populations, in addition to the noticeable advancement in big data analysis methods, has revolutionized the research field of pharmacoepidemiology (150, 151). Another factor that accelerates research in the field of pharmacoepidemiology is the intrinsic limitations of the gold standard in examining the efficacy and safety of pharmacological interventions, namely randomized clinical trials (RCT) (152). These limitations include small sample size, lack of population representativeness, high costs, and short duration (153). Such limitations are absent in pharmacoepidemiological studies, which use large population electronic health records, and which are characterized by large sample sizes, representativeness of the whole population, low costs, and ability to cover long durations of medication use (152). However, this does not imply that pharmacoepidemiological studies are without limitations. The observational nature of these studies means that it is difficult to control confounding factors that may affect research outcomes (154). Additionally, inherent limitations to observational pharmacoepidemiological

studies include missing data, subjection to different types of bias (e.g. information and ascertainment bias), and possible breaching of patients' confidentiality.

1.6.2.2 Drug Utilization Research

An extensive definition of drug utilization research was presented in one of the pharmacoepidemiology textbooks as follows: "an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes" (155).

Although the terms 'drug utilization research' and 'pharmacoepidemiology' are sometimes used interchangeably in the literature (148), some differences between these two fields have been proposed. One difference is that pharmacoepidemiology mainly focuses on the quantitative risks and benefits of medications on large cohorts of the population (148). On the other hand, drug utilization research provides quantitative and qualitative methods that evaluate medication use and prescribing patterns in different settings in addition to the factors that affect these uses and patterns (148, 156). Drug utilization research involves pharmacoepidemiological concepts that can be used in health service research, which subsequently may influence care decisions and policy implementations related to medication use (148, 155) (Figure 1-2). Additionally, drug utilization research helps to enhance knowledge and awareness of medication use and prescribing patterns, detects inappropriate drug use, and provide tools to assess the efficacy and feasibility of interventions that are designed to enhance drug use (148, 157).

Figure 1-2- Relationship between pharmacoepidemiology, drug utilization research, and health services research

Wettermark et al. (148).

Drug utilization research can be classified into descriptive and analytical methods (148). Descriptive methods, by their very nature, focus on describing the pattern of medication use and assessing whether this pattern is in accordance with the efficacy and safety information related to use of this medication (148). Analytical methods, on the other hand, focus more on factors that affect medication use (e.g. physicians' characteristics, patients' characteristics, etc.) and the outcomes resulting from such use (e.g. quality of care and health outcomes) (148). Descriptive and analytical methods in drug utilization research have been used extensively since the inception of research in this field; however, a major shift toward the analytical method has occurred in the last decade, with more research focusing on health outcomes and quality of care (158).

1.6.2.3 Prescriber adherence to national guidance and literature recommendations as a measurement tool for good prescribing.

Adherence to national prescribing guidelines could be evaluated by measuring prescribing patterns, and doing so would help in defining factors that affect prescribing, such as sex, age, socioeconomic status, education, drug pricing, and

other disparities (144, 156). While good prescribing has been defined in the literature as adherence to national guidelines, this definition is not comprehensive, given the various factors that affect provider decisions, including but not limited to drug availability, patients' choices, drug cost, and biological and genetic factors (159). However, adherence to national guidelines is often the only possible way to define and examine good prescribing, especially when using electronic databases that lack the majority of social patient-level data (156). Therefore, information extracted from both descriptive and analytical drug utilization studies, such as the incidence and prevalence of medication use, can be used by policy makers and regulators to examine the extent to which prescribers are prescribing in accordance with national guidelines and which factors affect their clinical decisions, which altogether would help the regulators in planning and implementing the necessary regulations to guarantee the best health outcomes (152).

1.6.3 Eisenberg's Framework of Clinical Decision-Making and Judgment

In studies of prescribing patterns, it is important to evaluate factors that affect prescribing decisions. In order to achieve this, Eisenberg, in his paper "Sociologic influences on decision-making by clinicians", proposed a framework that explained clinical decision factors (146).

Eisenberg argued in his framework that a complex interplay between patients, physicians, patient-physician interactions, and health-system characteristics is responsible for physicians' clinical decisions (146) (Figure 1-3).

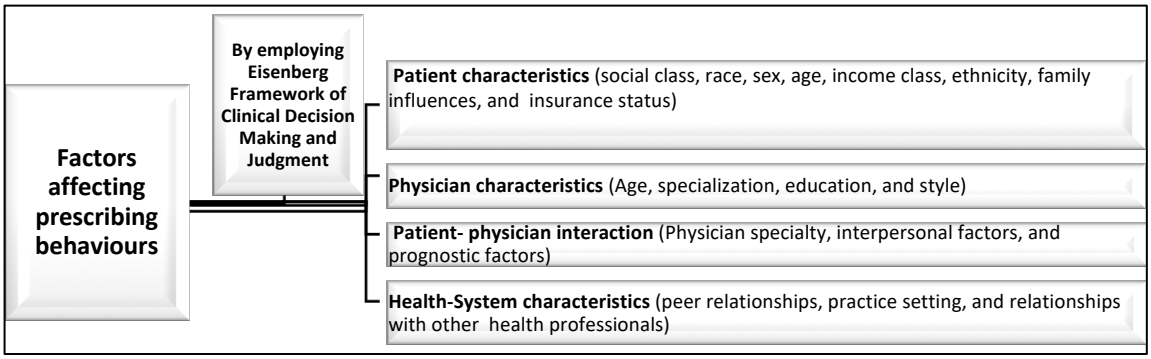


Figure 1-3- Eisenberg's Framework of Clinical Decision-Making and Judgment

As shown in Figure 1-3, there are four sociological factors that affect physicians' decisions in clinical practice. Those factors are patients' characteristics, physicians' characteristics, the relationship between patients and physicians, and finally, the impact of the health care system and peer pressure (146).

Firstly, regarding patients' characteristics, Eisenberg proposed the following characteristics as factors that affect clinical decision-making: patients' sex, social class, ethnicity, family influence, and others (146). Eisenberg provided some examples in the literature to support his argument. For example, females are more likely to receive suboptimal care after cardiovascular disease. Additionally, patients with lower social class or from minority races are more likely to not receive optimal care (146). Family may also influence physicians' decision-making about care home placement and resuscitation.

Secondly, physicians' characteristics have a significant impact on their clinical decisions. For example, physician's specialty has an impact on clinical decisions. Internal medicine physicians and psychiatrists tend to make slow and measured decisions, while surgeons make rapid and less reflective decisions (146). Physicians' age also has an impact on their clinical decisions, according to Eisenberg. Older physicians have been shown to prescribe drugs less appropriately compared to younger physicians. Physicians' personality is another factor that affects clinical decisions. Interventionist physicians who tend to

intervene in patients with medical problems more frequently are disease-oriented and tend to take immediate actions. On the other hand, health maintenance oriented physicians are patient-oriented and tend to observe the situation (146).

Thirdly, the relationship between physician and patient can affect clinical decisions in various ways. For example, the type of relationship is very important in clinical decision-making. Three types of patient-physician relationship have been proposed by Eisenberg. The activity-passivity relationship is the one which the patient is totally passive in respect of any clinical decision made and the physician makes the entire decision without any patient interaction. Surgeons may be involved in this kind of relationship as a result of frequent exposure to events that necessitate immediate decisions. The second type of patient-physician relationship is the guidance-cooperation relationship, in which the physician is expected to provide recommendations to the patient, and the patient is expected to follow these recommendations. The third type is the mutual participation relationship, in which the physician is more involved in patients' care by helping them to help themselves. Psychiatrists and paediatricians may be involved in this kind of mutual relationship. Patients with chronic diseases who need to monitor their symptoms for a long time are more likely to adopt a mutual relationship with their physicians (146).

The fourth factor that Eisenberg proposed in his framework is the impact of the health care system and peer pressure. For example, it is evident that the quality of care provided by physicians is influenced by the work environment more than by the physicians' medical training. In addition, the organization's bureaucratic structure may have an impact on the decisions made by the physicians who work in this organization. Physicians who work in bureaucratic organizations tend to have less autonomy and follow a structured process during decision-making compared to their counterparts who work in less or non-bureaucratic

organizations. Peer pressure is another factor that affects the decision-making process. Some studies have shown that the adoption of newly marketed drugs is strongly influenced by relationships among physicians themselves (146).

To summarize, the Eisenberg Framework of Clinical Decision-Making and Judgment is a suitable framework that explains a range of clinical decision-making factors. Although this framework was published in 1979, it is still valid and has been utilized in many prescribing studies (160, 161). One caveat to this framework is that it does not link clinical decision factors to health outcomes. Therefore, it was merged in this thesis with the Integrated Framework of Risk Management and Population Health proposed by Krewski et al. (147) in order to link the prescribing pattern of antiparkinsonian agents to the concept of population health.

1.6.4 Integrated Framework for Risk Management and Population Health

Krewski and colleagues have discussed the concepts of risk management and population health in their proposed framework (147). They argued that the risk management field has grown independently of the population health field. While the risk management field focused on managing all risks that the population might encounter, including health, environmental, and social risks, population health focuses on the effects of lifestyle changes and improving the physical and social environment, which in turn can improve the population's health more than the health system (147). To combine the population health field with the risk management field, Krewski and colleagues came up with the following integrated framework (Figure 1-4).

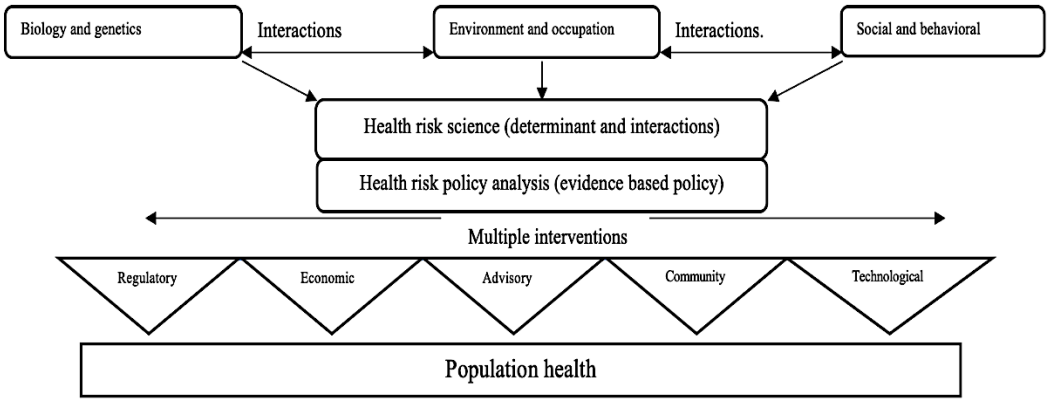


Figure 1-4- Integrated Framework for Risk Management and Population Health

(Adapted from Krewski et al., 2007 (147)).

The health determinants in this framework have been classified into three categories: biology and genetics; environment and occupation; and social and behavioural determinants, in addition to their interactions. These health determinants are factors associated with either improving population health, or exposing the population to health risks. Health determinants can be identified using both qualitative and quantitative methods. Results of such studies can be assessed by health policy makers and multiple interventions can be implemented at that point in order to mitigate possible health risks and improve population health. These interventions include regulatory, economic, advisory, community, and technological interventions, which in turn help in improving population health (147).

In this thesis, the health issue that will be discussed is the inappropriate prescribing of antiparkinsonian agents, which can be determined by the degree of prescribers' adherence to prescribing guidelines. Indeed, It is evident that

inappropriate prescribing, especially in elderly people, is linked to increases in the rates of morbidity and mortality, the risk of hospitalization, and wastage of heath resources (162). Therefore, inappropriate prescribing which leads to all of those health risks will be considered in this thesis as a health risk in itself. Another health risk that will be discussed in this thesis is the association between PD medications and certain side effect (i.e. the association between L-dopa and ischemic heart disease (IHD). Quantitative methods will be used to evaluate the prescribing pattern of antiparkinsonian agents and the factors that affect this pattern in Wales. This will provide the policy makers and regulators with some evidence, which may lead them to implement multiple interventions that improve the health of patients with Parkinson's disease (PD).

1.6.5 The combined framework for the thesis

The purpose of this combined framework is to confirm that the field of drug utilization research is a bridge between pharmacoepidemiology and health service research: i.e., health risk outcomes. This framework combines three multiple concepts, namely pharmacoepidemiology and drug utilization research, the Eisenberg Framework of Clinical Decision-Making and Judgment, and the Integrated Framework for Risk Management and Population Health. In drug utilization research, prescribers' adherence to prescribing guidelines will be considered as a tool to measure appropriate prescribing. Adherence to prescribing guidelines will be affected by multiple factors, which are explained by the Eisenberg framework. The Integrated Framework for Risk Management and Population Health is used as a link between the effects of prescribing behaviours and health risk outcomes (Figure 1-5).

1.6.6 Conclusion

The main reason for drug utilization research is to improve population health and avoid possible health risks. Drug prescribing pattern studies can be used to examine the extent to which the drug prescribers are acting in accordance with prescribing guidelines. A combined framework has been developed in order to guide the research process in this thesis. This framework is a combination of pharmacoepidemiological concepts and two theoretical frameworks.

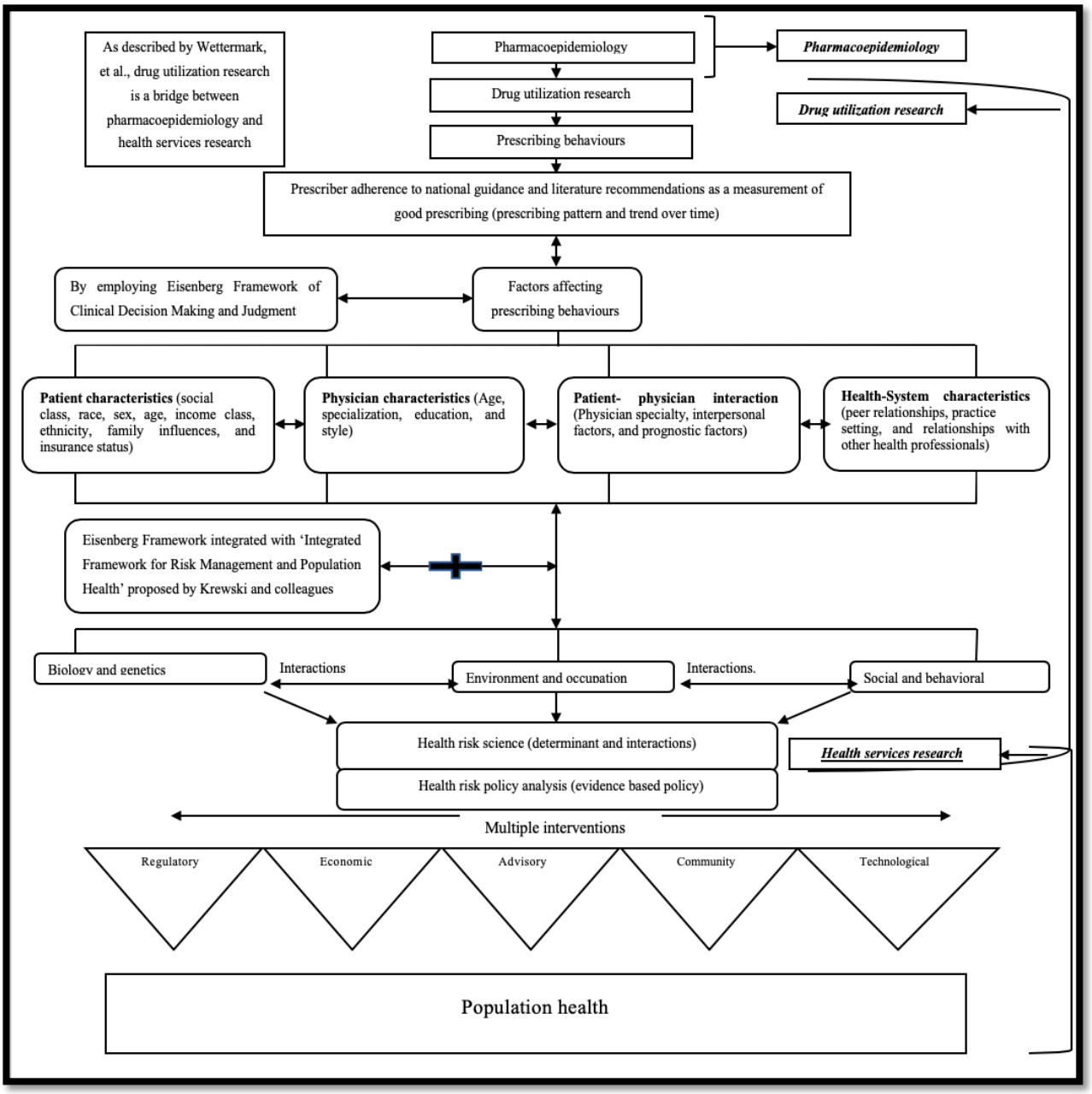


Figure 1-5- The combined framework for the thesis

1.7 Aims and Objectives

1.7.1 Aims

PD can have a substantial and complex impact on PwP, patients' carers, and on society as a whole. Despite this, the epidemiology and pharmacoepidemiology of PD in Wales have yet to be explored and various questions remain to be answered. Thus, this study will aim to provide updates on the previous epidemiological studies and give new insight into the pharmacoepidemiology of PD in Wales.

1.7.1.1 Validating the database

Computerized primary care data records can help to answer several questions regarding prescribing trends and patterns and to determine issues that affect trends and pattern changes, such as demographic and socioeconomic factors (151). Although researchers in the UK can use primary care data to answer a large number of research questions, can the accuracy of clinical codes entered by GPs be validated in order to avoid biased and invalid outcomes caused by incorrect or missed clinical coding?

By assessing whether the GP records of all prescriptions, particularly PD prescriptions, in the Secure Anonymised Information Linkage (SAIL) Databank are complete, it could be established whether PD prescriptions in the SAIL Databank are complete and valid. Additionally, by comparing the estimates of incidence and prevalence of PD in the SAIL Databank to previous studies in the UK, this could be considered as a step towards validating the accuracy of the PD diagnosis in SAIL.

1.7.1.2 Treatment

Medications available to treat the condition target the motor disorder, but as the disease progresses, greater comorbidities are evident and there is increased use of medications to manage psychotic events, dementia and mental health issues. There were continuous changes in the PD treatment literature and guidelines in the last twenty years. Recently, the National Institute for Health and Care Excellence (NICE) published updated treatment guidelines for PD, which included recommendations regarding those changes in the literature and how to implement them in clinical practice (31). But the question currently unanswered in the UK, are there patient-related factors that affect prescribing behaviours?

By determining the prescribing trends of antiparkinsonian medications in PwP in Wales with respect to several factors, including age, sex, social deprivation status, and co-morbidities, the pattern of medication use in PwP can be evaluated.

1.7.1.3 Health outcomes

Several studies have linked the use of levodopa to an increase in homocysteine levels, which can lead eventually to ischemic heart disease (IHD) in PwP (163, 164). There is a lack of large population studies investigating the cardiovascular safety of levodopa. With the utilisation of the data can the risks of IHD within 1 year of L-dopa initiation be evaluated?

By examining the association between L-dopa use in PwP and the risk of IHD, all cardiovascular risk, and all-cause mortality, and by examining the factors that may affect the association between L-dopa use and these risks in PwP (such as

Charlson comorbidity score, the presence of previous cardiovascular events before initiating L-dopa, age, sex, etc.), this gap in research will be filled.

1.7.2 Objectives

Chapter 2: Patterns and determinants of prescribing for Parkinson's disease: A systematic literature review.

- Evaluate prescribing patterns and determinants of PD medication utilisation worldwide and examine the extent to which these patterns accord with the changes occurring in the safety and efficacy profiles of PD medications.

Chapter 4: Validating SAIL databank prescriptions for PD Medications

- Assess whether the GP records of all prescriptions, particularly PD prescriptions, in the SAIL Databank between January 2014 and December 2016 are complete and whether they can be used to evaluate the prescribing trends and patterns of PD medications in Wales.
- Calculate the total prescriptions and population in both datasets (GP Data Extract and SAIL Databank between January 2014 and December 2016) and the average number of prescriptions per person every month and per year.
- Compare the number of PD prescriptions per 100,000 population between the two datasets and investigate whether they share the same prescription rates and trends.

Chapter 5: Incidence and prevalence of Parkinson's disease (PD) in Wales

- Define the characteristics of PwP with a definitive PD diagnosis using SAIL.
- Compare the incidence and prevalence of PD in Wales between 2000 and 2017 to previous UK studies.

Chapter 6: Trends in first line therapy for Parkinson's disease (PD) in Wales: A 16-year Observational Study

- Explore first line therapy in PwP across the years of the study using incidence cases.
- Perform univariate and multivariate logistic regressions to examine the potential factors that may affect the prescribing choice of each antiparkinsonian medication as a first line therapy.

Chapter 7: L-dopa and risk of ischemic heart disease (IHD)

- To investigate associations of IHD hospitalization risk, all-cardiovascular hospital events, and all-cause mortality among users of L-dopa and non-ergot DAs compared with users of MAO-B inhibitors among individuals with newly diagnosed PD.

CHAPTER 2: Patterns and Determinants of Prescribing for Parkinson's Disease: A Systematic Literature Review

2.1 Introduction

Since the first detailed description of PD in 1817, extensive efforts have been devoted to finding a cure. In the late 1960s, George Cotzias described the efficacy and safety of oral L-dopa in treating the motor symptoms of PD. He determined that when the L-dopa dose was increased gradually, motor symptoms improved for a longer duration with minimal gastrointestinal adverse effects (165, 166). Other compounds were tested alongside L-dopa, including amantadine, which Schwab et al. (167) discovered suppressed tremors. Problematically, although highly effective at treating the motor symptoms, it was determined early on that L-dopa induces dyskinesia and motor fluctuations often develop, limiting use of the drug. There remained a need to search for a drug that could improve motor symptoms without these issues, and even more desirably, could have disease modifying properties (168, 169). In 1974 (see Figure 2-1), the ergot dopamine agonist, bromocriptine, was tested, demonstrating a longer half-life than L-dopa and fewer motor fluctuations (170). One year later, a combination of L-dopa and dopa decarboxylase inhibitor (carbidopa) was found to reduce the gastrointestinal side effects compared to L-dopa alone (171-173). The safety and efficacy of the monoamine oxidase B (MAO-B) inhibitor selegiline (Deprenyl), as an adjunct to L-dopa therapy, was then demonstrated in 1977 (174). From 1982 to 1992, several dopamine agonists (DAs) were introduced to the market, to be used either as L-dopa adjuncts in patients with long-term complications or as *de novo* therapy in place of L-dopa (175). In 1997, tolcapone, the catechol-O-methyl transferase inhibitor (COMT inhibitor), was approved in Europe as a treatment to reduce the motor fluctuations caused by L-dopa (175). Since then, no new pharmacological class has been introduced in clinical practice; however, some new medications from previous classes have been introduced, including entacapone (COMT inhibitor) (1999), rasagiline (MAO-B inhibitor) (2005), rotigotine patch (non-ergot dopamine agonist) (2006), safinamide (MAO-B inhibitor) (2016), and opicapone

(COMT inhibitor) (2016) (121, 176-179). Additionally, since the early 2000s, new pharmaceutical formulations such as infusion therapies (subcutaneous apomorphine and Levodopa-carbidopa intestinal gel (LCIG)) became available in several countries with the promise of tackling the motor complications (mainly the wearing-off phenomenon) caused by the oral form of L-dopa in patients in the advanced stage of PD (180).

DAs were introduced to the market with the hope of improving motor symptoms and avoiding the complications caused by L-dopa. Several clinical trials conducted between 1989 and 2006 compared L-dopa to different DAs, such as bromocriptine, ropinirole, pramipexole, and pergolide; these trials concluded that starting a therapy with DAs was associated with delaying dyskinesia or motor fluctuations or both (181-185). These trials led to guidelines recommending starting therapy with DAs and not using L-dopa unless the DAs failed to manage the motor symptoms (113, 186, 187), or starting therapy with L-dopa or DAs without any preference (136, 186). The impact of the motor fluctuations caused by L-dopa on patients' quality of life (QOL) was not clear until 2014, when the PD-MED study used the quality of life (QoL) scale as a primary outcome. The study's main finding was that early initiation of L-dopa resulted in a better QoL in the long term than initiating DAs and MAO-B inhibitors (188, 189) .

With regard to neuroprotection, DAs and MAO-B inhibitors were initially proposed to have potential neuroprotective properties; however, the PDRG-UK (190), CALM.PD (191), and PROUD studies (192) failed to find evidence of possible neuroprotective properties of DAs (bromocriptine and pramipexole). With regard to MAO-B inhibitors, an open-label study was undertaken in 2009, extending the TEMPO trial with 6.5 years of follow-up. This study indicated a significant reduction in motor symptoms in patients who were administered rasagiline in the early stages of PD (193). In the same year, the ADAGIO trial

found that early-start treatment with 1 mg of rasagiline resulted in improved motor symptoms, which could not be explained solely by symptomatic effects (125). The same study revealed that 2 mg of rasagiline did not have the same beneficial effect as a 1 mg dose, which made it harder to claim that rasagiline had neuroprotection properties (194). These studies did not convince the American Food and Drug Administration (US FDA) to approve an expanded indication for rasagiline as a neuroprotective (194). Following the US FDA decision, the ADAGIO trial follow-up study published in 2016 failed to find any difference between the long-term benefits of early-start vs. delayed-start rasagiline, thus failing to support claims of its neuroprotective properties (195). Recently, the National Institute for Health and Care Excellence (NICE) in the UK has published updated treatment guidelines for PD, and has not changed its original conclusion that no evidence of neuroprotective properties can be found in PD medication (31, 136).

Another major force that drove drug discoveries and approvals of new PD medications, and which might affect the choice of therapy in PwP, is the drugs' safety profiles. Different studies have drawn attention to the safety profiles of some PD medications. For example, in 2003, two significant side effects were identified that cast doubt on the safety of DAs. The first side effect was the pathological gambling (one of the ICDs forms) associated with DAs (196). Other forms of ICDs, such as hypersexuality, were discovered subsequently (197, 198) The second side effect was the association between the use of ergot DAs and valvular heart toxicity (199). Although non-ergot derivatives were not initially associated with heart toxicity, some experts were concerned about this issue and recommended continuous vigilance (200). Since 2012, several studies have reported a possible risk of heart failure associated with pramipexole (a non-ergot DA) (112, 201-204), but this association could not be confirmed by other studies (205-207) The option of ergot DAs in early PD was not excluded in some guidelines, such as NICE (2006); however, non-ergot DAs were preferred over

ergot DAs according to NICE (2006) (136). After the NICE (2006) guidelines were issued, several side effects for both ergot and non-ergot DAs were reported, among them valvular cardiac toxicity of pergolide, which was reported in a large-scale UK study and led to the voluntary withdrawal of the drug in the USA and Canada in 2007 (208, 209), and the gambling precaution that was added to the pramipexole profile in 2008 (210). A DOMINION cross-sectional study conducted in 2010 found that ICDs were significantly associated with usage of DAs (198).

Apart from DAs, other types of PD medications also had some safety concerns. In 2000, the hepatotoxicity risk of tolcapone was demonstrated (129). Other non-approved safety concerns include the possible high rates of mortality in selegiline users. This was suggested by a PDRG-UK trial in 1995 (211), but was later debated by a meta-analysis that found no association between selegiline use and mortality increase (212). Additionally, in 2010, the US FDA expressed some concern about the possible cardiovascular risk of the L-dopa–carbidopa-entacapone combination (Stalevo®) (213); however, this concern was negated by the FDA itself in 2015 (214). (Figure 2-1 shows a summary of changes in efficacy, safety, and approvals of PD medications since the discovery of L-dopa).

Increased knowledge of efficacy and safety, and the growing number of drugs on the market, would be expected to impact on prescribing decisions and drug utilisation rates of PD medications. One means through which adherence to national prescribing guidelines and awareness of the changes in efficacy and safety in the medications' profiles can be evaluated is by examining prescribing patterns. Doing so would help to determine the factors that affect prescribing, including factors such as sex, age, socioeconomic status, education, and drug pricing (144, 156). Various studies have been conducted worldwide and this review draws together prescribing patterns and determinants of PD medication

utilisation across the globe to examine the extent to which these patterns accord with the changes occurring in the safety and efficacy profiles of PD medications.

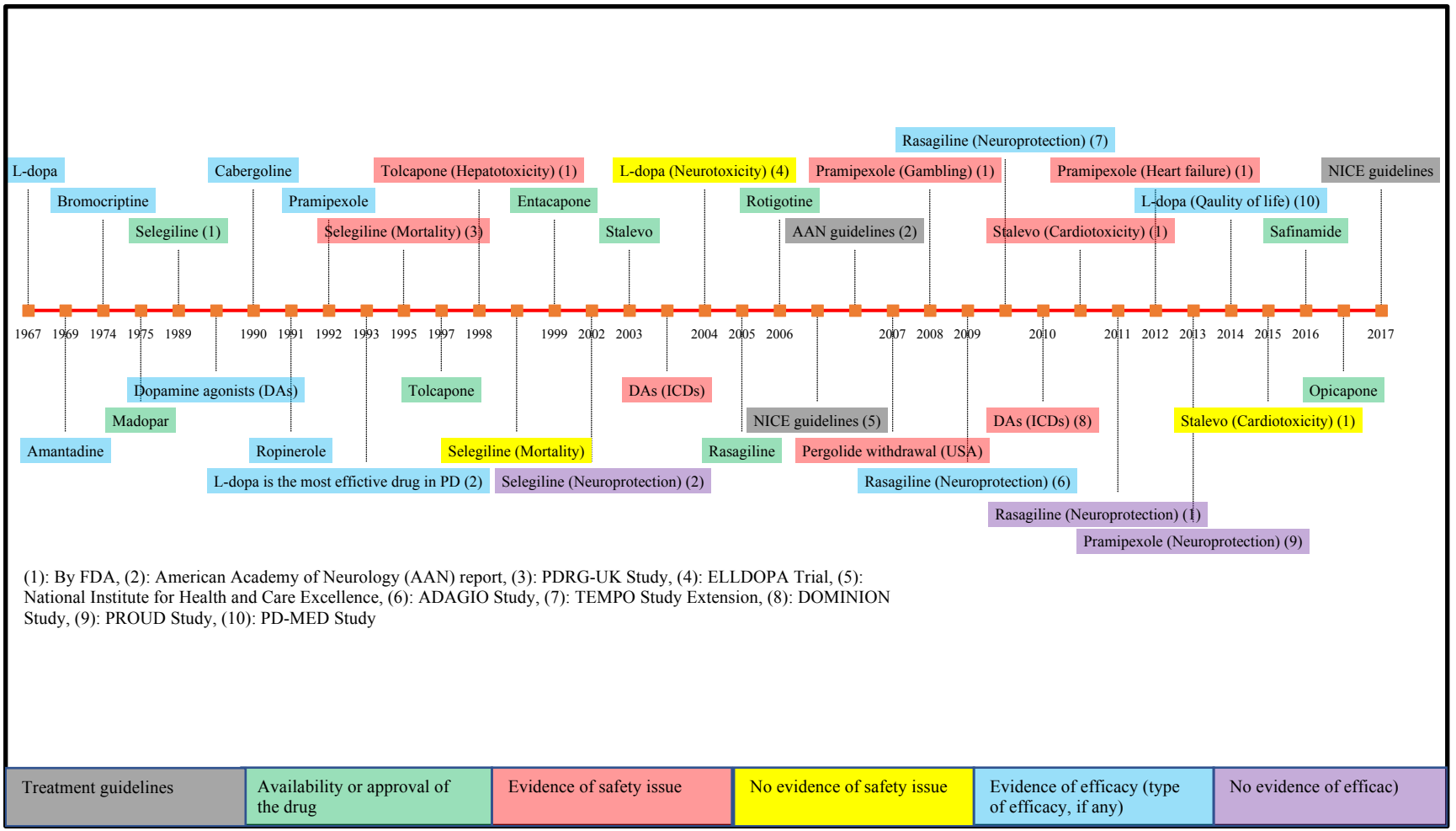


Figure 2-1- The evolution of pharmacotherapy for Parkinson's disease with key discoveries in efficacy, safety, and approvals of medications since the discovery of L-dopa.

The horizontal line represents years from 1967 to 2017. Coloured boxes around the horizontal line represent the event types mentioned in the coloured boxes shown at the bottom of the figure.

2.2 Methods

2.2.1 Search strategy

A comprehensive and systematic literature search was conducted using EMBASE (1947-March, 2018), Ovid MEDLINE(R) ALL (1946 to March 16, 2018), PsycINFO (1806 to March Week 2, 2018), and PubMed to identify all studies measuring prescribing patterns of PD medications (Figure 2-2). The key words used were "drug utilization" or "prescribing pattern" or "pharmacoepidemiology" or "prescribing trend" or "inappropriate prescribing" or "prescribing factors" or "prescribing determinants" or "prescribing behaviour," combined with "Parkinson's disease" or "idiopathic Parkinson's disease" or "Primary Parkinsonism" or "Paralysis Agitans" or "Antiparkinson drugs" or "Antiparkinsonians" or "Antiparkinsonian agents" or "Levodopa" or "L-dopa" or "dopamine agonists" or "apomorphine" or "cabergoline" or "lisuride" or "pergolide" or "pramipexole" or "ropinirole" or "rotigotine" or "amantadine" or "Catechol O-Methyltransferase Inhibitors" or "entacapone" or "tolcapone" or "Monoamine Oxidase Inhibitors" or "rasagiline" or "selegiline" or "anticholinergics or "orphenadrine" or "procyclidine" or "trihexyphenidyl". Manual reference research and the Google Scholar service were also used in the review (Appendix 1). The literature search was updated on 15 December 2019, although new articles published between 16 March 2018 and 15 December 2019 were not included in this chapter. The main results of these new studies can be seen in Appendix 2.

2.2.2 Inclusion and exclusion criteria

All English-language studies that measured the prescribing pattern and/or prescribing and drug utilisation determinants of one or more than one class of PD medication at any time point were included in the review. Since the purpose of this review was to examine all studies of prescribing patterns and determinants, the only exclusion criterion was if the study was published only as a conference poster. Non-English language studies were excluded from both the main analysis and the quality assessment due to the lack of translation resources; however, when possible, the English abstracts of these studies were screened and obtained (Appendix 3 and 4).

2.2.3 Data extraction and quality assessment checklist

Where information was available, the following data were extracted from each study: study design, source of data, country, year of study, number of patients and/or prescriptions, unit of analysis, prescribing determinants, main findings and the utilisation percentages of PD medications. The selected studies were classified into two categories: studies that examined the prescribing patterns of PD medications with or without prescribing determinants and studies that examined prescribing determinants without measuring prescribing patterns of PD medications.

The studies selected for this review had heterogeneous designs, which made it difficult to apply the commonly used quality and reporting assessment checklists for cross-sectional observational studies such as the STROPE checklist (215) and the National Institutes of Health Quality Assessment tool for Observational Cohort and Cross-sectional Studies (216). Most published quality and reporting

assessment checklists have not been designed to be applied to pharmacoepidemiological and drug utilisation studies (217). All the studies selected in this review were descriptive in nature and did not measure outcomes caused by exposures in the study participants. For this reason, and to assess and critique the quality of the selected studies, a critical appraisal tool that addresses prevalence studies was used (218). This tool was chosen because the drug utilisation rate of PD medications is the primary interest of this review. The prevalence of PD medication use was used to estimate the prevalence of PD itself in several studies (219-222). For the purpose of this review, the "Joanna Briggs Institute Critical Appraisal Tool for Use in Prevalence Studies" was used (Appendix 5). This tool poses 10 questions which can be answered by yes, no, unclear, or not applicable. The questions relate to the sample representativeness of the target population, the method used to recruit study participants, the sample size adequacy, the detailed description of study subjects, the sufficiency of the coverage of the selected sample during analysis, the objectivity of the criteria used in measuring the condition, the reliability of the criteria used to measure the condition, the appropriateness of the statistical analysis considering potential confounding factors, and finally, the objectivity of the criteria used to identify subpopulations (218). In this review, the sample (patients, prescriptions) would be taken to be representative of the PD population in the area of the study if it covered: (1) patients of all ages; (2) patients of both genders; (3) all disease severity levels; (4) all PD medications available in the area of the study; (5) different morbidities; and (6) different care settings (hospitals, community, and nursing homes). In relation to questionnaires distributed to prescribers, the sample would be considered to be representative if it included at least two types of prescriber (e.g. general practitioners and neurologists) in the study sample. Sample size in this review would be considered adequate if one of the two following conditions were fulfilled: (1) the study used a large national representative sample (national drug claim databases, national electronic medical records, etc.); or (2) the sample size was calculated in the

study. Other than that, the sample size will be considered as not being adequate. In terms of "objectivity of criteria used in measuring the condition", if the study used an electronic database to obtain the prescribing pattern of PD medications, the database should be validated against standard and accurate databases (medical records, general practitioners (GPs) questionnaire, etc.). If the study used patients' interviews as a source of information, the diagnosis should be made by an expert in PD medical diagnosis. For other types of method, the decision is made based on the contents of the article and the measures used to address this issue. With respect to the statistical analyses in the selected studies, if the study examined changes in the trend of PD medications' prescription rates, it is expected that an appropriate statistical test that examined the significance of such changes were conducted, such as the Cochrane-Armitage test, chi square test, or regression test. If none of these tests were used, the statistical analysis would be deemed inappropriate. On the other hand, if the study examined only the prescribing pattern of PD medications, the descriptive analysis would be deemed appropriate. However, if the study examined the differences between different subgroups in the study, an appropriate statistical test should be applied. With regard to the issue of addressing confounding factors, the study must include at least age, gender, and disease severity. In relation to all of the criteria mentioned above, the answer "yes" with one score was given if the study fulfilled the criterion; the answers "no", "unclear", or "not applicable" with a zero score would be given if the criterion was not fulfilled. After answering all the questions, all the scores were added and a net score was assigned for every study. Due to lack of evidence, no specific quality level (e.g. good, moderate, or poor) was assigned to the selected studies; however, the resulting net score (from 0 to 10) gives an estimation of the quality level of the studies.

After obtaining a quality score for each study, a Kruskal-Wallis test was used to compare the prescribing rates at different tiers of quality scores (for this purpose only, quality scores were classified into three tiers: from 1 to 3, 4 to 6, > 6).

Additionally, a Kruskal-Wallis test also was used to compare the prescribing rates according to the source of data. The significance level was set at $p < 0.05$ in both tests.

2.3 Results

2.3.1 Search results and characteristics of the drug utilisation studies

The initial search of the databases used in this review resulted in the retrieval of 682 studies (Appendix 1). Twenty-six additional studies were identified through other sources (manual reference research and the Google Scholar service). After removing duplicated and non-relevant studies, 415 studies remained. The abstracts of these 415 studies were screened and this resulted in the removal of 364 studies which did not examine prescribing patterns or determinants, thus leaving 51 studies. A further 7 studies were excluded because they were published only as conference posters. In total, therefore, 44 studies remained that examined the prescribing pattern and determinants in 17 countries and these were included in this review (Figure 2-2) (219, 223-265). Of the 44 studies, 40% (n = 18) were undertaken in Europe [Italy (n = 4), England (n = 2), Germany (n = 2), Spain (n = 2), Sweden (n = 3), Norway (n = 2) whole of Europe (n = 1), Finland (n = 1), France (n = 1), UK (n = 1)]; 29% (n = 13) were undertaken in the USA; 25% (n = 11) were undertaken in Asia [Japan (n = 4), India (n = 3), Taiwan (n = 2), China (n = 1)] and 7% (n = 3) were undertaken in other countries [Australia (n = 1), New Zealand (n = 1), South Africa (n = 1)]. Two studies were conducted in two different countries at once: the USA and Japan jointly (239) and Sweden and Norway jointly (264). This explains why the total of the percentages quoted above exceeds 100% (Tables 2-1 and 2-2). The results of the Kruskal-Wallis tests indicated no significance differences between prescribing rates of PD medications across different levels of study quality scores and across the several data sources that were used in the studies (Appendix 6 and 7). The only

exception was L-dopa, which was prescribed significantly more in studies which used patients' interviews, questionnaires, or surveys compared to studies which used insurance claims, prescription registries, or drug sales databases ($p = 0.011$) (Appendix 6).

Of the 44 studies, 35 were designed to examine the prescribing pattern of PD medications with or without measuring prescribing determinants (Table 2-1) (219, 223-228, 230, 231, 233-255, 263, 264), and 9 studies measured the prescribing determinants and utilisation factors without measuring prescription rates of PD medications (Table 2-2) (229, 232, 256-262). The sources of the data were varied according to each study design. Insurance claims, prescription registries, or drug sales databases were used in 16 studies (219, 226, 227, 233, 234, 236-238, 241, 242, 244, 245, 252, 255, 261, 263); medical charts and administrative databases were used in 12 studies (223, 224, 228, 230, 231, 246-250, 259, 262, 265); patients' interviews, questionnaires, or surveys were used in 12 studies (225, 235, 239, 240, 243, 251, 253, 254, 256-258, 264); and finally, 3 studies (229, 232, 260) were designed as post-hoc studies that used previously conducted clinical trials to find the prescribing patterns and determinates of PD medications (Tables 2-1 and 2-2). The timeframe of the studies that were reviewed was from 1986 to 2017. Of the studies that examined prescribing patterns, 19 were cross-sectional in design and calculated the prescription rates of PD medications in a particular period without comparing the rates to other periods (219, 223-225, 228, 230, 235, 237, 240, 244, 248, 249, 251, 253-255, 263-265) and 15 were designed to compare the prescribing patterns in two or more different periods (226, 227, 231, 233, 234, 236, 238, 239, 241-243, 245-247, 252). In one study that was conducted in Singapore, it was not possible to establish the year of the study (250). Study settings in prescribing pattern studies varied and included a community setting only (n = 20) (223-227, 235, 237, 239, 242, 243, 245-251, 253, 255, 264), inpatient and community settings (n = 9) (219, 230, 234, 236, 238, 240, 241, 252, 254), inpatient setting only (n = 2) (231, 265),

community and care home settings (*n* = 2) (228, 233), inpatient, community and care home settings (*n* = 1) (244), and, finally, care home setting only (*n* = 1) (263). The general characteristics of the drug prescribing studies that were reviewed are summarised in Table 2-1. In the prescribing pattern studies, the number of patients treated per 100,000 inhabitants, the number of prescriptions, the number of patients prescribed a particular medication, defined daily doses (DDD) per 1,000 inhabitants per day (DID), and the number of person-years were used as units of analysis in all studies, except for one study conducted in England that used drug sales as a unit of analysis (238). In the studies that used the number of patients prescribed a particular medication (219, 223, 224, 227, 228, 231, 234, 235, 239-241, 246, 248-251, 253-255, 263, 264) or the number of person-years (244) as units of analysis, the total prescription rates of all PD medications may not add up to 100% due to the possibility that the patients were prescribed combination therapy. On the other hand, in the studies that used the number of prescriptions or DID as units of analysis (233, 237, 242, 245, 247, 252), the total prescription rates of all PD medications may not add up to 100% due to rounding to the nearest percent or due to the inability to calculate some categories of PD medications prescription rates. One exception to these rules was a study carried out in Taiwan that used the number of prescriptions as a unit of analysis (226). The total prescription rate of all PD medications exceeds 100% due to the fact that some prescriptions include more than one medication. The prescription rates could not be calculated for any of the PD medications in four studies (225, 230, 236, 243).

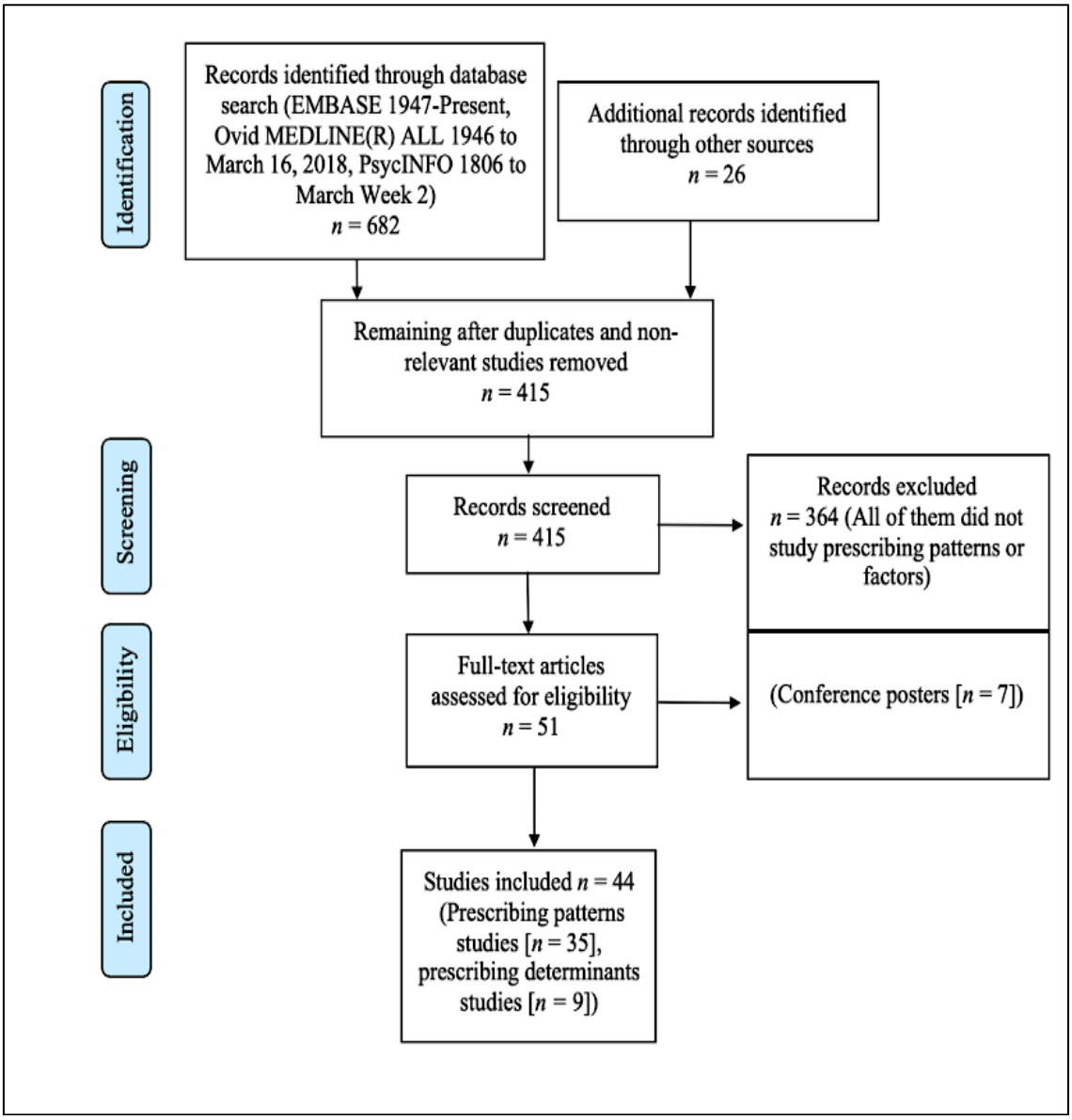


Figure 2-2- PRISMA flow chart for systematic research of prescribing patterns and studies of determinants

Table 2-1- Studies that examined PD medications prescribing patterns

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Ezat et al. **(265)**	Norway	Retrospective study from three hospitals in Norway	2009-2013 No comparison	Inpatient setting	262 patients	Number of patients treated per 100,000 inhabitants	Geographical location	Of all PD medication, the study examined prescribing of L-dopa intestinal gel alone. There is a significant variation of L-dopa intestinal gel prescribing in Norwegian counties (Rogaland county has the highest rate of prescribing).	3
Tripathi et al. **(224)**	India	Retrospective chart review from a neurology clinic in India	2014 No comparison	Community	100 patients	Percentage of patients prescribed each drug/drug class/drug combinations	N/A	L-dopa monotherapy is the most commonly prescribed regimen. L-dopa + anticholinergic is the second most common regimen, followed by L-dopa + DA.	4
Surathi et al. **(223)**	India	Cross-sectional prescriptions review study	2011-2014 No comparison	Community	800 patients	Percentage of patients prescribed each drug/drug class/drug combinations	N/A	L-dopa monotherapy is the most commonly prescribed regimen. Anticholinergic medication is the second most common regimen.	4
Jost et al. **(225)**	Germany	Cross-sectional surveys with patients and physicians.	2017	Community	4,485 patients, and 271 physicians	Percentage of patients prescribed each drug/drug class/drug combinations	N/A	The most commonly prescribed medication is L-dopa (90.27%) followed by DAs (40.66%).	4
Dahodwala et al. **(219)**	USA	Retrospective cohort from a random sample of annual 5% Medicare Part A&B claim	2007-2010 No comparison	Inpatient and community settings	9,482 to 9,626 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age, gender, race, income, comorbidities, and neurology clinic visits.	Most PwP receive PD medications. African American and patients not seen by neurologists are undertreated.	9
Liu et al. **(226)**	Taiwan	Retrospective cohort from Taiwan National Health Insurance Database	2004/2011	Community	19,302 patients in 2004 and 41,606 patients in 2011	Percentage of prescriptions. (one prescription may include more than one prescribed medication)	Age	General increase in L-dopa monotherapy prescribing. More than doubling of DA prescribing for younger patients. Most of the DA prescriptions are non-ergot derivatives after 2008.	8
Keränen et al. **(227)**	Finland	Retrospective cohort from a drug insurance reimbursement register	2005/2012	Community	1,436 patients in 2005 and 1,607 patients in 2012	Percentage of patients prescribed each drug/drug class	Age	L-dopa is the most prescribed medication in patients aged >75 y. DAs and MAO-B inhibitors are the most prescribed medications in patients aged <60 y. Prescribing changes are in accordance with changes in guidelines.	4
Hand et al. **(228)**	England	Retrospective study used by the Northumbria Healthcare NHS Foundation Trust PD service	2015	Community and care home settings	377 patients	Percentage of patients prescribed each drug/drug class/drug combinations and L-dopa equivalent daily dose (LEDD)	Care settings	This study examined patients with any type of parkinsonism. Age and disease stage were higher in these living in care homes. LEDD was lower in these living in care homes.	6

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Degli Esposti et al. **(230)**	Italy	This retrospective study used databases of three Italian Local Health Authorities	2009-2011 No comparison	Inpatient and community settings	1,607 patients on selegiline or rasagiline	Percentage of patients prescribed each drug/drug class/drug combinations	Age and gender	63.3% of patients were on selegiline while 36.2% were on rasagiline. DAs and L-dopa were more prescribed in rasagiline group.	5
Crispo et al. **(231)**	USA	Retrospective cohort from the Cerner Health Facts database	2001/2011	Inpatient	16,785 patients	Percentage of patients prescribed each drug/drug class	Age and gender	L-dopa was the most prescribed medication from 2001–2011. Decline in DA use over 2007–2011. Stable rate of DA use in patients aged >= 80 y over 2001–2011.	7
Pitcher et al. **(233)**	New Zealand	Retrospective cohort from national prescription database in New Zealand	1995/2011	Community and rest (care) homes. No comparison.	N/A	Defined daily doses (DDD) per 1,000 inhabitants per day	N/A	General increase in L-dopa prescribing over 1995–2011. Slight decrease in DA prescribing over the same interval. Slight increase in COMT inhibitor and amantadine prescribing. An increase in pergolide prescriptions even after 2007.	3
Nakaoka et al. **(234)**	Japan	Retrospective cohort from medical claim database in JMDC, Tokyo, Japan	2005/2010	Inpatient and community settings	714 patients	Percentage of patients prescribed each drug/drug class	Age.	L-dopa is the most prescribed medication over 2005–2010. Of newly diagnosed patients, 30% are prescribed anticholinergics. Non-ergot DA prescribing increases after 2007 in accordance with label revision of ergot DAs.	8
Junjaiah et al. **(235)**	India	Prospective study that included interviews with PwP	2011-2013 No comparison	Community	100 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Disease duration	48% of PwP received L-dopa alone. 52% of PwP received combination therapies.	5

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Gaida et al. **(237)**	South Africa	Retrospective cohort from national community pharmacy group in South Africa	2010 No comparison	Community	5,168 patients and 25,523 prescriptions.	Percentage of prescriptions	Age and gender.	The most commonly prescribed medications are L-dopa + COMT inhibitors. The second most commonly prescribed medications are non-ergot DAs. Patients aged 50–59 y are prescribed DAs more than L-dopa while >70 y group are prescribed more L-dopa.	5
Skogar et al. **(264)**	Sweden and Norway	Using questionnaires with PwP	2010-2013 No comparison	Community	1,553 patients in Sweden and 1,244 patients in Norway	Percentage of patients prescribed each drug/drug class/drug combinations	NA	L-dopa products were the most common used PD medications in both countries. Selegiline was significantly used more in Norway than in Sweden.	4
Morrish **(238)**	England	Retrospective study that used online statistics at the National Health Service (NHS) Information Centre	1999/2010	All drug sales in both inpatients and community settings	N/A	Total net ingredient cost for PD medication in pound (£)	N/A	The total net ingredient cost of PD medication was increased from £37 million in 1998 to £130 million in 2010. There was a decrease in ergot-DAs spending especially after 2004.	3
Hattor et al. **(239)**	USA/Japan	Using questionnaires with PwP followed by interviews with PwP.	2003 in USA-2008 in Japan	Community	300/3,548 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Drug side effects.	Patients who had already experienced dyskinesia were less concerned about L-dopa dyskinesia. The most commonly prescribed medication was L-dopa in both countries followed by DAs.	2
Schroder et al. **(240)**	Germany	A cross-sectional survey of neurologists	2004 No comparison	Inpatient and community settings	60 neurologists complete the medical charts of 320 patients.	Percentage of patients prescribed each drug/drug class/drug combinations	Age and disease severity	53% of patients aged <70 years were used DAs without L-dopa. In patients aged >70 years, 50-52% were used L-dopa without dopamine agonists.	5
Ooba et al. **(241)**	Japan	Retrospective study used the National Japanese database vendor	2005/2008	Inpatient and community settings	547 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age, gender, and pergolide withdrawal from USA market in 2007	Percentage of patients prescribed cabergoline or pergolide did not decrease, rather, it tended to increase after 2007.	5
Hollingworth et al. **(242)**	Australia	Retrospective study using Medicare Australia.((DUSC) databases	1995/2009	Community	5,078,242 prescriptions	Defined daily doses (DDD) per 1,000 inhabitants per day	Age, gender, and type of prescriber.	Decline in anticholinergics and DAs over 14 years. General increase in L-dopa use over 14 years.	4

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Fayard et al. **(243)**	France	A population-based study that included interviews with PwP	≤2000->2000	Community	308 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age and type of prescriber.	Agreement with the French recommendations increased after 2000 compared to before 2000. For patients aged <60 years, 35% increase in DAs prescribing after 2000. For patients aged >70 years, about 1% increase in L-dopa prescribing after 2000.	8
Wei et al. **(244)**	USA	Retrospective study used the Medicare Current Beneficiary Survey and Medicare claims	2000-2003 No comparison	Inpatient, community, and nursing home settings	571 patients	Percentage of person years prescribed each drug/drug class/drug combinations	Age, sex, race, education, marital status, annual income, care setting, and comorbidity scores.	Half of the patients did not use any PD medication in the period of the study. L-dopa was the most PD medication prescribed as a monotherapy or as a combination therapy. Age, prescription drug coverage, residing in an institution, education, dementia, and depression had an effect on PD medication use.	5
Rosa et al. **(245)**	Europe	Retrospective study that used ‘‘Intercontinental Marketing Services’’) Health, (26 European countries)	2003/2007	Community	A value of 663 million antiparkinsonian consumption in 2003 and 717 million in 2007	Defined daily doses (DDD) per 1,000 inhabitants per day	N/A	Levodopa and DAs accounted for half of the drug use in most countries. Between 2003 and 2007, the hugest increase in sales occurred with L-dopa and MAO-B inhibitors.	5
Trifiro et al. **(246)**	Italy	Retrospective study used the Arianna database (GPs database)	2003/2005	Community	1,479 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age	Stable prevalence of PD medication use during the years of the study. L-dopa was the most PD medication prescribed as a monotherapy or as a combination therapy. Non-ergot DAs use was increased in 2005 especially in elderly people.	6
Osinaga et al. **(247)**	Spain	Retrospective study used database of the Spanish Ministry of Health	1992/2004	Community	N/A	Defined daily doses (DDD) per 1,000 inhabitants per day	N/A	L-dopa was the most PD medication prescribed. Consumption of PD medications has increased during the years of the study.	4
Swarztrauber et al.**(248)**	USA	Retrospective study used the Pacific Northwest Veterans Health Administration (VHA) Data Warehouse	1998-2004 No comparison	Community	530 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age and type of prescriber	29% of the initial antiparkinsonian therapy was initialled by neurologists. 20% of patients younger than 65 years received DAs. Initial antiparkinsonian therapy is strongly influenced by the prescriber’s specialty. Additionally, it is mostly initiated by primary care physicians (without PD expertise).	7

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Huse et al. **(249)**	USA	Retrospective study used Medstat's MarketScan Research Databases	1999-2001 No comparison	Community	4,846 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age, gender, comorbidity (Charlson index), and type of insurance.	L-dopa was the most PD medication prescribed as a monotherapy or as a combination therapy regardless age or type of insurance. DAs are the second most PD medication prescribed, but it only accounted for about 15% of patients younger than 65 years.	6
Tan et al. **(250)**	Singapore	Retrospective study used patients' charts at a tertiary referral centre. Then factors that influence neurologists' decisions were examined by surveying a sample of neurologists.	N/A	Community	306 patients. 11 neurologists participated in the survey.	Percentage of patients prescribed each drug/drug class/drug combinations	Age, disease severity, intolerance of side effects, drug side effects, drug availability, clinical experience with the drug, drug cost, patient's preference, and drug company sponsorship	92.3% of patients were on L-dopa. Most of patients who were on L-dopa were older and had a higher stage of PD severity scale (Hoen & Yahr). 26.8% of patients were on DAs. From surveying the neurologists, the most important factors influencing their prescribing behaviors were severity of symptoms, intolerance of side effects, and efficacy. The real prescribing behaviours showed a significant positive association of medication usage with cost subsidy by the hospital. There was no mention in the manuscript when this study was conducted, although it was published in 2005.	8
Grandas et al. **(251)**	Spain	A population-based study that included surveying 241 physicians	1999	Community	1,803 patients and 241 physicians	Percentage of patients prescribed each drug/drug class/drug combinations	Type of prescriber	L-dopa was the most PD medication prescribed (90.4%) regardless type of prescriber. DAs was the second common PD medication prescribed (44%). Movement disorders specialists tended to prescribe DAs and COMT inhibitors more than other prescribers followed by neurologists. General physicians used to prescribe anticholinergics more than other prescribers.	6

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Askmark et al. **(252)**	Sweden	Retrospective study that used the prescription sales of 906 community pharmacies and 89 hospital pharmacies.	1995/2001	Inpatient and community settings	N/A	Defined daily doses (DDD) per 1,000 inhabitants per day	Age and number of neurologists in a particular county	Between 1995 and 2001, L-dopa prescriptions sales increased. After 1997, there has been an increase in sales of DAs (cabergoline, pramipexole and ropinirole). There was no correlation between the sales of all PD medications and the densities of neurologists or population ages in any particulate county in the study.	5
Leoni et al. **(253)**	Italy	Cross-sectional surveys with patients.	1997-1998 No comparison	Community	130 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Age, disease severity, and duration of the disease	L-dopa was the most PD medication prescribed (98.5%) followed by DAs (43.7%). Use of PD medications increased with duration and severity of the disease.	7
Lapane et al. **(263)**	USA	Retrospective study that used all Medicare- or Medicaid-certified nursing Homes (in 5 states in USA)	1992-1996 No Comparison	Nursing homes	24,402 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Gender, race, age and cognitive function	44% of all PwP in nursing homes received one of the PD medications. DAs were the most common PD medications prescribed (75%) followed by L-dopa (52.27%), MAO-B inhibitor (20.45%), and anticholinergics (18.18). Female, African Americans, and older age patients were less likely to receive PD medication in nursing homes.	7
Fukunaga et al. **(254)**	Japan	Cross-sectional surveys with patients.	1994-1996 No comparison	Inpatient and community settings	104 patients	Percentage of patients prescribed each drug/drug class/drug combinations	Duration of the disease	L-dopa was the most prescribed PD medication (78.84%) followed by DAs (76.92%). Combination therapies (2-3 PD medications) were common in patients with a duration of disease less than 5 years. The combination therapy of 4 PD medications was common in patients with a duration of disease of 7-9 years.	4
Menniti-Ippolito et al.**(255)**	Italy	Retrospective study that used prescriptions of drugs included in the National Drug Formulary	1986-1991 No comparison	Community	6,572 patients	Percentage of patients prescribed each drug/drug class/drug combinations	N/A	L-dopa was the most PD medication prescribed (86.2%) followed by selegiline (24.6%).	6

Table 2-2-Studies that examined PD medications prescribing determinants only

Study	Country	Type of study	Year	Number of patients	Prescribing determinants	Comments/ main findings	Quality score (out of 10)
Goudreau et al. [49]	USA	Using data from a clinical trial of creatine versus placebo in participants with early, mild PD on stable doses of dopaminergic therapy. The trial is called NINDS Exploratory Trials in PD (NET-PD) Long-Term Study-1 (LS1)	2007-2010 No Comparison	1,616 patients	Age, gender, race, education level, insurance statue, duration of the disease, comorbidity score, and using of MAO-b inhibitors	This study examined the characteristics of PwP who enrolled in NET-PD-LS1 study. It compared between patients with L-dopa vs patients with DAs vs patients with a combination therapy (L-dopa + DAs) in terms of proposed prescribing determinates. Higher education level, longer duration of the disease, younger age, and using of MAO-b inhibitors were strongly more common in patients who used DAs.	9
Umeh et al. [52]	USA	Using data from a clinical trial of creatine versus placebo in participants with early, mild PD on stable doses of dopaminergic therapy. The trial is called NINDS Exploratory Trials in PD (NET-PD) Long-Term Study-1 (LS1)	2007-2010 No Comparison	1,741 patients	Gender and education level	This study examined the characteristics of PwP who enrolled in NET-PD-LS1 study. It compared between patients with L-dopa vs patients with DAs vs patients with a combination therapy (L-dopa + DAs) in terms of proposed prescribing determinates. There was no association between patients' genders and the type of PD medications that were received. There was no association between patients' education levels and the type of PD medications that were received.	6
Chen et al. [76]	China	The cross-sectional questionnaire-based survey was distributed to 612 doctors.	2010-2011	N/A	Age, type of prescribers, cognitive impairment (CI), and wearing off phenomenon.	42.9%, 33.5% of doctors preferred using DAs, L-dopa, respectively, for patients aged less than 65 years without CI. 48.3% of doctors preferred switching from immediate release L-dopa to controlled release L-dopa for patient with wearing off phenomenon. Movement disorder specialists were better than GPs and general neurologists in improving patient's quality of care and sticking to national guidelines.	5
Hu et al. [77]	UK	The cross-sectional questionnaire- was distributed to 340 PwP.	2007-2008	340 patients	Age, cognition, mobility, education level and tremor.	The sub-optimal care was defined as: (1) more than one year gap between PD diagnosis and first consultation by a specialist, and (2) more than one year gap with no evidence of consultant review. Poor cognition, older age, and worse mobility were strongly associated with sub-optimal care.	7

Hemming et al. [78]	USA	The cross-sectional questionnaire- was distributed to 1090 PwP	2003-2008	1,090 patients	Race, income, and educational level.	African American PwP were: less likely to use dopaminergic medications and specially the newer PD medications, prescribed less PD medications, and prescribed more antipsychotics compared to white Americans. Generally, there was no difference between using of PD medications across different levels of incomes and educational levels except that these with lower income or/and low educational level were less likely to be prescribed newer PD medications, and they were more likely to be prescribed antipsychotics.	7
Nyholm et al. [79]	Sweden	Retrospective study that used patients' medical files and national drug registries.	2006-2007	504 patients	Age and gender	The median levodopa daily dose was 465 mg for men and 395 mg for women. The likelihood of dyskinesia was the same in the patients regardless of their total L-dopa dose. Patients' ages were associated inversely with L-dopa dose.	5
Yacoubian et al. [80]	USA	Retrospective study that used the National Institute of Neurological Disorders and Stroke-sponsored REGARDS study.	2003-2007	190 patients	Gender, race, and health insurance	PwP without health insurance were less likely to receive PD medications. PD medications use was more common in White-Americans than African-Americans. PD medications use was more common in men compared to women. There was no association between PD medications use and educational level, income, and geographical residence.	4
Dahodwala et al. [81]	USA	Retrospective study that used Pennsylvania State Medicaid claims.	1999-2003	307 patients	Age, gender, race, county, and type of prescriber.	African-Americans were four times less likely to receive PD medications comparing to whites. Older age was associated with not receiving PD medications.	4
Cheng et al. [82]	USA	Retrospective study that used an administrative database (the Network 22 VISN Data Warehouse).	2001-2002	309 patients	Age, race, comorbidity (Charlson index), outpatients' visits, and type of prescriber.	An expert panel has determined multiple indicators for quality of PD care including adding DAs, COMT inhibitors, amantadine, and MAO-b inhibitors if the patient developed wearing-off phenomenon. Adherence to previous quality indicator was more common in non-Hispanic white people than African American. Adherence to previous quality indicator was associated positively with a high Charlson index, short time from PD diagnosis, more outpatients' visits, and involvement of movement disorder specialists in patient's care.	5

2.3.2 Quality of the studies

The quality assessment of the selected studies using the Joanna Briggs Institute Critical Appraisal Tool is illustrated in Table 2-3. Of the prescribing pattern and determinants studies (*n* = 44), two studies were given a quality score of 9 out of 10 (9/10) (219, 229), four studies were given 8/10 (226, 234, 243, 250), seven studies were given 7/10 (231, 236, 248, 253), six studies were given 6/10 (228, 232, 246, 249, 251, 255), eleven studies were given 5/10 (230, 235, 237, 240, 241, 244, 245, 252), ten studies were given 4/10 (223-225, 227, 242, 247, 254), three studies were given 3/10 (233, 238, 265), and finally, one study was given 2/10 (239).

2.3.3 Prescribing patterns

PD medication prescription rates in all the countries included in this review are presented in Table 2-4 and Table 2-5. Additionally, Table 2-6 shows a grand summary of PD medications' prescribing pattern.

2.3.3.1 L-dopa

All of the studies except five (225, 228, 230, 236, 243) calculated the prescription rate of L-dopa. Of the studies that calculated L-dopa prescription rates, four calculated the prescription rates of L-dopa + carbidopa and L-dopa + carbidopa + entacapone combinations separately (224, 238, 242, 264); seven studies calculated the prescription rates of both L-dopa- carbidopa and L-dopa + carbidopa + entacapone combinations altogether, without distinction (219, 227, 231, 237, 240, 244, 245), and the rest of the studies calculated only L-dopa + carbidopa prescription rates (223, 226, 233-235, 239, 241, 246-255, 263). None

of the studies that used hospital data mentioned whether the LCIG prescribing rate was calculated, except for one Norwegian study (265). The Norwegian study found the average number of patients using L-dopa gel to be 2.6 per 100,000 population, which was less than the number of patients using deep brain stimulation (DBS) (2.9 per 100,000 population) (265).

Except for a few studies (233, 241, 242, 263), L-dopa was the most commonly prescribed medication in all of the studies regardless of the year or the design of the study, accounting for between 37.42% (in Spain) and 100% (in India) of all PD medications.

L-dopa prescription rates were the highest (ranging from 46.50% to 100%) compared to other PD medications in several cross–sectional studies in Italy (253, 255), Japan (254), Spain (251), Singapore (250), USA (219, 244, 249), Sweden and Norway (264), South Africa (237) and India (223, 224, 235). The lowest L-dopa prescription rates were 21% in 2005 and 2008, found in a Japanese study that used the national Japanese database vendor to examine the effect of pergolide withdrawal from the USA market on PD medications prescribing patterns in Japan by applying a time interrupted series model (241). L-dopa did not account for the majority of prescription rates in New Zealand (24.86% in 1995) (233) and Australia (36.50% in 1995) (242). However, both studies reported that L-dopa prescription rates had increased and accounted for the majority of prescription rates in 2011 in New Zealand (48.76%) and in 2009 in Australia (52.30%).

Studies carried out in other countries found an increase in the prescription rates of L-dopa in different years. Figure 2-3a shows that L-dopa prescriptions increased in Sweden, Spain, and Europe in general (245, 247, 252). Inversely, Figure 2-3a shows a decrease in the prescription rates of L-dopa over the years in Southern Italy, Japan, USA, Finland, and Taiwan (226, 227, 231, 234, 246).

2.3.3.2 Dopamine agonists

All bar five studies calculated the prescription rates of DAs (ergot, non-ergot, or both) (225, 230, 236, 243, 255). Studies that calculated prescribing patterns of DAs can be classified under studies that calculated both ergot and non-ergot DAs prescription rates (224, 231, 233, 234, 238, 241, 242, 246, 247, 251, 253); DAs prescription rates in general without specifying what type of DAs (219, 223, 226, 227, 239, 240, 244, 245, 248, 249, 252, 263, 264); ergot DAs only (250, 254); or, non-ergot DAs only (228, 235, 237).

In general, DAs were the second most common PD medication prescribed after L-dopa in 16 studies, with the prescription rate ranging from 7.63% to 85% (219, 226-228, 231, 234, 237, 239, 244, 246, 248-251, 253, 254, 264). One study that examined the pattern of prescribing in nursing homes in five states in the USA found that DAs were the most commonly prescribed PD medication to the members of the study sample, surpassing even L-dopa (75% of 10,738 PD medications users) (263). In a small number of studies, anticholinergics bumped DAs into third place, ranging from 10.90% to 29% either throughout the study, as in India (223, 224, 235), New Zealand (233), and Japan (241), or at least at one point during the study, as in Spain in 1992 (247) and Australia in 2009 (242). In only one retrospective study in Sweden, DAs' prescription rates were third after L-dopa and MAO-B inhibitors (252), although DA agonist prescribing continued to grow. Aligned with the Swedish study, a gradual increase in the trend of DAs' prescription rates over the years is evident in many countries (226, 227, 231, 233, 234, 241, 242, 246, 247) (Figure 2-4c). Studies from Australia, New Zealand, Spain, and Italy revealed a slight increase in the use of apomorphine after it became available in these countries (233, 247, 253, 266). There were no data from other countries regarding apomorphine usage.

2.3.3.2.1 Ergot-based DAs

Of all prescribing pattern studies, thirteen studies calculated the exact prescription rates of ergot DAs (224, 231, 233, 234, 238, 241, 242, 246, 247, 250, 251, 253, 254). There was a wide range in the prescription rates of ergot DAs, which ranged from 0.50% to 76.92%. For studies that calculated the rate of prescribing at only one point of time, there was often an association between the year of the study and the prescription rates. For example, studies carried out prior to 2000 showed higher prescription rates of ergot DAs than did those carried out after 2000. Studies that examined the changes in prescription rates across a number of years found a general decrease in prescription rates of ergot DAs (231, 233, 234, 238, 241, 247), ranging from a 3% decrease in prescription rates in Japan between 2005 and 2008 (241) to a 30.69% sales costs decrease in England between 1999 and 2010 (238). The exception was two studies in Australia and Southern Italy, which showed a slight increase in ergot DAs' prescription rates (242, 246). The Australian study revealed an increase in ergot DAs' prescription rates from 4.10% in 1995 to 4.80% in 2009 (242) and the Italian study found about a 5% increase in the prevalence of ergot DAs' use per 100,000 inhabitants between 2003 and 2005 (246) (Figure 2-4a).

2.3.3.2.2 Non-ergot DAs

Fourteen studies measured the exact prescription rate of non-ergot DAs (224, 228, 231, 233-235, 237, 238, 241, 242, 246, 247, 251, 253). Of these, nine calculated the prescription rates at only one time and found that the prescription rates of non-ergot DAs ranged from 5.9% in Australia (242) to 39.80% in South Africa (237). An increase in the trend of non-ergot DAs' prescription rates was observed in several countries (231, 234, 238, 241, 246). This increase was dramatic in some studies: for instance, in England, there was a 49.2% increase in non-ergot DAs' sales rates between 1999 and 2010 (238).

Typically, though, a more modest increase in prescription rates of non-ergot DAs was observed; for instance, in the USA (13% increase between 2001 and 2011) (231), Japan (28.2% increase between 2005 and 2010 or 5.2% increase between 2005 and 2008) (234, 241), and Southern Italy (1.88% increase between 2003 and 2005) (246). Although there was a general increase in non-ergot DAs prescription rates in an American study carried out in an inpatient setting across a number of years, the prescription rate of non-ergot DAs decreased from 33.4% in 2008 to 27.9% in 2011 following the addition of the gambling precaution to the pramipexole profile in 2008 (231) (Figure 2-4b).

2.3.3.3 COMT inhibitors

The pattern of prescribing of COMT inhibitors was examined in several studies (219, 224, 227, 231, 233-235, 237-242, 244, 245, 247, 249-253). While only two studies calculated the prescription rate of the entacapone combination (L-dopa + carbidopa + entacapone combination) with a clear distinction between rates of L-dopa- carbidopa and L-dopa + carbidopa + entacapone combinations (224, 264), several studies have considered L-dopa + carbidopa and L-dopa + carbidopa + entacapone combinations as being one group without clear distinctions (219, 227, 231, 237, 238, 240, 244, 245). For monotherapy with COMT inhibitors, some studies calculated the prescription rates of tolcapone monotherapy (253), entacapone monotherapy (224, 234, 235, 238, 241, 242, 247, 249, 251), or both (219, 231, 233, 239, 244, 245, 250, 252). COMT inhibitors monotherapy prescription rates in the cross-sectional studies ranged from 1.01% in the USA in 1999-2000 (249) to 29% in the USA in 2003 (239). An increase in prescription rates for COMT inhibitors monotherapy was observed in the USA (2.9% in 2001 to 10.6% in 2012) (231), New Zealand (0.73% in 1998 to 3.53% in 2011) (233), and Japan (2.80% in 2007 to 8.80% in 2010) (234). On the other hand, studies based in Australia, Europe, and Spain have shown a slight decrease in prescribing of COMT inhibitors (242, 245, 247) (Figure 2-3b). Although a

previous study in Europe found this decrease in prescription rates for COMT inhibitors, it revealed a significant increase in L-dopa + carbidopa and L-dopa + carbidopa + entacapone combination sales by 68% between 2003 and 2007. As it is accompanied by a decrease in entacapone monotherapy prescribing over the same period, this likely reflects increasing sales of L-dopa + carbidopa + entacapone combinations (245). There was no way to calculate the prescription rates of L-dopa + carbidopa + entacapone combinations in these studies, which did not distinguish them from the L-dopa + carbidopa combinations (219, 227, 231, 237, 238, 240, 244, 245).

2.3.3.4 MAO-B inhibitors

Prescribing patterns for MAO-B inhibitors were explored in the majority of the identified studies (219, 224, 227, 228, 231, 233-235, 237-242, 244, 245, 247-253, 255, 264). Of the two MAO-B inhibitors available, the selegiline prescription rate was measured in 17 studies (233, 234, 237, 240-242, 244, 247-253, 255, 263, 264), both selegiline and rasagiline prescription rates were measured in six studies (227, 228, 231, 235, 238, 245), and the rest of the studies measured MAO-B inhibitors as a group without specifying the name of the drug (219, 239). There were variations in the prescription rates of MAO-B inhibitors in the cross-sectional studies, which ranged from 2.12% in South Africa (237) to 42% in Japan (239). Other studies that examined changes in the trend of prescription rates over the years revealed varying trends. Selegiline prescribing was either maintained or decreased (233, 234, 241, 242, 247, 252) (Figure 2-5a). Decreases were particularly notable in Sweden between 1995 and 2001 (28% decrease in sales) (252) and New Zealand (18.76% in 1995 to 3.88% in 2011) (233). A relatively steady prescription rate of selegiline was seen in Japan (234, 241), Australia (242), and Spain (247) (Figure 2-5a). Some studies calculated selegiline rates in the beginning of the study and subsequently calculated both selegiline and rasagiline rates (as a group) when rasagiline became commercially available

(227, 231, 238, 245). Two of the studies revealed a slight increase in prescribing of MAO-B inhibitors over time (9.90% in 2005 and 14.10% in 2012 in Finland, and 3.89% in 2003 and 5.80% in Europe) (227, 245), while one study in the USA found a slight decrease from 9.80% in 2001 to 5.80% in 2011 (231) (Figure 2-5a).

2.3.3.5 Amantadine

A total of 20 studies measured prescription rates of amantadine (219, 223, 224, 228, 231, 233-235, 237, 240-242, 244, 245, 248-251, 253, 254). Among cross-sectional studies, there was wide variation, ranging from 0.2% in Italy (253) to 44.23% in Japan (254). In trend studies, a relatively steady prescription rate of amantadine was observed in the USA (6.20% in 2001 and 6.80% in 2012) (231), Australia (2.90% in 1995 and 3.50% in 2009) (242), and Europe (1.86% in 2003 and 1.10% in 2007) (245). In Japan, two studies showed two different trends: Nakaoka et al. found a decrease in amantadine prescription rates from 30% in 2005 to 22.10% in 2010 (234), while Ooba et al. found no major changes in prescription rates between 2006 and 2008 (11% and 10%, respectively) (241). A noticeable increase in amantadine prescribing was seen in New Zealand (1.26% in 1995 and 6.71% in 2011) (233) (Figure 2-5b).

2.3.3.6 Anticholinergics

A significant variation was noticed in the cross-sectional studies that examined prescription rates for anticholinergics in PwP. Two relatively recent studies in the USA examined anticholinergics prescribing in inpatient and community settings and revealed low prescription rates of anticholinergics (5% and 6. 6%) (219, 244). This suggests a decreasing trend overall when compared to an earlier study (18.18% between 1992 and 1996) (263). In some Asian countries (India, Japan, and Singapore), anticholinergics prove more popular, with a relatively high prescription rate, ranging from 22.9% in Singapore to 40.4% in India (223, 250).

In trend studies, most studies have shown a decrease in prescription rates of anticholinergics across years. This decrease was slight in the USA (6.70% in 2001 to 6.10% in 2012) (231) and limited to one study in Japan (47.80% in 2006 to 43% in 2008) (241), Europe (4.40% in 2003 to 2.91% in 2007) (245), and Southern Italy (24.95% in 2003 to 24.21% in 2005) (246). A more observable decrease was seen in other countries, including New Zealand (44.30% in 1995 to 25.44% in 2011) (233), Australia (48.70% in 1995 to 24.10% in 2009) (242), and Spain (31.28% in 1992 to 16.99% in 2004) (247) (Figure 2-5c).

Table 2-3- Quality appraisal checklist using the Joanna Briggs Institute Critical Appraisal Tool

Study[a]	Representative sample	Appropriate recruitment	Adequate sample size	Reporting of study subjects and setting	Data coverage of the identified sample is adequate	Objective, standard criteria used for measurement of the condition	The condition was measured reliably and objectively	Appropriate statistical analysis	Ensuring confounding factors/subgroups/differences are identified and accounted for.	Subpopulations identified using objective criteria	Quality score
Ezat et al. **(265)**	**UC**	**UC**	**N**	**Y**	**N**	**Y**	**UC**	**Y**	**N**	**N**	**3**
Tripathi et al. **(224)**	N	N	N	Y	NA	Y	Y	Y	N	N	4
Surathi et al. **(223)**	N	UC	UC	Y	NA	N	UC	Y	Y	Y	4
Jost et al.**(225)**	N	N	Y	Y	Y	N	UC	Y	N	N	4
Dahodwala et al.**(219)**	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y	9
Liu et al. **(226)**	N	Y	Y	Y	Y	Y	UC	Y	N	Y	8
Keränen et al. **(227)**	N	UC	Y	Y	N	UC	UC	Y	N	Y	4
Hand et al. **(228)**	N	UC	Y	Y	Y	N	N	Y	Y	Y	6
Goudreau et al.**(229)**	Y	UC	Y	Y	Y	Y	Y	Y	Y	Y	9
Degli Esposti et al. **(230)**	N	UC	Y	Y	Y	UC	UC	Y	N	Y	5
Crispo et al. **(231)**	N	Y	Y	Y	Y	Y	UC	Y	N	Y	7
Umeh et al.**(232)**	N	Y	N	Y	UC	Y	UC	Y	Y	Y	6
Pitcher et al.**(233)**	N	NA	Y	Y	Y	N	N	N	N	NA	3
Nakaoka et al.**(234)**	N	Y	Y	Y	Y	Y	UC	Y	Y	Y	8
Junjaiah et al. **(235)**	N	Y	N	Y	Y	N	N	Y	Y	Y	5
Guo et al. **(236)**	Y	UC	Y	Y	Y	N	N	Y	Y	Y	7
Gaida et al.**(237)**	N	UC	Y	Y	Y	N	N	Y	N	Y	5
Skogar et al. **(264)**	N	UC	Y	Y	Y	N	N	Y	N	NA	4
Morrish **(238)**	Y	NA	Y	Y	NA	N	N	N	N	NA	3
Hattor et al.**(239)**	N	UC	N	Y	Y	N	N	N	N	UC	2

Study[a]	Representative sample	Appropriate recruitment	Adequate sample size	Reporting of study subjects and setting	Data coverage of the identified sample is adequate	Objective, standard criteria used for measurement of the condition	The condition was measured reliably and objectively	Appropriate statistical analysis	Ensuring confounding factors/subgroups/differences are identified and accounted for.	Subpopulations identified using objective criteria	Quality score
Chen et al. **(256)**	Y	Y	UC	Y	Y	NA	NA	Y	N	UC	5
Schroder et al. **(240)**	N	Y	N	Y	UC	Y	UC	Y	N	Y	5
Ooba et al. **(241)**	N	UC	Y	Y	Y	N	N	Y	N	Y	5
Hu et al. **(257)**	N	Y	N	Y	UC	Y	Y	Y	Y	Y	7
Hollingworth et al. **(242)**	N	NA	Y	Y	Y	N	N	N	N	Y	4
Hemming et al. **(258)**	N	N	UC	Y	Y	Y	Y	Y	Y	Y	7
Fayard et al. **(243)**	N	Y	UC	Y	Y	Y	Y	Y	Y	Y	8
Wei et al.**(244)**	N	UC	Y	Y	Y	N	N	Y	N	Y	5
Rosa et al. **(245)**	Y	NA	Y	Y	Y	N	N	Y	N	NA	5
Nyholm et al. **(259)**	Y	NA	Y	Y	UC	N	N	Y	N	Y	5
Yacoubian et al. **(260)**	N	UC	UC	Y	Y	N	N	Y	N	Y	4
Dahodwala et al. **(261)**	N	UC	N	Y	Y	N	N	Y	N	Y	4
Trifiro et al. **(246)**	N	UC	N	Y	Y	Y	Y	Y	N	Y	6
Cheng et al. **(262)**	N	UC	N	Y	Y	N	N	Y	Y	Y	5
Osinaga et al. **(247)**	Y	NA	Y	Y	Y	N	N	N	N	NA	4
Swarztrauber et al.**(248)**	N	UC	Y	Y	Y	Y	Y	Y	N	Y	7
Huse et al. **(249)**	N	UC	Y	Y	Y	N	N	Y	Y	Y	6
Tan et al. **(250)**	N	Y	N	Y	Y	Y	Y	Y	Y	Y	8
Grandas et al. **(251)**	Y	UC	Y	Y	Y	UC	UC	Y	N	Y	6

Study[a]	Representative sample	Appropriate recruitment	Adequate sample size	Reporting of study subjects and setting	Data coverage of the identified sample is adequate	Objective, standard criteria used for measurement of the condition	The condition was measured reliably and objectively	Appropriate statistical analysis	Ensuring confounding factors/subgroups/differences are identified and accounted for.	Subpopulations identified using objective criteria	Quality score
Askmark et al. **(252)**	Y	NA	Y	Y	Y	N	N	N	N	Y	5
Leoni et al. **(253)**	N	UC	N	Y	Y	Y	Y	Y	Y	Y	7
Lapane et al. **(263)**	N	Y	Y	Y	Y	Y	UC	Y	N	Y	7
Fukunaga et al. **(254)**	N	UC	N	Y	Y	N	N	N	Y	Y	4
Menniti-Ippolito et al.**(255)**	Y	Y	N	Y	Y	N	N	NA	Y	Y	6

a) Yes (Y), No (N), Unclear (UC) or Not/Applicable (NA)

Table 2-4- PD medications prescription rates*

Country	Year	L-dopa[d] only[a]	L-dopa combination[b]	COMT inhibitors	Ergot DAs	Non-ergot DAs	All DAs	MAO-B inhibitors	Amantadine	Anticholinergics
Norway[e] **(265)**	2009-2013	—[c]	—	—	—	—	—	—	—	—
India **(224)**	2014	94.8	—[c]	—	—	—	23.2	—	17.2	40.4
India **(223)**	2011-2014	86	92	6	2	27	29	12	2	31
Germany[f] **(225)**	2017	—	—	—	—	—	—	—	—	—
USA[g] **(219)**	2010	—	90	6	—	—	29	11	7	5
Taiwan **(226)**	2004/2011	91.38/89.24	—	—	—	—	26.52/27.54	—	—	—
Finland **(227)**	2005/2012	—	59/55.30	—	—	—	21.70/23.9	9.90/14.10	—	—
England **(228)**	2015	—	—	—	—	38.5/13.2[h]	38.5/13.2	12.2/1.1	7.3/4.4	—
Italy[i] **(230)**	2009-2011	—	—	—	—	—	—	—	—	—
USA **(231)**	2001/2011	—	89.10/85.10	2.90/10.10	6.60/0.50	14.90/27.90	21.5/28.50	9.80/5.80	6.20/6	6.70/5.40
New Zealand **(233)**	1995/2011	24.68/48.76	—	—/3.53	11.07/2.82	—/8.38	11.07/11.2	18.67/3.88	1.26/6.71	44.30/25.44
Japan **(234)**	2005/2010	58.20/51	—	—/8.80	41.80/13.90	9.10/37.30	50.90/51.20	10.90/10.50	30/22.10	15.50/31.40
India **(235)**	2011-2013	100	—	≈4[j]	—	≈18	≈18	≈9	≈5	≈30
Taiwan[k] **(236)**	2000/2010	—	—	—	—	—	—	—	—	—
South Africa **(237)**	2010	—	46.50	—	—	39.80	39.80	2.12	1.80	9.20
Sweden and Norway **(264)**	2010-2013	—	≈59/76[l]	—	—	—	≈52/30	≈10/35[m]	—	—
England[n] **(238)**	1999/2010	≈47.5/16	≈—/26	≈3.75/3.63	≈32.5/1.81	≈11.25/60.45	≈43.75/62.26	≈6.25/7.27	—	—
USA/Japan **(239)**	2003/2008[o]	(70-80)/95	—	29/25	—	—	57/85	—/42	—	—

Table 2-5- PD medications prescription rates*

Country	Year	L-dopa[d] only[a]	L-dopa combination[b]	COMT inhibitors	Ergot DAs	Non-ergot DAs	All DAs	MAO-B inhibitors	Amantadine	Anticholinergics
Germany **(240)**	2004	—	54.45/89.92[p]	—	—	—	79.58/43.41	14.13/13.17	23.56/24.03	—
Japan[q] **(241)**	2005/2008	21/21	—	—/1	13/10	3.8/9	16.8/19	4/5	11/10	47.8/43
Australia **(242)**	1995/2009	36.50/52.30	—/55.90	—/2.90	4.10/4.80	—/5.90	4.10/10.90	7.90/2.10	2.90/3.50	48.70/24.10
France[r] **(243)**	≤2000/>2000	—	—	—	—	—		—	—	—
USA**(244)**	2000-2003	—	75.10	13.31	—	—	34.84	9.63	7.79	6.16
Europe[s] **(245)**	2003/2007	—	25.63/30.49	10.50/5.61	—	—	53.69/54.06	3.89/5.80	1.86/1.10	4.40/2.91
Italy **(246)**	2003/2005[t]	≈49.91/43.73	—	—	≈8.48/13.53	≈16.63/18.51	≈25.11/32.04	—	—	≈24.95/24.21
Spain **(247)**	1992/2004	37.42/49.75	—	—/0.24	16.25/6.31	—/11.89	16.25/18.68	15.03/14.56	—	31.28/16.99
USA **(248)**	1998/2004	46.48/82.10[u]	—	—	—	—	19.81/7.63	0/1.67	14.41/4.29	18.91/3.81
USA **(249)**	1999-2001	70.92	—	1.01	—	—	13	5.05	5.92	—
Singapore **(250)**	—	92.3	—	6.8	26.8	—	26.8	21	2.9	22.9
Spain **(251)**	1999	90.4	—	5.8	28.9	15.1	44	31	2.8	9.6
Sweden[v] **(252)**	1995/2001	≈50.54/63.84	—	≈—/7.50	—	—	≈1.44/9.21	≈48.1/19.79	—	—
Italy **(253)**	1997-1998	98.5	—	3.1	36.1	7.6	43.7	2.3	0.8	8.5
USA **(263)**	1992-1996	52.27	—	—	—	—	75	20.45	—	18.18
Japan **(254)**	1994-1996	78.84	—	—	76.92	—	76.92	—	44.23	30.76
Italy **(255)**	1986-1991	86.2	—	—	—	—	—	24.6	—	—

* A summary of the prescribing pattern or studies through which the percentage of patients prescribed each drug and drug class can be calculated (this includes studies that have examined the drug sales differences). Entries below the drug names are the percentages of all prescriptions, drug sales prices, or all patients for that row and year. If there are two years mentioned in the "year" column, they indicate the first and last year of the study if they are separated by the slash symbol (/), and the prescription rates represented these years unless stated otherwise. If the two years are separated by the dash symbol (-), that means that the

prescription rates were calculated for these years cross-sectionally at the same time, unless stated otherwise. (Articles are ordered by year of publication).

a. "L-dopa only" = L-dopa + dopamine decarboxylase inhibitors (carbidopa or benserazide).
b. "L-dopa combination" = L-dopa + dopamine decarboxylase inhibitors and L-dopa + dopamine decarboxylase inhibitors + COMT inhibitors.
c. "—" = data unavailable or not applicable
d. L-dopa, levodopa; COMT, catechol-O-methyl transferases; DAs, dopamine agonists; MAO-B, monoamine oxidase inhibitors; NA, not applicable.
e. The study examined only L-dopa intestinal gel, so prescribing rate cannot be estimated.
f. Based on the data presented in the study, it was impossible to calculate prescription rates for every medication.
g. The study covered the period from 2007 to 2010; however, it did not examine the changes in the trend. Therefore, the last year of the study was included in the table, taking into account that there were no big differences in the prescription rates over the years of the study.
h. This study examined the difference in PD prescribing pattern between community and care homes. "/" = separates data for PwP living in their homes and patients living in care homes, respectively.
i. This study examined the prescription rate of PD medications that were used only by selegiline/rasagiline users. Therefore, the prescription rate for each PD medication/class cannot be calculated.
j. "≈" = the rate was estimated from a graph in the study and there were no specific numbers in the manuscript.
k. This study examined the pattern of initial therapy in PwP from 2000 to 2010. It divided the years of the study into two periods: 2000-2005 and 2006-2010. Therefore, the total prescription rate per year cannot be calculated. The individual prescription rates of every PD medication cannot be calculated because the study has classified PD medications as L-dopa only (which means any L-dopa product with or without any PD medication other than DAs); and DAs only (which means any DA with or without any PD medication other than L-dopa).
l. "/" = separates data for PwP in Sweden and Norway respectively.
m. The prescription rate of selegiline only.
n. This study examined the total net ingredient costs of PD medications in England between 1999 and 2010. All the sales percentages were estimated from a graph in the study because they were not mentioned in the manuscript.
o. This was a drug utilisation comparison study between the USA and Japan. The American study was conducted in 2003, and the Japanese study was conducted in 2008.
p. "/" = separates data for PwP aged <70 years and PwP aged >70 years in the year of study, respectively.

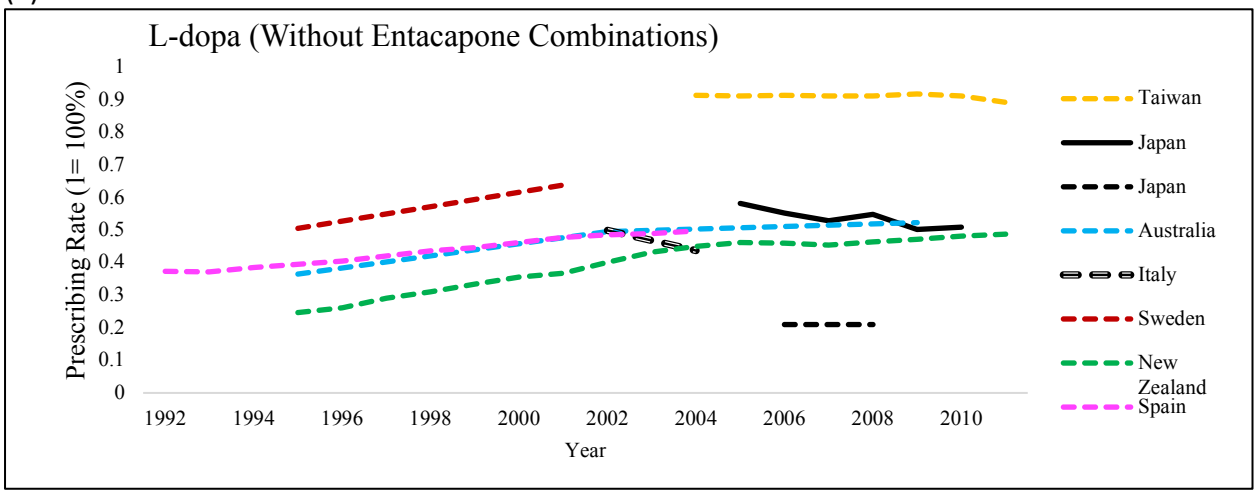
q. The study examined the effect of pergolide withdrawal from the US market by applying a time interrupted series model. The year “2005” covered the period from September 2005–March 2007, while “2008” covered the period from April 2007–October 2008.
r. The study did not specify exactly in which year the prescription rates were calculated. Additionally, all medications were presented as a combination with other medications: therefore, the prescription rates cannot be calculated.
s. The study examined the changes in PD medications sales in 26 European countries. The unit of analysis was DID (DDD per 1000 inhabitants daily). DID cannot be calculated for the whole of Europe. However, the difference in PD medication sale prices between 2003 and 2007 was calculated and presented in the table.
t. “/” = separates data for the difference in percentage of the prevalence of a particular PD medication use per 100,000 inhabitants out of the total percentages of prevalence of all PD medications use per 100,000 inhabitants between 2003 and 2005.
u. The study examined the initial antiparkinsonian therapy in newly diagnosed PwP from 1998 to 2004. “/” = separates data for PwP aged <65 years and PwP aged ≥65 years in the years of the study, respectively.
v. The study examined the changes in PD medication sales in Sweden. The unit of analysis was DID (DDD per 1000 inhabitants daily). The difference in DIDs for PD medications between 1995 and 2001 was estimated from a graph in the study and presented in the table.

	L-dopa	Dopamine Agonists (DAs)	COMT inhibitors	MAO-B inhibitors	Amantadine	Anticholinergics
General prescribing pattern	L-dopa was the most commonly prescribed medication in most studies regardless of the year or the design of the study, ranging from 37.42% (in Spain) to 100% (in India). Only one Norwegian study examined the prescribing rate of L-dopa intestinal gel (LCIG).	DAs (mainly non-ergots) were the second most common PD medication prescribed in 16 studies, with the prescription rate ranging from 7.63% to 85%. Studies carried out prior to 2000 showed higher prescription rates of ergot DAs than did those carried out after 2000.	Large variation in the prescribing rates of COMT inhibitor monotherapy, ranging from 1.01% in the USA to 29%, also in the USA.	There were variations in the prescription rates of MAO-B inhibitors, ranging from 2.12% in South Africa to 42% in Japan.	There was wide variation, ranging from 0.2% in Italy to 44.23% in Japan.	A significant variation was noticed in the cross-sectional studies that examined anticholinergic use in PD. In some Asian countries (India, Japan, and Singapore), anticholinergics prove more popular.
Trend of prescribing across years	There was an increase in L-dopa prescribing across time in Sweden, Spain, and Europe. A decrease in L-dopa prescribing across time was observed in Southern Italy, Japan, USA, Finland, and Taiwan.	A general decrease in prescription rates of ergot DAs and an increase in the trend of non-ergot DAs prescription rates were observed in several countries, especially after 2000.	Prescribing increase was observed in the USA, New Zealand, and Japan. On the other hand, studies based in Australia, Europe, and Spain showed a slight decrease in prescribing.	Selegiline prescribing was either maintained or decreased across years. Only two studies revealed a slight increase in prescribing of MAO-B inhibitors over time in Finland and Europe.	Across years, a relatively steady prescribing rate of amantadine was observed in the USA, Australia, and Europe.	Most studies have shown a decrease in prescription rates of anticholinergics across years
Patient factors						
Age	Elderly patients (age ≥ 65 years) were more likely to be prescribed L-dopa than younger patients.	DAs use was less common in elderly patients with some exceptions as in some USA hospitals.	N/A	N/A	N/A	In two studies, elderly patients were less likely to be prescribed or initiated on anticholinergics.
Gender	Multiple studies found no difference between men and women in the likelihood of L-dopa prescribing.	Multiple studies found no difference between men and women in the likelihood of DAs prescribing.	N/A	One Italian study found that rasagiline was more commonly prescribed to men than selegiline.	N/A	N/A
Race	N/A	In the USA, DAs prescribing was more common in non-Hispanic white people when compared to African Americans, although this finding was not statistically significant.	In the USA, COMT inhibitors prescribing was more common in non-Hispanic white people when compared to African Americans.	In the USA, MAO-B inhibitors prescribing was more common in white people when compared to African Americans.	In the USA, amantadine prescribing was more common in white people when compared to African Americans.	N/A
Duration of the disease	Number of years since PD diagnosis was lower in L-dopa monotherapy users than in DAs monotherapy users.	Number of years since PD diagnosis was lower in L-dopa monotherapy users than DAs monotherapy users.	N/A	N/A	N/A	N/A
Comorbidities	N/A	DAs prescribing was more common in patients with a high comorbidity score.	COMT inhibitor prescribing was more common in patients with a high comorbidity score.	MAO-B inhibitor prescribing was more common in patients with a high comorbidity score.	Amantadine prescribing was more common in patients with a high comorbidity score.	Patients with PD and dementia were prescribed anticholinergics as initial therapy more commonly than non-dementia patients.
Socioeconomic status and care settings	L-dopa equivalent daily dose (LEDD) prescribed to care home residents was lower than that prescribed to patients in the community.	Patients with a higher education level were prescribed DAs more often than patients with a lower education level. Patients residing in institutions were less commonly prescribed DAs than residents within the community.	COMT inhibitor prescribing was higher in patients living in their homes compared to care homes patients.	MAO-B inhibitor prescribing was higher in patients living in their homes compared to care homes patients.	N/A	N/A

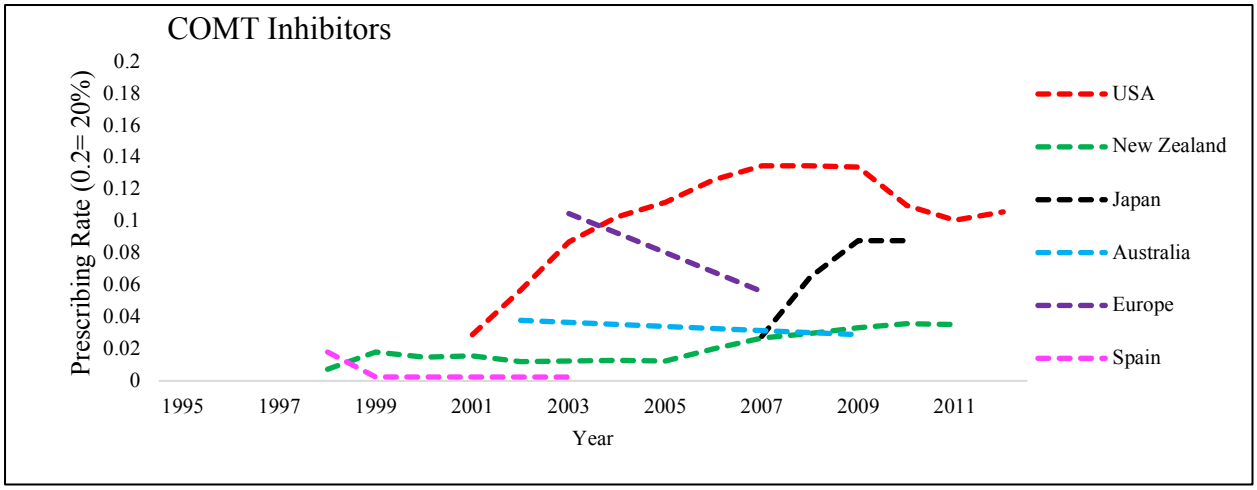
Table 2-6- Summary of prescribing trends of PD medications and factors associated with their use.

Figure 2-3- Prescribing trends of PD medications

(a)



(b)

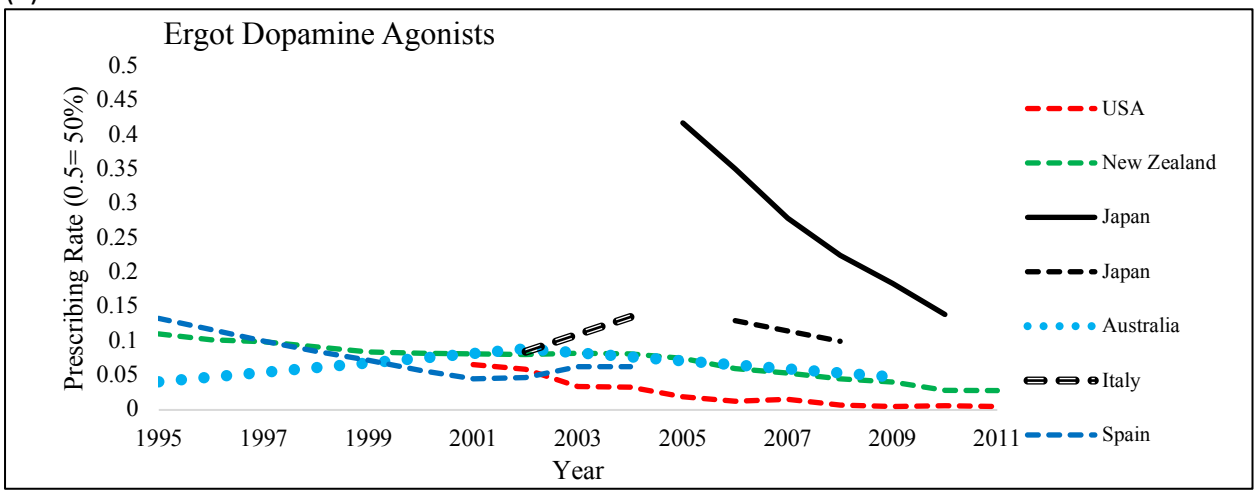


Japan, (——) = Nakaoka et al. (234)
Japan, (– – –) = Ooba et al. (241)

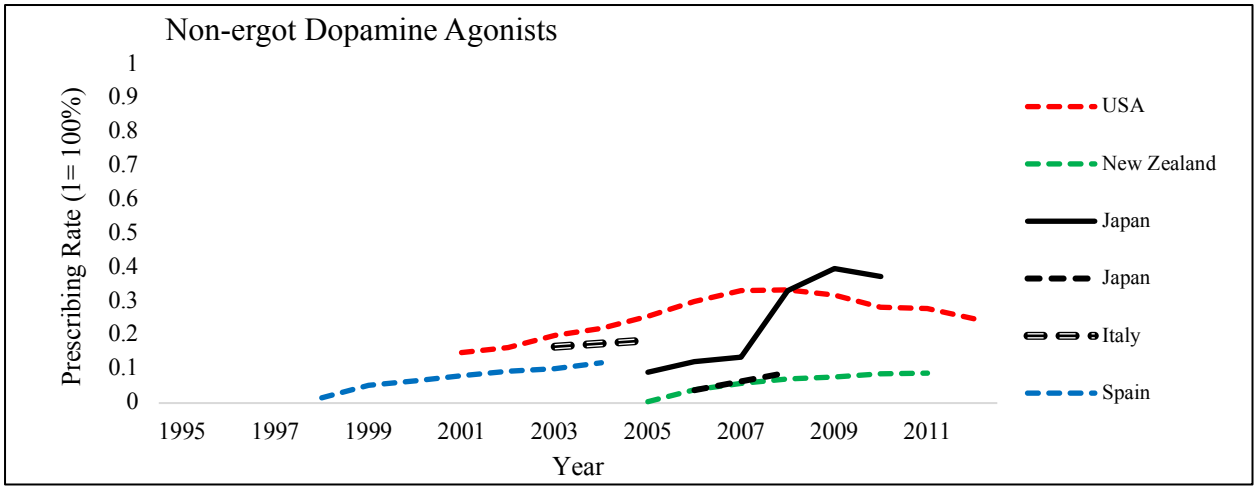
Note: this applies to the next two sets of figures.

Figure 2-4- Prescribing trends of PD medications

(a)



(b)



(c)

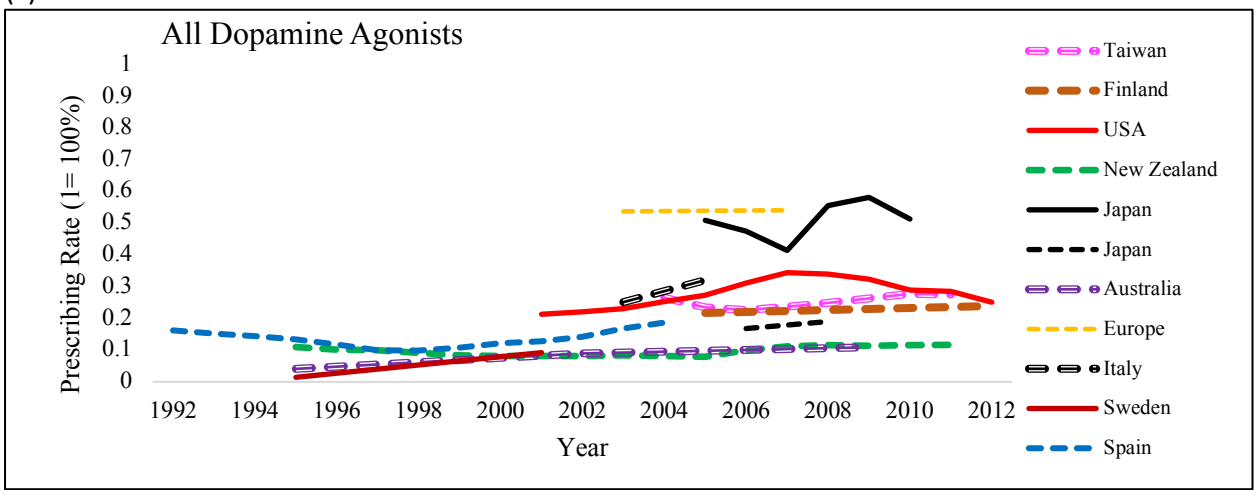
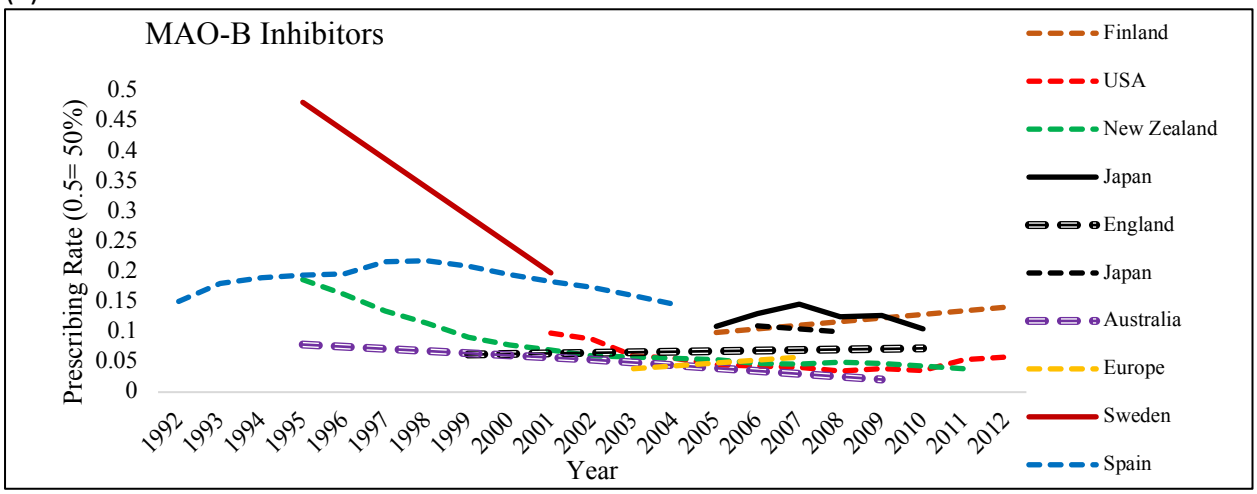
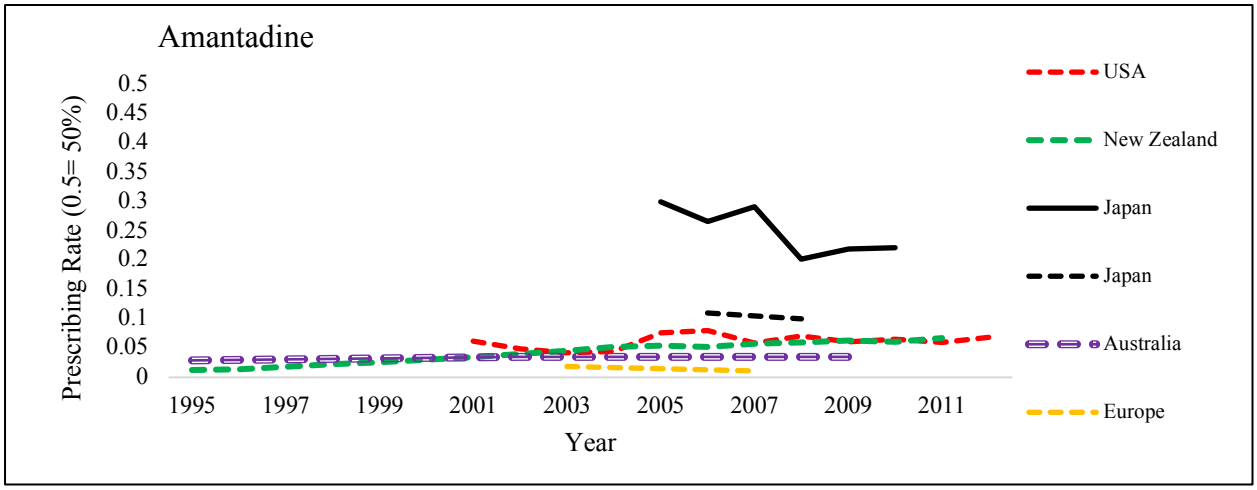


Figure 2-5- Prescribing trends of PD medications

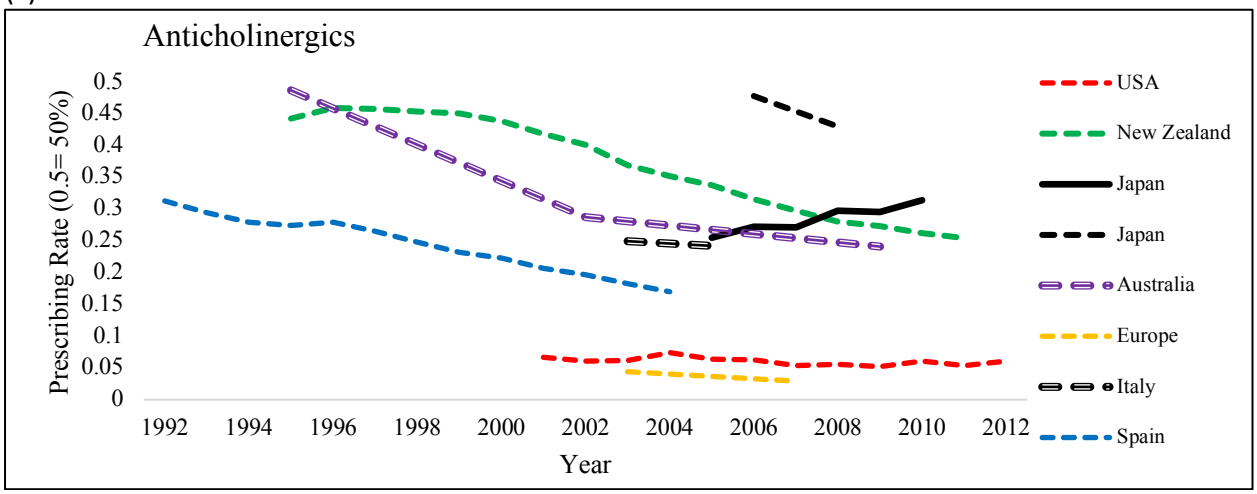
(a)



(b)



(c)



2.3.4 Prescribing and drug utilisation determinants

Once the determinants of the prescription and utilisation of PD medications had been extracted, they could be classified according to patients' factors (with several subcategories) and prescribers' factors (with only one subcategory). Table 2-6 shows a summary of prescribing determinants of PD medications.

2.3.4.1 Patients' factors

2.3.4.1.1 Age

Several studies have shown that elderly patients (age ≥ 65 years or age ≥ 70 years) were more likely to be prescribed L-dopa than younger patients. The L-dopa dose was inversely associated with age in an examination of 33,534 L-dopa users in Sweden (259). Moreover, in two studies, elderly patients were less likely to be prescribed (234) or initiated on anticholinergics (248). In contrast to the use of L-dopa, and consistent with guidance of preferred L-dopa use in the elderly, the use of DAs was less common in elderly patients (219, 231). However, there were studies that were discrepant: Crispo et al. found that elderly people in inpatient hospital settings in the USA were regularly prescribed DAs regardless of national guidelines (231). Studies have looked at the overall likelihood of receiving PD medications based on age, two of which suggested that older patients (>85) were less likely to be medicated (244, 263). Conversely, Dahodwala et al. in the USA determined that older patients were more likely to receive PD medications than younger patients (OR = 1.67, 95% CI, 1.17–3.27)(261). On the other hand, a study of younger patients (≤ 60 years, or ≤ 65 years) revealed a different pattern of prescribing than that pertaining to older patients. Younger patients were more likely to be prescribed DAs in multiple studies and tended to receive more than one medication to treat PD (219, 226,

227, 229, 231, 237, 240, 243, 259). There is significant country-to-country variation in the management of younger patients with PD, with one US study finding that the majority of younger patients in the study were prescribed L-dopa, while only 20% of younger patients (or ≤ 65 years) were on DAs (248). MAO-B inhibitors and anticholinergics were more likely to be prescribed as an initial therapy to younger patients than L-dopa in a Taiwanese study (236). With regard to MAO-B inhibitors, a comparative Italian study that examined 1,607 MAO-B users found that rasagiline utilisation was more common in younger patients than selegiline (230). In trend studies, a Finnish study found that use of MAO-B inhibitors was increased during the duration of the study (from 2005 to 2011) in younger patients (227).

2.3.4.1.2 Sex

Multiple studies found no difference between men and women in terms of prescription rates for L-dopa and DAs (231, 232, 244, 246, 249). However, where differences were observed, they generally indicated that men were receiving higher doses or were more likely to receive multiple medications (219, 259, 260, 263). The effect of sex on the prescribing of other types of PD medications (other than L-dopa and DAs) was not evaluated in all the studies in this review. However, in one study, it was found that rasagiline was more commonly prescribed to men than selegiline: i.e. 45.2% of selegiline users (n = 1024) and 57.8% of rasagiline users (n = 583) were men (p = 0.001)(230).

2.3.4.1.3 Race

The effect of patients' race on the prescription and general utilisation of PD medications was evaluated only in the US-based studies. These studies found that, in inpatient and community settings, African American PwP were less likely to use dopaminergic medications, especially the newer PD medications; were

prescribed less PD medications; and were prescribed more antipsychotics than white Americans (258, 260, 261). In nursing home settings, African Americans were less likely to receive PD medications in the USA, but this was not statistically significant (OR = 0.89, 95% CI 0.79-1.01) (263). Another study found that adding medications that reduce L-dopa-induced motor fluctuations (DAs, MAO-B inhibitors, COMT inhibitors, and amantadine) was more common in non-Hispanic white people when compared to African Americans, although this finding was not statistically significant (262).

2.3.4.1.4 Duration of the disease

Some studies measured the duration of the disease as a prescribing determinant. The use of multiple PD medications was positively associated with the duration of the disease in two studies (235, 253). Another study used data from a clinical trial of creatine versus placebo in participants with early, mild PD (NET-PD LS1) and found that the number of years since PD diagnosis was lower in L-dopa monotherapy users than in DAs monotherapy users (1.45 years vs 1.60 years respectively, p = 0.02) (229).

2.3.4.1.5 Comorbidities

Dahodwala et al. found that patients with high morbidity scores (prescription drug hierarchical condition category (RxHCC) risk score) were less likely to receive multiple PD medications (OR = 0.53, 95% CI 0.49–0.57, p = <0.001) (219). Different results were observed in another American study that conducted a logistic regression to find the effect of total comorbidity scores on the chance of receiving single or multiple PD medications in elderly PD Medicare beneficiaries (244). The study found no association between PD medication use and patient's total comorbidity scores (244). However, the same study found that some specific types of comorbidities might have an impact on the chance of receiving

single or multiple PD medications. For example, patients with depression were more likely to receive PD medications than non-depressed patients (OR = 1.25, 95% CI 1.02–1.53, p = <0.05) (244). On the other hand, patients with dementia were less likely to receive PD medications than non-dementia patients (OR = 0.62, 95% CI 0.48–0.80, p = <0.001) (244). Similar findings were observed in nursing home settings in the USA where patients with severe cognitive impairment were less likely to receive PD medications than patients with normal cognitive functions (OR = 0.79, 95% CI 0.73-0.85) (263). Also, another study found that patients with dementia were prescribed anticholinergics as initial therapy more commonly than were non-dementia patients, but this finding was not statistically significant (p = 0.11) (248). Another study revealed that the addition of medications that reduce L-dopa-induced motor fluctuations was significantly more common in patients with a high comorbidity score (Charlson Index of 5 or more) (p = 0.03) (262).

2.3.4.1.6 Socioeconomic status and care settings

All the studies that examined the effect of socioeconomic status (SES) on PD drug utilisation were conducted in the USA and they reported conflicting results. Yacoubian et al. failed to find an association between PD medication use and patients' educational level, income, and geographical residence (260). Another study found no association between PD medication use and patients' income and marital status (244). However, the same study revealed that the chance of being prescribed any of the PD medications was higher for patients with a higher education level (high school diploma or more) than for patients with a lower education level (OR = 1.51, 95% CI 1.04–2.19; p < 0.05) (244). Hemming et al. found no difference in the use of PD medications across patients with different levels of income and educational level except for the fact that these with lower income and/or a low education level were less likely to be prescribed newer PD medications and were more likely to be prescribed antipsychotics (258). Another

study found that patients with a higher education level were prescribed DAs more often than those with a lower education level (229). With regard to the effect of health insurance on prescriptions, one study carried out in the USA confirmed that PwP without health insurance received fewer PD medications than patients who had health insurance of any type ($p = 0.001$) (260).

Regarding patients' care settings, an American study found that only 44% of a total of 24,402 nursing home residents with PD in the USA received PD medications (263). Another US study based on Medicare claims for PwP from 2000 to 2003 revealed that patients residing in institutions were more likely to receive PD medications than residents within the community (OR = 1.78, 95% CI 1.17-2.71; $p < 0.01$) (244). The same study found that patients residing in institutions were less commonly prescribed DAs than residents within the community (15.7% vs 35% respectively) ($p < 0.001$ (244). In the UK, Hand et al. compared PD medication use in the community vs. care homes in a retrospective study using the Northumbria Healthcare NHS Foundation Trust PD service in England (228). They found that the L-dopa equivalent daily dose (LEDD) prescribed to care home residents was lower (median LEDD = 400 mg, 95% IQR 250-610) than that prescribed to the patients in the community (median LEDD = 657.5 mg, 95% IQR 447.5-1048) ($p = < 0.001$) (228). The same study found that use of DAs, MAO-b inhibitors, and COMT inhibitors was relatively higher in patients living in their homes (228).

2.3.4.1.7 Geographical location

This factor has been examined only in one Norwegian study that found that patients who live in Rogaland county were prescribed significantly more L-dopa intestinal gel than were those living in other counties in Norway (265). This

difference was attributed in the study to the amount of knowledge patients had about the advanced therapy options in Norway (265).

2.3.4.2 Prescribers' factors

2.3.4.2.1 Type of prescriber

Eleven studies examined the association between prescriber type and prescribing pattern of PD medications (219, 236, 239, 242, 243, 248, 250-252, 256, 262). Prescribers in these studies could be classified as: general practitioners (GPs), family physicians, mental health providers, geriatricians, neurologists, and movement disorder specialists.

A US survey evaluating 54 family physicians, 328 neurologists, and 74 movement disorder specialists determined that half of the family physicians and almost one-third of the neurologists prescribed L-dopa as a starting therapy for PwP immediately after diagnosis (239). In Spain, no significant difference was found in the percentages of prescribers of L-dopa among family physicians, geriatricians, neurologists, and movement disorder specialists (87.3%, 86.1%, 91.2%, 91.9% respectively) (251), although movement disorders specialists tended to prescribe DAs more often and exclusively prescribed amantadine (251). In the USA, family physicians were more likely to prescribe L-dopa, while neurologists and movement disorder specialists were more likely to prescribe DAs (248). Likewise, in Australia, around 80% of the total DID of L-dopa was prescribed by family physicians, while 10% to 20% was prescribed by neurologists, with minimal variation between 2003 and 2009 (242).

In the USA, mental health providers were more likely to prescribe anticholinergics as an initial therapy than other prescribers (OR = 76, 95% CI 31.7-181.7) (248), whilst in Spain, the percentage of patients treated with

anticholinergics was higher if they were treated by family physicians (17.8%) as opposed to geriatricians (11.1%), neurologists (8.6%) or movement disorder specialists (7%) (251).

Polytherapy and therapy switching were another two issues that only a few studies examined. In USA, Dahodwala et al. found that patients who were treated by neurologists were more likely to receive multiple PD medications than were those who were treated by others (non-neurologists) (219). In a study in Taiwan that examined the type of initial therapy in PwP from 2000 to 2010, it was found that 79.3% of L-dopa and DAs combination therapy was initiated by neurologists and 20.7% was initiated by non-neurologists (236). The same study noted that patients who were treated by neurologists were switched more commonly to another drug within one year of the study (236).

The impact of the type of prescriber on adherence to national guidelines was another parameter that was evaluated in two studies (243, 256). The French study failed to find a significant difference between neurologists and non-neurologists in adherence to the type of initial therapy that was recommended in French treatment guidelines of PD in 2000 (243). Conversely, the Chinese study found that movement disorder specialists were more successful than GPs and general neurologists in improving a patient's quality of care and adhering to Chinese national guidelines, which included several recommendations on how to reduce L-dopa-induced motor fluctuations by adding COMT inhibitors, MAO-B inhibitors, or others (256). Likewise, Cheng et al. found that medications that reduced L-dopa-induced motor fluctuations were more commonly prescribed by movement disorder specialists than general neurologists and GPs in the USA (262).

2.4 Discussion

To the best of found knowledge, this review is the first that assessed the pharmacoepidemiological studies in PD. The number of PD-related drug utilisation studies identified for review in this study was limited, taking into account the non-negligible prevalence of PD (3, 6). Most of the studies that were included were conducted in the USA and Europe (68% of all studies), which has limited the geographical spread. This may relate to the high prevalence of PD cases in these countries, exemplified by a recent meta-analysis examining 47 prevalence studies globally, which determined that PD prevalence was higher across all ages in Europe, North America, and Australia than in Asia (3). However, in terms of prevalence, South America surpassed them all (3); but no drug utilisation study in South America was identified for review.

The source of drug utilisation data varied in the reviewed studies, with 38% of the data being sourced from insurance claim, prescription registry, or drug sales databases. Data sourced from insurance claims or similar sources may include a large number of patients, which makes it possible to generalise the study results to the whole population, but it is also highly possible that these databases include patients who have other diseases that have mistakenly been diagnosed as PD (e.g. secondary parkinsonism), since these data lack detailed patient clinical information. Several studies that used this source of data that were included in this review acknowledged this drawback and considered the possibility of overestimation of PD medication prescription rates (219, 226, 234, 236, 244, 261, 263). About 26% of the studies reviewed here used patients' interviews, questionnaires, and surveys to estimate the drug utilisation rates. Although this approach might give a more accurate estimate of medication prescribing patterns, given that the data is based on a more accurate diagnosis by PD experts (224, 225, 243), the relatively small sample sizes restrict the generalisability of the findings. Use of Electronic Medical Records (EMR) and GP

data may overcome the problems of small sample size and misdiagnosis in drug utilisation studies. However, to avoid the inherent drawbacks of EMR (missing data and data entry errors), it is essential to validate these records against standard criteria such as the actual paper files of the patients, GP questionnaires, or linking data to other databases (267, 268). In all the studies that used EMR and GP data included in this review (28%), none were validated against standard criteria. However, in general, the impact of source of data on PD medications prescribing was minimal in most studies. The exception was L-dopa, which was reportedly more prescribed than other PD medications in studies using interviews, questionnaires, and surveys in their methodology. However, this increase is most likely due to the time of these studies (most of which were conducted before 2000), when the current portfolio of dopaminergic drugs was either not clinically available or efficacy was not well-established (Appendix 7). Therefore, no valid conclusion could be drawn from a simple comparison of L-dopa prescribing according to the source of data.

2.4.1 Prescribing patterns

In this review, studies of prescribing patterns of PD medications worldwide were reviewed and the extent to which these patterns accorded with the changes occurring in the safety and efficacy profiles of PD medications was determined. In the majority of studies, regardless of the study year or location, unsurprisingly L-dopa plus a dopa decarboxylase inhibitor (carbidopa or benserazide) persists as the most commonly prescribed PD medication (with or without the COMT inhibitor, entacapone), with no significant changes over time. Where an increase was identified over time (New Zealand, Australia, Sweden and Spain) (233, 242, 247, 252), this was hypothesised to be due to an increase in PD incidence, an increase in the duration of the disease, or an increasing preference for L-dopa therapy over DAs in the early stages of the disease. Determining which is not

possible from this data, but a real increase in PD incidence is unlikely. It is likely that some trends might have evidenced the changing recommendations in DA vs. L-dopa use. In the early 2000s, multiple studies reported that long-term L-dopa use could contribute to neurotoxicity (269, 270). The ELLDOPA trials in 2004 (271) refuted these findings by showing no evidence of neurotoxicity of L-dopa. There was vigorous debate in the field at this time on the benefits of commencing therapy with DA agonists to delay the onset of L-dopa-induced dyskinesia (LID) and other potential benefits of reduced development of LID might have altered prescribing, but this was only evident in marginal trends (272, 273). Indeed, the PD-MED study only supported part of this rationale; it used the QoL scale and determined that initiating patients with L-dopa actually resulted in a better QoL than using DAs and that reducing motor fluctuations by delaying L-dopa initiation was not associated with better results over the long term (101).

Early reports of potential neuroprotective effects of DAs may have contributed to a general increase in DAs prescribing in the early 2000s (274-278), but in 2006, the AAN report stated that there was no evidence of neuroprotection for DAs (126), and subsequent reports and clinical trials confirmed the AAN recommendation (190-192, 279). These reports might explain why some studies found a slight decrease in DA prescription rates, especially post-2005 (231, 234). A slight increase or consistent rate in prescribing DAs was seen in other studies (227, 233, 236, 241, 242), which might be due to the fact that DAs were still the recommended treatment in the guidelines as a starting therapy, especially with younger patients (280-282). Recently, the UK NICE guidelines recommended starting therapy with DAs or other dopaminergic therapies (MAO-B inhibitors or L-dopa) in the early stages of PD if the motor symptoms do not impact patients' quality of life (31).

Within the subtypes of the DAs, several cross-sectional studies have shown a wide range of prescription rates for ergot DAs. The relatively high prescription

rate seen in the studies conducted before 2000 may be due to the cumulative effect of reports of L-dopa neurotoxicity in the late 1990s and early 2000s (269, 270), the hope that ergot DAs might possess neuroprotective properties (274, 283, 284), and the fact that ergot DAs' side effects, such as cardiac fibrosis, had not yet been discovered. In the trend studies, most showed a decrease in the prescription of ergots even though the results of a large-scale UK study that led to a voluntary withdrawal of this drug from the US and Canadian markets in 2007 had not yet been published (208, 209). For example, in the USA, there was a 5.1% decrease in the prescription of ergots between 2001 and 2007 (231). The same phenomenon was seen in New Zealand, Japan, Italy, and Spain, in parallel with an increase in non-ergot DAs prescription (233, 234, 246, 251). An association between the use of ergot DAs (pergolide initially) and valvular heart toxicity was reported in the early 2000s (199). Whilst non-ergot DAs might have seemed an obvious alternative, reports then emerged of side effects associated with their use (112, 201-204). Although in several studies the non-ergot prescription rate increased, particularly after pergolide withdrawal (226, 227, 231, 233, 234, 242), prescription rates decreased in the USA in 2011 (231). This could be explained by reports of several side effects of non-ergot DAs that appeared between 2006 and 2017. Examples of these side effects, in addition to reports of the risk of heart failure associated with pramipexole, include the gambling precaution that was added to the pramipexole profile in 2008 (210). A DOMINION cross-sectional study that was conducted in 2010 found ICDs to be significantly associated with DAs (198).

Prescribing rates of COMT inhibitors were largely consistent, with both slight increase (231, 233, 234) and slight decrease (242, 245, 247) reported. In some studies, differentiating the exact prescription rate of COMT inhibitors without considering the L-dopa prescription rate is difficult, since the prescription rate of the L-dopa + carbidopa + entacapone combination was reported in the studies but not the rate of entacapone alone (219, 227, 231, 237, 238, 240, 244, 245).

Tolcapone monotherapy was explicitly measured in one study in Italy in 1997-1998 and showed a very low prescription rate (1.3% of the total prescriptions) (253), which is probably linked to the FDA black box warning about the hepatotoxicity risk in 1998 (129) and its very recent approval. Post-2000, any increase in entacapone plus tolcapone prescription rates, as in the USA (231) and New Zealand (233), might have been due to entacapone alone, since tolcapone prescriptions were restricted due to its hepatotoxicity. No conclusion could be drawn regarding the prescription rates of the L-dopa + carbidopa + entacapone combination in a number of the studies which did not distinguish between its prescription rate and the prescription rates for L-dopa + carbidopa combinations (219, 227, 231, 237, 238, 240, 244, 245).

Although it was still in clinical-trials testing for possible neuroprotective properties after its approval in 2006, the prescription rate for rasagiline (an MAO-B inhibitor) was only examined in six of the studies (227, 228, 231, 235, 238, 245), whilst the prescription rate for selegiline showed great variation between studies The decrease in prescribing around 1995 can be linked to the PDRG-UK trial, which suggested an association with an increased mortality rate (211) although this was subsequently debated through a meta-analysis (212). Furthermore, the decline in use has continued, with the purported neuroprotective properties suggested by a range of clinical trials (TEMPO (193); ADAGIO (125)) being unsupported by the guidance (31). Safinamide is an MAO-B inhibitor that has been recently approved as an add-on therapy to L-dopa in patients who develop motor fluctuations, and with its relatively recent appearance, its place on the PD stage has yet to evolve significantly.

A huge variation in amantadine prescription rates can be seen, characterised by very low and consistent rates in all but Japan, for which there is no explanation (234). Unlike other PD medications, amantadine has not been subjected to significant changes in safety or efficacy profiles since the Schwab trail in 1969

that suggested its clinical efficacy in treating PD symptoms (167). The main indication for amantadine, based on Schwab's work, was to treat the early symptoms of PD, but this was not enough to avoid adding or switching to L-dopa therapy in the long run (285). In the late 1990s, several studies showed the antidyskinetic effect of amantadine to treat L-dopa-induced dyskinesia (286, 287). In 2017, the extended release form of amantadine was the first medication that was approved by the US FDA to treat L-dopa induced dyskinesia (288). How this formulation and approval affects prescribing in future remains to be seen.

Anticholinergics were routinely used in the treatment of PD before the discovery of L-dopa; however, due to their troublesome side effects, their use is limited at present to managing severe tremor in younger patients who do not suffer from cognitive problems (86). Notwithstanding this fact, anticholinergic prescription rates were generally high in most Asian studies (223, 224, 234, 235, 241, 250), but are generally reducing over time through replacement with other strategies. This was explained, for example, in one Japanese study by the fact that the treatment guidelines in Japan in the early 2000s recommended anticholinergics as the first option (234). An Indian study attributed this high rate of prescribing anticholinergics to the fact that they were cheaper than most of the other PD medications in India (224). In the USA, two cross-sectional studies showed a very low rate of anticholinergics prescriptions, possibly reflecting an awareness of anticholinergics' side effects, especially in older patients (219, 244). Conversely, Lapane et al. found a high rate of prescriptions for anticholinergics (18.18%) in nursing home settings in the USA (263). This data is confounded by the use of anticholinergics in neuroleptic-induced parkinsonism and other conditions.

2.4.2 Prescribing determinants

The patient's age was one of the most common factors affecting the use of PD medications. In a number of studies, older patients were less likely to receive PD medications than younger patients. This is likely to be linked to fear of side effects, interactions or increased morbidity, consistent with findings that old age in general has a positive association with high morbidity scores in PwP (289).

Whilst L-DOPA has been demonstrated to be the most effective medication for all age groups in PD (85, 282, 290), several studies demonstrated a clear preference for younger patients to be prescribed DA agonists, withdrawing them in older people, consistent with the guidelines. L-dopa causes fewer side effects than DAs in elderly people (109) and DAs are three times more likely to cause hallucinations than L-dopa (108, 182, 291). Additionally, DAs cause a higher rate of somnolence and sleep attacks in PwP (108, 182, 291), and could be significantly more likely to trigger impulse control disorders (ICDs) such as hypersexuality and pathological gambling (196, 198, 292). However, notwithstanding these recommendations, Cirspo et al. found that in inpatient settings in the USA, there was a continuous high rate of prescription of DAs for elderly patients, which raised a question regarding the awareness of treatment guidelines (231). In relation to the L-dopa dose given, a Swedish study found that older patients were associated with a lower L-dopa dose than younger patients (259), which may be due to the pharmacokinetics (L-dopa had greater bioavailability and less clearance volume in elderly people) (293, 294).

Overall, according to the studies included in this review, it seems that the several guidelines published after 2000 (113, 282, 295) recommending starting therapy with DAs or MAO-B inhibitors in younger patients and starting L-dopa in older patients might have had an impact on clinical practice. However, according to the results of the PD-MED study, the recent NICE guidelines did not consider age

as a factor in choosing the first line treatment. Instead, patients' quality of life was the major factor that affected the treatment decision. According to the NICE guidelines, if motor symptoms do not affect patients' quality of life, then starting therapy with DAs or other dopaminergic therapies (MAO-B inhibitors or L-dopa) is recommended (31). L-dopa, on the contrary, should be used if motor symptoms affect the patients' quality of life (31).

Gender was examined in multiple studies but with conflicting outcomes. Whilst several studies found no gender relationship in prescription rates for L-dopa and DAs (231, 232, 244, 246, 249), other studies found that women had lower odds of being prescribed L-dopa (219), were less likely to receive PD medications (both polytherapy and monotherapy) (219, 260, 263), and received lower L-dopa daily doses (259). Whilst this may be linked to pharmacokinetics, this matter is under-researched and more investigation is required into the differences in responses between medications and sensitivity to side effects.

In most countries, the patients' race was not investigated as a factor influencing prescription. However, a few studies in USA revealed inequalities relating to African Americans when it comes to PD medication prescriptions, particularly with regard to the newly approved medications, which are generally more expensive (258, 260-263). Similar inequalities exist across broad tranches of the US health care system in relation to PD (296, 297) and other conditions, which may be linked to the fact that African Americans in general are less likely to have medical insurance and have less access to health care facilities than white Americans in the USA (298).

Residence in long-term care facilities such as care homes can be a factor affecting access to health care in PwP. One study, which included a large number of PwP in care home settings in the USA, found that about 56% of patients did not receive any PD medication (263). The study did not consider this

phenomenon as a sign of health inequality; rather, it suggested that these patients had most likely been admitted to nursing homes due to debilitating side effects, such as psychosis caused by PD medications. This claim was supported by Hand et al., who compared PD medication use in the community vs. care homes in England and found that LEDD was lower in care home residents than in patients in the community (228). Although there is a difference in the endpoints of the two previous studies – i.e. the first study examined any single use of PD medication (263), while the second measured the total dose of PD medications taken (228) – both reached the same conclusion. According to the two studies, the reason behind the lower use or lower dose of PD medications in care homes was to avoid psychotic episodes caused by PD medication. In PwP, psychosis can occur as a consequence of the disease itself, or it can be caused by the PD medications (50). Thus, it is crucial, when managing psychosis in PwP, to titrate the PD medication doses first, before considering prescribing antipsychotics (42). Despite previous evidence that attributed the lack of PD medication utilisation in care homes to a plausible clinical reason – i.e. to avoid the side effects of PD medications – some studies found inappropriate management for PwP in care homes (263, 299). This could be explained by lack of access to secondary clinics or switching to a new GP which resulted in suboptimal care (300). Telemedicine (the approach that uses new technology such as video teleconferencing to link health care providers to PwP directly) is one tool that could potentially resolve the issue of lacking access to health care due to difficulty accessing health care facilities (301).

Among the countries covered in this review, there were differences in health care systems, prescribing guidelines and in the eligibility of the patients, which limit the value of making comparisons between countries. However, there were some common observations that are worth mentioning in relation to the prescribers themselves. In the only studies identified, movement disorders specialists and neurologists, more than family physicians or GPs, were more

likely to prescribe DAs according to some of the studies (242, 248, 251), whereas family physicians and GPs were more likely to prescribe L-dopa or anticholinergics (242, 251). Since these studies predate many of the changes in guidance, more up-to-date examination of the relative roles and trends in prescribing would be valid.

This study has several limitations. First, the reviewed studies were heterogeneous in terms of design, duration, and data sources. This makes direct comparisons of the prescription rates of different PD medications very difficult. This type of difficulty has been previously identified in other studies (302, 303). Second, although quality scores were assigned to each study, no study was excluded on the basis of its quality score due to lack of evidence. However, the study score might indicate its quality level. Future studies should focus on developing a quality assessment tool that would help researchers to make decisions in drug utilisation research. Third, the fact that this review included only English studies could introduce language bias. However, we tried to minimize this bias by identifying relevant non-English-language studies in our literature searches. The fourth limitation is the assumption that has been made in the discussion section, which has attributed the changes in prescribing patterns of PD medication to awareness or non-awareness of the guidelines. Other factors such as drug availability and patient preferences might explain some prescribing behaviours. Therefore, caution should be taken when interpreting the results reported in this review.

In conclusion, worldwide, since its discovery, L-dopa has been the most commonly prescribed PD medication. The prescription rates of ergot-derived DAs decreased in several countries due to cardiac toxicity issues, while the use of non-ergot DAs increased. Significant country-to-country variation in the prescribing rates of COMT inhibitors, MAO-B inhibitors, amantadine, and anticholinergics were found. Alongside this, patient age was the most common

factor that affected prescribing in most studies. The most recent third-generation MAO and COMT inhibitors have not been considered in any study, as they are so new to the portfolio and new guidance has recently been released in the UK.

CHAPTER 3: General Methods

3.1 Source of data and study data overview

3.1.1 SAIL Databank

The Secure Anonymised Information Linkage (SAIL) Databank is a central repository that was set up by the Health Information Research Unit (HIRU) in the school of medicine at Swansea University (304). The main target of the SAIL Databank is to provide opportunities for researchers to utilise the maximum number of electronic data resources related to people resident in Wales by linking person-level data together in an anonymised and double-encrypted way that protects patients' confidentiality (304). The person-level data contained in the SAIL Databank include but are not limited to primary care (GPs), hospital episodes, outpatient visits, demographics, and mortality data (305). At the time of writing this thesis, SAIL contains about 80% of GPs' data for the general population of Wales. After obtaining the required governance approval, researchers can access the relevant data through a remote gateway that enables them to look up and analyse the data in a safe environment enriched with several analytical and statistical software programs that help them in answering their research questions (306).

In the following sub-sections, a more detailed description of how the SAIL Databank is operated will be discussed, including the safety measures employed by SAIL to prevent/minimize risks of breaching patients' data privacy.

3.1.1.1 Data transfer

The data are transferred to the SAIL Databank after formal permission has been obtained from data providers and data sharing agreements have been signed in accordance with Information Governance (306). The information and

instructions on how to transfer data from the data provider system to SAIL are provided by the SAIL technical team to the data providers (306). Efforts have been made to secure the process of transferring data from the data providers to SAIL. For example, the data providers cannot transfer their data to SAIL through unsafe methods; rather, the data providers are given access to a secure electronic gateway that allows a safe and protected data transfer process (305).

3.1.1.2 Split file process, matching, anonymisation and encryption

With the help of the SAIL technical team, the data provider should send the data to SAIL using the split file process approach (306). This means that the data provider separates patients' data into two files: the first one contains the identified demographic data, such as name, gender, date of birth, NHS number, and address. The second file contains the clinical-related data, which cannot be used to identify patients' identities, such as diagnosis codes and drugs (306). The two files contain a unique identifier number for every patient, which can be used later to relink the patient data in SAIL. The first file (demographics file) will then be sent to a Trusted Third Party (TTP), which is the NHS Wales Informatics Service (NWIS), while the second file will be sent to SAIL directly. Upon receiving the first file, NWIS conducts the process of anonymisation and matching, by which the identified demographic data are encrypted by assigning a unique Anonymised Linkage Field (ALF) to each patient in the first file (306). Additionally, NWIS assigns a Residential Anonymous Linking Field (RALF) for every address. RALF is a unique code that results from matching the Welsh demographic data at NWIS against the addresses registered at Royal Mail Postal Address Files. After that, NWIS matches every ALF with its related RALF and sends these data to SAIL (307). After matching the data against the Welsh Demographic Service, a third file which contains the patients' ALFs, RALFs, unique identifier numbers, and minimal demographic data (week of birth,

gender code and Lower Super Output Area (LSOA) (which constitutes a population of roughly 1,500 in Wales and is used instead of the post code as an estimation of the address in SAIL)) is sent to the SAIL Databank. SAIL staff, in turn, link the second file (which they already have) with the third file using the unique identifier numbers. A second encryption of ALF and RALF is conducted in SAIL, which results in ALF-E and RALF-E (305) (Figure 3-1).

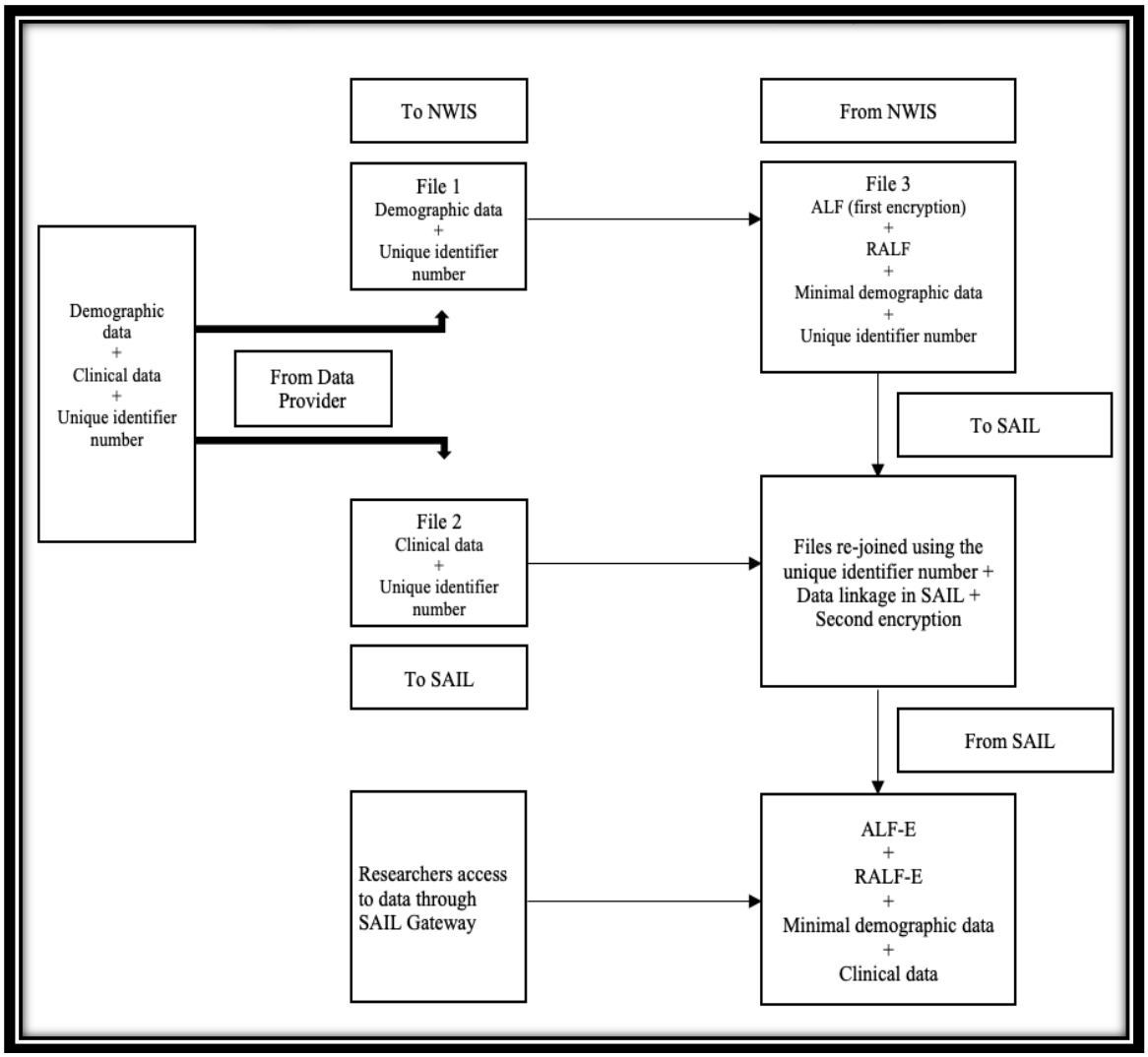


Figure 3-1- Split file process in SAIL Databank

3.1.1.3 Disclosure control

In order to prevent/minimize the risk of breaching data confidentiality and mitigate the risk of any re-identification of patients' identities, the SAIL Databank has developed several safety and privacy measures. The first measure SAIL has considered is the process of anonymisation, which removes all person-level data that may identify the patients' identities. As mentioned in the split file process, it is the NWIS that conducts the anonymisation process and assigns an ALF for every patient. Concerns about the possibility of re-identifying patients' identities have led SAIL to conduct a second privacy measure, which involves assigning a second encryption to ALFs and RALFs, thus making it impossible for SAIL staff and NWIS to re-identify patients' identities. Other privacy measures in the SAIL Databank by which researchers must abide include data aggregation and suppression when required. The researchers must ensure that no datasets consisting of small numbers (<5) are published, as well as ensuring that no potentially identifiable subgroups or cohorts are communicated via their results (306).

3.1.1.4 Data linkage process in the SAIL Databank

The SAIL technical team uses the ALFs that were created by NWIS to link patients' data from a dataset to another dataset in the SAIL Databank. Using the ALF as a unique 10-digit number for every patient in SAIL is preceded by a reliable matching process that uses several matching algorithms with a high sensitivity and a lower error rate (304). Two types of record linkages are used in SAIL: Deterministic Record Linkage (DRL) and Probabilistic Record Linkage (PRL). In DRL, a unique identifier of the individual (e.g., NHS number) is used to link multiple records from different datasets. This approach is characterized by a high specificity (linking the required individuals records correctly), and a relatively low

sensitivity (missing individuals in questions due to an error or missing values in the unique identifiers). In PRL, the likelihood of matching is calculated based on the agreement between two records in various variables (not unique identifiers like first name, family name, post code, and gender). In contrast to DRL, PRL is characterized by a low specificity due to an increased possibility of linking two records wrongly, and a high sensitivity due to including all possible matchings (308). In SAIL, both DRL and PRL are used under one algorithm, called the Matching Algorithm for Consistent Results in Anonymous Linkage (MACRAL) (304). Upon linking multiple records, it has been shown that MACRAL has a high sensitivity (99.9% for GPs records, and 99.3% for hospital records) at a matching probability threshold of 50% (304). These results confirm that ALFs, which are used in linking the data in the SAIL Databank, are valid and can consistently be used to link data in SAIL.

3.1.1.5 Information governance compliance

Another privacy and safety measure that SAIL has set is that all researchers who are interested in using SAIL data must submit their proposals to the independent panel called the Information Governance Review Panel (IGRP). This panel includes members from the National Research Ethics Service, the British Medical Association, NWIS, Public Health Wales, and the Consumer Panel for Data Linkage Research (a representative from the public to encourage public involvement in research) (305). IGRP members check all research applications in terms of the research questions, the research design, the rationale of the data specifications, the analysis plan and how it is related the data requested, and finally, data confidentiality, whereby they ensure that the researcher will take all the necessary measures to mitigate any risk of re-identifying patients' identities. After the researcher has obtained the IGRP approval and has completed and passed an obligatory training session on the safe use of data, a project-specific

data view is created for every project, and the researcher is contacted by the SAIL team and is allocated a SAIL Gateway user account.

3.1.1.6 Data access (SAIL Gateway)

The SAIL gateway is a remote gateway that enables researchers wherever they are to access and analyse data provided by the SAIL Databank in a safe, powerful environment. In addition to the researcher having the privilege of getting access to the SAIL data remotely, the SAIL gateway provides a powerful analytical environment that contains several software programs that can be used to conduct Structured Query Language (SQL) queries and/or statistical analysis. The SAIL Gateway also has a robust system that controls all files transferred out from the gateway. This is done by requiring researchers to upload their results and outcomes to the gateway and to await the approval of release from the SAIL analyst who acts as the data guardian in this case. Upon receiving the research results and outcomes, the SAIL analyst makes sure that these results are in accordance with the previously approved IGRP application, and that there are no small numbers (<5) in the results. The SAIL Gateway also provides the opportunity for researchers to benefit from other SAIL Gateway users. This is achieved by searching through the WIKI that is provided in the gateway. The WIKI includes a large number of inputs from SAIL users regarding training materials, data dictionaries, clinical codes, SQL queries, general PowerPoint presentations related to SAIL or data linkage in general, and other interesting information that SAIL users may need during their research (306).

3.1.1.7 Databases used from the SAIL Databank in the thesis

In this thesis, the GP database (Welsh Longitudinal General Practice Dataset (WLGP)) was the main database that was used to discover the prescribing

pattern and trend of PD drugs in PwP. Other databases that were used include the Welsh Demographic Service Dataset, whereby demographic data of PwP were found. Hospital admission data that could be used to identify the comorbidities in PwP (Charlson index components) and to measure the cardiovascular hospitalization episodes after PwP had been prescribed L-dopa were obtained from the Patient Episode Database for Wales. Mortality data that were used to measure the survival rate after L-dopa had been prescribed were available in the Annual District Death Extract. In the following subsections, a brief description of all the databases used in this thesis is presented.

3.1.1.7.1 Welsh Demographic Service dataset (WDS)

In 2009, the NHS Wales Administrative Register was replaced by the Welsh Demographic Service (WDS) (309). The WDS dataset (WDS) contains the demographic data of GP practice-registered patients in Wales. These data include each patient's name, address, sex, NHS number, and GP practice. For data that can be changed over time, like address and GP practice, the WDS provides all modifications of addresses and GP practices in addition to the time-point of these modifications (310).

3.1.1.7.2 Welsh Longitudinal General Practice Dataset (WLGP)

Before the SAIL Databank started collecting primary care data from GP practices in Wales, no comprehensive primary care dataset was available in Wales. However, since launching the SAIL Databank in 2007 until the time of writing of this part of the thesis, SAIL has collected about 80% of GP data in Wales (305). The data imported from the computer system of GP practices to SAIL include patients' health records, like disease signs and symptoms, results of laboratory

tests, diagnoses, prescriptions, and referrals to secondary care services. Most GP practices use version 2 of the Read code system in recording patients' GP events.

The Read code system is characterized by a hierarchical structure that covers a large number of clinical and medical terms, including diagnoses, symptoms, surgical procedures, and drugs. The hierarchical structure means that there will be an increase in the level of detail with increasing numbers. For example, dq… is used to record antiparkinsonian dopaminergic drugs, dq1.. is used for levodopa and dq11. for levodopa 125 mg capsules. In the early 1980s, the British general practitioner Dr James Read developed the first version of the Read code, which had the 4-Byte Read scheme. This scheme was composed of four characters: this was later extended to five characters and formed the second version of the Read code scheme (5-Byte Read) in the early 1990s. Since the second version of the Read code was developed in the early 1990s, a third version of the scheme has been developed to overcome some technical and clinical limitations in the second version (311). The clinical terms in the Read code system can be cross-mapped to other clinical code systems, such as the International Statistical Classification of Disease (ICD9 and ICD10) and the Operation Classification System's (OPCS) Classification of Interventions and Procedures version 4 (311). To facilitate searching the appropriate Read codes, the SAIL Gateway enables researchers to navigate the Read codes by browsing through an NHS Clinical Terminology Browser (306). Additionally, several researchers have made the Read codes they used in their projects available for all SAIL users in the SAIL WIKI.

3.1.1.7.3 Hospital admissions data: Patient Episode Database for Wales (PEDW)

PEDW holds data on hospital admissions and inpatient activity for all patients treated in NHS Wales facilities and Welsh patients treated in NHS England

facilities (312). PEDW contains records going back to 1991, and mandatory changes were made to PEDW in 1997, when all admission and inpatient data were changed to adopt the format of the Admitted Patient Care (APC) dataset (312). The reason for adopting the APC format in PEDW was to make the format of inpatient and hospital data similar to its counterpart in England to allow for benchmarking and comparison between the two countries (312).

The PEDW Data Acquisition Team collect, process, and monitor the data received from the Information Technology Departments in the NHS health boards in Wales or England (for Welsh patients) (312). About 100,000 episodes (diagnoses or procedures) are processed every month in PEDW. The data include clinical information for every patient. The clinical data include the diagnostic details (using the clinical codes of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)) and the procedure episodes (using the clinical codes of version 4 of the OPCS (OPCS-4)) (312). Furthermore, PEDW holds some administrative data for every episode, such as information about the NHS health board that treats the patient, the date of admission, the method of admission (elective vs. emergency), and the total time of a single hospital episode (spell) (312). Additionally, each patient's demographic data are held in PEDW, such as sex, age, and address. The address can be used to derive the Lower Layer Super Output Area (LSOA), which, in turn, can be used to estimate the social deprivation status of the patient using the Welsh Index of Multiple Deprivation (WIMD) score (313).

3.1.1.7.4 Mortality data: Annual District Death Extract (ADDE)

Mortality data in England and Wales are generated from the Office of National Statistics (ONS) (314). The ONS obtains mortality data when deaths are certified and registered (314). There are three main sources of mortality data: the

information given by the doctor when the death is certified, the information given to the registrar by the informant (e.g., close friend or family member), or the death details provided by the coroner (314). The General Register Office is responsible for the registration of deaths (in addition to other registrations, such as births, civil partnerships, and marriages). The death information is then submitted to the ONS, including the deceased's date of birth, sex, marital status, residence, place of death, date of death, and cause of death (314). Since January 2001, the ONS has generated the cause of death by using ICD-10 clinical codes after switching from the old version (ICD-9) in accordance with the World Health Organization's (WHO) recommendation (314). In the ONS deaths operating system, there two types of dataset for the death events. The registration database contains mainly the textual data obtained from the death certificate. The second dataset is the statistical dataset that includes the coded data of every death event.

Upon recording the cause of death in the Medical Certificate of the Cause of Death (MCCD), the underlying cause of death should be recorded in the lowest completed line in the section for cause of death in the MCCD, while the direct cause of death should be recorded in the first line of the section. Any intermediate causes lying between the underlying cause and the direct cause should be recorded in the middle (314).

3.1.1.7.5 Socio-economic deprivation data

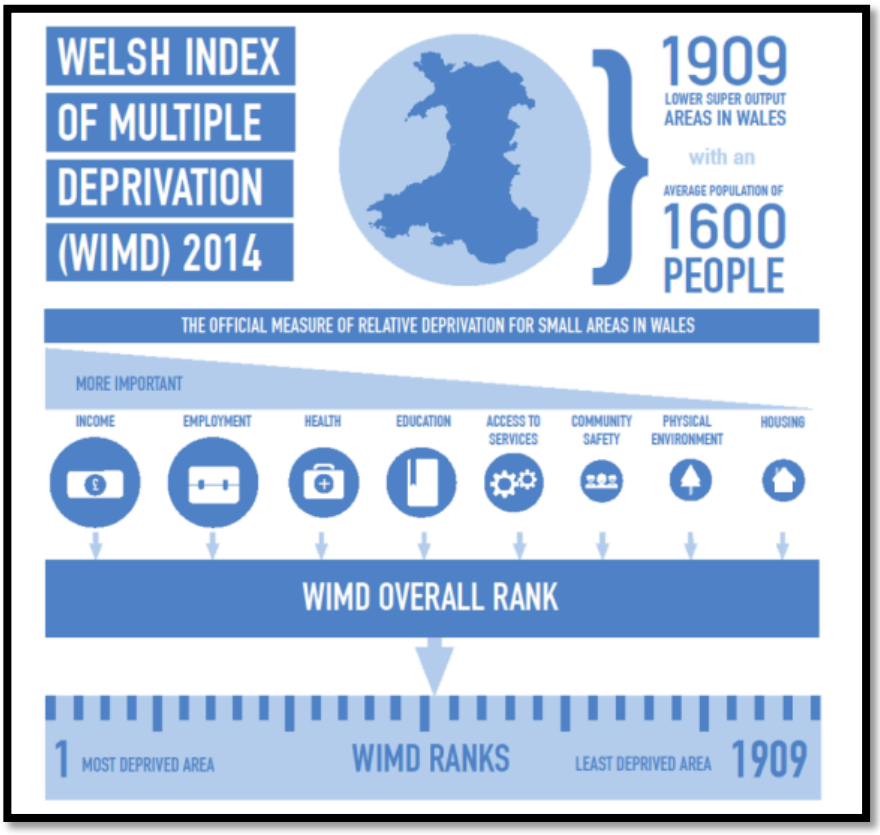
Deprivation can be defined as "a state of observable and demonstrable disadvantage, relative to the local community or the wider society or nation to which an individual, family or group belongs" (315). Based on this definition, this observable disadvantage can take different forms. For example, when this disadvantage is related to a lack of access to resources and goods, it is called

"material deprivation", while if it is related to an individual's relationship with society, then it is called "social deprivation" (315). When there is more than one form of deprivation, it is called "multiple deprivation".

There are different scales that can be used measure the deprivation status in the UK. In Wales, the Welsh Index of Multiple Deprivation (WIMD) is officially used to measure deprivation in Wales at the Lower Super Output Area (LSOA) level (316). Based on the most up-to-date WIMD (2014), the whole population of Wales has been divided into 1909 LSOAs, each with approximately 1,600 people. An LSOA of 1 is considered the most deprived area, and an LSOA of 1909 is considered the least deprived area. This grouping is based on eight domains (i.e. income, employment, health, education, access to services, community safety, physical environment, and housing) as seen in Figure 3-2. The WIMD 2011 is similar to the WIMD 2014 (Figure 3-2) in terms of the number of domains. Few differences have been reported between the two indices in the domains' inclusion criteria. However, the general picture and its implications remain largely similar between the two indices (316).

The SAIL Databank contains several measures of social deprivation in Wales, including WIMD 2005, WIMD 2008, WIMD 2011, and Townsend 2001. These data were linked to the SAIL Databank from another project which used SAIL data, namely the Wales Electronic Child Cohort. In this thesis, WIMD 2011 was used to measure the social deprivations status of PwP.

Figure 3-2- Welsh Index of Multiple Deprivation (WIMD) 2014



Welsh Government Website (31)

3.2 Data management

3.2.1 SAIL data

3.2.1.1 Data access permission

As discussed above in section 3.1.1.5, “Information Governance compliance”, it is mandatory to obtain the approval of the Information Governance Review Panel (IGRP) to have access to the SAIL data. The project application was approved (SAIL project number 0729) and access to the data granted (see Appendix 8).

3.2.1.2 Data specification

As discussed before (see Section 3.1.1.7), five core datasets in the SAIL Databank would be used in the current project (i.e., demographic dataset, social deprivation dataset, primary care dataset, hospital dataset, and mortality dataset). Therefore, an algorithm was created that contained the data that needed to be extracted by the SAIL analyst. This algorithm included three important things: the variables that were needed from each dataset, the criteria for selecting data rows in all datasets, and the relationships between the variables in the datasets’ tables.

Regarding the first part of the algorithm, which was specifying the variables needed from each dataset, for every dataset, a specific number of variables was requested. These variables can be linked by a unique Project-specific Anonymised Linkage Field (PSALF) for every patient.

For the demographic dataset, the following variables were requested: PSALF, sex, and week and year of birth. For the primary care dataset, in addition to

PSALF, the following variables were specified: event clinical code (Read code), event date, and description of the event. For the social deprivation dataset, PSALF and WIMD (2011) quintile, which ranged from quintile 1 (more deprived area) to quintile 5 (least deprived), were requested. Regarding the hospital dataset, in addition to PSALF, for every single hospital admission (spell), the following variables were requested: spell number, start date, end date, diagnostic clinical code (ICD-10 in this case), and admission method. Finally, for the mortality dataset, the following variables were requested: PSALF, death date, codes of primary cause and underlying cause of death (ICD-10).

The second part of the algorithm was to set up the criteria for selecting data rows in all datasets. For the demographic dataset, two main criteria were specified: 1: patients who were born in or before 1977 (to exclude people aged less than 40 years in 2017), and 2: patients who had data in the GP data that had been submitted to the SAIL databank.

For the social deprivation dataset, no specific criteria were required except that PSALF in this dataset must be present in the demographic dataset.

For the primary care dataset, the selection criteria stated that PSALF in this dataset must be present in the demographic dataset as well as the event clinical code of any Read code related to the project's questions (see Appendix 9). To identify the required Read codes in this project, it was essential to find an appropriate way to help capture all the clinical events related to the research questions (Read codes of PD diagnosis, PD drugs, secondary parkinsonism (for exclusion), psychosis, antipsychotics, depression, antidepressants, dementia, and antidementia (Appendix 9)), and to avoid using any Read codes not used in clinical practice. Therefore, four steps were taken to identify the Read codes. First, previous UK studies that examined the same clinical conditions as in the

current project were reviewed and the related codes were extracted (317-322). Second, two clinical specialists (Dr Kathryn Peall, a Clinical Senior Lecturer at the Neurosciences and Mental Health Research Institute in Cardiff, UK, and Dr Biju Mohamed, a Consultant Physician and Geriatrician at the Cardiff and Vale University Health Board) were consulted to assist in defining and refining the PD diagnostic codes. Third, a website that acts as a clinical codes repository in the UK (ClinicalCodes.org) was reviewed (323). Finally, access to the Technology Reference Data Update Distribution (TRUD) website was granted and extensive research was conducted to find all the project-related Read codes in the website (324). The final table that should be generated from the primary care dataset would cover patients' PSALFs that had a PD diagnosis or/and PD drugs and their associated clinical conditions and prescriptions (psychosis, antipsychotics, depression, antidepressants, dementia, or antidementia).

For the hospital dataset, the first specified criterion was that the patient denoted by PSALF should have a PD diagnosis and/or PD drugs in the primary care data. The second criterion was the presence of the related ICD-10 clinical codes. These codes included all hospital spells related to cardiovascular events, and other comorbidities that constitute the Charlson comorbidity index (see Appendix 9). In this project, the total score of the Charlson comorbidity index was not used because of the absence of one component from SAIL, namely the HIV diagnosis. Additionally, dementia is one of the index components, and as dementia is closely related to PD diagnosis and medication in some patients, it should be considered separately. Therefore, the Charlson index score was converted to a binary variable that indicated the presence or absence of the disease.

For the mortality dataset, death data for all patients with PD diagnosis and/or PD drugs in the primary care data were extracted and linked by PSALF. If the cause of death was related to cardiovascular events, the death event would be called a

cardiovascular death; otherwise, it would be considered a non-cardiovascular death.

The third part of the data extraction algorithm was to determine the relationships between the variables in the datasets' tables. As it was expected that the volume of extracted data would be very large, the extracted data was divided into 9 datasets that would be easier to manage (see Figure 3-3). Before submitting these tables to the SAIL analyst, an Excel file that included the whole list of Read codes and ICD-10 codes related to the current project was created. Prior to data extraction, all team members were consulted.

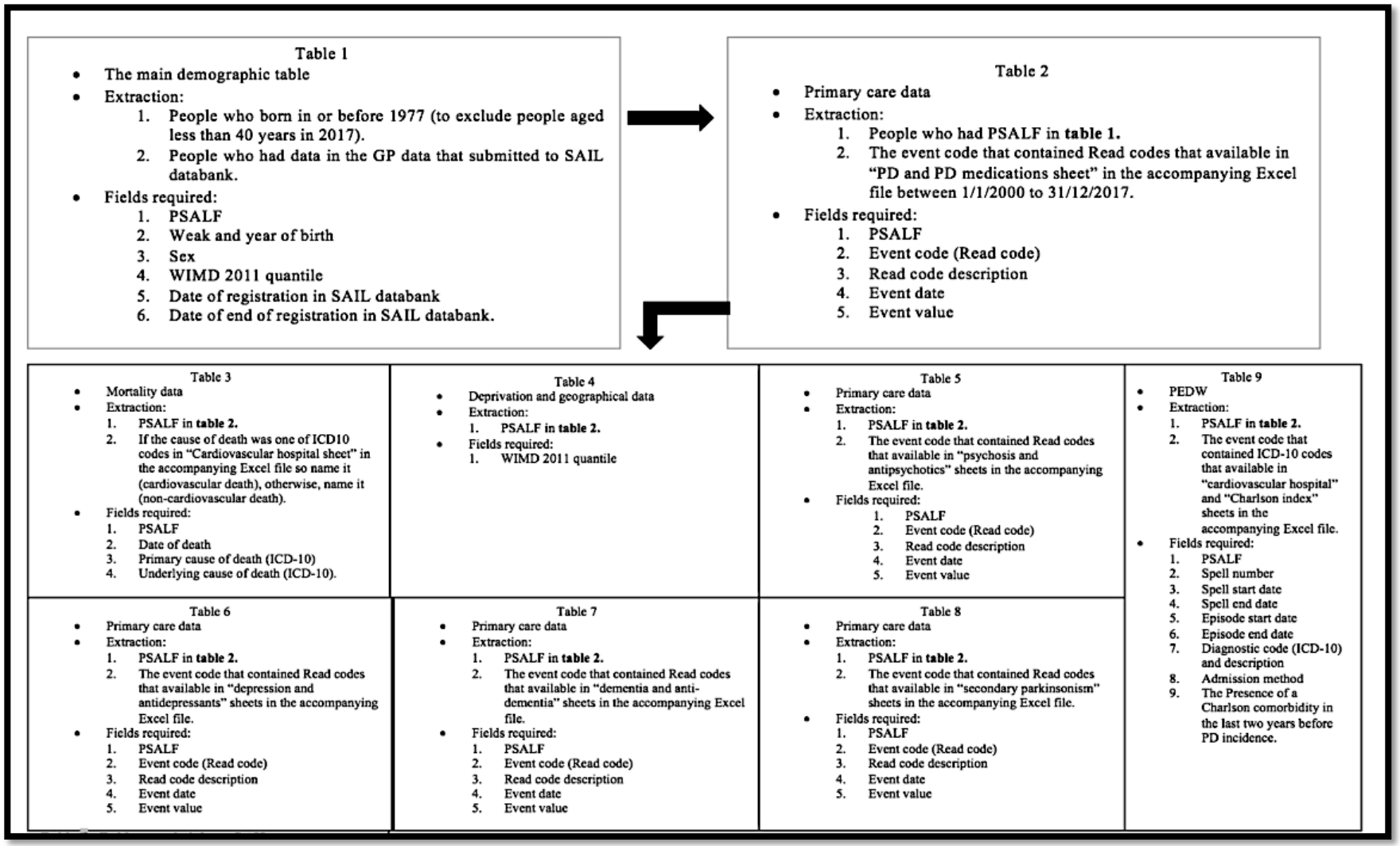


Figure 3-3- Tables submitted to SAIL analyst for data extraction

3.2.1.3 Identifying the study cohort

After the tables had been submitted to the SAIL analyst, it was essential to define exactly the main study cohort (PwP) by specifying which Read codes would be used to extract all other relevant data. The original list of Read codes of PD that was submitted to the SAIL analyst included three categories of codes that could be used to identify PwP based on the previous literature (317, 318): definitive diagnosis of PD, suggestive diagnosis of PD, and PD drugs. The Read codes for those categories can be seen in Table 3-1.

Read code categories					
Definitive PD diagnosis		Suggestive PD diagnosis		PD drugs	
Read code	Definition	Read code	Definition	Read code	Definition
F12..00	Parkinson's disease	2987	On examination: Parkinson flexion posture	dq…	Dopaminergic drugs
F120.00	Paralysis agitans	2987.11	On examination: Parkinson posture	dr…	Anticholinergics
F12z.00	Parkinson's disease not otherwise specified	2994	On examination: festination/Parkinson gait		
147F.00	History of Parkinson's disease	2994.11	On examination: Parkinson gait		
		297A.00	On examination: Parkinsonian tremor		
		8T06.00	Referral to Parkinson's service		
		8T06000	Referral to community Parkinson's service		
		TJ64z00	Adverse reaction to anti-parkinsonism drugs not otherwise specified		
		U606711	[X] Adverse reaction to anti-parkinsonism drug		
		U606712	[X] Adverse reaction to amantadine		
		U606713	[X] Adverse reaction to levodopa, L-dopa		
		U606714	[X] Adverse reaction to trihexyphenidyl		
		U606718	[X] Adverse reaction to anti-parkinsonism drugs not otherwise specified		
		F1303	Parkinsonism and orthostatic hypotension		

Table 3-1- Read codes of the three categories that could be used to identify PwP

To identify exactly which category should be used in this project, it was necessary to compare the incidence and prevalence of these codes in the SAIL data with the PD prevalence and incidence in previous UK studies (317, 325-329).

To achieve this, the SAIL analyst extracted very broad figures regarding the number of prevalence and incidence cases (for the three categories) in the study period (2000 to 2017). The prevalence cases were defined by having the Read code of interest recorded in SAIL on or before 31 December of the year . The incidence cases were defined by having the first record of the Read code of interest recorded in SAIL on or after January 1st of the year. If there is less than 6 months between the date of registration in SAIL GP data and the incidence date, this case will not be considered as an incidence case; rather, it will be considered as a prevalence case. The denominator was the total mid-year population in GP data in every calendar year (from 2000 to 2017). They were all patients who were alive and registered in the GP data in SAIL at 1st July in every calendar year (from 2000 to 2017). There were no age or gender stratifications in this step, since it was meant to identify which cohort was to be used in the project, and the demographic dataset had not yet been linked to the primary care dataset. The numerator and denominator in this step were not age restricted; however, in future chapters, the inclusion criteria will be limited to people aged 40 years or older in every year. Table 3-2 shows the total number of cases and the mid-year populations in the years of the study (2000-2017) for both prevalence and incidence for all three categories (people with a definitive PD diagnosis, people with a suggestive diagnosis, and people with PD drugs).

Year	Mid-year population	Number of incidence cases			Number of prevalence cases		
		Definitive	Suggestive	PD drugs	Definitive	Suggestive	PD drugs
2000	2,172,046	534	74	1,079	3,386	224	7,985
2001	2,189,260	509	102	1,124	3,541	248	8,503
2002	2,207,857	596	183	1,041	3,700	349	9,034
2003	2,230,740	672	82	830	3,889	449	9,,475
2004	2,276,792	631	58	860	4,143	484	9,816
2005	2,294,513	619	53	760	4,268	481	10,083
2006	2,314,907	605	31	1,012	4,405	471	10,419
2007	2,333,906	566	45	1,361	4,543	469	11,135
2008	2,351,265	625	43	1,152	4,647	462	11,937
2009	2,359,930	640	40	1,193	4,757	462	12,511
2010	2,369,160	608	26	1,231	4,864	459	13,257
2011	2,382,544	612	43	1,340	4,968	458	13,934
2012	2,401,062	694	27	1,326	5,081	456	14,680
2013	2,424,732	689	59	1,326	5,273	454	15,421
2014	2,442,847	672	38	1,407	5,407	472	16,130
2015	2,454,032	707	31	1,244	5,397	464	16,674
2016	2,496,650	669	43	1,364	5,449	460	17,226
2017	2,515,231	451	33	1,022	5,439	464	17,749

Table 3-2- Number of incidence and prevalence cases across the years of the study

Based on the previous three categories that could be used to identify PwP, five sub-cohorts were defined as follows (Table 3-3):

1- PD definitive diagnosis only sub-cohort (sub-cohort 1)

2- PD definitive and suggestive diagnosis sub-cohort (sub-cohort 2)

3- PD drugs sub-cohort (sub-cohort 3)

4- PD definitive diagnosis and PD medication sub-cohort (sub-cohort 4)

5- PD definitive and suggestive diagnosis and PD drugs sub-cohort (sub-cohort 5)

Total PD cohort				
Category 1 (Definitive PD diagnosis)		Category 2 (Suggestive PD diagnosis)	Category 3 (PD drugs)	
Sub-cohort 1 = Category 1	Sub-cohort 2 = Category 1 and/or Category 2. (Excluding secondary parkinsonism)	Sub-cohort 3 = Category 3. (Excluding secondary parkinsonism)	Sub-cohort 4 = Sub-cohort 1 + Category 3.	Sub-cohort 5 = sub-cohort 2 + Category 3.

Table 3-3- PD sub-cohorts

To identify the appropriate study cohort in the current project, the incidence and prevalence were calculated for all sub-cohorts in all years of the study. The incidence and prevalence were estimated per 100,000 population, and a 95% confidence interval was calculated, assuming a Poisson distribution. Table 3-4 shows the estimated incidence and prevalence in the five sub-cohorts.

Year	Incidence per 100,000 population (95% CI)					Prevalence per 100,000 population (95% CI)				
	Sub-cohort 1	Sub-cohort 2	Sub-cohort 3	Sub-cohort 4	Sub-cohort 5	Sub-cohort 1	Sub-cohort 2	Sub-cohort 3	Sub-cohort 4	Sub-cohort 5
2000	24.59 (22.54-26.76)	27.99 (25.81-30.31)	49.68 (46.76-52.73)	74.26 (70.68-77.98)	77.67 (74.01-81.47)	155.89 (150.68-161.23)	166.2 (160.82-171.71)	367.63 (359.61-375.78)	523.52 (513.94-533.23)	533.83 (524.16-543.64)
2001	23.25 (21.27-25.36)	27.91 (25.74-30.21)	51.34 (48.38-54.43)	74.59 (71.02-78.3)	79.25 (75.56-83.07)	161.74 (156.46-167.16)	173.07 (167.6-178.67)	388.4 (380.18-396.74)	550.14 (540.36-560.05)	561.47 (551.59-571.48)
2002	26.99 (24.87-29.25)	35.28 (32.85-37.85)	47.15 (44.33-50.1)	74.14 (70.6-77.83)	82.43 (78.69-86.31)	167.58 (162.23-173.07)	183.39 (177.78-189.13)	409.18 (400.78-417.7)	576.76 (566.78-586.86)	592.57 (582.45-602.81)
2003	30.12 (27.89-32.49)	33.8 (31.43-36.3)	37.21 (34.72-39.83)	67.33 (63.97-70.83)	71.01 (67.55-74.59)	174.34 (168.9-179.9)	194.46 (188.72-200.34)	424.75 (416.24-433.39)	599.08 (588.97-609.33)	619.21 (608.93-629.63)
2004	27.71 (25.59-29.96)	30.26 (28.04-32.61)	37.77 (35.29-40.38)	65.49 (62.2-68.9)	68.03 (64.69-71.51)	181.97 (176.47-187.59)	203.22 (197.41-209.17)	431.13 (422.65-439.75)	613.1 (602.97-623.36)	634.36 (624.05-644.79)
2005	26.98 (24.89-29.19)	29.29 (27.11-31.59)	33.12 (30.81-35.56)	60.1 (56.97-63.36)	62.41 (59.22-65.73)	186.01 (180.47-191.67)	206.97 (201.13-212.94)	439.44 (430.9-448.1)	625.45 (615.26-635.77)	646.41 (636.05-656.9)
2006	26.13 (24.09-28.3)	27.47 (25.38-29.69)	43.72 (41.06-46.5)	69.85 (66.49-73.34)	71.19 (67.79-74.71)	190.29 (184.71-195.99)	210.63 (204.76-216.63)	450.08 (441.48-458.81)	640.37 (630.1-650.76)	660.72 (650.29-671.27)
2007	24.25 (22.29-26.33)	26.18 (24.14-28.34)	58.31 (55.26-61.5)	82.57 (78.92-86.34)	84.49 (80.81-88.31)	194.65 (189.03-200.4)	214.75 (208.84-220.78)	477.1 (468.28-486.04)	671.75 (661.28-682.35)	691.84 (681.21-702.6)
2008	26.58 (24.54-28.75)	28.41 (26.3-30.65)	48.99 (46.21-51.91)	75.58 (72.1-79.17)	77.41 (73.89-81.04)	197.64 (192-203.4)	217.29 (211.37-223.33)	507.68 (498.62-516.87)	705.32 (694.63-716.14)	724.97 (714.13-735.94)
2009	27.12 (25.06-29.3)	28.81 (26.69-31.06)	50.55 (47.72-53.5)	77.67 (74.16-81.31)	79.37 (75.81-83.04)	201.57 (195.89-207.38)	221.15 (215.19-227.23)	530.14 (520.89-539.52)	731.72 (720.84-742.71)	751.29 (740.27-762.43)
2010	25.66 (23.66-27.79)	26.76 (24.72-28.93)	51.96 (49.1-54.95)	77.62 (74.11-81.25)	78.72 (75.19-82.38)	205.3 (199.58-211.16)	224.68 (218.68-230.8)	559.57 (550.08-569.17)	764.87 (753.77-776.09)	784.24 (773.01-795.6)
2011	25.69 (23.69-27.81)	27.49 (25.43-29.68)	56.24 (53.27-59.34)	81.93 (78.33-85.65)	83.73 (80.1-87.49)	208.52 (202.76-214.4)	227.74 (221.72-233.88)	584.84 (575.17-594.63)	793.35 (782.08-804.75)	812.58 (801.17-824.1)
2012	28.9 (26.79-31.14)	30.03 (27.88-32.3)	55.23 (52.29-58.28)	84.13 (80.5-87.88)	85.25 (81.6-89.03)	211.61 (205.84-217.51)	230.61 (224.57-236.76)	611.4 (601.55-621.37)	823.01 (811.58-834.57)	842 (830.44-853.69)
2013	28.42 (26.33-30.62)	30.85 (28.68-33.14)	54.69 (51.78-57.71)	83.1 (79.51-86.81)	85.54 (81.89-89.3)	217.47 (211.64-223.42)	236.19 (230.11-242.39)	635.99 (625.99-646.11)	853.46 (841.87-865.16)	872.18 (860.46-884.01)
2014	27.51 (25.47-29.67)	29.06 (26.97-31.28)	57.6 (54.63-60.69)	85.11 (81.49-88.84)	86.66 (83.01-90.43)	221.34 (215.48-227.32)	240.66 (234.55-246.89)	660.3 (650.14-670.56)	881.64 (869.9-893.49)	900.96 (889.09-912.94)
2015	28.81 (26.72-31.01)	30.07 (27.94-32.32)	50.69 (47.91-53.59)	79.5 (76.01-83.11)	80.77 (77.25-84.4)	219.92 (214.1-225.87)	238.83 (232.76-245.03)	679.45 (669.18-689.85)	899.38 (887.55-911.32)	918.28 (906.33-930.35)
2016	26.8 (24.8-28.91)	28.52 (26.46-30.69)	54.63 (51.77-57.61)	81.43 (77.93-85.05)	83.15 (79.61-86.81)	218.25 (212.5-224.13)	236.68 (230.68-242.79)	689.96 (679.7-700.35)	908.22 (896.43-920.12)	926.64 (914.74-938.66)
2017*	17.93 (16.31-19.66)	19.24 (17.57-21.04)	40.63 (38.18-43.2)	58.56 (55.61-61.63)	59.88 (56.89-62.98)	216.24 (210.53-222.07)	234.69 (228.74-240.75)	705.66 (695.32-716.12)	921.9 (910.08-933.85)	940.35 (928.4-952.41)

Table 3-4- Incidence and prevalence of PD according to the Read codes of different sub-cohorts

*The data in 2017 spanned from January until September (so, there were missing data for three months). This data missing was not discovered until the results of Chapter 5 of this thesis titled (Incidence and prevalence of PD in Wales) were analysed.

After the incidence and prevalence of all the sub-cohorts had been calculated, the results were compared to previous UK literature (317, 325-329). Figures 3-4 and 3-5 show comparisons between the incidence and prevalence of the sub-cohorts in this study and previous UK studies. These figures can be summarized as follows.

1- Choosing patients with PD drugs (sub-cohort 3, 4, and 5) resulted in very high incidence and prevalence rates, which were far higher than in all previous studies (317, 325-329). For example, the incidence of PD in North-East England was 15.9 per 100,000 population in 2010 (326), while in the same year, the incidences were 51.96, 77.62, and 78.72 per 100,000 population in sub-cohorts 3, 4, and 5 respectively. Another example of this huge difference in the prevalence figure can be seen in 2015, when the prevalence of PD in the study conducted by Parkinson's UK was 286.50 per 100,000 population in Wales (317), while sub-cohorts 3, 4, and 5 have shown prevalence rates of 679.45, 899.38, and 918.28 respectively. It is worth noting that this difference is expected, since it is not necessary that all PD drugs users have a PD diagnosis, as some PD medications could be used in conditions other than PD, such as using pramipexole and ropinirole in treating restless leg syndrome (330). Therefore, sub-cohorts 3, 4, and 5 have been excluded from consideration in the current project due to these large differences in incidence and prevalence compared to previous UK studies.

2- As sub-cohorts 3, 4, and 5 were excluded from consideration, the decision had to be made to choose between sub-cohort 1 (definitive PD diagnosis) and sub-cohort 2 (definitive and suggestive PD diagnosis). Figure 3-4 shows the incidence of PD in the two sub-cohorts and reveal a very similar pattern in both of them compared to the previous literature. Figure 3-5 shows the same comparison

except for the prevalence proportions, and they represented a similar pattern in the two cohorts compared to the previous literature. Given the obvious similarity in the incidence and prevalence in the two cohorts, it was necessary to justify using any of them. Finally, sub-cohort 1 (PD definitive diagnosis) was chosen to be the main study cohort in the current project.

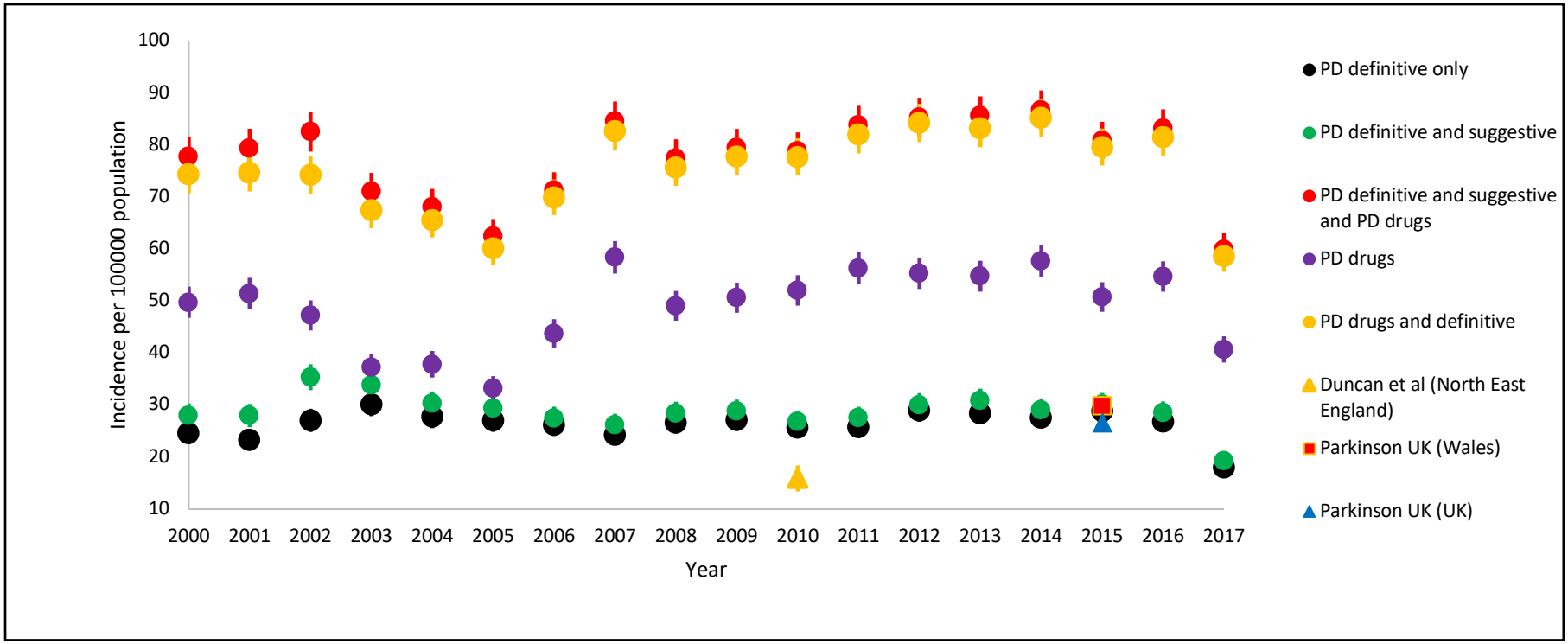


Figure 3-4- Comparison of incidence of PD between study sub-cohorts and previous UK studies

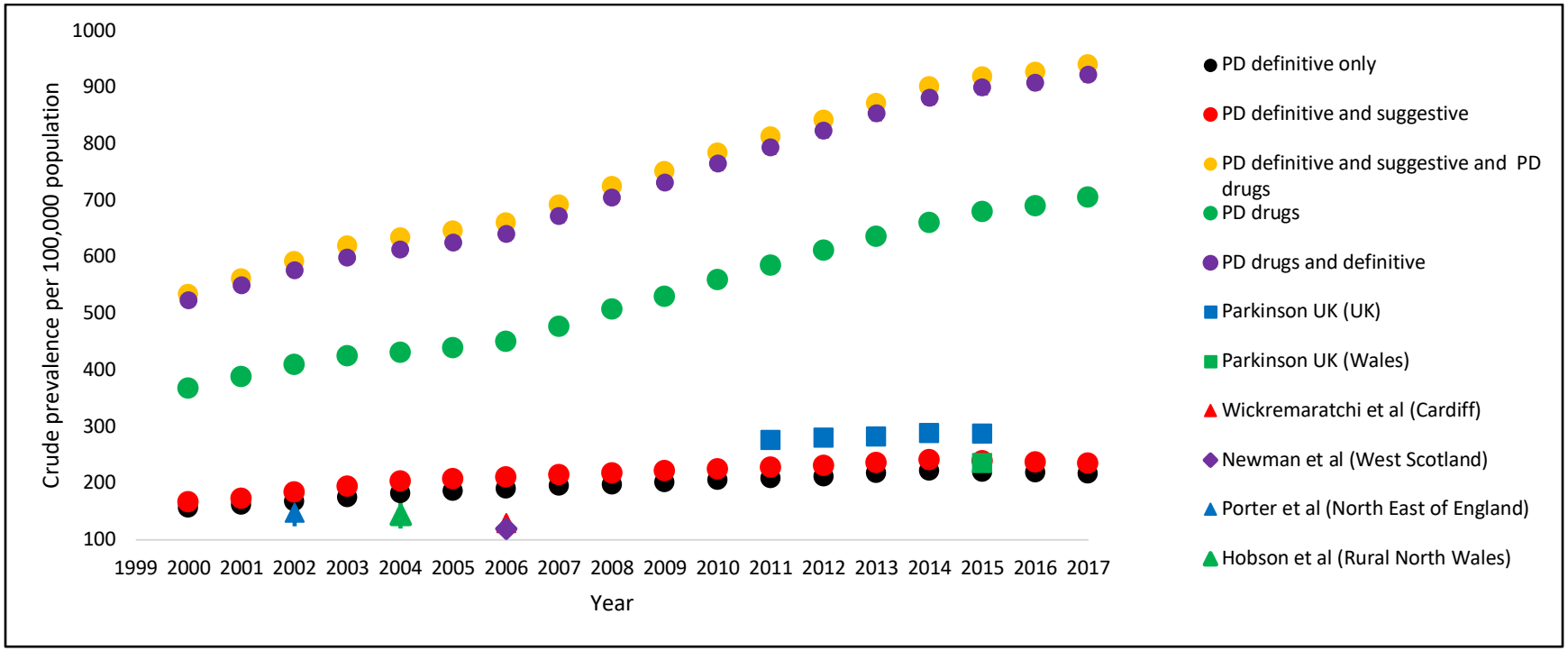


Figure 3-5- Comparison of prevalence of PD between study sub-cohorts and previous UK studies

This decision could be justified because of the similarity in incidence and prevalence of this sub-cohort to a previous population-based study. Parkinson's UK has conducted a population-based study using the Clinical Practice Research Datalink (CPRD) database to calculated the incidence and prevalence of PD in the UK (317). The study, which included 2.5 million patients throughout the UK, used the Read codes of (PD definitive diagnosis) in the analysis based on advice from clinical experts. Compared to the incidence and prevalence numbers of PD definitive diagnosis in the current project, the study by Parkinson's UK revealed similar incidence and prevalence numbers in Wales in 2015. For instance, the incidences of PD were 28.8 (95% CI 26.72-31.01) and 29.8 (95% CI 27.92-31.78) per 100,000 population in SAIL (current project) and CPRD (Parkinson's UK study) respectively. With regard to PD prevalence, a very slight difference was seen between the two studies. Indeed, the prevalence in the current study was 219.92 (95% CI 214.09-225.87), while the prevalence in the Parkinson's UK study was 234.70 (95% CI 229.2 -240.2). Therefore, in the case of the current study, it was reasonable to follow the advice offered by experts to the Parkinson's UK study.

3.2.1.4 Data extraction

After comparing the previous five sub-cohorts and choosing one of them (PD definitive diagnosis) as the main cohort in this project, the SAIL analyst extracted all the Read codes of PD definitive diagnosis in SAIL between 2000 and 2017 (Table 3-1). These Read codes were linked to patients' PSALFs, which in turn, were used to link the primary care dataset to other datasets in SAIL (Figure 3-3). The extracted tables were accessed through the SAIL Gateway and imported to SPSS (version 25.0; SPSS, Chicago, IL, USA) inside the gateway for cleaning and analysis.

3.2.1.5 Data preparation

As this project deals with secondary data that were not collected originally for research purposes, it was expected that the data extracted by the SAIL analyst would not be perfectly clean and ready for analysis. Therefore, some data and variables had to be manipulated and cleaned in a way that facilitated the process of analysis. Data manipulation included adding and deleting some variables.

3.2.1.5.1 Adding of variables

In general, three new types of variable were extracted from the already existing variables. Age is one of the most important variables in this project. Patients' ages were calculated based on the week of birth provided in the demographic table (Figure 3-3). The age of the patient was calculated as the difference between the week of birth and the year of interest. Therefore, eighteen new variables were created to show the age of patients in the whole study period (from 2000 to 2017). One of those variables, of course, would be the age at the index data (age at the time of diagnosis). In order to consider the date of death for those who died during the study period, syntaxes were created in SPSS to recode all age variables that happened after the year of death and change them to missing values. Therefore, they were not considered during the analysis of these values, since SPSS could be ordered to cancel them. Table 3-5 shows a fictitious example of two people in which one of them has died during the study period and the other one has survived until the end of the study period. Then, all age variables were classified to seven age groups: 40-50 years, 51-60 years, 61-70 years, 71-80 years, 81-90 years, and 91 years and older, and 39 years and younger. Later, all patients in the last category (39 years and younger) were excluded from this project.

Furthermore, to estimate the incidence rates in some parts of the project, the Person Year at Risk (PYAR) was used as a denominator. PYAR in this project could be defined as the amount of time for which each person in the population (SAIL population) was at risk of having PD. PYAR began accumulating at the latest of the patient registration dates in SAIL or the 1st of January of the year of interest. PYAR ended at the earliest of the PD diagnosis date, the death date, the end registration date, or the end of the study period (31-12-2017) (the end of the study period was changed to (30-09-2017) after three months missing data in 2017 were discovered in Chapter 5). Therefore, eighteen new variables were created in the demographic table (Table 1 in Figure 3-3). Every variable included the number of PYAR for every individual at all years of the study.

	Person 1	Person 2
Week of birth	08-02-1960	13-05-1946
Date of death	15-11-2010	Still alive
PD diagnosis date	04-08-2005	06-09-2008
Age at 2000	40	54
Age at 2001	41	55
Age at 2002	42	56
Age at 2003	43	57
Age at 2004	44	58
Age at 2005	45 (Age at diagnosis, (age at index date))	59
Age at 2006	46	60
Age at 2007	47	61
Age at 2008	48	62 (Age at diagnosis (age at index date))
Age at 2009	49	63
Age at 2010	50 (Age at death)	64
Age at 2011	Missing	65
Age at 2012	Missing	66
Age at 2013	Missing	67
Age at 2014	Missing	68
Age at 2015	Missing	69
Age at 2016	Missing	70
Age at 2017	Missing	71

Table 3-5- A fictitious example of adding age variables in the data preparation process

The third type of newly added variable was the disease duration. It was calculated by subtracting the year of interest from the year of PD diagnosis. This step resulted in eighteen new variables (one for each year of the study). The values of variables that related to the years before the year of diagnosis or after the year of death were recorded as missing.

3.2.1.5.2 Deletion of variables

Event value (see Figure 3-3) was one variable that the SAIL analyst was asked to extract from the primary care dataset. The rationale behind choosing this variable was an assumption made by the researcher that this variable might contain the dose instructions and drug quantity in prescribing events in the primary care data. This information – if present in the SAIL databank - would be important to calculate the levodopa equivalent daily dose (LEDD). Unfortunately, all cells under the event value variable were empty. At the time of the research, SAIL did not provide this kind of information; rather, it only provided the event (type and strength of medications) and the event date. Therefore, this variable was deleted and excluded entirely from any further analysis or consideration.

3.2.1.6 Data quality

3.2.1.6.1 Data availability

The study period spanned 18 years (from January 2000 to December 2017). To gather information on the medical history of PwP, the data extraction period in the primary care datasets was extended to include the six months before 1/1/2000. This was to exclude all PD prevalence cases that happened before

2000 from the incidence cases that happened after 2000. Additionally, the hospital data (PEDW dataset) were extended to cover two years before 1/1/2000. This was done to consider all the comorbidities that constituted the Charlson index. The SAIL analyst extracted these comorbidities for each person at their diagnosis date by using hospital admission data up to two years prior to the diagnosis date.

The availability of data varied between the different datasets. The demographic data obtained from WDS covered the registration history (with all the demographic data) of all Welsh residents from 1990 until the present. Therefore, it was expected that the demographic data of the current study cohort would be complete. For primary care data (WLGP), the availability of data varied between GP practices. In general, the WLGP period spanned from January 2000 until the present, which covered the whole study period. However, some GP practices had some inconsistent data before this time, and they were used to exclude prevalence cases before 1/1/2000. For hospital data, the PEDW dataset covered all hospital admissions from 1998 until the present day. Thus, it covered the entire study period, and the components of the Charlson index of PD incidence cases in 2000 could be extracted up to two years before PD diagnosis. For mortality data (ADDE), the dataset covered the period from 2003 until the present day. However, ONS had death records prior to 2003 (up to 2000, as far as this study is concerned). Therefore, the mortality data are expected to be complete for the whole study period.

3.2.1.6.2 Data accuracy and completeness

All UK residents are covered by the NHS, and there is evidence that in Wales, for example, almost all people are registered with a GP (309). The SAIL databank stores data from about 80% of GP practices in Wales (305). This large sample size

could be easily generalized to the whole population of Wales. Therefore, the GP records in Wales should represent the whole Welsh population, since all of them are registered. However, GP registration did not necessarily mean that all clinical codes of diagnosis and prescriptions were recorded. Therefore, it was necessary to examine the accuracy of PD diagnosis and the completeness of PD prescriptions in the current project. Regarding the accuracy of diagnosis in this project, PD-related clinical data could not be accessed using the primary care and hospital data in SAIL. Usually, these data are present in the databases of secondary clinics (Parkinson's clinic, COTE clinics, etc.), and these databases are not available in SAIL. Therefore, the only feasible way to examine the accuracy of diagnosis was to compare the estimates of incidence and prevalence in the SAIL Databank to previous studies in the UK. If these estimates in SAIL were comparable to those in the previous UK literature, this could be considered as a validation step to the accuracy of the PD diagnosis in SAIL. This comparison and validity are explored in Chapter 5.

Comparing prescription records from GP systems in Wales (using SAIL) with records released by NHS Wales that contain complete data for all prescriptions issued by Welsh GPs (GP Data Extract) is a unique way of assessing the completeness of PD prescriptions. In Chapter 4, the number of prescriptions for all PD medications in Wales in the GP Data Extract was compared with those from SAIL from January 2014 to December 2016.

3.2.1.6.3 Missing and duplicate data

After the tables (Figure 3-3) had been imported into SPSS, all the variables underwent a cleaning process, including finding and fixing missing and duplicate data.

There were no missing data for all patients in the study cohort (PD definitive diagnosis), in the demographic, mortality, and social deprivation tables. For primary care data and hospital data, it was impossible to discover whether there were any missing data, since the data in these datasets included the outcomes of interest in this project (diagnosis and medications). However, the validation studies (discussed in the previous section) could resolve this issue and ensure the completeness of the records of PD diagnosis and PD medications in SAIL.

Additionally, all tables were searched carefully to find any duplicate values. In the demographic tables, some patients in the study cohorts had more than one row, since they had more than one registration date. This was non-problematic in all patients in the study cohort, since all demographic data (week of birth, WIMD 2011, sex) were exactly the same in all rows for any single patient. Therefore, one row for every patient was retained, and new variables were created for every patient that included different registration dates in SAIL. In the primary care data, any single Read code which was repeated twice or more in the same event date was removed. It was understood that it was possible for the GPs to generate two prescriptions for the same medication with two different quantities, which should not be considered as a "duplicate value"; however, as the drug quantity data were not available in SAIL, only one prescription for the same medication was retained in the study. For hospital data, if the same ICD-10 code was repeated in the same event date twice, it was removed; otherwise, all ICD-10 codes were retained. For mortality data, as one record should be enough for every deceased patient (only one mortality event), only one record was retained for everyone. This was done after making sure that all multiple records for the same patients had the same death date, and this was the case for all deceased patients in the study cohort. For the social deprivation tables (WIMD 2011 quintile), all duplicates were removed if the patient had the same value during the study period. If the patient had more than one registration date with

a different WIMD 2011 value, then new variables were added to every patient that showed the different WIMD 2011 values across the years of the study.

3.3 Study design

Unless mentioned otherwise in the relevant chapter, a repeated cross-sectional study design was implemented in this project. This approach is quantitative and observational in nature, and it allowed for applying the cross-sectional design to every year during the 18-year period from 2000 to 2017.

3.4 Study cohort

The study cohort included all adults (aged 40 years or older) with an incidence of "PD definitive diagnosis" in the SAIL Databank between January 2000 and December 2017. Time of entrance into the study was defined by the first record of "PD definitive diagnosis" (index date). If there was less than six months between the date of registration in SAIL GP data and the index date, this case was not considered as an incidence case; rather, it was considered as a prevalence case.

3.5 Statistical tests

The statistical analysis in this thesis was carried out based on advice that was sought from biostatisticians (data clinic @ Cardiff University). The data analysis in this study was conducted using Microsoft Excel 2016 (Microsoft, Redmond, WA, US), SPSS 24 (BM, Armonk, NY, USA), and R 3.5.0 software. The significance level was set at 0.05. A Poisson regression model was used to calculate adjusted incidence rate ratios of PD (IRRs), and the Wald test was used to calculate the associated p-values (Chapter 5). Multilevel and single-level logistic regression models were built to investigate the factors that affect the prescribing of the first

line therapy in PD (Chapter 6). Cox regression (proportional hazards regression) was used to examine the association between the first PD prescription and ischemic heart disease and other cardiovascular diseases (Chapter 7). Details of these statistical approaches are discussed in each respective chapter.

3.6 Ethical consideration

This project was approved by SAIL's IGRP (project 0729). The Research Ethics Committee in the School of Pharmacy at Cardiff University confirmed that anonymised data obtained from the SAIL Databank did not require any new ethical approval. The committee allocated a project number of 1718-26 for this project.

CHAPTER 4: Validating SAIL Databank Prescriptions for PD Medications

4.1 Background

An investigation of the prescribing trends of PD medications and other types of medications requires comprehensive data with high quality measures. Computerized primary care data records can help to answer several questions regarding prescribing trends and patterns and to determine issues that affect trends and pattern changes, such as demographic and socioeconomic factors (151). Although researchers in the UK can use primary care data to answer a large number of research questions, the accuracy of clinical codes entered by GPs should be validated in order to avoid biased and invalid outcomes caused by incorrect or missed clinical coding. In the UK, several studies have validated different disease diagnosis codes used in the GP electronic system (331), but studies validating the completeness and validity of prescriptions in the GP electronic system are scarce (332, 333). In general, drug prescriptions are expected to be well recorded in the GP electronic system, since GPs use it to generate prescriptions. However, Over-the-Counter (OTC) prescriptions, private prescriptions, and medications prescribed in secondary care cannot be captured by the system (331).

Most PwP are managed by Care of the Elderly (COTE) physicians or neurologists and PD nurses, who in turn provide GPs with recommendations regarding initiating, titrating, or changing PD medication regimens. Thus, it is expected that most PD medication prescriptions should be recorded in the GP data system.

The SAIL Databank contains the records of approximately 80% of the GP practices in Wales (305). An extensive search of the relevant literature in the Databank yielded only one article that examined the validity of a specific prescription type (antiepileptic prescriptions) (334); however, the article examined the validity of prescriptions in the context of epilepsy diagnosis and did not compare the total number of antiepileptic prescriptions to the national

dispensing system. In the PD field, it is important to examine the validity and completeness of PD medication prescriptions in the GP electronic system before conducting any pharmacoepidemiological study of the medications themselves. Comparing prescription records on the GP systems in Wales (using the SAIL Databank) to national records released by NHS Wales containing complete data for all prescriptions administered by GPs in Wales is one way to assess the validity and completeness of PD prescriptions in GP data held in the SAIL Databank. The national reference used in this study is the General Practice Prescribing Data Extract (GP Data Extract) released by the NHS Wales Shared Services Partnership every month, which contains all prescriptions administered in all GP practices in Wales (335).

4.2 Aim and objectives

The general aim of the study is to assess whether the GP records of all prescriptions, particularly PD prescriptions, in the SAIL Databank between January 2014 and December 2016 are complete and whether they can be used to evaluate the prescribing trends and patterns of PD medications in Wales. The objectives of this study are to:

1. Calculate the total prescriptions and population in both datasets (GP Data Extract and SAIL Databank between January 2014 and December 2016) and the average number of prescriptions per person every month and per year.
2. Compare the number of PD prescriptions per 100,000 population between the two datasets and investigate whether they share the same prescription rates and trends.

4.3 Method

4.3.1 Data source and study population

4.3.1.1 SAIL Databank

A detailed description of the SAIL Databank is provided in the general method chapter. This chapter focuses on the Welsh Longitudinal General Practice Dataset (WLGP). The WLGP contains data relating to approximately 80% of all GP practices in Wales. It also contains the GP events of all the patients registered with GP practices that are registered on the SAIL Databank. These GP events include drugs prescriptions (305). Any prescription of interest in the WLGP is recorded as a single GP event which can be searched using its Read code. The GP events of prescriptions contain no information about drug dispensing or actual patient intake. Rather, they detail the type of medication prescribed and the date of prescription.

4.3.1.2 General Practice Prescribing Data Extract (GP Data Extract)

Since April 2013, the NHS Wales Shared Services Partnership has released a monthly report of the prescriptions made in all the GP practices in Wales (335). The prescriptions in the GP Data Extract include those prescribed by the GPs themselves and by non-medical prescribers who prescribe on GPs' behalf. The report includes data from all prescriptions made in Wales and dispensed in Wales or England. Therefore, any prescription written in a GP practice outside Wales and dispensed in Wales cannot be captured by the report. In addition, any prescription written in a Welsh GP practice and not dispensed at all will not be captured. However, the SAIL Databank contains information regarding medications prescribed in GP practices in Wales regardless of whether they are dispensed to the patient or not. Therefore, if the prescription rates for the GP

Data Extract are greater than the SAIL Databank rates, this indicates that dispensing exceeds prescribing, which might be due to incomplete recording in the SAIL Databank. In contrast, if prescription rates for the GP Data Extract are lower than the SAIL Databank rates, this indicates that prescribing exceeds dispensing, which may be because the medication was prescribed but not dispensed. The GP Data Extract presents aggregated data extracted from the Primary Care Service dispensing system. These data include the total number of every medication identified by its British National Formulary (BNF) code.

4.3.2 Data extraction and outcome measures

In order to identify all PD medications in both datasets, a matching process was carried out between the Read codes (the clinical code dictionary in the SAIL Databank) and the BNF codes (the clinical code dictionary in the GP Data Extract) of the PD medications, which were extracted based on a manual search using the NHS Digital website (324, 336) (Table 4-1).

For the GP Data Extract, 36 Excel files were downloaded from the NHS Wales Shared Services Partnership website (including the quantity of prescriptions of 36 months between January 2014 and December 2016) (335). The total number of all prescriptions (for PD and non-PD medications) was calculated manually for every single month and divided by the total population in Wales that month to obtain the number of prescriptions per person per month. This manual calculation was confirmed by validating the number of prescriptions per person per year in the GP Data Extract against a previous report published by the Welsh government (337). Then, the number of all PD prescriptions was calculated and stratified by medication type (dopaminergic vs. anticholinergic) and by every single PD medication, as shown in Table 4-1.

For the SAIL Databank, the WinSQl software in the SAIL Gateway was used to calculate the total number of all prescriptions in the WLGP (GPs') records for every single month from January 2014 to December 2016. Then, the total number of prescriptions for every month was divided by the total population in the SAIL Databank at every month to obtain the number of prescriptions per person per month and per year. Additionally, in a similar manner to the GP Data Extract, the number of all PD prescriptions was calculated and stratified by each PD medication type, as presented in Table 4-1. All cells containing a number less than 5 were removed from the analysis in accordance with the SAIL Databank information governance rules.

The outcome measures in this study were the number of prescriptions per person per month, the number of prescriptions per person per year, and the number of prescriptions per 100,000 population per month in both the GP Data Extract and the SAIL Databank. In order to measure the denominator in both datasets, the total population of both was used. For the SAIL Databank, the total population was calculated using WinSQl software for every single month. The total population for GP data in the SAIL Databank included individuals who were alive and registered in the GP data on the first day of every calendar month. Everyone in this population was assumed to contribute one person-month of follow-up. Then, to calculate the number of prescriptions per 100,000 population per month, the total number of prescriptions of the drug of interest was divided by the total population and multiplied by 100,000. If a particular medication had an average of less than 5 prescriptions per 100,000 population in all 36 months, the prescription rate of this medication was removed from the analysis and no comparison was made between the SAIL Databank and the GP Data Extract in this case. For the GP Data Extract, the total populations for the three years of the study (2014, 2015, and 2016) were obtained from the mid-year population of Wales information produced by the Office for National Statistics (ONS) (338). In

order to calculate the total population for every single month, the annual increase for the year of interest was obtained from the ONS website and divided by 12. Then this was added to the mid-year population for every single month accumulatively. The number of prescriptions per 100,000 population was calculated in the same way as for the SAIL Databank.

A comparison was conducted between the prescription rates of all PD medications for the GP Data Extract and the SAIL Databank from January 2014 to December 2016. This time period was chosen because the NHS Wales Shared Services Partnership website made the data (prescriptions for every month) available for the current financial year and the next two years. As the website started releasing these data in April 2013, the data of all prescription numbers from January 2014 to December 2016 were available on the website at the time of this study (335). Furthermore, three years of comparison between the two datasets was enough to obtain valid and robust results that were not affected by seasonal changes in the prescriptions trends.

Drug	BNF code (in the GP Data Extract)	Read code (in SAIL)	Type of PD Medication
Levodopa	0409010I0	dq1..	Dopaminergic
Co-Beneldopa (Benserazide/Levodopa)	0409010K0	dq2..	Dopaminergic
Co-Careldopa (Carbidopa/Levodopa) and (Carbidopa/Levodopa/Entacapone)	0409010N0 and 0409010X0	dq3..	Dopaminergic
Amantadine Hydrochloride	0409010B0	dq4..	NA
Bromocriptine	0607010B0	dq5..	Dopaminergic
Selegiline Hydrochloride	0409010T0	dq6..	Dopaminergic
Lisuride Maleate	0409010L0	dq7..	Dopaminergic
Pergolide Mesilate	0409010P0	dq8..	Dopaminergic
Apomorphine Hydrochloride	0409010A0	dq9..	Dopaminergic
Ropinirole Hydrochloride	0409010H0	dqA..	Dopaminergic
Cabergoline	0409010U0	dqB..	Dopaminergic
Tolcapone	0409010S0	dqC..	Dopaminergic
Entacapone	0409010V0	dqD..	Dopaminergic
Pramipexole	0409010W0	dqE..	Dopaminergic
Rasagiline Mesilate	0409010Y0	dqF..	Dopaminergic
Rotigotine	0409010Z0	dqG..	Dopaminergic
Trihexyphenidyl Hydrochloride	0409020C0	dr1..	Anticholinergic
Orphenadrine Hydrochloride	0409020N0	dr2..	Anticholinergic
Benzatropine Mesilate	4.09E+05	dr3..	Anticholinergic
Biperiden Hydrochloride or Biperiden Lactate	0409020G0 and 0409020H0	dr4..	Anticholinergic
Metixene Hydrochloride	0409020L0	dr5..	Anticholinergic
Procyclidine Hydrochloride	0409020S0	dr6..	Anticholinergic

Table 4-1- Read and BNF Codes matching between the two datasets

4.3.3 Statistical analysis

The difference between the numbers of prescriptions per 100,000 for each dataset was calculated for every month. The mean of these differences was then also calculated for every month. As the GP Data Extract was the reference used for comparison, the SAIL prescription rates were subtracted from the GP Data Extract prescription rates. If the difference was zero, there was no difference between the prescription rates of the two datasets. If the difference was a positive number, this indicated that there might be an incomplete recording in the SAIL data. If the difference was a negative number, the SAIL prescription rates exceeded the GP Data Extract prescription rates, and this indicated that medication had been prescribed but not dispensed. The data analysis in this study was carried out using Microsoft Excel 2016 (Microsoft, Redmond, WA, US) and SPSS 24 (BM, Armonk, NY, USA).

4.3.4 Ethical considerations

The data for the GP Data Extract was publicly available through the NHS Wales Shared Services Partnership. It was also aggregated and contained no personal information. Furthermore, the researcher abided by the Open Government Licence (OGL) instructions recommended by NHS Wales for dealing with this type of data (339). For the data collected from the SAIL Databank, ethical approval (number 1729) was obtained from the Information Governance Review Panel (IGRP) of the SAIL Databank, as discussed in the General Method chapter.

4.4 Results

4.4.1 Total population and number of prescriptions

Table 4-2 presents the results of validating the manual calculation of the number of all prescriptions in the GP Data Extract against the report published by the Welsh government.

	GP Data Extract	Welsh Government	SAIL Databank	Difference between GP and SAIL data
Number of Prescriptions per Person per Year in 2014	25.2	25.4	25.8	-0.6
Number of Prescriptions per Person per Year in 2015	25.4	25.6	25.9	-0.5
Number of Prescriptions per Person per Year in 2016	25.5	25.8	26.1	-0.6

Table 4-2- Validating the Number of Prescriptions per Person per Year in the GP Data Extract Against a National Published Report

Table 4-3 shows the total population and number of prescriptions in the GP Data Extract and the SAIL Databank between January 2014 and December 2016. Throughout this period, the total population in the SAIL Databank constituted ~77-79% of the total population estimated on the ONS website. The same table (Table 4-3) shows that the total number of prescriptions recorded in the SAIL Databank during the 36 months of the study accounted for ~75-84% of the total number of prescriptions recorded in the GP Data Extract. The average number of prescriptions per month and the trend in both datasets are presented in Table 4-3 and Figure 4-1, respectively. Calculating the average difference between the number of prescriptions per person per month for each dataset in the whole study period revealed that the rates were very similar, although numbers of

prescriptions written in the SAIL Databank tended to be slightly higher than the dispensed prescriptions in the GP data extract. After adding up all the monthly averages to obtain the overall annual average for both datasets, the GP data extract showed averages of 25.2, 25.4, and 25.5 prescriptions per person per year in 2014, 2015, and 2016, respectively. In contrast, the annual averages of the number of prescriptions per person in the SAIL Databank in 2014, 2015, and 2016 were 25.8, 25.9, and 26.1, respectively.

4.4.1 Prescriptions rates of PD medications in both datasets

In general, dopaminergic PD medications constituted the majority of prescriptions in all months of the study, with an average of 585 prescriptions per 100,000 population in the GP Data Extract, exceeding the prescription rate in the SAIL Databank by one prescription per 100,000 population (Figures 4-2 and 4-3). On the other hand, prescription rates for anticholinergic PD medications (average of 205.17 prescriptions per 100,000 population) exceeded the prescribing and dispensing rates of the GP Data Extract by 5.34 prescriptions per 100,000 population (see Figure 4-2a and Table 4-4). L-dopa (without benserazide or carbidopa), lisuride, tolcapone, benztropine, biperiden, and metixene were removed from the analysis because the average prescription rates per 100,000 population of these medications were less than 5 per 100,000 population.

Among the dopaminergic PD medications, the number of prescriptions per 100,000 population was slightly higher in the GP Data Extract for six medication types — careldopa (carbidopa/levodopa and carbidopa/levodopa/entacapone), bromocriptine, selegiline, pergolide, and entacapone — and ranged from a negligible increase of 0.08 to a more observable increase of 1.85 prescriptions per 100,000 population compared to the SAIL Databank (Table 4-4). Noticeably higher rates were also observed for amantadine prescriptions in the GP Data

Extract, with an average rate of 8.26 prescriptions per 100,000 population more than the SAIL Databank (Table 4-4). In contrast, apomorphine, cabergoline, pramipexole, rasagiline, and rotigotine were found to have slightly higher prescriptions rates in the SAIL Databank, ranging from 0.29 to 1.20 prescriptions per 100,000 population more than the GP Data Extract (Table 4-4). Furthermore, the SAIL Databank gave observably higher rates than the GP Data Extract for co-beneldopa (benserazide/levodopa) and ropinirole prescriptions, with 5.32 and 3.34 prescriptions per 100,000 population more in the SAIL Databank, respectively (Table 4-4).

Among the anticholinergic PD medications, trihexyphenidyl prescription rates were slightly higher in the GP Data Extract, with a rate of 0.26 prescriptions per 100,000 population, whereas orphenadrine and procyclidine showed a more obvious increase in the SAIL Databank (1.46 and 4.24 respectively) (Table 4-4).

Month	GP Data Extract			SAIL Databank		
	Total number of prescriptions	Total number of populations (from ONS website)	Average number of prescriptions per person	Total number of prescriptions and percentage out of the total number in the GP Data Extract	Total number of population and percentage out of the total number in the ONS website	Average number of prescriptions per person
Jan-14	6,507,446	3,092,000	2.10	5,198,136 (79.88%)	2,397,489 (77.54%)	2.17
Feb-14	5,901,802	3,092,592	1.91	4,700,110 (79.64%)	2,395,620 (77.46%)	1.96
Mar-14	6,337,872	3,093,183	2.05	5,092,001 (80.34%)	2,397,460 (77.51%)	2.12
Apr-14	6,419,352	3,093,775	2.07	5,250,477 (81.79%)	2,388,160 (77.19%)	2.20
May-14	6,572,490	3,094,367	2.12	5,123,551 (77.95%)	2,390,708 (77.26%)	2.14
Jun-14	6,374,477	3,094,958	2.06	5,147,683 (80.75%)	2,393,319 (77.33%)	2.15
Jul-14	6,778,717	3,095,550	2.19	5,448,813 (80.38%)	2,393,754 (77.33%)	2.28
Aug-14	6,241,459	3,096,142	2.02	4,870,296 (78.03%)	2,393,747 (77.31%)	2.03
Sep-14	6,557,050	3,096,733	2.12	5,312,907 (81.03%)	2,407,369 (77.74%)	2.21
Oct-14	7,110,888	3,097,325	2.30	5,382,618 (75.70%)	2,408,159 (77.75%)	2.24
Nov-14	6,253,774	3,097,917	2.02	4,827,663 (77.20%)	2,406,843 (77.69%)	2.01
Dec-14	7,026,112	3,098,508	2.27	5,619,011 (79.97%)	2,405,401 (77.63%)	2.34
Jan-15	6,493,737	3,099,100	2.10	5,104,425 (78.61%)	2,408,038 (77.70%)	2.12
Feb-15	6,036,263	3,100,275	1.95	4,812,703 (79.73%)	2,406,662 (77.63%)	2.00
Mar-15	6,648,387	3,101,450	2.14	5,533,987 (83.24%)	2,397,118 (77.29%)	2.31
Apr-15	6,518,956	3,102,625	2.10	5,126,105 (78.63%)	2,396,718 (77.25%)	2.14
May-15	6,300,272	3,103,800	2.03	4,902,027 (77.81%)	2,395,511 (77.18%)	2.05
Jun-15	6,607,234	3,104,975	2.13	5,390,318 (81.58%)	2,399,794 (77.29%)	2.25
Jul-15	6,884,673	3,106,150	2.22	5,425,174 (78.80%)	2,399,705 (77.26%)	2.26
Aug-15	6,172,486	3,107,325	1.99	4,837,870 (78.38%)	2,411,063 (77.59%)	2.01
Sep-15	6,690,654	3,108,500	2.15	5,452,581 (81.50%)	2,423,371 (77.96%)	2.25
Oct-15	6,993,108	3,109,675	2.25	5,249,468 (75.07%)	2,426,255 (78.02%)	2.16
Nov-15	6,493,198	3,110,850	2.09	5,173,280 (79.67%)	2,406,187 (77.35%)	2.15
Dec-15	7,156,243	3,112,025	2.30	5,491,557 (76.74%)	2,404,056 (77.25%)	2.28
Jan-16	6,261,813	3,113,200	2.01	4,963,636 (79.27%)	2,414,839 (77.57%)	2.06
Feb-16	6,341,041	3,114,200	2.04	5,161,564 (81.40%)	2,414,240 (77.52%)	2.14
Mar-16	6,749,838	3,115,200	2.17	5,448,890 (80.73%)	2,421,298 (77.73%)	2.25
Apr-16	6,673,811	3,116,200	2.14	5,198,407 (77.89%)	2,429,411 (77.96%)	2.14
May-16	6,507,154	3,117,200	2.09	5,249,978 (80.68%)	2,428,935 (77.92%)	2.16
Jun-16	6,709,001	3,118,200	2.15	5,406,044 (80.58%)	2,431,448 (77.98%)	2.22
Jul-16	6,576,084	3,119,200	2.11	5,093,294 (77.45%)	2,433,973 (78.03%)	2.09
Aug-16	6,627,807	3,120,200	2.12	5,549,640 (83.73%)	2,435,810 (78.07%)	2.28
Sep-16	6,814,140	3,121,200	2.18	5,352,474 (78.55%)	2,455,753 (78.68%)	2.18
Oct-16	6,704,069	3,122,200	2.15	5,264,977 (78.53%)	2,452,022 (78.54%)	2.15
Nov-16	6,799,193	3,123,200	2.18	5,535,594 (81.42%)	2,450,866 (78.47%)	2.26
Dec-16	6,973,468	3,124,200	2.23	5,407,742 (77.55%)	2,443,325 (78.21%)	2.21

Table 4-3- Total populations and number of prescriptions in the study datasets

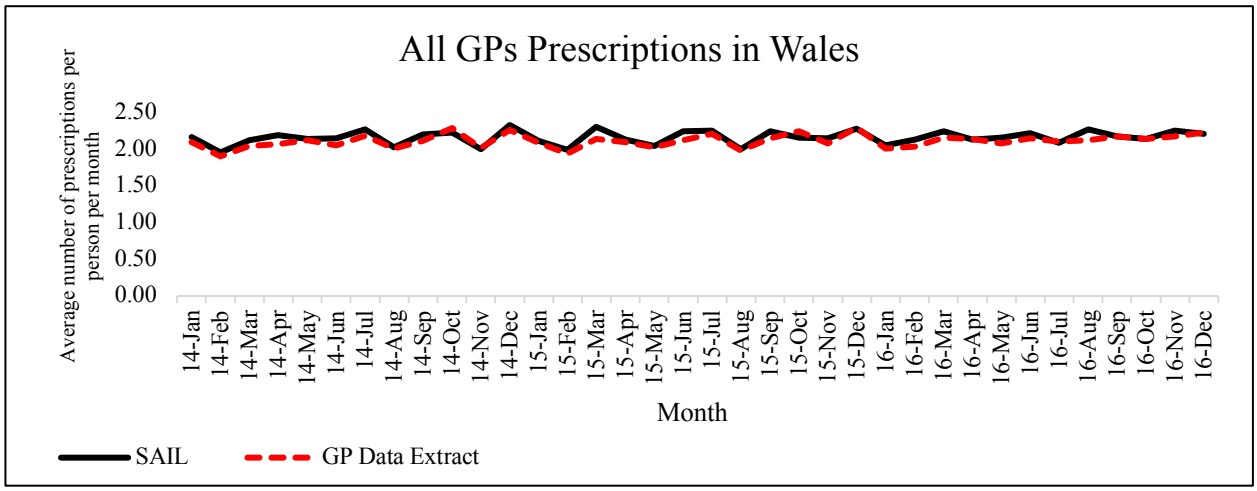


Figure 4-1- Average Number of Prescriptions per Person per Month in the Study Datasets

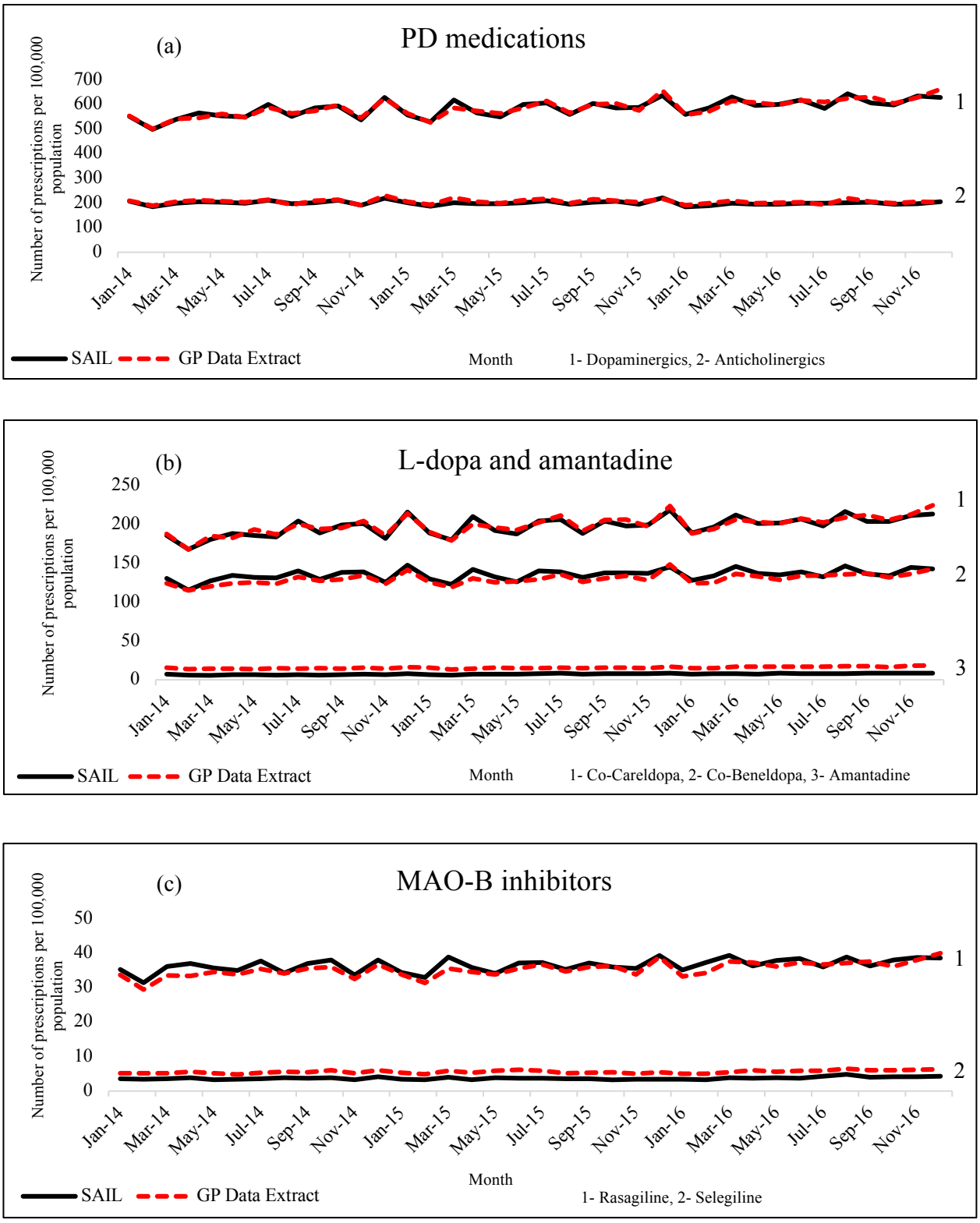
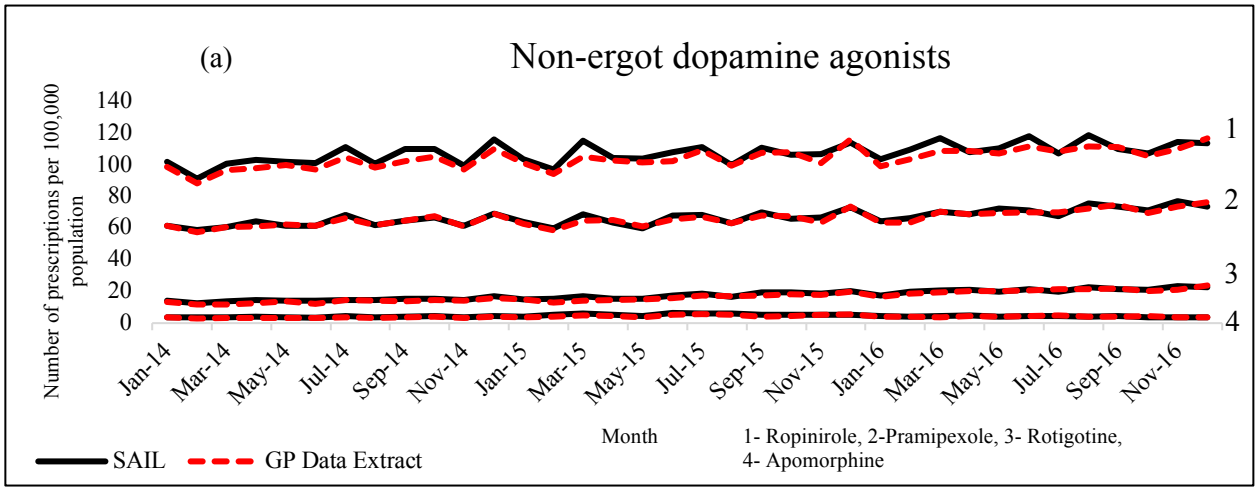
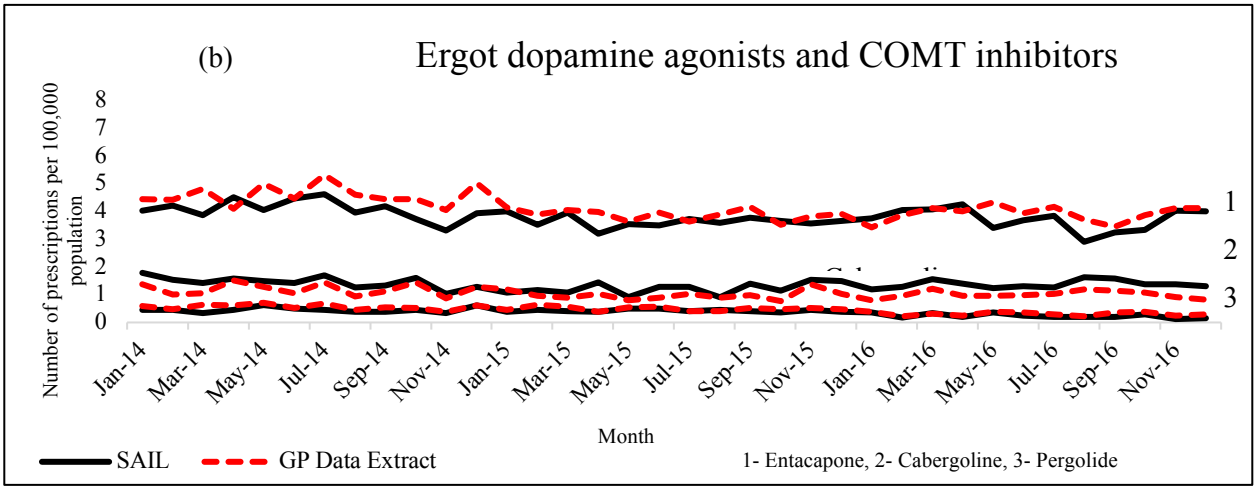


Figure 4-2- Number of Prescriptions of PD Medications Per 100,000 Population in the Study Datasets (Part 1)





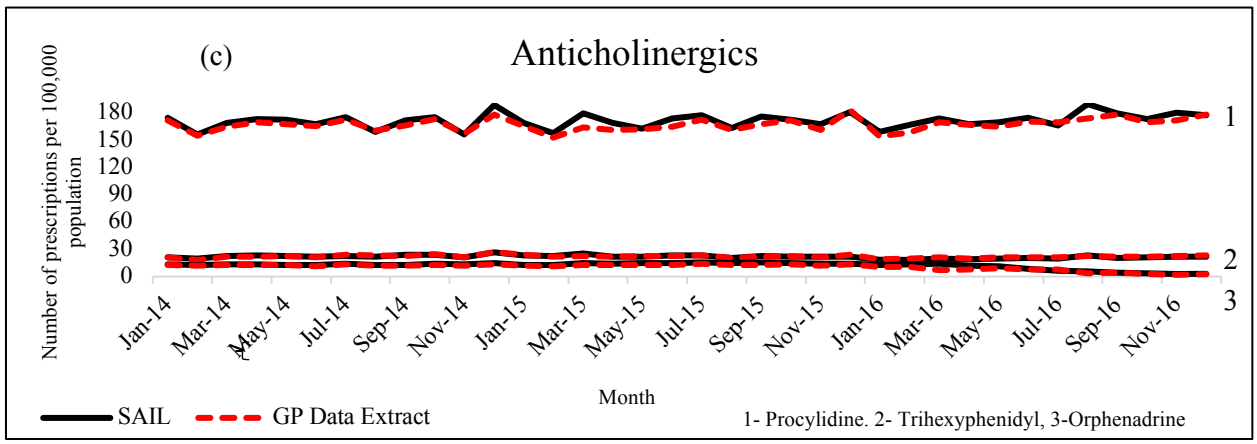


Figure 4-3- Number of prescriptions of PD medications per 100,000 population in the study datasets (Part 2)

Month / Drug	Jan-Mar (14)	Apr-Jun (14)	Jul-Sep (14)	Oct-Dec (14)	Jan-Mar (15)	Apr-Jun (15)	Jul-Sep (15)	Oct-Dec (15)	Jan-Mar (16)	Apr-Jun (16)	Jul-Sep (16)	Oct-Dec (16)	Mean difference
Co-Beneldopa (Benserazide/Levodopa)	-4.61	-8.34	-6.32	-4.26	-6.60	-6.02	-5.31	-3.03	-7.65	-5.31	-2.81	-3.57	-5.32
Co-Careldopa (Carbidopa/Levodopa) and (Carbidopa/Levodopa/Entacapone)	2.06	1.91	-0.87	1.72	-3.00	2.24	3.16	3.92	-3.03	0.51	1.83	4.84	1.27
Amantadine Hydrochloride)	8.35	7.74	8.27	8.27	7.63	7.54	7.63	8.05	8.08	9.03	9.27	9.23	8.26
Bromocriptine	1.37	1.40	1.35	1.48	1.44	1.66	1.42	1.56	1.49	1.59	1.62	1.38	1.48
Selegiline Hydrochloride	1.63	1.68	1.71	2.00	1.76	2.12	1.86	1.94	1.71	2.04	1.76	2.00	1.85
Pergolide Mesilate	0.15	0.08	0.16	0.03	0.14	0.05	0.02	0.09	0.02	0.06	0.08	0.12	0.08
Apomorphine Hydrochloride	-0.30	-0.51	-0.59	-0.45	-0.92	-0.92	-0.84	-0.23	-0.47	-0.05	-0.18	0.12	-0.45
Ropinirole Hydrochloride	-3.37	-3.82	-5.61	-4.35	-5.27	-3.24	-1.85	-0.81	-6.25	-3.09	-1.56	-0.91	-3.34
Cabergoline	-0.43	-0.21	-0.26	-0.11	-0.09	-0.31	-0.23	-0.34	-0.36	-0.34	-0.38	-0.41	-0.29
Entacapone	0.52	0.18	0.53	0.85	0.20	0.45	0.19	0.13	-0.15	0.30	0.44	0.25	0.32
Pramipexole	-0.55	-0.83	-0.73	0.01	-2.21	0.00	-1.11	-0.51	-1.44	-1.28	0.02	-0.81	-0.79
Rasagiline Mesilate	-2.05	-2.02	-1.27	-1.48	-1.80	-1.06	-0.78	-0.60	-2.27	-0.68	0.03	-0.43	-1.20
Rotigotine	-1.06	-1.41	-0.59	-0.85	-1.68	-0.76	-1.03	-0.87	-1.06	-0.48	0.16	-0.53	-0.85
Trihexyphenidyl Hydrochloride	-0.97	-0.43	0.40	0.47	-0.70	0.23	-0.11	0.69	0.83	0.80	0.89	1.02	0.26
Orphenadrine Hydrochloride	-0.93	-0.73	-0.72	-1.36	-1.46	-1.68	-2.21	-1.33	-3.80	-2.28	-0.30	-0.72	-1.46
Procyclidine Hydrochloride	-2.85	-3.49	-2.17	-4.04	-7.93	-5.71	-5.41	-1.33	-5.95	-3.20	-4.71	-4.07	-4.24
Total number of dopaminergic PD medications	1.65	-4.19	-4.26	2.82	-10.46	1.71	3.06	9.29	-11.41	2.28	10.25	11.25	1.00
Total number of anticholinergic PD medications	-4.61	-4.57	-2.32	-4.81	-9.99	-7.04	-7.57	-1.86	-8.81	-4.61	-4.10	-3.81	-5.34

Table 4-4- Differences between the number of prescriptions per 100,000 population in the study data

4.5 Discussion

This is the first study that has examined the completeness of prescription recording for all prescriptions in general, and particularly for PD prescriptions in the SAIL Databank compared to the national dispensing system in Wales (GP Data Extract). Several previous studies have shown that prescription recording in the GP systems in the UK is likely to be more complete than diagnosis recording and of a higher quality in the Clinical Practice Research Datalink (CPRD) (340-342). In a comparison with a national dispensing database, one study found that the rates of prescriptions of GP smoking cessation medication recorded in The Health Improvement Network (THIN) database and the UK's National Health Service (NHS) prescriptions service in England were highly comparable (332). However, no similar studies have used the SAIL Databank to validate GP prescription recording. Hence, the current study is the first to carry out this kind of validation.

This study's comparison of the manually-calculated GP Data Extract number of prescriptions with a previous report published by the Welsh government revealed a small discrepancy in the prescription rates. For example, in 2016, the number of prescriptions per person per year was 25.5 in the GP Data Extract published by the NHS Wales Shared Services Partnership (335) and 25.8 in the report published by the Welsh government (337) (Table 4-2). This discrepancy is understandable, since the Welsh government report included — in addition to the GP prescriptions — the prescriptions given by dentists, nurses, and hospital doctors which were dispensed in the community, whereas the GP Data Extract included only the prescriptions written in the GP practices. Given that the majority of prescriptions in the Welsh government's report were prescribed by GPs (337), the manual calculation of the number of prescriptions in the GP Data Extract seems to have produced highly comparable results to the report; thus it

could be used as a reference to examine the completeness and validity of prescription records in the SAIL Databank.

Jones et al. stated that the SAIL Databank contained records for approximately 80% of all GP practices in Wales (305). Although the current study found that 77%-79% of the total Welsh population was registered in the SAIL Databank during the study period, it was unable confirm that this population represented the same percentage (77%-79%) of all GP practices in Wales. For example, there was a large variation in the number of registered patients and the number of GP practices in Wales in 2017 (343). Nevertheless, the percentage of population in the current study remains highly representative of the total Welsh population.

In the current study, the annual averages of prescriptions per year in the study period for the GP Data Extract and the SAIL Databank were highly comparable, and ranged from 25.23 to 26.14. This suggests that the level of prescription completeness and validity in the SAIL Databank was very high during the study period.

In general, the average number of prescriptions per person per month was higher in the SAIL Databank, although the difference between the datasets was very small (0.05 prescriptions per person per month) (Figure 4-1). This indicates that, generally, the prescribing exceeded the dispensing very slightly and there were few prescriptions that were not dispensed by the community pharmacies. This very low rate of undispensed prescriptions is notable, given that a previous literature review that examined 79 international studies showed that the average prescription non-fulfilment rate ranged between 11% and 19% either of all prescriptions or all patients, according to every study design (344). The high dispensing rate in Wales might be due to the free prescriptions policy implemented in the country in April 2007 (345). Indeed, some studies have

demonstrated that, since 2007, the dispensing rate in general has tended to be higher in Wales than in England, where this kind of policy has not been implemented (337, 346, 347). However, it is optimistic to expect high compliance with the medications based on this high dispensing rate, because the high dispensing rate does not mean that the medications were taken by the patients as instructed; therefore, rates of compliance are difficult to determine. Other research approaches, such as qualitative interviews, can be used to address these kinds of questions.

In terms of PD medications, the current study found that the prescription rates of PD medications per 100,000 population in the SAIL Databank were highly similar to their rates in the GP Data Extract. Although there were small differences between some medications, these differences were consistent across the months of the study; thus, they did not affect the similarity in the trends of the prescription rates in the two datasets (Figure 4-2 and Figure 4-3).

The differences in prescription rates per 100,000 population were varied, and some medications — such as co-careldopa, procyclidine, and ropinirole — had a noticeably higher prescribing rate in the SAIL Databank (with averages of 5.32, 4.24, and 3.34 more prescriptions per 100,000 population, respectively (Table 4-4) compared to the GP Data Extract). This may indicate that some prescriptions were not dispensed during the time period studied. The reasons for not dispensing these kinds of medications cannot be easily speculated. Although several factors of non-adherence to PD medications from the patients' perspective have been suggested in the literature — such as younger age, polypharmacy, complex regimen, and others (348) — it is difficult to link those factors to the lower dispensing rates of co-careldopa and ropinirole due to the aggregated nature of the existing data and the lack of personal dispensing records for PD medications. Nevertheless, the higher number of prescription

rates in the SAIL Databank will not preclude their use in further drug utilization trend studies, as the differences were not significant and were consistent over time, having a minimal effect on prescribing trends. This is especially true for smaller prescribing rate differences, such as those for pramipexole and apomorphine (Table 4-4).

Amantadine was the only obvious medication among the PD medications with a higher prescribing rate in the GP Data Extract than the SAIL Databank, with an average increase of 8.26 prescriptions per 100,000 population. This could be explained by incomplete recording of amantadine prescriptions in the SAIL Databank. However, there is no clear reason why this occurred with amantadine across all months of the study. Nevertheless, the difference in amantadine prescriptions between the two datasets was persistent. Therefore, the accuracy of examining the prescribing trend of amantadine using the SAIL Databank would not be altered by the differences between the prescribing rates in the two datasets, although precautions should be taken when calculating the exact prescribing rate (regardless of the trend over time) of amantadine, because it might be possible to underestimate the number of amantadine prescriptions truly prescribed in GP practices in Wales.

Due to the high similarity between the prescription rates of all medications in general, and the PD prescriptions in particular, in the SAIL Databank and the GP Data Extract in Wales, the SAIL Databank could be used as a valid and reliable resource to measure the prescribing trends of PD medications in Wales. Additionally, the factors that affect the prescribing trends of PD medications, such as the socioeconomic status and demographic characteristics of patients, could be investigated by using the SAIL Databank. The SAIL Databank could also be used to determine the reason for prescription and diagnosis, because some PD medications can be used in the treatment of other medical conditions: for

example, bromocriptine, which can be used to prevent lactation; and anticholinergics, which can be used in other movement disorders, such as dystonia and essential tremor. Although the total prescription rates of all medications were highly comparable in this study, this does not mean that all specific medication types will show the same level of similarity and comparability. Thus, further studies are important to validate the prescribing rates of other types of medications. The current study covered three years of data (2014-2016), and therefore its results should be taken with caution when generalizing the results to other years.

4.6 Conclusion

The prescription rates for PD medications were highly similar, with very small and consistent differences over time between the SAIL Databank and Welsh national dispensing data (GP Data Extract). Therefore, the SAIL Databank could be used to monitor the prescribing trends of PD medications in Wales, and hence could be used to evaluate the impact of new treatment guidelines or safety issues and their effects on the general trends of PD medication prescriptions.

CHAPTER 5: Incidence and Prevalence of Parkinson's Disease (PD) in Wales

5.1 Introduction

Findings from studies published over the last six decades have shown that the incidence of PD rises with age in both males and females, with noticeable differences within older age groups (349, 350). Two published systematic reviews have found that the highest peak of PD incidence was observed in the 70-79 year age group (349, 350). Hirsch et al. conducted a meta-analysis, examining twenty-seven studies of PD incidence, and found that the overall incidence rate of PD in males older than 40 years was 61.21 per 100,000 person-years (350). Female incidence, in contrast, was estimated to be 37.55 per 100,000 person-years (350). Additionally, the results of the meta-analysis have shown that the incidence of PD in males was significantly higher than the incidence in females in the 60-69 year and 70-79 year age groups (350). These age and sex associations with PD are not the only patterns seen in incidence studies: the prevalence of PD has a similar association. A recent meta-analysis that examined 47 prevalence studies has found a significant association between PD prevalence and age, with an increase in prevalence from 41 per 100,000 population in the 40-49 year age group to 1903 per 100,000 population in patients older than 80 years (3). This meta-analysis revealed a higher prevalence of PD in males compared to females, particularly in those aged 50-59 years (3).

Socioeconomic status has been shown to correlate with either an increase or a decrease in the incidence of several diseases (351); however, studies have reported conflicting results regarding the association between PD incidence and prevalence and patients' socioeconomic status. These studies can be classified into three groups: studies which reported an increase in PD incidence and/or prevalence in patients with lower socioeconomic status (352), studies which reported no difference in PD incidence and/or prevalence across patients of different socioeconomic status (353), and studies which reported an increase in PD incidence and/or prevalence in patients with higher socioeconomic status

(318, 354, 355). This variation might be due to the methods used and how the level of socioeconomic status was defined. For example, Yang et al. (355), Lix et al. (352), and Frigerio et al. (354) respectively used occupation, income, and education level as proxies for socioeconomic status, which made it more difficult to reach a valid conclusion regarding the overall effect of socioeconomic status on PD risk. In Wales, the WIMD scale includes eight domains of deprivation components (see Section 3.1.1.7.5), which seems to be more comprehensive than scales used in previous studies.

In the UK, several studies have calculated the incidence and prevalence of PD (Tables 5-1 and 5-2). Wickremaratchi et al. conducted a meta-analysis regarding the trend of PD prevalence across time and revealed a stable prevalence rate of PD in the UK, despite the increase in population ages (325). The study suggested that the reason for this stability might be due to the decrease in PD incidence across years, although this claim opposes previous international studies that reported stability in PD incidence across years from 1976 to 2007 (352, 356). To examine the time trend in the UK, Horsfall et al., using the Health Improvement Network (THIN) database, examined the incidence trend of PD in the UK and found a slight decline in PD incidence between 1999 and 2009 (318). Although the results might confirm the claim made by Wickremaratchi et al., Horsfall et al. attributed this decline to a change in recording patterns across years and the recognition of other types of parkinsonism which might be recorded as PD in patient files.

In general, most UK studies are community-based and restricted to small geographical locations. Although this kind of study can be more accurate in the case ascertainment of PD, the relatively smaller study population could impede the representativeness of the study results. Few studies in the UK have used population-based data to estimate the incidence and/or prevalence of PD. The

first study used the THIN database to estimate the incidence of PD in the UK from 1999 to 2009 (318). The second study was published as a report from Parkinson's UK and used Clinical Practice Research Datalink (CPRD) to estimate the prevalence and incidence of PD in the UK from 2011 to 2015 (317).

Study	Study period	Study type	Study population	Age groups (years)	Incidence per 100,000 (population or person year at risk (PYAR)
Sutcliffe et al., 1995 **(357)** Northampton District, England	1982-1992	Community-based	302,000	All	12
Cockerell et al., 1996 **(358)**. Buckinghamshire and Kent, England	1993	Community-based	26,636	All	26
Macdonald et al., 2000 **(359)**, London, England	1996	Community-based	100,230	45-49 60-64 65-69 70-74 75-79 85-89	20 50 37 222 100 116
Foltynie et al., 2004 **(360)**, Cambridge, England	2000-2003	Community-based	708,715	40-49 50-59 60-69 70-79 ≥80	2 9.6 41.2 75.5 86.2
Carslake et al., 2013 **(353)**, North East Scotland	2006-2010	Community-based	1,176,552 PYAR	40-49 50-59 60-69 70-79 80-89 ≥90	4.5 11.9 29.7 129.1 149.3 35.4
Horsfall et al., 2013 **(318)**, UK	1999-2009	Routinely collected data using THIN database	10,900,000 PYAR	50-59 60-69 70-79 80-89 ≥90	14 56.2 164.8 232.8 147.5
Duncan et al., 2014 **(326)**, Newcastle and Gateshead, England	2009-2011	Community-based	488,576	40-49 50-59 60-69 70-79 ≥80	3.6 6.9 36.5 110 81.6
Parkinson's UK, 2017 **(317)**, UK	2011-2015	Routinely collected data using CPRD database	16,051,520 PYAR	40-49 50-59 60-69 70-79 80-89 ≥90	4 13.3 47.7 140.4 192 115.1

Table 5-1- Previous incidence studies of PD in the UK

Study	Study period	Study type	Study population	Age groups (years)	Prevalence per 100,000 population
Mutch et al., 1986 **(361)**, Aberdeen, Scotland	1983-1984	Community-based	151,616	40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85	12.5 76.1 82.6 72.6 239.8 268.5 707.4 1019.6 1792.1 2205.3
Sutcliffe et al., 1995 **(357)** Northampton District, England	1992	Community-based	302,000	40-44 45-49 55-54 55-59 60-64 65-69 70-74 75-79 80-84 ≥85	4 10 76 111 159 343 664 856 1400 1044
Schrag et al., 2000 **(362)**, London, England	1997	Community-based	121,608	40-49 50-59 60-69 70-79 ≥80	12 109 342 961 1265
Hobson et al., 2005 **(327)**, Rural areas in North Wales	1998	Community-based	77,388	40-49 50-59 60-69 70-79 ≥80	32 63 228 537 653
Porter et al. 2006 **(328)**, North Tyneside, North East England	2002-2003	Community-based	108,597	40-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-90 >90	7 51 65 228 369 724 1,115 814 837 1,134
Wickremaratchi et al. 2009, **(325)**, Cardiff, Wales	2006	Community-based	292,637	40-49 50-59 60-69 70-79 ≥80	9.9 74 272 738 1297
Parkinson's UK, 2017 **(317)**, UK	2015	Routinely collected data using CPRD database	2,551,470	40-49 50-59 60-69 70-79 80-89 ≥90	14.2 94.5 369.6 1046.3 1669.1 1230.2

Table 5-2- Previous prevalence studies of PD in the UK

Of all the studies conducted in the UK, there have been only two community-based studies that calculated the prevalence of PD in Wales: one of them was conducted in a rural area of North Wales (327), and the second was conducted in Cardiff (325). There has been no community-based study that examined the incidence of PD in Wales. Additionally, the two population studies that used THIN and CPRD data included only a small percentage of Welsh populations, since the THIN and CPRD databases covered roughly 6.2% (363) to 8% (364) respectively of the whole UK population. Although the results from the THIN and CPRD databases could be generalized to the whole UK population, they do not necessarily reflect the accurate figures and numbers in Wales. Therefore, a Welsh population-based study is required to estimate the incidence and prevalence of PD in comparison to previous studies conducted inside or outside the UK. This chapter aims to utilize the SAIL Databank, which covers about 80% of the Welsh population, to estimate the prevalence and incidence of PD in Wales between 2000 and 2017.

5.2 Objectives of the study

There are two main objectives in this chapter. The first objective aims to define the characteristics of patients with a definitive diagnosis of PD using SAIL. The second objective is to estimate the incidence and prevalence of PD in Wales between 2000 and 2017 and to examine the associated factors such as age, gender, and social deprivation.

5.3 Methods

5.3.1 Data source and study population

The SAIL Databank was used to estimate the incidence and prevalence of PD in Wales (see General Methods chapter for more details about SAIL).

This study used four datasets in SAIL as follows:

1- The Welsh Demographic Service (WDS) dataset was used to obtain the demographic data of the study population.

2- The Welsh Longitudinal General Practice Dataset (WLGP) was used to find all Read codes related to PD diagnosis (PD definitive diagnosis in this study) and smoking status.

3- Hospital admissions data from PEDW (Patient Episode Database for Wales) was used to define the ICD-10 codes of the Charlson index comorbidities that existed in patient files at the time of first PD diagnosis.

4- A socio-economic deprivation dataset was used to obtain the social deprivation quintile of every patient (WIMD 2011).

The study population comprised patients with a definitive PD diagnosis who were aged 40 years or older and contributed to SAIL data up to December 31, 2017.

5.3.2 Extraction and identification of PwP (the study cohort)

As discussed in the methodology chapter, the cohort most likely to resemble the previous incidence and prevalence UK literature was the PD definitive diagnosis cohort (Table 5-3).

Definitive PD diagnosis	
Read code	Definition
F12..00	Parkinson's disease
F120.00	Paralysis agitans
F12z.00	Parkinson's disease not otherwise specified
147F.00	History of Parkinson's disease

Table 5-3- Read codes that define the PD definitive diagnosis

The initial extraction of PwP from SAIL was conducted by using all possible Read codes that might define the PD diagnosis, including PD definitive diagnosis, PD suggestive diagnosis, secondary parkinsonism, and PD medications (see Appendix 9 for all related Read codes). After extracting these codes, all patients' PSALFs were defined in order to identify exactly the patients with a definitive PD diagnosis. Figure 5-1 shows the steps that were followed to identify the study cohort.

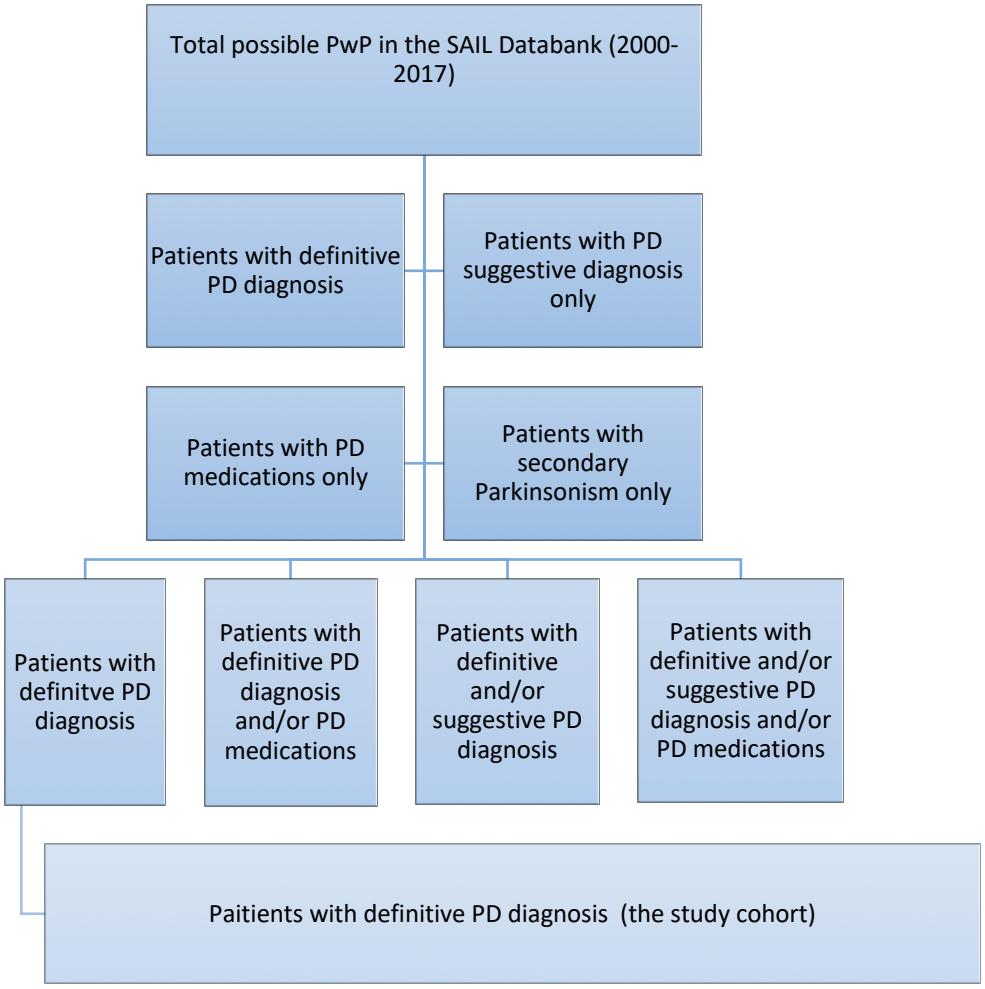


Figure 5-1- Steps of building the study cohort

After defining all PwP with a definitive PD diagnosis, additional exclusion criteria were applied. All patients with a PD diagnosis before 1/1/2000 were excluded from the study cohort. However, when calculating the prevalence of PD in any single year, all patients with a definitive PD diagnosis were included regardless of whether or not they were diagnosed before 1/1/2000. Furthermore, all patients who were diagnosed before the age of 40 were excluded, since PD risk is very low in this group of patients and they might have other diseases that are mistakenly diagnosed as PD. Patients who were on antipsychotics within one year before PD diagnosis were excluded because antipsychotics are well known to cause extrapyramidal symptoms, which could be mistakenly diagnosed as PD (see Appendix 9 for all related Read codes). Except for prevalence calculations,

exclusion criteria also included all patients who had their first PD diagnosis within six months of their SAIL registration in order to avoid considering prevalence cases as incidence cases (Figure 5-2).

Upon investigating the registration dates of PwP in SAIL, some patients' first record of PD (date of diagnosis) predated the registration date in SAIL. There was no way to find the reason for this phenomenon. However, in order to avoid underestimating the incidence cases, those cases were included in the study if they had not been prescribed any PD medication before the diagnosis date.

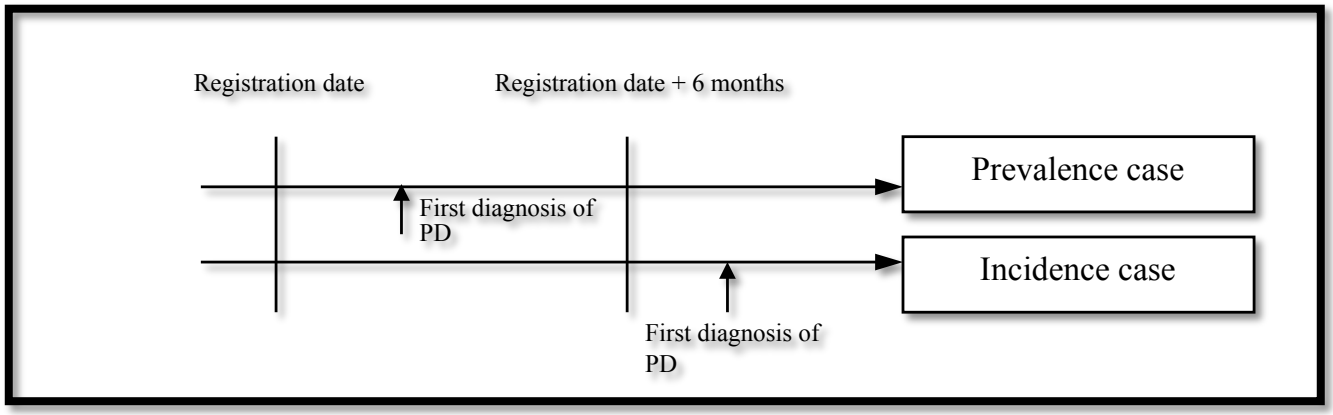


Figure 5-2 - Defining incidence and prevalence cases in the study

5.3.3 Describing the characteristics of the study cohort

The main demographic characteristics of PwP, such as age, social deprivation quintile, sex, and smoking status at the time of diagnosis, were quantified and tabulated. The age of PwP was calculated at the time of first recording of PD diagnosis in SAIL. The social deprivation quintile was extracted at the time of the first PD diagnosis by using the WIMD 2011 index, which is available in SAIL. The scores on the WIMD 2011 index were grouped into five deprivation quintiles which ranged from 1 (most deprived) to 5 (least deprived). The smoking status at the time of diagnosis was classified into three categories: never-smoker, ex-

smoker, and smoker. The Read codes for smoking status were obtained from a previously published article (365) (see Appendix 9 for the list of Read codes). To define the smoking status at the time of PD diagnosis, all GP events of smoking status that happened after the date of PD diagnosis were removed. Then, if there was a GP event which related to smoking status at the same date as PD diagnosis, then this GP event was considered as the smoking status of the patient. Otherwise, the closest GP event date before the time of PD diagnosis was considered as the patient's smoking status.

Furthermore, the number of patients' comorbidities at the time of PD diagnosis was calculated using the components of the Charlson comorbidities index. This was done by using hospital admission data up to two years prior to the diagnosis date.

5.3.4 Definition of study variables (exposure and outcome)

The exposure in this study was any record of PD definitive diagnosis in the SAIL Databank during the study period (2000-2017). The outcomes were the incidence and prevalence of PD in Wales between 2000 and 2017.

5.3.5 Calculating the overall incidence rate of PD

The overall incidence rate of PD was calculated for all years of the study (2000-2017). The study population was restricted to patients aged 40 years or older. The incidence cases were defined by having the first record of PD definitive diagnosis recorded in SAIL on or after January 1st of the year. The denominator was the total person years at risk (PYAR) of follow-up for all living patients who registered at SAIL during the calendar year. The whole observation period for this population started from the earlier of the patient's first registration date or

1st January of the year of interest. This observation period finished on whichever of the following dates was the latest: the last GP practice collection date, the date of patient transfer out, date of death, 31 December of the year of interest, or time of PD diagnosis. The incidence rate was calculated by dividing the total number of new PD cases in a calendar year by the total person years (PYAR) in the same calendar year multiplied by 100,000, as in the following equation:

Incidence rate =

$$\frac{\text{Number of new cases of PD}}{\text{Total person years in the year of interest}} \times 100{,}000$$

The incidence per 100,000 person years and the 95% confidence interval were calculated assuming a Poisson distribution.

5.3.6 Calculating the incidence rate of PD stratified by age, sex, social deprivation, and calendar year

The crude incidence rate of PD was stratified by age at the time of diagnosis, sex, social deprivation level (WIMD quintile), and each calendar year. The age at the time of diagnosis was classified into six categorical groups: 40-50 years, 51-60 years, 61-70 years, 71-80 years, 81-90 years, and 91 years and older. Sex was classified into males and females. The social deprivation scores were grouped into five quintiles. The calendar years were the years of the study (from 2000 to 2017). For each group, the new PD incidence cases were considered as the numerator, while the denominator was the total person years contributed by this group of the population in SAIL. The incidence rate was calculated by dividing the total number of new PD cases in every group by the total person years (PYAR) in the same group multiplied by 100,000, as in the following equation: Incidence rate = $\frac{\text{Number of new cases of PD in the group}}{\text{Total person years contributed by the group}} \times 100{,}000$

Poisson regression with robust error variance was used to calculate adjusted incidence rate ratios (IRRs) with 95% confidence intervals. The Wald test was used to calculate the associated p-values. Offset was corrected by considering the logarithm of the total person years of follow-up as an offset variable in the regression model. Reference categories chosen for each variable were: age (91 years and older), sex (female), social deprivation (WIMD fifth quintile), and calendar year (2000).

5.3.7 Calculating the overall prevalence rate of PD

A repeated cross-sectional design was used to calculate the prevalence of PD in every year of the study. Prevalence cases were defined as patients with a definitive diagnosis of PD from the first date of diagnosis onward. For every calendar year, the prevalence cases were defined by patients who were alive and registered in a SAIL practice and who had the Read code of interest recorded in SAIL on or before 31 December of the year. The prevalence was calculated by dividing the total number of PD cases in the year of interest by the total mid-year population aged 40 years or older and registered in SAIL on the first of July of the same year, as in the following equation:

Prevalence =

$$\frac{\text{Number of all cases of PD in the year of interest}}{\text{Total mid} - \text{year population aged 40 years or older in the same year}} \times 100{,}000$$

The difference in prevalence across the years of the study (2000-2017) was tested using the Poisson regression test. The 95% confidence intervals were calculated. P-value was calculated using the Wald test.

5.3.8 Calculating the prevalence rate of PD stratified by age and sex

A repeated cross-sectional design was used to calculate the prevalence of PD stratified by age and sex in every year of the study. For each group, all PD prevalence cases in a calendar year were considered as the numerator, while the denominator was the total mid-year population of this group in SAIL on the first of July of the same year. The prevalence was calculated by dividing the total number of PD cases in every group by the total mid-year population of the same group multiplied by 100,000, as in the following equation:

$$\frac{\text{Number of all cases of PD in the group}}{\text{Total mid} - \text{year population of the same group}} \times 100{,}000$$

Poisson regression was used to examine the difference in prevalence among different age and sex categories across the years of the study.

5.4 Results

5.4.1 Study cohort

The total number of possible PwP registered in the SAIL Databank between 2000 and 2017 was 43,225 (Figure 5-3). This number included patients with a definitive PD diagnosis, a PD suggestive diagnosis, PD medications, and secondary parkinsonism.

After screening patients' files and excluding all Read codes except for PD definitive diagnosis codes, 14,139 patients (the study cohort) were identified to have Read codes of PD definitive diagnosis (Figure 5-3). After excluding patients diagnosed before 2000 (n = 3059), patients diagnosed before the age of 40 (n = 15), patients on antipsychotics within one year before PD diagnosis (n = 24), and patients diagnosed within 6 months from SAIL registration date (n = 397), the total number of incidence cases of PD definitive diagnosis was 10,644 patients (Figure 5-3).

There were some patients who had a first record of PD (date of diagnosis) before the registration date in SAIL (n = 1,608). They have been included in the study because none of them had a record of PD prescriptions before the diagnosis date.

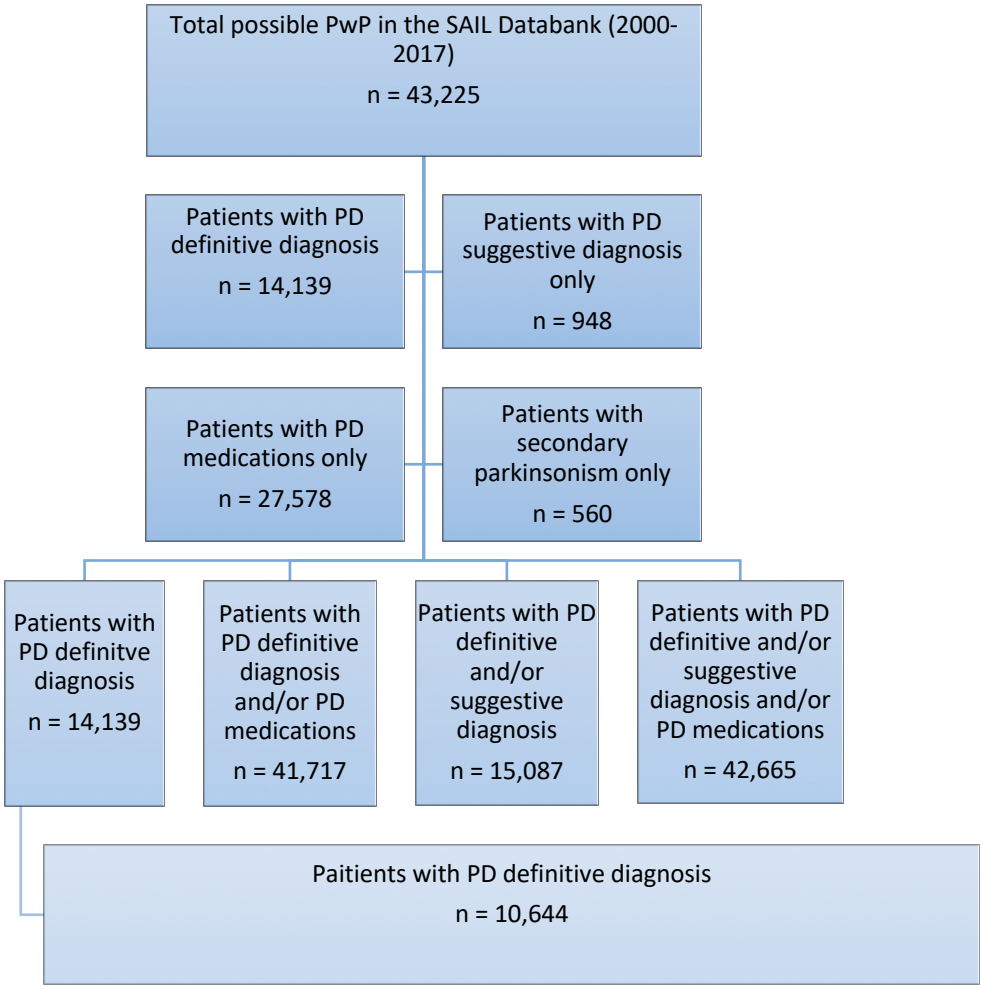


Figure 5-3- Summary of extracting PwP from SAIL Databank

5.4.2 Characteristics of the study cohort

The study cohort included a total of 10,644 PwP, of whom 6,226 (58.5%) were males (Table 5-4). The mean age at the time of first record of PD was 73.52 years (maximum = 106 years, minimum = 40 years, SD = 9.8). The most frequent age category in the cohort was the age category of 71-80 years (40.1%). The age categories of 61-70 years and 81-90 years roughly equally shared the second

most common age category in the cohort (23.9% for the former and 23.6% for the latter).

The social deprivation data (WIMD quintiles) revealed that 41.6% of newly diagnosed PwP were above the third quintile (Table 5-4). In terms of comorbidities at the time of first diagnosis, 78.5% of PwP had no records of any comorbidity in their hospital data in the previous two years that preceded the PD first diagnosis. Within the study cohort, diabetes represented the most common comorbidity (7.4%), followed by pulmonary diseases (6%). Regarding smoking status, a large portion of the study cohort (41.6 %) were ex-smokers at the time of first PD diagnosis. The majority of the study cohort (44.1%) had no information in the GP data about patients' smoking status.

Characteristics	No. of PwP (%) n = 10,644
Age at first record of PD (years)	
40-50	229 (2.2)
51-60	891 (8.4)
61-70	2,547 (23.9)
71-80	4,271 (40.1)
81-90	2,514 (23.6)
>90	192 (1.8)
Sex	
Males	6,226 (58.5)
Females	4,418 (41.5)
Welsh Index of Multiple Deprivation (WIMD) quintile	
1 (most deprived)	1,826 (17.2)
2	2,007 (18.9)
3	2,388 (22.4)
4	2,095 (19.7)
5 (least deprived)	2,328 (21.9)
Co-morbidities and other disorders	
Diabetes	787 (7.4)
Pulmonary disease	636 (6.0)
Cerebral vascular accident	424 (4)
Acute myocardial infarction	387 (3.6)
Dementia	343 (3.2)
Congestive heart failure	250 (2.3)
Renal disease	199 (1.9)
Cancer	185 (1.7)
Peripheral vascular disease	136 (1.3)
Connective tissue disorder	110 (1.0)
Paraplegia	85 (0.8)
Diabetes complications	75 (0.7)
Peptic ulcer	45 (0.4)
Metastatic cancer	39 (0.4)
Liver disease	14 (0.1)
Severe liver disease	6 (0.1)
Number of co-morbidities at the time of first PD record	
0	8,354 (78.5)
1	1,373 (12.9)
2	575 (5.4)
3	225 (2.1)
4	72 (0.7)
>4	42 (0.4)
Smoking status at the time of first PD record	
Never-smoker	0 (0)
Ex-smoker	4,429 (41.6)
Smoker	1,521 (14.3)
No information	4,694 (44.1)

Table 5-4 - Characteristics of newly diagnosed PwP (n = 10,644)

5.4.3 Overall incidence rate of PD

After analysing 17,485,834 single person-years during 2000-2017, the incidence rate ranged from 54.74 to 68.04 per 100,000 person years across the study period. The overall incidence rate of PD in patients who were 40 years of age or older in Wales between 2000 and 2017 was 60.87 per 10,000 person years of the SAIL population (Table 5-5).

5.4.4 Incidence rate of PD stratified by age, sex, social deprivation, and calendar year

Generally, the age categories of 81-90 years and 71-80 years possessed the highest incidence rates of PD, which were 205.65 per 100,000 person years for the former and 155.16 per 100,000 person years for the latter in the whole study period (Table 5-5). The incidence rate decreased dramatically in patients older than 90 years (99.24 per 100,000 person year); however, it was still higher than the incidence rates for the 40-50 year and 51-60 year age categories (Table 5-5). The same effect of age on incidence rates was seen in both males and females, as shown in Figure 5-4. Poisson regression results showed that the incidence rates in patients aged 40-50 years and 51-60 years were significantly lower than the incidence rate in patients older than 90 years (reference group) in all years of the study (IRR ranged from 0.01 to 0.08 in the 40-50 year age category; and IRR ranged from 0.04 to 0.18 in the 51-60 year age category) (Tables 5-6 and 5-7). A significantly lower incidence rate of PD was also seen, albeit to a lesser extent and not in all years of the study, in patients aged 61-70 years compared to patients older than 90 years (IRR ranged from 0.18 to 0.71) (Tables 5-6 and 5-7). There was no significant difference in incidence rates between patients aged 71-80 years and patients older than 90 years in all years of the study. There was a significantly higher incidence rate in patients aged 81-90 years compared to the

reference group in only four years of the study, namely 2000, 2005, 2007 and 2016 (IRR ranged from 1.19 to 3.06) (Tables 5-6 and 5-7).

Regarding sex, the incidence rate in males was 73.7 per 100,000 person years in all years of the study, while females had a lower incidence rate (i.e., 48.88 per 100,000 person years) (Table 5-6). Poisson regression results showed that over all years of the study, males had a significantly higher incidence rate of PD compared to females (IRR = 1.50, 95%CI 1.44-1.57). The significantly higher incidence rate in males was also seen in every individual year of the study. Tables 5-6 and 5-7 showed that incidence rates of PD in males were significantly higher in every calendar year (IRR ranged from 1.53 to 2.72).

In terms of social deprivation status, the incidence rates of PD were not hugely different between different WIMD quintiles. The incidence rate of PD in the first quintile (most deprived) was 54.16 per 100,000 person years, while the fifth quintile had an incidence rate of 63.72 per 100,000 person years (Table 5-5). Although the results of the Poisson regression in every individual year of the study showed no significant difference in incidence rates between different quintiles except for two years (i.e., 2000 and 2016) (Tables 5-6 and 5-7), the incidence rate of PD in all the years collectively was significantly lower in the most deprived quintile compared to the least deprived quintile (IRR = 0.82, 95%CI 0.77-0.87).

		Number of cases	Person years (PYAR)	Incidence rate per 100,000 person year (95 % CI)
Age				
All 40+	All	10,644	17,485,833.66	60.87 (59.72-62.03)
40-50	All	204	4,890,892.91	4.17 (3.62-4.78)
	Males	147	2,478,834.70	5.93 (5.01-6.97)
	Females	57	2,412,057.71	2.36 (1.79-3.06)
51-60	All	827	4,445,949.41	18.6 (17.35-19.91)
	Males	539	2,230,457.38	24.17 (22.17-26.29)
	Females	288	2,215,492.04	13 (11.54-14.59)
61-70	All	2450	3,879,947.22	63.15 (60.67-65.7)
	Males	1545	1,913,047.70	80.76 (76.78-84.89)
	Females	905	1,966,893.52	46.01 (43.06-49.11)
71-80	All	4216	2,717,174.22	155.16 (150.51-159.92)
	Males	2435	1,258,152.58	193.54 (185.93-201.38)
	Females	1781	1,459,021.60	122.07 (116.46-127.87)
81-90	All	2719	1,322,121.12	205.65 (198-213.53)
	Males	1467	507,822.48	288.88 (274.29-304.05)
	Females	1252	814,298.64	153.75 (145.35-162.51)
>90	All	228	229,748.78	99.24 (86.77-112.99)
	Males	93	59,703.83823	155.77 (125.73-190.83)
	Females	135	170,044.9374	79.39 (66.56-93.97)
Sex				
Males		6226	8,448,018.68	73.70 (71.87-75.55)
Females		4418	9,037,808.44	48.88 (47.45-50.34)
Welsh Index of Multiple Deprivation (WIMD) quintile				
1 (most deprived)		1826	3,371,315.82	54.16 (51.71-56.71)
2		2007	3,426,516.36	58.57 (56.04-61.19)
3		2388	3,719,226.16	64.21 (61.66-66.83)
4		2095	3,315,139.80	63.19 (60.52-65.96)
5 (least deprived)		2328	3,653,635.53	63.72 (61.16-66.36)

Table 5-5- Incidence rate of PD per 100,000 person years (2000-2017)

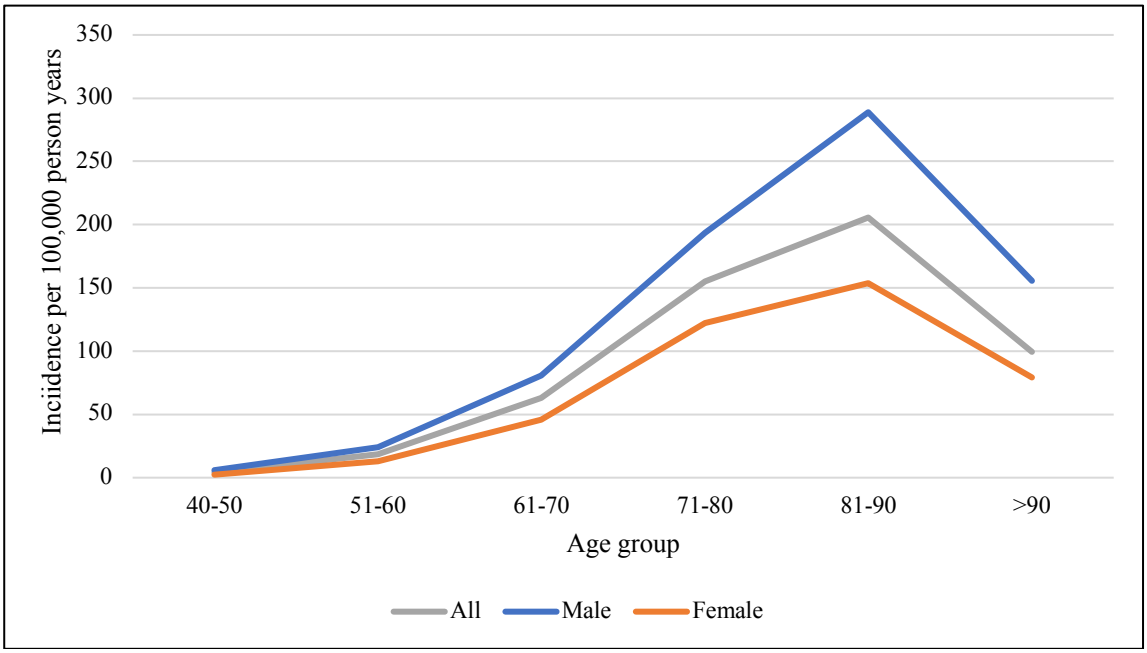


Figure 5-4- Age and sex-specific incidence of PD (per 100,000 person years)

Year	2000			2001			2002			2003			2004			2005			2006			2007			2008		
	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value
Age																											
Age 40-50	0.04	0.01-0.14	<0.0001	0.02	0.01-0.05	<0.0001	0.01	0-0.05	<0.0001	0.00	0-0.02	<0.0001	0.02	0.01-0.05	<0.0001	0.01	0-0.04	<0.0001	0.01	0-0.03	<0.0001	0.02	0.01-0.07	<0.0001	0.01	0-0.03	<0.0001
Age 51-60	0.14	0.05-0.37	<0.0001	0.08	0.04-0.17	<0.0001	0.11	0.05-0.24	<0.0001	0.06	0.03-0.11	<0.0001	0.08	0.04-0.17	<0.0001	0.08	0.04-0.17	<0.0001	0.07	0.03-0.13	<0.0001	0.07	0.03-0.16	<0.0001	0.07	0.04-0.15	<0.0001
Age 61-70	0.77	0.31-1.91	0.577	0.39	0.19-0.78	0.008	0.43	0.21-0.86	0.017	0.26	0.15-0.44	<0.0001	0.33	0.18-0.6	<0.0001	0.39	0.2-0.77	0.006	0.25	0.14-0.45	<0.0001	0.34	0.16-0.71	0.004	0.26	0.14-0.48	<0.0001
Age 71-80	1.84	0.75-4.49	0.183	0.98	0.5-1.92	0.942	1.42	0.73-2.78	0.305	0.84	0.51-1.39	0.505	1.16	0.65-2.08	0.618	1.21	0.64-2.3	0.559	0.95	0.54-1.67	0.853	1.25	0.61-2.55	0.542	0.94	0.52-1.69	0.826
Age 81-90	3.06	1.24-7.52	0.015	1.73	0.87-3.42	0.118	1.94	0.98-3.83	0.057	1.16	0.7-1.93	0.558	1.62	0.89-2.93	0.112	1.92	1.01-3.67	0.047	1.19	0.67-2.13	0.547	2.13	1.04-4.37	0.039	1.28	0.7-2.32	0.427
Age >90	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
Sex																											
Male	1.75	1.41-2.17	<0.0001	1.91	1.53-2.38	<0.0001	1.53	1.26-1.87	<0.0001	1.70	1.41-2.06	<0.0001	1.88	1.55-2.28	<0.0001	1.58	1.29-1.93	<0.0001	1.77	1.44-2.17	<0.0001	2.03	1.63-2.53	<0.0001	1.66	1.34-2.05	<0.0001
Female	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
WIMD																											
1 (most deprived)	0.81	0.59-1.1	0.173	0.83	0.58-1.18	0.296	1.05	0.77-1.44	0.753	0.95	0.7-1.3	0.744	1.00	0.74-1.37	0.978	1.11	0.8-1.53	0.526	0.95	0.69-1.31	0.766	0.88	0.62-1.24	0.452	0.84	0.6-1.17	0.305
2	0.51	0.35-0.72	<0.0001	0.94	0.67-1.31	0.702	1.11	0.81-1.5	0.524	1.10	0.82-1.48	0.525	1.04	0.77-1.4	0.818	1.14	0.83-1.56	0.407	0.85	0.62-1.18	0.334	0.98	0.7-1.36	0.902	0.80	0.57-1.11	0.176
3	0.73	0.54-1	0.046	1.08	0.79-1.49	0.629	0.92	0.67-1.25	0.584	1.07	0.8-1.44	0.627	1.15	0.86-1.53	0.337	1.05	0.77-1.43	0.775	0.98	0.72-1.32	0.888	0.97	0.71-1.34	0.870	1.06	0.78-1.42	0.722
4	0.67	0.49-0.93	0.017	0.91	0.65-1.28	0.602	1.01	0.74-1.38	0.960	1.16	0.86-1.55	0.336	1.04	0.77-1.4	0.806	1.08	0.79-1.49	0.632	0.88	0.64-1.21	0.431	0.99	0.71-1.37	0.933	0.85	0.61-1.17	0.315
5 (least deprived)	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	

Table 5-6- Summary of the outputs from multivariate Poisson regression to identify the effects of sex, age, and social deprivation on PD incidence over time (part 1)

*IRR: incidence rate ratio adjusted for all other variables, **Ref: reference, Red colour denotes p-values that are significant at an alpha level of 0.05.

Year	2009			2010			2011			2012			2013			2014			2015			2016			2017		
	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value
Age																											
Age 40-50	0.03	0.01-0.08	<0.0001	0.01	0-0.03	<0.0001	0.02	0.01-0.05	<0.0001	0.03	0.01-0.09	<0.0001	0.02	0.01-0.05	<0.0001	0.02	0-0.05	<0.0001	0.03	0.01-0.07	<0.0001	0.08	0.02-0.3	<0.0001	0.03	0.01-0.17	<0.0001
Age 51-60	0.04	0.02-0.1	<0.0001	0.06	0.03-0.13	<0.0001	0.05	0.03-0.11	<0.0001	0.07	0.03-0.19	<0.0001	0.09	0.05-0.18	<0.0001	0.10	0.04-0.21	<0.0001	0.10	0.05-0.2	<0.0001	0.18	0.06-0.54	0.002	0.12	0.04-0.38	<0.0001
Age 61-70	0.34	0.17-0.68	0.002	0.21	0.11-0.4	<0.0001	0.18	0.1-0.34	<0.0001	0.42	0.19-0.93	0.031	0.21	0.11-0.4	<0.0001	0.23	0.11-0.45	<0.0001	0.25	0.13-0.49	<0.0001	0.71	0.25-1.96	0.502	0.34	0.12-0.98	0.046
Age 71-80	1.09	0.56-2.15	0.796	0.80	0.44-1.45	0.467	0.73	0.41-1.29	0.272	0.99	0.46-2.13	0.975	0.68	0.37-1.24	0.208	0.78	0.41-1.51	0.467	0.84	0.45-1.57	0.585	1.38	0.5-3.8	0.531	1.39	0.51-3.83	0.522
Age 81-90	1.67	0.84-3.29	0.143	1.28	0.7-2.33	0.420	1.21	0.68-2.15	0.527	2.30	1.07-4.96	0.033	1.50	0.82-2.72	0.187	1.75	0.91-3.37	0.091	1.32	0.7-2.48	0.392	2.87	1.04-7.89	0.041	1.16	0.4-3.35	0.779
Age >90	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
Sex																											
Male	1.89	1.51-2.35	<0.0001	2.07	1.65-2.59	<0.0001	2.37	1.87-3	<0.0001	1.71	1.35-2.18	<0.0001	2.42	1.9-3.09	<0.0001	2.19	1.7-2.82	<0.0001	2.09	1.63-2.68	<0.0001	2.72	2.01-3.67	<0.0001	2.54	1.74-3.71	<0.0001
Female	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
WIMD																											
1 (most deprived)	1.09	0.78-1.54	0.607	1.16	0.83-1.62	0.397	1.20	0.84-1.71	0.329	1.05	0.71-1.56	0.807	1.31	0.91-1.88	0.152	1.11	0.75-1.65	0.600	0.80	0.54-1.21	0.292	1.00	0.63-1.59	0.993	1.00	0.57-1.74	0.986
2	0.94	0.66-1.33	0.713	0.85	0.59-1.21	0.366	1.02	0.71-1.47	0.925	1.37	0.95-1.97	0.091	1.11	0.77-1.61	0.578	1.14	0.78-1.68	0.496	1.07	0.74-1.55	0.715	0.89	0.55-1.43	0.620	0.98	0.57-1.71	0.955
3	1.08	0.78-1.5	0.643	1.01	0.73-1.41	0.942	1.18	0.84-1.66	0.335	1.14	0.79-1.64	0.499	1.24	0.87-1.76	0.238	1.13	0.78-1.64	0.529	0.98	0.68-1.41	0.918	1.11	0.72-1.7	0.649	0.92	0.54-1.58	0.758
4	1.07	0.77-1.5	0.688	1.08	0.77-1.51	0.669	1.09	0.77-1.56	0.621	1.17	0.8-1.7	0.424	1.08	0.74-1.57	0.691	1.16	0.8-1.7	0.433	1.17	0.82-1.67	0.394	1.61	1.08-2.42	0.021	1.07	0.63-1.82	0.815
5 (least deprived)	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	

Table 5-7- Summary of the outputs from multivariate Poisson regression to identify the effect of sex, age, and social deprivation on PD incidence over time (part 2)

*IRR: incidence rate ratio adjusted for all other variables, **Ref: reference, Red colour denotes p-values that are significant at an alpha level of 0.05.

Figure 5-5 shows the overall incidence rates of PD in every calendar year of the study (2000-2017). The incidence rate ranged from 54.73 to 68.04 per 100,000 person years across the years of the study. Figure 5-5 also shows the sex-stratified incidence rate across the years of the study. The male incidence rate ranged from 65.23 to 82.86 per 100,000 person years, while the female incidence rate ranged from 40.54 to 61.66 per 100,000 person years across the years of the study.

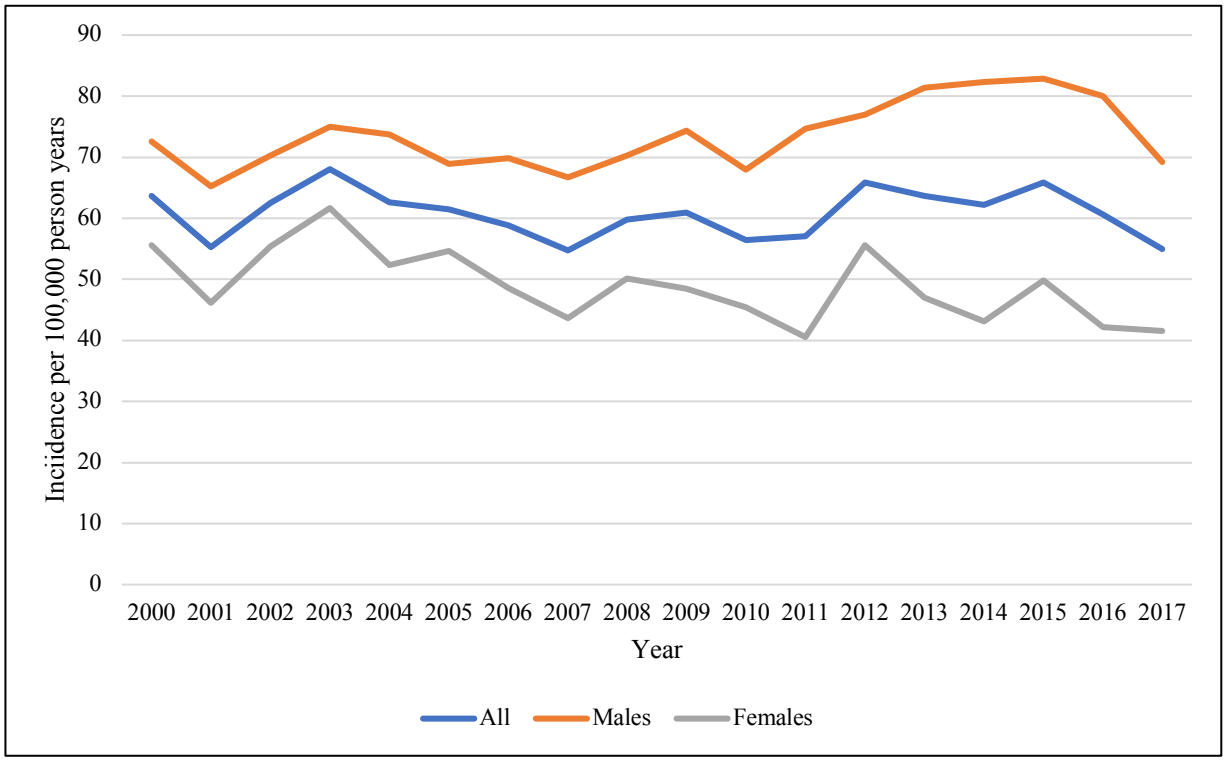


Figure 5-5 - Incidence rate of PD per 100,000 person years across the years of the study

The results of the Poisson regression showed that the incidence rate did not differ significantly between the reference group (calendar year of 2000) and the majority of years of the study period. Table 5-8 shows the difference in incidence rates of PD between calendar years in the whole cohort and stratified by age and sex. There were no significant differences in the incidence rates of PD in the

whole cohort between the reference group and 14 years from the study period. However, compared to 2000, the incidence rates in 2003 and 2015 were significantly higher (IRR = 1.21, 95%CI 1.07-1.36 for 2003; and IRR = 1.13, 95%CI 1.01-1.27 for 2015). The incidence rates of PD were significantly lower in 2017 compared to 2000 in the whole cohort and in all age and sex stratified groups except for the age categories of 71-80 years and older than 90 years (Table 5-8). In all age and sex stratified groups, there were no statistically significant differences between the incidence rate in 2000 and the majority of subsequent years (up to 2016). Among the few examples which showed statistically significant differences in incidence rates, these differences were inconsistent and varied in terms of their IRR value (higher or lower than 1). The incidence rate in patients older than 90 years did not differ significantly between 2000 and all subsequent years (up to 2017) (Table 5-8).

	All			Male			Female			Age 40--50			Age 51-60			Age 61-70			Age 71-80			Age 81-90			Age >90		
Year	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value	IRR*	95% CI	p-value
2000	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
2001	0.9	0.79-1.02	0.100	0.93	0.79-1.1	0.41	0.86	0.71-1.04	0.119	0.55	0.18-1.63	0.278	0.91	0.59-1.39	0.659	0.83	0.64-1.07	0.148	0.91	0.74-1.12	0.372	0.93	0.72-1.2	0.583	1.49	0.58-3.83	0.414
2002	1.07	0.95-1.21	0.250	1.06	0.9-1.25	0.502	1.09	0.91-1.3	0.341	1.73	0.75-4	0.200	0.93	0.61-1.41	0.731	0.87	0.68-1.12	0.276	1.24	1.02-1.49	0.028	1.04	0.81-1.33	0.773	1.28	0.49-3.37	0.615
2003	1.21	1.07-1.36	0.002	1.17	0.99-1.37	0.060	1.26	1.06-1.49	0.009	0.84	0.32-2.17	0.712	1.26	0.85-1.86	0.253	0.97	0.76-1.23	0.782	1.36	1.13-1.63	0.001	1.18	0.93-1.5	0.174	2.32	0.97-5.51	0.057
2004	1.11	0.99-1.25	0.078	1.15	0.98-1.35	0.091	1.07	0.89-1.27	0.477	0.92	0.36-2.31	0.852	1.15	0.78-1.72	0.478	0.98	0.77-1.25	0.880	1.2	0.99-1.45	0.064	1.09	0.86-1.39	0.469	1.89	0.78-4.6	0.159
2005	1.09	0.97-1.23	0.153	1.07	0.91-1.26	0.414	1.11	0.93-1.32	0.237	0.89	0.36-2.25	0.812	1.21	0.82-1.8	0.333	0.95	0.75-1.21	0.666	1.14	0.94-1.38	0.194	1.13	0.89-1.44	0.301	1.5	0.6-3.76	0.386
2006	1.04	0.92-1.17	0.525	1.08	0.92-1.27	0.346	0.99	0.82-1.18	0.869	1.46	0.64-3.33	0.372	1	0.66-1.51	0.998	0.92	0.72-1.16	0.472	1.22	1.01-1.47	0.042	0.89	0.7-1.14	0.365	1.57	0.64-3.9	0.328
2007	0.97	0.86-1.09	0.572	1.03	0.88-1.21	0.739	0.88	0.74-1.06	0.189	1.25	0.53-2.91	0.612	0.84	0.55-1.28	0.413	0.79	0.61-1.01	0.056	1.08	0.89-1.31	0.428	1.01	0.79-1.28	0.944	0.99	0.37-2.65	0.978
2008	1.05	0.93-1.18	0.401	1.08	0.92-1.26	0.353	1.01	0.85-1.21	0.883	1.13	0.48-2.69	0.779	1.08	0.72-1.62	0.700	0.87	0.69-1.1	0.249	1.15	0.95-1.39	0.153	1.04	0.82-1.32	0.733	1.53	0.62-3.78	0.361
2009	1.07	0.95-1.2	0.273	1.14	0.97-1.33	0.111	0.98	0.82-1.17	0.798	1.68	0.76-3.75	0.202	0.87	0.57-1.34	0.534	0.91	0.72-1.15	0.436	1.26	1.05-1.52	0.016	0.95	0.74-1.21	0.671	1.07	0.41-2.81	0.890
2010	0.99	0.88-1.11	0.827	1.04	0.89-1.22	0.649	0.92	0.77-1.1	0.345	0.65	0.24-1.75	0.396	1.07	0.71-1.6	0.761	0.81	0.64-1.03	0.083	1.11	0.92-1.35	0.277	0.91	0.71-1.16	0.438	1.64	0.68-3.99	0.273
2011	1	0.89-1.13	0.987	1.14	0.98-1.33	0.096	0.82	0.68-0.99	0.035	1.4	0.61-3.19	0.430	0.89	0.58-1.35	0.577	0.8	0.63-1.02	0.067	1.14	0.94-1.37	0.192	0.95	0.75-1.21	0.685	1.4	0.57-3.43	0.464
2012	1.12	1-1.25	0.060	1.14	0.97-1.33	0.108	1.09	0.91-1.29	0.351	1.03	0.43-2.48	0.954	0.96	0.63-1.45	0.839	0.94	0.75-1.18	0.602	1.19	0.99-1.44	0.069	1.19	0.94-1.49	0.147	0.94	0.37-2.44	0.905
2013	1.1	0.98-1.23	0.115	1.22	1.05-1.43	0.010	0.93	0.78-1.12	0.453	0.66	0.25-1.77	0.408	1.1	0.74-1.64	0.629	0.84	0.66-1.06	0.139	1.2	1-1.45	0.052	1.1	0.87-1.39	0.429	1.85	0.79-4.33	0.157
2014	1.07	0.95-1.2	0.272	1.23	1.06-1.44	0.008	0.85	0.71-1.03	0.091	0.57	0.2-1.61	0.292	0.96	0.64-1.45	0.853	0.88	0.7-1.11	0.291	1.1	0.91-1.33	0.303	1.15	0.91-1.45	0.248	0.97	0.38-2.45	0.939
2015	1.13	1.01-1.27	0.038	1.24	1.06-1.44	0.006	0.99	0.83-1.18	0.872	2.05	0.94-4.48	0.071	0.82	0.54-1.26	0.367	0.92	0.73-1.16	0.502	1.16	0.97-1.4	0.113	1.15	0.92-1.45	0.227	1.13	0.45-2.79	0.800
2016	1.05	0.93-1.18	0.420	1.15	0.99-1.34	0.070	0.88	0.74-1.06	0.181	1.5	0.66-3.43	0.334	0.83	0.54-1.26	0.377	0.86	0.68-1.09	0.212	1.18	0.98-1.42	0.080	0.93	0.73-1.18	0.540	0.73	0.27-1.95	0.526
2017	0.72	0.63-0.82	<0.0001	0.79	0.67-0.93	0.006	0.63	0.51-0.76	<0.0001	1.03	0.42-2.54	0.947	0.42	0.25-0.7	0.001	0.45	0.34-0.59	<0.0001	0.95	0.78-1.15	0.564	0.6	0.46-0.78	<0.0001	0.49	0.17-1.47	0.204

Table 5-8- Summary of the outputs from univariate Poisson regression to identify the effect of calendar year on PD incidence

*IRR: incidence rate ratio, **Ref: reference, Red colour denotes p-values that are significant at an alpha level of 0.05

5.4.5 Overall prevalence rate of PD

The overall prevalence rate of PD in patients who were aged 40 or older in Wales increased from 319.45 per 100,000 population in 2000 to 370.05 per 100,000 population in 2016. The prevalence of PD dropped slightly in 2017 (350.64 per 100,000 population) (Table 5-9).

	Number of cases	Population (40 years or older)	Prevalence rate per 100,000 population (95 % CI)
Year			
2000	3,562	1,115,047	319.45 (309.04-330.11)
2001	3,626	1,136,369	319.09 (308.78-329.64)
2002	3,780	1,158,759	326.21 (315.89-336.78)
2003	4,011	1,180,617	339.74 (329.3-350.42)
2004	4,159	1,203,725	345.51 (335.09-356.17)
2005	4,298	1,224,107	351.11 (340.69-361.77)
2006	4,376	1,243,323	351.96 (341.61-362.55)
2007	4,444	1,260,166	352.65 (342.36-363.18)
2008	4,558	1,276,955	356.94 (346.65-367.46)
2009	4,661	1,291,099	361.01 (350.72-371.53)
2010	4,721	1,302,967	362.33 (352.06-372.81)
2011	4,790	1,313,260	364.74 (354.48-375.22)
2012	4,917	1,325,171	371.05 (360.75-381.57)
2013	4,998	1,334,702	374.47 (364.16-384.99)
2014	5,083	1,343,543	378.33 (368-388.87)
2015	5,086	1,347,994	377.3 (367-387.82)
2016	4,988	1,347,942	370.05 (359.85-380.46)
2017	4,712	1,343,823	350.64 (340.7-360.8)

Table 5-9- Prevalence rates of PD in the whole cohort over the years of the study

The results of the Poisson regression showed that the prevalence rate differed significantly between the reference group (calendar year of 2000) and the majority of years of the study period. Table 5-10 shows the difference in

prevalence rates of PD between calendar years in the whole cohort. There were significant differences in the prevalence rates of PD in the whole cohort between the reference group and 15 years from the study period. For example, compared to the reference group, the prevalence rate of PD in 2003 was significantly higher (prevalence risk ratio (PRR) = 1.06, 95%CI 1.02-1.11). The prevalence rate was far higher in the later years, such as in 2016, where the PRR = 1.16 and the 95%CI = 1.11-1.21.

5.4.6 Prevalence rate of PD stratified by age and sex

Figure 5-6 shows the age-specific prevalence of PD per 100,000 population across the years of the study. In the age stratified groups (71-80 and 81-90), there were statistically significant increases in the prevalence rates between 2000 and the majority of subsequent years (up to 2017) (Table 5-10). In Table 5-10, it can be seen that the age categories of 40-50 and older than 90 years showed a significant decrease in prevalence rate between 2000 and some of the subsequent years.

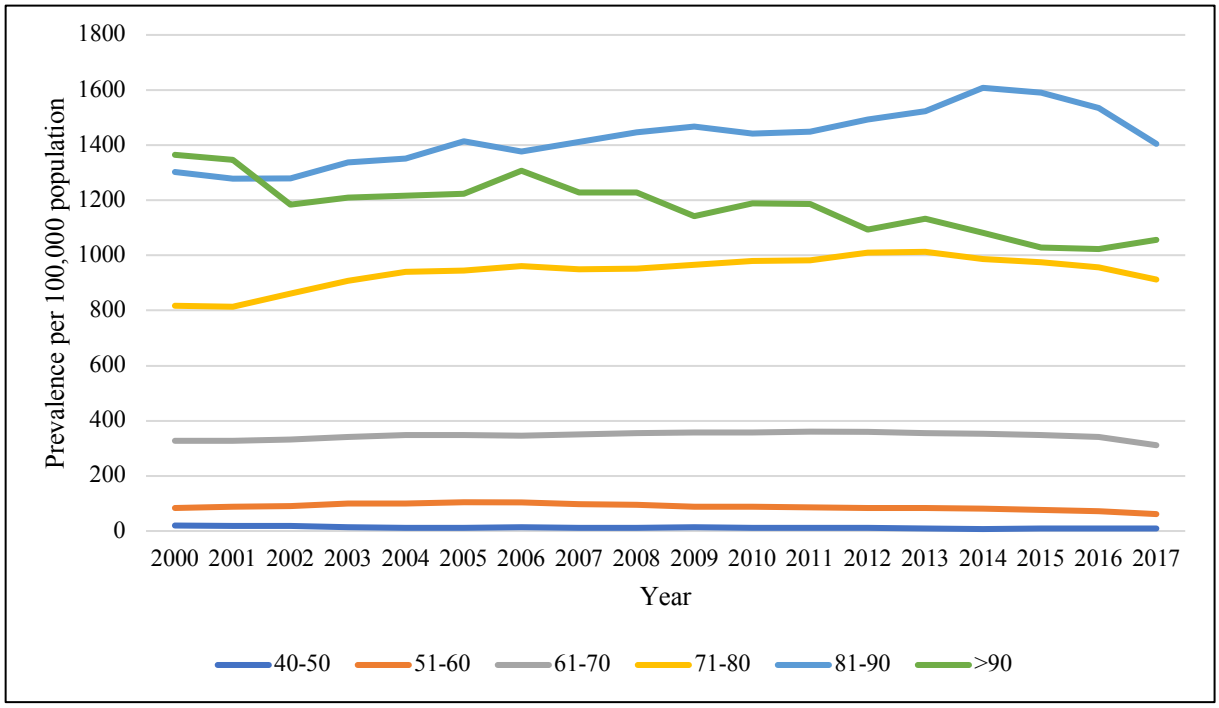


Figure 5-6- Age-specific prevalence of PD per 100,000 population

Figure 5-7 shows the sex-specific prevalence of PD per 100,000 population across the years of the study. The prevalence of PD in males increased from 342.4 per 100,000 population in 2000 to 427.08 per 100,000 population in 2017. This increase in prevalence was absent in females. A relatively stable prevalence rate was seen in females that ranged from 298.74 per 100,000 population to 277.67 per 100,000 population in 2017 (Figure 5-7). This increase in prevalence in males was statistically significant, according to the Poisson regression results. For example, compared to 2000, the prevalence rate of PD in 2017 was statistically higher (PRR = 1.25, 95%CI 1.18-1.32) in males. In females, there was no statistically significant increase or decrease in the prevalence rate of PD across the years of the study (Table 5-10).

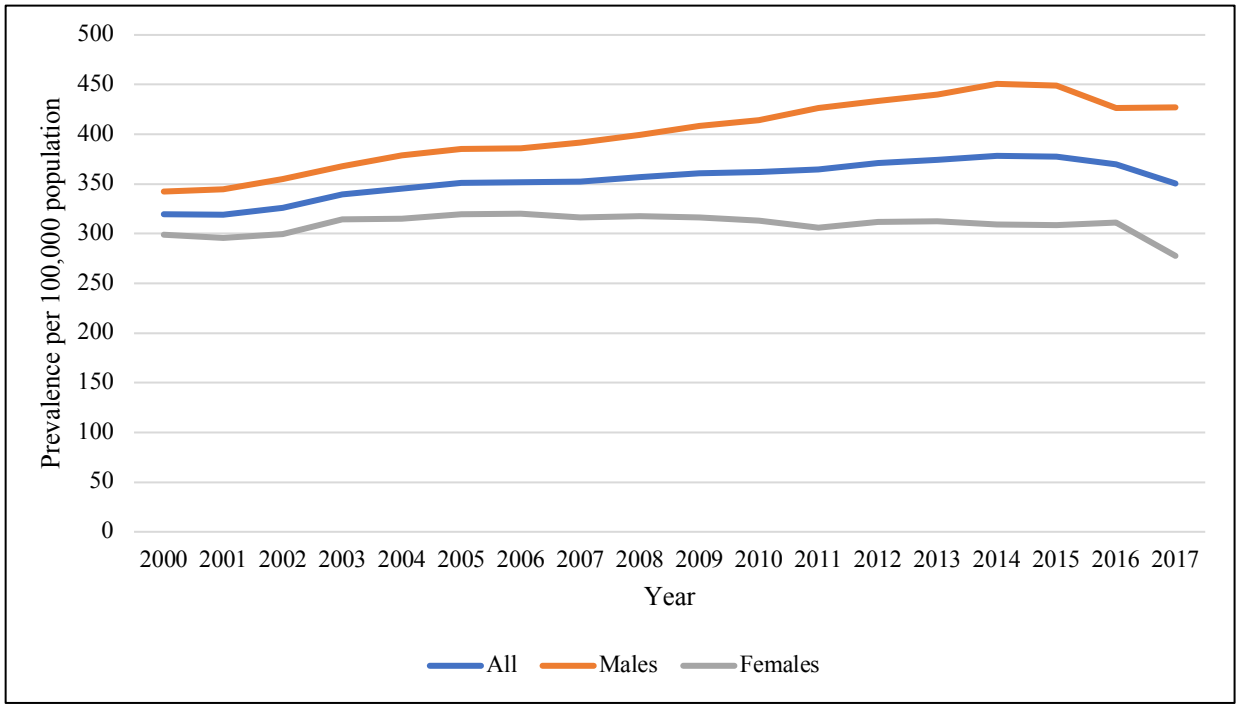


Figure 5-7- Sex-specific prevalence of PD per 100,000 population

	All			Male			Female			Age 40--50			Age 51-60			Age 61-70			Age 71-80			Age 81-90			Age >90		
Year	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	PRR*	95% CI	p-value	IRR*	95% CI	p-value
2000	1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**		1.00	Ref**	
2001	1.00	0.95-1.05	0.962	1.01	0.94-1.07	0.836	0.99	0.93-1.06	0.767	0.91	0.65-1.28	0.594	1.05	0.88-1.24	0.609	1.00	0.9-1.1	0.935	1.00	0.93-1.07	0.909	0.98	0.9-1.07	0.670	0.99	0.79-1.23	0.91
2002	1.02	0.98-1.07	0.370	1.04	0.97-1.11	0.267	1.00	0.94-1.07	0.908	0.97	0.68-1.37	0.839	1.07	0.9-1.27	0.465	1.01	0.91-1.12	0.812	1.05	0.98-1.13	0.151	0.98	0.9-1.07	0.691	0.87	0.69-1.09	0.215
2003	1.06	1.02-1.11	0.007	1.07	1.01-1.14	0.027	1.05	0.99-1.12	0.128	0.65	0.45-0.94	0.023	1.19	1-1.4	0.044	1.04	0.94-1.15	0.446	1.11	1.03-1.19	0.004	1.03	0.94-1.12	0.563	0.89	0.71-1.11	0.283
2004	1.08	1.03-1.13	0.001	1.11	1.04-1.18	0.002	1.05	0.99-1.12	0.107	0.62	0.43-0.9	0.012	1.19	1.01-1.41	0.038	1.06	0.96-1.17	0.257	1.15	1.07-1.24	<0.0001	1.04	0.95-1.13	0.415	0.89	0.72-1.11	0.301
2005	1.10	1.05-1.15	<0.0001	1.12	1.06-1.2	<0.0001	1.07	1-1.14	0.037	0.61	0.42-0.88	0.008	1.23	1.04-1.45	0.014	1.06	0.96-1.17	0.242	1.16	1.08-1.24	<0.0001	1.08	1-1.18	0.063	0.90	0.72-1.11	0.321
2006	1.10	1.05-1.15	<0.0001	1.13	1.06-1.2	<0.0001	1.07	1.01-1.14	0.033	0.66	0.46-0.94	0.023	1.23	1.05-1.45	0.013	1.06	0.96-1.16	0.289	1.18	1.1-1.26	<0.0001	1.06	0.97-1.15	0.210	0.96	0.78-1.18	0.689
2007	1.11	1.06-1.15	<0.0001	1.14	1.08-1.22	<0.0001	1.06	0.99-1.13	0.079	0.62	0.43-0.9	0.011	1.15	0.97-1.36	0.108	1.07	0.97-1.18	0.170	1.16	1.08-1.25	<0.0001	1.08	1-1.18	0.062	0.90	0.73-1.11	0.332
2008	1.12	1.07-1.17	<0.0001	1.17	1.1-1.24	<0.0001	1.06	1-1.13	0.062	0.60	0.41-0.87	0.007	1.12	0.95-1.33	0.178	1.08	0.98-1.19	0.110	1.17	1.09-1.25	<0.0001	1.11	1.02-1.21	0.014	0.90	0.73-1.12	0.336
2009	1.13	1.08-1.18	<0.0001	1.19	1.12-1.27	<0.0001	1.06	1-1.13	0.072	0.72	0.51-1.02	0.064	1.05	0.88-1.24	0.594	1.09	0.99-1.2	0.066	1.18	1.1-1.27	<0.0001	1.13	1.04-1.22	0.005	0.84	0.67-1.04	0.105
2010	1.13	1.09-1.19	<0.0001	1.21	1.14-1.29	<0.0001	1.05	0.98-1.12	0.146	0.62	0.43-0.89	0.009	1.04	0.87-1.23	0.688	1.09	0.99-1.2	0.078	1.20	1.12-1.29	<0.0001	1.11	1.02-1.2	0.017	0.87	0.71-1.08	0.201
2011	1.14	1.09-1.19	<0.0001	1.25	1.17-1.32	<0.0001	1.03	0.96-1.09	0.451	0.62	0.43-0.89	0.009	1.02	0.86-1.22	0.796	1.10	1-1.21	0.049	1.20	1.12-1.29	<0.0001	1.11	1.02-1.21	0.013	0.87	0.71-1.07	0.189
2012	1.16	1.11-1.21	<0.0001	1.27	1.19-1.34	<0.0001	1.04	0.98-1.11	0.186	0.58	0.4-0.84	0.004	0.98	0.82-1.17	0.814	1.10	1-1.21	0.051	1.24	1.15-1.32	<0.0001	1.15	1.06-1.24	0.001	0.80	0.65-0.99	0.036
2013	1.17	1.12-1.22	<0.0001	1.29	1.21-1.36	<0.0001	1.05	0.98-1.11	0.170	0.42	0.28-0.64	<0.0001	0.98	0.82-1.16	0.808	1.09	0.99-1.19	0.088	1.24	1.16-1.33	<0.0001	1.17	1.08-1.27	<0.0001	0.83	0.68-1.02	0.074
2014	1.18	1.14-1.24	<0.0001	1.32	1.24-1.4	<0.0001	1.04	0.97-1.1	0.271	0.35	0.23-0.55	<0.0001	0.96	0.81-1.14	0.618	1.08	0.98-1.18	0.124	1.21	1.13-1.29	<0.0001	1.23	1.14-1.34	<0.0001	0.79	0.65-0.97	0.027
2015	1.18	1.13-1.23	<0.0001	1.31	1.24-1.39	<0.0001	1.03	0.97-1.1	0.304	0.49	0.33-0.73	<0.0001	0.90	0.76-1.08	0.257	1.07	0.97-1.17	0.190	1.19	1.12-1.28	<0.0001	1.22	1.12-1.32	<0.0001	0.75	0.61-0.93	0.007
2016	1.16	1.11-1.21	<0.0001	1.25	1.18-1.32	<0.0001	1.04	0.98-1.11	0.220	0.48	0.32-0.72	<0.0001	0.84	0.7-1	0.053	1.04	0.95-1.14	0.423	1.17	1.1-1.25	<0.0001	1.18	1.09-1.28	<0.0001	0.75	0.61-0.92	0.007
2017	1.11	1.05-1.15	<0.0001	1.25	1.18-1.32	<0.0001	0.93	0.87-0.99	0.027	0.46	0.31-0.7	<0.0001	0.73	0.61-0.87	0.001	0.95	0.86-1.05	0.298	1.12	1.04-1.2	0.002	1.08	0.99-1.17	0.078	0.78	0.63-0.95	0.016

Table 5-10- Summary of the outputs from univariate Poisson regression to identify the effect of calendar year on PD prevalence

*PRR: prevalence risk ratio, **Ref: reference, Red colour denotes p-values that are significant at an alpha level of 0.05

5.5 Discussion

5.5.1 Summary of the main findings

The first aim of this study was to identify the number and characteristics of the study cohort (with a definitive PD diagnosis). The study cohort that was identified in this chapter (n = 10,644) will be used in the following chapters, which will deal with PD incidence cases in studying the prescribing patterns of PD medications.

This study is the first to use a large Welsh population database (SAIL) to estimate the incidence and prevalence of PD in Wales. The overall incidence rate of PD in Wales in this study was estimated to be 60.87 (95% CI 59.72-62.03) per 100,000 person years. The incidence rate across the years of the study ranged from 54.73 to 68.04 per 100,000 person years. The incidence of PD was significantly higher in males compared to females. The incidence of PD in this study was higher in the 71-80 and 81-90 year age categories. For the whole study period, the incidence of PD was significantly lower in the most deprived areas (quintile 1) compared to the least deprived areas (quintile 5). However, this difference in incidence rates between different deprivation quintiles mostly disappeared when the incidence rates were stratified by calendar year. This difference in the results might be due to the power of the study. Considering all years of the study in the analysis has resulted in a larger sample size compared to every individual year; this increased the power of the study and allowed for the detection of small differences that could not have been detected if the incidence in every individual year had been calculated.

The overall prevalence rate of PD in Wales between 2000 and 2016 increased by 15.83% (from 319.44 per 100,000 population in 2000 to 370.04 per 100,000 population in 2016). The increase in PD prevalence was present in

the 71-80 and 81-90 year age categories and in males, but to different degrees.

5.5.2 Incidence of PD compared to previous literature

The overall incidence rate of PD in this study was comparable to incidence rates in previous studies in the UK and some parts of Europe (317, 318, 366). The populations of these studies were broadly similar to the population of the current study (i.e. 40 years or older). Based on these studies, the overall incidence rate ranged from 61.6 to 109 per 100,000 population (317, 318, 366). Of these studies, Parkinson's UK used the CPRD database to estimate the overall incidence rate of PD in the UK population aged 45 years or older between 2011 and 2015 (317). The incidence rate of PD in this population in CPRD was estimated to be 61.6 (95% CI 58.5-61.6) per 100,000 person years. Interestingly, this rate is almost identical to the incidence rate in the current study: i.e. 60.87 (95% CI 59.72-62.03) per 100,000 person years. However, there was a difference in the study populations between the Parkinson's UK study (i.e. population aged 45 years and older) and the current study (i.e. population aged 40 years and older), which means that the incidence rate in the current study was relatively higher than that in the Parkinson's UK study. The reason for this is because the denominator in the current study was higher and new cases of PD in patients aged 40-45 years are assumed to be very low. Therefore, the denominator of the current study is inflated, while the numerator is assumed to be stable compared to the Parkinson's UK study (317). Thus, it can be concluded from the data in this study and the Parkinson's UK study that the incidence rate of PD in Wales is slightly higher than in the UK as a whole.

The overall incidence rate in the current study was substantially higher than the incidence rates in two community-based studies conducted in some parts of England (12 per 100,000 population in Northampton, and 26 per 100,000 population in Buckinghamshire and Kent) (357, 358). The obvious reason for

this huge difference is because community-based studies usually cover a small portion of the population, which increases the uncertainty in the resulting estimates. Additionally, the two studies used all age cohorts as denominators.

The current study found an association between high incidence of PD and increase in age. This phenomenon is consistent with the previous epidemiologic studies in the UK and worldwide (317, 318, 350, 353). In line with previous studies, the incidence of PD in this study peaked at the age of 81-90 years and then dropped in patients older than 90 years (317, 318, 353, 367). The drop in incidence rate of PD in patients older than 90 years is not necessarily attributed to PD risk reduction in this category; rather, symptoms attributed to the natural aging process could mask PD and lead to underestimation of its incidence in this age group (368). The incidence rate of PD in the 71-80 and 81-90 year age categories in this study was similar to that reported by Parkinson's UK, using CPRD data for the whole UK population (317). However, the incidence rate for the 81-90 year age category was higher in a previous study that used the THIN database for the whole UK population (318). This difference could be explained by the fact that the current study used exactly the same Read Codes that were used by the Parkinson's UK study to identify PD cases, whereas the THIN study added several Read Codes such as 'Parkinson' Disease Dementia', which may explain the higher incidence rates in this very elderly age group (369). In general, the incidence rates in most age categories in the current study and in previous UK population studies (using the CPRD and THIN databases) (317, 318) were higher than incidence rates in previous UK community-based studies (326, 353, 357, 359). Although community-based studies (such as door-to-door surveys) were theoretically expected to produce more accurate incidence estimates, since the identification of PD cases in these studies was more robust and based on clinical diagnosis, they covered only small geographical locations and included relatively small sample sizes, which impeded the generalization of their results to the whole of the UK. For this reason, funding

bodies and NHS place greater weight on large population-based studies to ensure that the funds benefit as many people as possible (370).

The current study found that the incidence rate of PD was significantly higher in males than in females over all years of the study and for every individual year. This phenomenon is in line with the findings of two previous global systematic reviews (349, 350) and with previous UK studies (317, 318, 353). Several explanations have been proposed to explain this phenomenon, such as the presence of oestrogen in females, which could play a role in protection from PD, and genetic and environmental factors (371). However, the main reason for this difference is not well known. Surprisingly, research has indicated that this sex bias is opposite in other neurodegenerative disease such as Alzheimer disease, which is more common in females, suggesting that there isn't a generalized susceptibility in neurodegenerative diseases (372).

Social deprivation status could play a role in the PD incidence rate, based on the results of the current study. Almost identical findings were presented by Horsfall et al., who used the THIN database and utilized the Townsend deprivation scale to examine the effect of social deprivation on PD incidence (318). They found that the population in the most deprived quintile had a significantly lower rate of PD compared to the least deprived quintile (IRR = 0.90, 95% CI 0.83-0.98) (318). The authors suggested that this difference might be due to differences in coding practice in the most deprived areas. However, this interpretation is oversimplified due to lack of evidence from scientific studies. In contrast, a community-based study conducted in north-east Scotland using the Scottish Deprivation Category (DepCat) found no association between social deprivation and PD incidence (353). Thus, there are clear differences in the proxies used to define social deprivation status in the current study and the two previous UK studies (318, 353), which makes it harder to reach a valid conclusion regarding the effect of social deprivation on PD risk. For example, unlike the WIMD scale used in the current study, the deprivation scale used in the two previous studies excluded health status

domain from consideration. It is evident that patients in more deprived areas suffer from chronic diseases more than other areas (373), which raises concerns that there could be a delay in PD diagnosis in PwP residing in more deprived areas because the early symptoms of PD may be underrecognized in these people as medical care may be more focused on the most obvious and serious diseases, such as cardiovascular disease, addiction problems, and other chronic issues (372). Several hypotheses have been suggested to explain the reason for the lower incidence rate in the most deprived areas. For example, higher physical activity and a higher smoking rate in the population in the most deprived areas could explain the reduction in PD risk in these areas (355). Another explanation is that people who live in deprived areas are more prone to have a delay in PD diagnosis (374). Although it is difficult to support these hypotheses based on the results of the current study, the results of the next chapter (Section 6.5.1) support the hypothesis of delay in PD diagnosis.

The current study found no significant difference in incidence rate of PD between the calendar year of 2000 and the majority of subsequent calendar years (up to 2016). There was a significant reduction in incidence rate of PD in 2017 in the whole cohort and in the majority of age and sex stratified groups. This was surprising; however, after asking SAIL about the completeness of data in 2017, it was found that there were approximately three months of data missing from the calendar year of 2017 due to the time at which the study data were obtained. Therefore, if there were no missed data, and based on the previous years, which showed no significant difference from the reference year (2000), it is highly likely that the incidence rate in 2017 would not differ significantly from the rest of the study years. The study findings were in line with two previous US studies that have shown no difference in incidence rate of PD between 1976 and 1990 (356) and between 1992 and 2005 (375). In contrast, the study findings contradicted a previous UK study which found a slightly significant decline in PD incidence between 1999 and 2009 (IRR = 0.94, 95% CI 0.94-0.95 per increase in

calendar year (318). On the other hand, the results of the current study disagreed with a previous US study that revealed an increase in PD incidence cases between 1976 and 2005 (376). The authors attributed this increase to a real increase in PD risk in recent years, which might be due to a decrease in smoking habits in the general population, given that smokers are at lower risk of developing PD (376). The large variation in the results of the previous studies could be due to the difference in the time of these studies, changes in the diagnostic criteria of PD over time, changes in recording practices, or an increase in recognition of other parkinsonism disorders that could be mistakenly recorded in the system as PD.

5.5.3 Prevalence of PD compared to previous literature

The overall crude prevalence of PD in the current study across the years of the study was consistent with previous global and UK prevalence studies. According to a recently published meta-analysis that studied 47 global prevalence studies, the overall pooled prevalence of PD in the general population was estimated to be 315 (95% CI 113-873) per 100,000 population (3). Between 1960 and 2014, the crude prevalence of PD in the previous UK studies ranged from 113 to 288.3 per 100,000 population (317, 325), which was lower than the prevalence in the current study. The reason for this might be due to the study design (community-based vs. population-based), the geographical location of the study, and the year of the study. The current study is a population study that includes about 80% of the Welsh population, while most of the previous prevalence studies were community-based and included a small geographical location in the UK (325, 327, 357).

In contrast to a previous meta-analysis that found a stable PD prevalence in the UK between 1966 and 2008 (325), the current study found a significant gradual increase in PD prevalence between 2000 and 2016. The prevalence in 2017 dropped slightly due to incomplete data in 2017, as mentioned above. The increase in prevalence across the years was seen in the 71-80 and 81-90

year age categories and in males. Given that the incidence rates in the current study were relatively stable across the years of the study, the increase in prevalence could be attributed to the increase in population aging in Wales. According to a governmental report released by the Welsh government (377), the number of people aged 65 years or older is expected to increase by 55% between 2012 and 2037. This link between the increase in prevalence and population aging is strengthened by the fact that the highest increase in PD prevalence between 2000 and 2016 in the current study was seen in the age category of 81-90 years, in which an increase by 17.75% between 2000 and 2016 was observed, followed by a 17.17% increase in incidence rate in the 71-80 year age category. Despite the stable incidence rate of PD in the 40-50 and over-90 year age categories, the prevalence in these groups has declined over time. There was no obvious reason for such declining trend; nonetheless, it did not change the trend direction of overall prevalence in the whole study cohort. As prevalence is affected by the rate at which new diagnoses occur and the average duration of disease, the fact that incidence was stable but prevalence was on the increase in males could suggest that survival in males was increasing over the years compared to females. A previous UK study found that the mortality rate in PwP has declined in both males and females between 1993 and 2006, but the decline rate was steeper in males in all age groups (378). Therefore, it is possible that the mortality rate in female PwP has reached a plateau, while that in males continues to decrease.

In general, the increase in PD prevalence in the current study is in line with several previous international studies (379-381), and this increase should raise concerns regarding the higher burden on the health system and the adequacy of financial resources to help PwP.

5.5.4 Strengths and weaknesses

The current study is the first population-based study to calculate the incidence and prevalence of PD in Wales over an 18-year period. The study used the SAIL Databank, which included data on about 80% of the Welsh population and is assumed to be representative of the whole population in Wales.

Generally, the findings of the current study were comparable to those reported in previous PD incidence and prevalence studies in the UK and around the world. Therefore, it is possible to claim that the diagnostic codes for PD in SAIL are valid and produce comparable results to previous studies. This in turn could manifest the strength of the SAIL Databank as a source of population-based data to examine the epidemiology of disease in the UK.

There were several limitations in the current study. First, although efforts have been made to improve ascertainment of the number of PD cases by including only patients with a definitive diagnosis of PD, it was beyond the capabilities of the study to confirm these PD diagnoses. This can be done by either linking the primary care data in SAIL to the data from Neurology or Care of the Elderly (COTE) clinics, which include more clinical details for PwP, or by contacting GPs and requesting their records for a random sample of PwP. These steps have not been taken in the current study because of time and cost constraints; however, similar studies have been conducted using GP data in the SAIL Databank without confirmation of diagnoses and assuming the validity of the database (382, 383). The second limitation in the current study is that the assumption has been made that the time of the first PD Read codes reflected the time of first diagnosis. It is possible that the real time of PD diagnosis was before the first record in the GP data, such as in people migrating to Wales after they have been diagnosed with PD in other countries. To overcome this caveat, patients with PD diagnosis codes less than six months from the time of GP registration were excluded. Additionally,

there could be a gap between the first time the patient contacted the GP after developing the PD symptoms and the time of referral to the specialist. However, theoretically, this gap seemed to be narrow: no more than six weeks, according to the 2006 NICE guidelines (136), which would not have a significant impact on the time of diagnosis in the GP system. Another limitation was that the incidence and prevalence rates were not standardised for age or gender. This was intentional since the purpose of the study was to compare the rates to previous UK rates (which were not standardised) (317, 318); however, future work should also consider standardising rates to allow comparison of Welsh prevalence and incidence rates with other global standardised rates.

As discussed above, another limitation in the study is that there were approximately three months of data missing from the 2017 calendar year due to the time at which these data were obtained from SAIL. This limitation will be considered in the next chapters of this thesis.

5.5.5 Conclusion

The current study supports the findings from the previous literature that PD incidence and prevalence are significantly associated with higher age and being male. The study also found a significant increase in PD incidence in the least deprived areas in Wales. The incidence of PD seemed to be stable over the time of the study, while the prevalence tended to increase over the 18-year period between 2000 and 2017. Epidemiological data from the SAIL Databank seems to be comparable to previous population-based studies in the UK, and this could be a sign of data validity.

CHAPTER 6: Trends in First Line Therapy for PD in Wales: A 16-Year Observational Study

6.1 Introduction

The options for the treatment of motor symptoms in PwP have increased in the last thirty years, which have seen several new classes of PD medications, such as DAs, MAO-B inhibitors and COMT inhibitors, introduced onto the market. Knowledge on the efficacy and safety of PD medications has also progressed. For example, in 2006, the American Academy of Neurology (AAN) ascertained that DAs, MAO-B inhibitors and L-dopa do not provide any neuroprotective properties (31, 126). Additionally, information on safety issues related to DAs, such as cardiotoxicity and ICDs, emerged from 2006 (198, 384) (other efficacy and safety issues have been discussed in detail in Chapter 2). On the other hand, the PD MED study in 2014 demonstrated that the early use of L-dopa in PwP resulted in a better QOL in the short and long term (101).

There has been an ongoing debate about the first line therapy for patients newly diagnosed with PD (385). This debate has been specifically focused on L-dopa and DAs and centres on which medications to start with as first line therapy. Recently, and based on the results of PD MED study and the discovered side effects of DAs, a shift in the literature to favour L-dopa as a first line therapy has been suggested (102). The recent NICE guidance was more neutral and suggested that for people whose motor symptoms affect QoL, L-dopa should be used; while for people whose QoL is not affected by motor symptoms, L-dopa, MAO-B inhibitors, and DAs are recommended (31).

There is a paucity of literature on the use of PD medications within the UK, and whether the levels of prescribing are reflective of the NICE guidance or academic literature, particularly with specific reference to Wales. One particular study examined the differences in the National Health Service's (NHS) spending for PD medications in England between 1998 and 2010 and found an increase in DA sales in the early 2000s and an increase in sales of newly approved medications (e.g. rasagiline and rotigotine) immediately

after their approval (238). This study was restricted to England and was based on the cost of the PD medications, not the exact number of prescriptions. Additionally, the factors that affect prescribing, such as the patient's age, sex, social deprivation status, year of prescribing, and comorbidities, were not examined in this study.

To address this knowledge gap, this chapter describes the actual utilisation of PD medications by PwP in Wales. By determining the prescribing trends of antiparkinsonian medications in PwP in Wales with respect to several factors, including age, sex, social deprivation status, and co-morbidities, the pattern of medication use in PwP can be evaluated.

6.2 Objectives of the study

The objectives of this chapter are to:

1. Identify individual PD medications prescribed to PwP.

2. Explore first line therapy in PwP across the years of the study using incidence cases.

3. Perform univariate and multivariate logistic regressions to examine the potential factors that may affect the prescribing choice of the first line therapy.

6.3 Method

6.3.1 The SAIL databases used and the study cohort

The study is a retrospective cohort study using the SAIL Databank. The WLGP database was used to identify the prescribing pattern and trend of PD drugs. The WDS database was used to obtain the demographic data of PwP. PEDW data were used to identify the comorbidities in PwP (Charlson index components). The study population for this chapter was the 10,644 patients

who were newly diagnosed with PD in SAIL between 1 January 2000 and 30 September 2017 (as previously explained in Chapter 5). To examine the first line therapy prescribed to newly diagnosed PwP, several exclusion criteria were applied. Patients who were newly diagnosed with PD in 2017 were excluded due to incomplete prescription data in 2017. Additionally, all patients prescribed any PD medication within one year before the first PD diagnosis were excluded. This was done to ensure that the prescriptions examined were truly prescribed as first line therapies. Finally, patients not prescribed any PD medications in the GP data in SAIL were excluded.

6.3.2 Identify individual PD medications

PD medications were identified in the GP data by browsing the Read codes using an NHS Clinical Terminology software in the SAIL gateway. Then, PD medications were classified into six main categories, as follows:

1. Anticholinergics (which included benztropine, orphenadrine, procyclidine, and trihexyphenidyl).

2. DAs (with two subcategories):

    2.1. Ergot DAs (which included bromocriptine, cabergoline, lisuride, and pergolide).

    2.2. Non-ergot DAs (which included apomorphine, pramipexole, ropinirole, and rotigotine).

3. L-dopa (which included L-dopa plus carbidopa, L-dopa plus benserazide, and L-dopa plus carbidopa plus entacapone).

4. MAO-B inhibitors (which included rasagiline and selegiline).

5. COMT inhibitors (which included entacapone and tolcapone).

6. Amantadine.

This chapter deals with two types of drug classification. The first, classifies PD medications into six main categories without specifying a particular medication for analysis. Within this classification, the two subcategories of DAs are considered separately. This classification helped to identify the factors that predicted the prescribing of a particular drug category as a first line therapy. The second classification divided the first line therapy into four groups:

1. L-dopa group (which included patients prescribed L-dopa alone or with other categories of PD medications other than DAs).

2. DAs group (which included patients prescribed DAs alone or with other categories of PD medications other than L-dopa).

3. L-dopa plus DAs group (which included patients prescribed L-dopa with DAs with or without other PD medications).

4. "Other" group (which included patients prescribed any PD medications other than L-dopa and DAs).

As explained in Chapter 3, the dose instructions and drug quantity data were not available in SAIL; therefore, the study is limited to the type of PD medication prescribed to newly diagnosed PwP.

6.3.3 Prescribing pattern of first line therapy stratified by age, sex, social deprivation status, health boards, year of prescribing, and comorbidities

First line therapy is defined as the first PD medication(s) prescribed to the patient following the first PD diagnosis. Any additional PD medication prescribed within 30 days of the first prescription is also considered as first line therapy.

To further characterise factors affecting prescribing, several possible explanatory variables were used (i.e. age, sex, social deprivations status, health board, year of prescribing, and comorbidities, previous use of antidepressants). Patient age was grouped into three categories: 40-60, 61-80, and 81 years or older. Social deprivation status was classified according to the WIMD 2011 scale (i.e. quintile 1 (most deprived) up to quintile 5 (least deprived)). The Welsh Health Boards were classified into seven Health Boards: Abertawe Bro Morgannwg, Aneurin Bevan, Betsi Cadwaladr, Cardiff & Vale, Cwm Taf, Hywel Dda, and Powys. In order to examine both the effects of the 2006 AAN report that found no evidence of neuroprotection properties for PD medications (126) and the evidence of behavioural and cardiac side effects of DAs that emerged between 2006 and 2011 (198, 384), the year of first prescribing was grouped into three categories: 2000-2005, 2006-2011, and 2012-2016. Comorbidities were extracted using hospital admission data (PEDW) up to two years prior to the diagnosis date. The 16 comorbidities identified were: diabetes, pulmonary disease, cerebral vascular accident, acute myocardial infarction, dementia, congestive heart failure, renal disease, cancer, peripheral vascular disease, connective tissue disorder, paraplegia, diabetes complications, peptic ulcer, metastatic cancer, liver disease, and severe liver disease. Each condition was treated as a binary variable in terms of whether or not the presence of the condition was mentioned. Regarding previous use of antidepressants, patients would be considered as users of antidepressants (BNF section 4.3) if they were on

antidepressants within one year prior to PD diagnosis. The rationale behind including this variable was to control for possible drug-drug interactions (serotonin syndrome) between MAO-B inhibitors and antidepressants (386).

6.3.4 Statistical tests

As every patient in the SAIL databank is registered with a particular GP practice, which in turn is nested within a particular health board, a series of multilevel logistic regression models were used. The dependent variables in the analysis were binary and included the specific medication categories used as first line therapies in PD. All six categories of PD medications mentioned in Section 1.3.2 were tested, except for COMT inhibitors and amantadine, whose role in *de novo* PwP is limited (31). Additionally, apomorphine was excluded from non-ergot DAs, since it is a rescue therapy and its pump formula may be delivered in the hospital with no record in the GP data. For the second classification, which divided the first line therapy into four groups, a multilevel logistic regression was conducted to compare the L-dopa group with the DAs group. These two groups were chosen because they constituted the majority of the first line therapies in the current study (about 90%).

An empty regression model (with no predictors) was run in R for every medication category and for the two groups of L-dopa and DAs. This model included the GP practice nested with the health board as a random effect and the Intraclass Correlation Coefficient (ICC) was calculated for each model based on the results (387). ICC represents the ratio of between-GPs variation in prescribing and the total variation of between-GPs variation + within GPs variation (387). If the ICC values were less than 10%, a single level logistic regression was run without considering the random effects of GP practice and health board (388). In line with best practice (389), a confirmatory step was needed to ensure the validity of the model outcomes. After adding the dependent variables in the models (as discussed below), the odd ratios and confidence intervals of the single and multi-level logistic regression models

were compared. It was found that they were highly similar in all the models: therefore, the single level logistic regression was applied.

6.3.4.1 Univariate logistic regression of factors affecting the prescribing choice of first line therapy

The first step in building the final regression model was to determine which independent variables to include in the model. As all independent variables in this study were binary or categorical, the weighted Wald test was conducted to determine whether the overall effect of each independent variable was significant in the model. A particular variable was included in the multivariate model if the p-value of the Wald test was ≤ 0.20 (390).

6.3.4.2 Multivariate logistic regression of factors affecting the prescribing choice of first line therapy

Based on the outcomes of the univariate analysis, a multivariate logistic regression, which included the candidate variables, was performed to understand the relationship between those variables and the prescribing choice of the first line therapy. The odds ratio (OR) and confidence intervals were obtained and the significance level was set at 0.05. Any variable that had fewer than five patients in any group was excluded from the analysis, as recommended by SAIL ethical rules. Since the main goal of the analysis was to predict the overall effect of factors in the prescription of PD first line therapy, the main effects model was used. Therefore, no interaction terms were incorporated in the models.

6.3.4.3 Model diagnostics and Goodness of Fit

Two “Goodness of Fit” tests were conducted to evaluate the fitness of the final regression model. The first was the Hosmer and Lemeshow test, which

examined the extent to which the model was well calibrated (390). The model is considered to be well calibrated if the p-value is > 0.05 (390). The second test conducted was the area under a ROC (Receiver Operating Characteristics) curve with the values exclusively lying between 0.5 and 1 (390). This model would have the ability to discriminate between the two possible outcomes of the dependent variable in the logistic regression model if the ROC is $\geq$ 0.7 (390).

6.3.4.4 Sensitivity analysis

To assess the robustness of the study outcomes, a sensitivity analysis that excluded patients with a history of dementia was conducted. All the previous models were re-examined without this group of patients. The rationale behind excluding these patients from the sensitivity analysis was to exclude potentially false PD cases, since symptoms of dementia with Lewy bodies (DLB) might overlap with PD symptoms such as tremor and rigidity (136).

6.4 Results

6.4.1 Study cohort

During the study period (2000-2016) and after applying the exclusion criteria, 9,142 newly diagnosed PwP who had initiated a first PD therapy were identified (Figure 6.1). Table 6.1 shows the overall characteristics of the study cohort in terms of their age, sex, WIMD quintile, health board, year of prescription, comorbidities, and previous use of antidepressants.

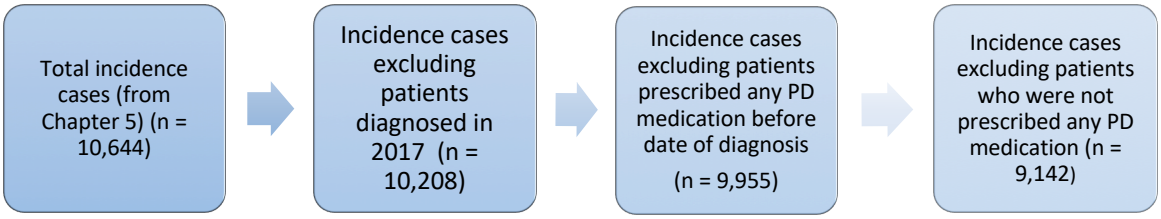


Figure 6-1- Summary of characteristics defining the study cohort

Character	Number of patients (total n = 9,142)
Age (years)	
40-60	845 (9.24%)
61-80	5,670 (62.02%)
>80	2,627 (28.74%)
Sex	
Male	5,358 (58.61%)
Female	3,784 (41.39%)
Welsh Index of Multiple Deprivation (WIMD) quintile	
1 (most deprived)	1,517 (16.59%)
2	1,685 (18.43%)
3	2,060 (22.53%)
4	1,794 (19.62%)
5 (least deprived)	2,086 (22.82%)
Health board	
Abertawe Bro Morgannwg	2,128 (23.28%)
Aneurin Bevan	1,408 (15.4%)
Betsi Cadwaladr	2,005 (21.93%)
Cardiff & Vale	1,275 (13.95%)
Cwm Taf	845 (9.24%)
Hywel Dda	1,158 (12.67%)
Powys	323 (3.53%)
Year of prescription	
2000-2005	2,602 (28.46%)
2006-2011	3,228 (35.31%)
2012-2016	3,312 (36.23%)
Comorbidities	
Diabetes	656 (7.18%)
Pulmonary disease	510 (5.58%)
Cerebral vascular accident	338 (3.7%)
Acute myocardial infarction	321 (3.51%)
Dementia	255 (2.79%)
Congestive heart failure	192 (2.1%)
Renal disease	160 (1.75%)
Cancer	156 (1.71%)
Peripheral vascular disease	105 (1.15%)
Connective tissue disorder	90 (0.98%)
Paraplegia	74 (0.81%)
Diabetes complications	58 (0.63%)
Peptic ulcer	41 (0.45%)
Metastatic cancer	31 (0.34%)
Liver disease	10 (0.11%)
Severe liver disease	5 (0.05%)
Antidepressants	
Previous use of antidepressants	2,076 (22.7%)

Table 6-1- Characteristics of the study cohort

6.4.2 Characteristics of the study cohort among different treatment groups

Of the six medication categories, L-dopa was the most common first line therapy (80.6%), followed by non-ergot DAs (12.9%) and MAO-B inhibitors (7.9%) (Table 6.2). Of the four medication groups, the L-dopa group constituted the majority of prescriptions (78%), followed by the DAs group (11.5%) and the "Other" group (7.9%) (Table 6.2). The L-dopa group was the most common in all age groups, but to a different extent for each group. Younger patients (40-60 years) were prescribed medication from the DAs group and the "Other" group (mainly MAO-B inhibitors) more than medications from the other categories. Very old patients (>80 years) were prescribed medications from the L-dopa group more commonly (about 94%), with a very low use of medications from the DAs and "Other" group (Table 6.2). A very low prescription rate for medications from the ergot DAs category was seen throughout the study (no more than 3.96%) (Table 6.2). The prescription rate of medications from the L-dopa group increased by 10% in 2000-2005 when compared to 2012-2016, and the prescription rate of medications in the DAs group decreased by 9% (Table 6.2 and Figure 6.2). The prescription rate of MAO-B inhibitors increased by 5% between 2000-2005 and 2012-2016. On the other hand, the prescription rates of anticholinergics and ergot DAs declined between the two periods. The prescription rate for non-ergot DAs increased by 4% between 2000-2005 and 2006-2011 and then decreased by 9% in 2012-2016 (Figure 3.6). For other characteristics of the study cohort among different treatment groups, see Table 6.2.

The first therapy*	L-dopa group (%)	DAs group (%)	L-dopa plus DAs group (%)	"Other" group (%)	First therapy includes Amantadine (%)	First therapy includes Anticholinergics (%)	First therapy includes COMT-inhibitors (%)	First therapy includes DAs (%)	First therapy includes ergot DAs (%)	First therapy includes non-ergot DAs (%)	First therapy includes L-dopa (%)	First therapy includes MAO-B inhibitors (%)
All PwP (n = 9142)	7,127 (78)	1,052 (11.5)	239 (2.6)	724 (7.9)	22 (0.2)	325 (3.6)	58 (0.6)	1,291 (14.1)	111 (1.2)	1,181 (12.9)	7,366 (80.6)	719 (7.9)
Age (years)												
40-60	374 (44.26)	300 (35.5)	31 (3.67)	140 (16.57)	NA*	51 (6.04)	12 (1.42)	331 (39.17)	23 (2.72)	309 (36.57)	405 (47.93)	143 (16.92)
61-80	4,307 (75.96)	699 (12.33)	160 (2.82)	504 (8.89)	15 (0.26)	221 (3.9)	31 (0.55)	859 (15.15)	78 (1.38)	781 (13.77)	4,467 (78.78)	501 (8.84)
>80	2,446 (93.11)	53 (2.02)	48 (1.83)	80 (3.05)	NA	53 (2.02)	15 (0.57)	101 (3.84)	10 (0.38)	91 (3.46)	2,494 (94.94)	75 (2.85)
Sex												
Male	4,150 (77.45)	640 (11.94)	135 (2.52)	433 (8.08)	12 (0.22)	169 (3.15)	32 (0.6)	775 (14.46)	63 (1.18)	712 (13.29)	4,285 (79.97)	473 (8.83)
Female	2,977 (78.67)	412 (10.89)	104 (2.75)	291 (7.69)	10 (0.26)	156 (4.12)	26 (0.69)	516 (13.64)	48 (1.27)	469 (12.39)	3,081 (81.42)	246 (6.5)
Welsh Index of Multiple Deprivation (WIMD) quintile												
1 (most deprived)	1,205 (79.43)	165 (10.88)	41 (2.7)	106 (6.99)	NA	89 (5.87)	14 (0.92)	206 (13.58)	17 (1.12)	189 (12.46)	1,246 (82.14)	78 (5.14)
2	1,332 (79.05)	185 (10.98)	46 (2.73)	122 (7.24)	NA	62 (3.68)	12 (0.71)	231 (13.71)	25 (1.48)	206 (12.23)	1,378 (81.78)	118 (7)
3	1,607 (78.01)	247 (11.99)	55 (2.67)	151 (7.33)	6 (0.29)	56 (2.72)	15 (0.73)	302 (14.66)	28 (1.36)	275 (13.35)	1,662 (80.68)	152 (7.38)
4	1,395 (77.76)	207 (11.54)	42 (2.34)	150 (8.36)	NA	54 (3.01)	9 (0.5)	249 (13.88)	19 (1.06)	230 (12.82)	1,437 (80.1)	154 (8.58)
5 (least deprived)	1,588 (76.13)	248 (11.89)	55 (2.64)	195 (9.35)	6 (0.29)	64 (3.07)	8 (0.38)	303 (14.53)	22 (1.05)	281 (13.47)	1,643 (78.76)	217 (10.4)
Health board												
Abertawe Bro Morgannwg	1,724 (81.02)	255 (11.98)	41 (1.93)	108 (5.08)	6 (0.28)	71 (3.34)	10 (0.47)	296 (13.91)	40 (1.88)	256 (12.03)	1,765 (82.94)	70 (3.29)
Aneurin Bevan	1,069 (75.92)	183 (13)	50 (3.55)	106 (7.53)	NA	60 (4.26)	16 (1.14)	233 (16.55)	12 (0.85)	221 (15.7)	1,119 (79.47)	94 (6.68)
Betsi Cadwaladr	1,563 (77.96)	213 (10.62)	43 (2.14)	186 (9.28)	7 (0.35)	48 (2.39)	15 (0.75)	256 (12.77)	19 (0.95)	237 (11.82)	1,606 (80.1)	242 (12.07)
Cardiff & Vale	942 (73.88)	141 (11.06)	43 (3.37)	149 (11.69)	NA	45 (3.53)	NA	184 (14.43)	15 (1.18)	169 (13.25)	985 (77.25)	171 (13.41)
Cwm Taf	656 (77.63)	108 (12.78)	23 (2.72)	58 (6.86)	NA	50 (5.92)	5 (0.59)	131 (15.5)	9 (1.07)	122 (14.44)	679 (80.36)	32 (3.79)
Hywel Dda	916 (79.1)	107 (9.24)	32 (2.76)	103 (8.89)	NA	42 (3.63)	9 (0.78)	139 (12)	15 (1.3)	125 (10.79)	948 (81.87)	96 (8.29)
Powys	257 (79.57)	45 (13.93)	7 (2.17)	14 (4.33)	NA	9 (2.79)	NA	296 (13.91)	NA	51 (15.79)	264 (81.73)	14 (4.33)
Year of prescription												
2000-2005	1,948 (74.87)	374 (14.37)	81 (3.11)	199 (7.65)	9 (0.35)	172 (6.61)	34 (1.31)	455 (17.49)	103 (3.96)	353 (13.57)	2,029 (77.98)	114 (4.38)
2006-2011	2,388 (73.98)	492 (15.24)	66 (2.04)	282 (8.74)	6 (0.19)	82 (2.54)	17 (0.53)	558 (17.29)	8 (0.25)	550 (17.04)	2,454 (76.02)	294 (9.11)
2012-2016	2,791 (84.27)	186 (5.62)	92 (2.78)	243 (7.34)	7 (0.21)	71 (2.14)	7 (0.21)	278 (8.39)	0 (0)	278 (8.39)	2,883 (87.05)	311 (9.39)

Table 6-2- Descriptive statistics for the type of the first therapy prescribed to PwP in Wales

* NA indicates that the cell had fewer than 5 patients

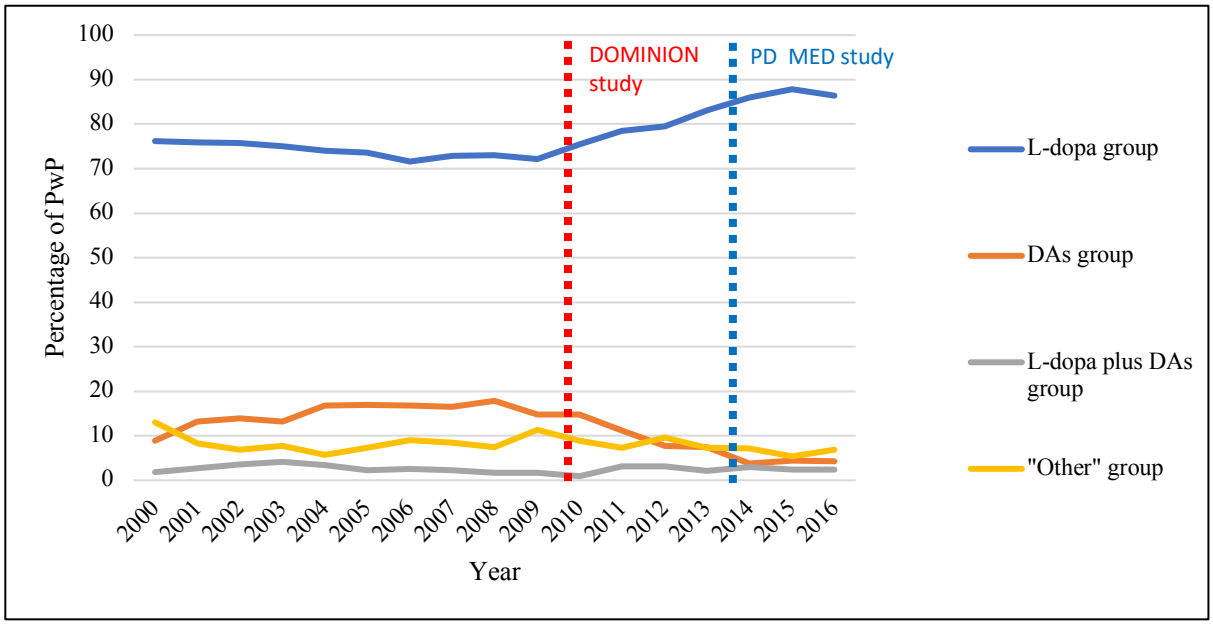


Figure 6-2- Changes in pattern of the initial therapy prescribed to PwP over time (medications groups)

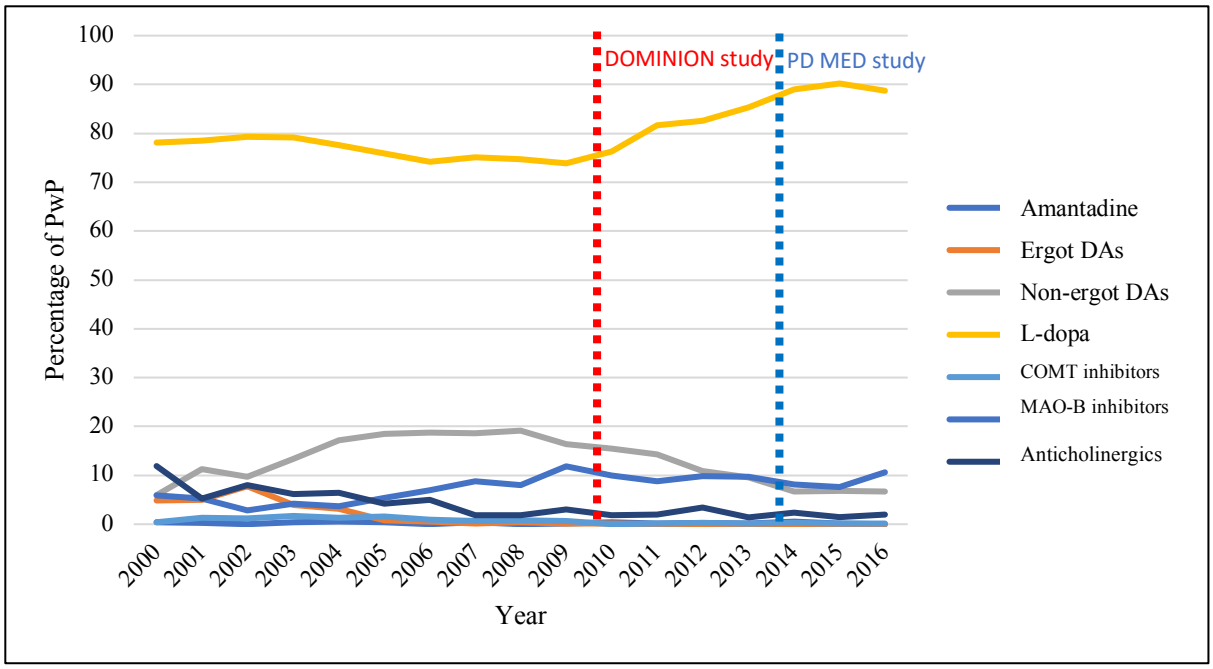


Figure 6-3- Changes in pattern of the initial therapy prescribed to PwP over time (medications categories)

6.4.3 Results of logistic regression models predicted factors affecting the prescribing choice of the first line therapy

6.4.4 Univariate analysis to identify predictors should be included in the multivariate logistic regression

Table 6.3 shows the results of the univariate analysis that was performed to identify independent variables associated with prescribing choice of the first line therapy in PwP. It can be seen that age and year of prescription were associated with prescribing choice of all medication models. Other variables had varied associations with the different types of medication model (Table 6.3).

The first therapy*	DAs group vs L-dopa group	First therapy includes Anticholinergics	First therapy includes DAs	First therapy includes ergot DAs	First therapy includes non-ergot DAs	First therapy includes L-dopa	First therapy includes MAO-B inhibitors
Variables	Adjusted Wald teats (p-value)						
Age categories	603 (<0.0001)*	33.43 (<0.0001)	560.23 (<0.0001)	27.47 (<0.0001)	503.59 (<0.0001)	735.13 (<0.0001)	169.28 (<0.0001)
Sex	2.56 (0.101)	6.03 (0.011)	1.25 (0.261)	1.15 (0.694)	1.57 (0.215)	2.96 (0.083)	16.45 (0.002)
Social deprivation score (WIMD)	2.45 (0.651)	29.84 (0.001)	1.46 (0.833)	2.27 (0.681)	1.92 (0.750)	8.56 (0.070)	36.93 (0.003)
Year of prescribing categories	170.20 (<0.0001)	91.38 (<0.0001)	134.81 (<0.0001)	58.25 (<0.0001)	106.55 (<0.0001)	138.93 (<0.0001)	58.32 (<0.0001)
Diabetes	27.75 (0.001)	1.34 (0.246)	33.63 (0.001)	NA	27.53 (0.001)	35.39 (0.001)	19.58 (0.001)
Pulmonary disease	10.28 (0.001)	1.02 (0.313)	11.34 (0.002)	NA	8.68 (0.001)	14.22 (0.002)	12.08 (0.001)
Cerebral vascular accident	20.60 (0.001)	2.19 (0.135)	19.16 (0.006)	NA	16.60 (0.005)	34.04 (0.004)	NA
Acute myocardial infarction	10.61 (0.002)	0.54 (0.461)	10.59 (0.001)	NA	7.57 (0.001)	18.06 (0.003)	9.54 (0.005)
Dementia	18 (<0.0001)	7.12 (<0.0001)	18.08 (<0.0001)	NA	15.32 (<0.0001)	20.53 (<0.0001)	NA
Congestive heart failure	12.91 (0.001)	NA	11.61 (0.002)	NA	10.66 (0.001)	21.13 (0.002)	5.61 (0.011)
Renal disease	8.81 (0.002)	NA	7.77 (0.002)	NA	7.18 (0.001)	16.86 (0.001)	NA
Cancer	2.97 (0.083)	NA	5.20 (0.021)	NA	4.67 (0.031)	4.33 (0.032)	4.41 (0.032)
Peripheral vascular disease	3.90 (0.043)	NA	3.55 (0.051)	NA	2.57 (0.101)	6.28 (0.015)	NA
Connective tissue disorder	3.51 (0.062)	NA	1.25 (0.262)	NA	1.29 (0.252)	8.36 (0.005)	NA
Paraplegia	NA**	NA	NA	NA	NA	8.16 (0.001)	NA
Diabetes complications	NA	NA	NA	NA	NA	7.08 (0.002)	NA
Peptic ulcer	NA	NA	0.00 (0.912)	NA	0.01 (0.811)	0.145 (0.721)	NA
Metastatic cancer	NA	NA	NA	NA	NA	1.78 (0.181)	NA
Liver disease	NA	NA	NA	NA	NA	0.00 (0.912)	NA
Severe liver disease	NA	NA	NA	NA	NA	0.00 (0.923)	NA
Previous use of antidepressants	5.84 (0.011)	1.88 (0.173)	8.68 (0.002)	4.29 (0.031)	5.76 (0.012)	21.85 (0.008)	59.79 (0.005)

Table 6-3- The results of univariate analysis (Adjusted Wald test) to examine which variables should be included in the multivariate logistic regression to examine factors that affect the choice of first therapy.

*The red colour indicates that the p-value was less than 0.20, hence included in the subsequent multivariate logistic regression ** NA indicated that the cell had fewer than 5 patients.

6.4.4.1 Multivariate analysis

6.4.4.1.1 DAs group vs L-dopa group model

Table 6.4 shows the results of the logistic regression model that calculated the odds of prescription of medicines from the DAs group compared to medicines from the L-dopa groups. Age was a significant factor in the model. Compared to the younger patients (40-60 years), older patients (61-80 and > 80 years) were 79.8% and 97.2% less likely, respectively, to be prescribed medicines from the DAs group, and hence more likely to be prescribed medicines from the L-dopa groups (p-value <0.0001 for both). There was no significant difference between males and females in the prescription of medicines from the DAs or L-dopa groups. Newly diagnosed PwP in the 2012-2016 period were 65.9% less likely to be prescribed medicines from the DAs group compared with the 2000-2005 period (p-value <0.0001). None of the comorbidities had a significant effect on the prescription of medicines from the DAs or the L-dopa groups, except diabetes and dementia. Diabetic and dementia patients were 41.8% and 65% less likely, respectively, to be prescribed medicines from the DAs group (p-value = 0.004 and 0.014 respectively) (Table 6.4).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercepts = 0.038 (3.8%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-1.599	0.202	0.169 -0.242	<0.0001 *
	> 80 years	-3.583	0.028	0.02 -0.038	<0.0001
Sex	Males (ref)				
	Females	0.017	1.017	0.880 -1.175	0.819
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	0.130	1.138	0.971 -1.334	0.109
	2012-2016	-1.077	0.341	0.28 -0.414	<0.0001
Diabetes		-0.541	0.582	0.402 -0.843	0.004
Pulmonary disease		-0.069	0.933	0.648 -1.344	0.711
Cerebral vascular accident		-0.577	0.561	0.313 -1.008	0.053
Acute myocardial infarction		-0.103	0.902	0.55 -1.48	0.683
Dementia		-1.048	0.351	0.152 -0.809	0.014
Congestive heart failure		-0.682	0.506	0.217 -1.18	0.115
Renal disease		-0.172	0.842	0.371 -1.908	0.680
Cancer		0.161	1.175	0.624 -2.212	0.618
Peripheral vascular disease		-0.129	0.879	0.361 -2.139	0.776
Connective tissue disorder		-0.279	0.756	0.292 -1.958	0.565
Previous use of antidepressants		0.172	1.188	0.999 -1.411	0.051

Table 6-4- Results of multivariate logistic regression model of DAs group vs L-dopa group

*Red colour denotes p-values that are significant at an alpha level of 0.05

6.4.4.1.2 Anticholinergic model

As shown in Table 6.5, age, sex, WIMD quintiles, year of prescribing, and dementia had significant effects on the odds of prescribing anticholinergics as a first therapy. Compared to the younger patients (40-60 years), older patients (61-80 and > 80 years) were 38.4% and 70.3% less likely, respectively, to be prescribed anticholinergics (p-value = 0.003 and <0.0001 respectively). Females were 32.2% more likely to be prescribed anticholinergics (p-value = 0.016). Patients who lived in the least deprived WIMD quintile area were 45% less likely to be prescribed anticholinergics compared to patients from the most deprived quintile area (p-value <0.0001). The odds of prescription of anticholinergics had significantly declined in the 2012-2016 period compared to the 2000-2005

period (p-value <0.0001). Patients with dementia had higher odds of being prescribed anticholinergics (p-value = 0.001) (Table 6.5).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board codes as random intercept = 0.015 (1.5%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-0.485	0.616	0.448 -0.847	0.003
	> 80 years	-1.214	0.297	0.198 -0.444	<0.0001
Sex	Males (ref)				
	Females	0.279	1.322	1.053 -1.659	0.016
Social deprivation score (WIMD)	1 (most deprived) (ref)				
	2	-0.453	0.636	0.454 -0.889	0.008
	3	-0.747	0.474	0.336 -0.669	<0.0001
	4	-0.620	0.538	0.379 -0.763	0.001
	5 (least deprived)	-0.599	0.550	0.394 -0.767	<0.0001
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	-0.973	0.378	0.289 -0.495	<0.0001
	2012-2016	-1.120	0.326	0.246 -0.433	<0.0001
Cerebral vascular accident		-0.580	0.560	0.257 -1.221	0.145
Dementia		0.897	2.452	1.442 -4.168	0.001
Previous use of antidepressants		0.136	1.145	0.883 -1.485	0.305

Table 6-5- Results of multivariate logistic regression model of anticholinergics category

6.4.4.1.3 DAs model

In the DAs' model, five factors were shown to have a significant effect on the prescription of DAs. Older patients (61-80 and > 80 years) were 71.3% and 93.4% less likely, respectively, to be prescribed DAs (p-value <0.0001 for both). Compared to the 2000-2005 period, the odds of being prescribed DAs declined significantly in the 2012-2016 period (p-value <0.0001). Diabetic and dementia patients were 46.5% and 51.5% less likely, respectively, to be prescribed medicines from the DAs' group (p-value <0.0001 and 0.023 respectively) (Table 6.6). Patients who used antidepressants within one year before PD diagnosis were 15.9% less likely to be prescribed DAs (p-value = 0.029).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercept = 0.026 (2.6%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-1.250	0.287	0.244 -0.336	<0.0001
	> 80 years	-2.711	0.066	0.052 -0.085	<0.0001
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	-0.005	0.995	0.862 -1.148	0.942
	2012-2016	-0.841	0.431	0.365 -0.509	<0.0001
Diabetes		-0.625	0.535	0.381 -0.752	<0.0001
Pulmonary disease		-0.116	0.891	0.643 -1.235	0.488
Cerebral vascular accident		-0.399	0.671	0.412 -1.092	0.108
Acute myocardial infarction		-0.096	0.909	0.584 -1.413	0.671
Dementia		-0.724	0.485	0.26 -0.905	0.023
Congestive heart failure		-0.385	0.680	0.349 -1.326	0.258
Renal disease		0.011	1.011	0.511 -2	0.975
Cancer		-0.152	0.859	0.464 -1.593	0.630
Peripheral vascular disease		-0.018	0.982	0.457 -2.112	0.963
Previous use of antidepressants		-0.173	0.841	0.721 -0.982	0.029

Table 6-6- Results of multivariate logistic regression model of DAs category

6.4.4.1.4 Ergot DA model

Table 6.7 shows that only two factors were shown to have a significant effect on the prescription of ergot DAs. Older patients (61-80 and > 80 years) were less likely to be prescribed ergot DAs compared to patients in the 40-60 year group (p-value = 0.004 and <0.0001 respectively). Patients with previous use of antidepressants also had less chance of being prescribed ergot DAs (p-value = 0.036) (Table 6.7).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercept = 0.011 (1.1%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-0.693	0.500	0.312 -0.801	0.004
	> 80 years	-1.993	0.136	0.065 -0.288	<0.0001
Previous use of antidepressants		-0.569	0.566	0.332 -0.964	0.036

Table 6-7- Results of multivariate logistic regression model of ergot DAs category

6.4.4.1.5 Non-ergot DA model

Table 6.8 shows that the outcomes of this model were largely similar to those reported in the DAs model (Table 6.6). However, some differences were noticed. Unlike DAs, the prescription of non-ergot DAs rose significantly by 35.3% in the period 2006-2011, and then significantly declined in 2012-2016 by 64.7%. The other difference was that there were no significant effects of dementia and previous use of antidepressants in this model (Table 6.8).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercept = 0.022 (2.2%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-1.250	0.287	0.244 -0.337	<0.0001
	> 80 years	-2.707	0.067	0.052 -0.086	<0.0001
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	0.302	1.353	1.163 -1.575	<0.0001
	2012-2016	-0.515	0.597	0.503 -0.71	<0.0001
Diabetes		-0.570	0.566	0.401 -0.799	0.001
Pulmonary disease		-0.103	0.902	0.647 -1.259	0.546
Cerebral vascular accident		-0.377	0.686	0.416 -1.13	0.139
Acute myocardial infarction		-0.027	0.973	0.625 -1.514	0.903
Dementia		-0.589	0.555	0.297 -1.036	0.064
Congestive heart failure		-0.417	0.659	0.328 -1.326	0.242
Renal disease		-0.088	0.916	0.448 -1.87	0.809
Cancer		-0.164	0.849	0.448 -1.61	0.616
Peripheral vascular disease		0.034	1.035	0.481 -2.224	0.931
Previous use of antidepressants		-0.142	0.868	0.74 -1.017	0.081

Table 6-8- Results of multivariate logistic regression model of non-ergot DAs category

6.4.4.1.6 L-dopa model

Table 6.9 shows that age was a significant factor in the model. Compared to the younger patients (40-60 years), older patients (61-80 and > 80 years) were 300.1% and 1,871.8% more likely, respectively, to be prescribed medicines from the L-dopa category (p-value <0.0001 for both). There was no significant difference between males and females in the prescription of medicines from the L-dopa category. Patients who lived in the least deprived WIMD quintile areas were 22.1% less likely to be prescribed L-dopa compared to patients from the most deprived quintile area (p-value = 0.007). Newly diagnosed PwP in the 2012-2016 period were 91.3% more likely to be prescribed L-dopa compared to newly diagnosed PwP in the 2000-2005 period (p-value <0.0001). None of the comorbidities had a significant effect on the prescription of medicines from the L-dopa category except for diabetes, congestive heart failure, and paraplegia. Patients with these conditions were significantly more likely to be prescribed L-dopa. Patients with previous use of antidepressants were 33.3% more likely to be prescribed L-dopa (see Table 6.9).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercept = 0.041 (4.1%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	1.386	4.001	3.43 -4.666	<0.0001
	> 80 years	2.982	19.718	15.723 -24.728	<0.0001
Sex	Males (ref)				
	Females	-0.054	0.948	0.845 -1.063	0.360
Social deprivation score (WIMD)	1 (most deprived) (ref)				
	2	-0.064	0.938	0.773 -1.138	0.518
	3	-0.124	0.884	0.736 -1.062	0.187
	4	-0.217	0.805	0.667 -0.971	0.023
	5 (least deprived)	-0.250	0.779	0.65 -0.933	0.007
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	-0.139	0.871	0.763 -0.993	0.039
	2012-2016	0.649	1.913	1.653 -2.214	<0.0001
Diabetes		0.320	1.377	1.042 -1.821	0.025
Pulmonary disease		0.052	1.053	0.792 -1.4	0.722
Cerebral vascular accident		0.372	1.450	0.899 -2.339	0.127
Acute myocardial infarction		0.201	1.222	0.821 -1.821	0.323
Dementia		0.358	1.430	0.883 -2.317	0.146
Congestive heart failure		0.724	2.062	1.063 -3.999	0.032
Renal disease		0.521	1.685	0.825 -3.439	0.152
Cancer		-0.174	0.840	0.502 -1.405	0.506
Peripheral vascular disease		0.144	1.155	0.572 -2.331	0.689
Connective tissue disorder		0.692	1.998	0.847 -4.718	0.114
Paraplegia		2.309	10.060	1.311 -77.223	0.026
Diabetes complications		1.174	3.233	0.765 -13.673	0.111
Metastatic cancer		0.645	1.907	0.538 -6.758	0.318
Previous use of antidepressants		0.287	1.333	1.157 -1.535	<0.0001

Table 6-9- Results of multivariate logistic regression model of L-dopa category

6.4.4.1.7 MAO-B inhibitors' model

Table 6.10 shows that patients aged 61-80 and > 80 years were 51.5% and 85.1% less likely to be prescribed MAO-B inhibitors (p-value <0.0001 for both). There was no significant difference between males and females in the prescription of MAO-B inhibitors. Patients who lived in the least deprived WIMD quintile area were 98.8% more likely to be prescribed MAO-B inhibitors compared to patients in the most deprived quintile area (p-value <0.0001). PwP were 144.3% more likely to be prescribed MAO-B inhibitors in the 2012-2016 period compared to patients in the 2000-2005 period (p-value <0.0001). Patients with diabetes or

pulmonary diseases were less likely to be prescribed MAO-B inhibitors (p-value = 0.004 and 0.041 respectively). A previous use of antidepressants also had a significant effect on the prescription of MAO-B (p-value <0.0001) (Table 6.10).

The Interclass Correlation (ICC) when the model was run with no predictors and with the GP practice and the health board as random intercept = 0.093 (9.3%)					
Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-0.725	0.485	0.394 -0.596	<0.0001
	> 80 years	-1.906	0.149	0.11 -0.2	<0.0001
Sex	Males (ref)				
	Females	-0.153	0.858	0.727 -1.012	0.069
Social deprivation score (WIMD)	1 (most deprived) (ref)				
	2	0.304	1.355	1.004 -1.83	0.047
	3	0.340	1.405	1.055 -1.871	0.020
	4	0.525	1.690	1.268 -2.252	<0.0001
	5 (least deprived)	0.687	1.988	1.513 -2.613	<0.0001
Year of prescribing categories	2000-2005 (ref)				
	2006-2011	0.817	2.263	1.805 -2.838	<0.0001
	2012-2016	0.893	2.443	1.95 -3.06	<0.0001
Diabetes		-0.665	0.514	0.327 -0.809	0.004
Pulmonary disease		-0.498	0.607	0.377 -0.979	0.041
Acute myocardial infarction		-0.538	0.584	0.304 -1.121	0.106
Congestive heart failure		-0.272	0.762	0.33 -1.762	0.525
Cancer		-0.511	0.600	0.242 -1.489	0.271
Previous use of antidepressants		-0.901	0.406	0.318 -0.52	<0.0001

Table 6-10- Results of multivariate logistic regression model of MAO-B inhibitors category

6.4.5 Results of model diagnostics and Goodness of Fit tests

Table 6.11, below, is a summary of the findings of the model diagnostics and Goodness of Fit tests used in this study. All of the models in this study had ROC of $\geq$ 0.7, which means that they have acceptable discriminatory power. Two exceptions were noted, namely the models for anticholinergics and ergot DAs, which were under the 0.7 cut-off. The Hosmer and Lemeshow test statistics indicated that there were three poorly fitting models (i.e. DAs, non-ergot DAs and L-dopa). Other models appeared to be a good fit (Table 6.11).

Logistic model	ROC curve statistic	Hosmer and Lemeshow test statistic	Hosmer and Lemeshow test p-value.
DAs vs. L-dopa	0.781	11.95	0.153
Anticholinergics	0.697	3.92	0.915
DAs	0.732	33.96	<0.0001
Ergot-DAs	0.651	0.357	0.949
Non-ergot DAs	0.729	25.96	0.001
L-dopa	0.748	18.44	0.018
MAO-B inhibitors	0.719	10.78	0.214

Table 6-11-Results of model diagnostics and Goodness of Fit tests

6.4.6 Results of sensitivity analysis

The outcomes of the sensitivity analysis were consistent after excluding dementia patients (data not shown).

6.5 Discussion

6.5.1 Trends in first line therapy for PD in Wales

This was the first study to present a detailed description of the factors associated with the prescription trends of antiparkinsonian medications in newly diagnosed PwP in Wales. Moreover, it was the first study to examine changes in first line therapy in PwP following the publication of the PD-MED study in 2014. The analysis examined 9,142 patients who were prescribed antiparkinsonian medications after the first diagnosis of PD. Between 2000 and 2016, there were significant changes in Wales in the initiation of antiparkinsonian medications in PD. These changes were most likely due to emerging evidence on the efficacy and safety of PD medications.

Overall, L-dopa was the most common first line therapy prescribed (80.6%), which was a pattern that has also been reported in other countries such as the USA, Japan, and Taiwan (234, 236, 248, 249). This study shows that, between 2000 and 2016, the trends in first line therapy underwent a significant switch towards L-dopa and away from non-ergot DAs (especially after 2010) in all Parkinson's patients, regardless of age. None of the previous studies examined the trend of L-dopa as a first line therapy across the years. However, several studies in Australia and New Zealand showed an increase in L-dopa prescriptions before 2010 for all treatment cases, i.e. both as a first line therapy and after the progression of PD (233, 242). In contrast, a recent American study found no change in L-dopa prescribing in the USA between 2010 and 2017 (391). An interesting finding of this study is that the switch to L-dopa and the move away from non-ergot DAs started in 2010. This was the year of publication of the results of the DOMINION study, which identified ICDs as being significantly associated specifically with DA usage (198). Furthermore, other safety concerns related to DAs were discovered around 2010, including an increased risk of heart

failure associated with pramipexole usage (201). These findings may explain the shift from prescribing DAs to prescribing L-dopa, which is both more effective and with has less severe side effects (85). A similar trend was noticed in other studies carried out in the USA, where the prescription rate of non-ergot DAs decreased by 5% between 2008 and 2011. This was for all PwP, regardless of whether or not they were newly diagnosed (231). A recent study that used the CPRD database in the UK found a lower rate of L-dopa prescribing when it was used as an initial therapy (29%) across the UK (392), whereas the current study found a much higher rate (80.6%) in Wales. This could be due to four reasons: (1) difference in time period covered (i.e., the CPRD study covered the years 2004-2015, whereas the current study covered a wider range of years (2000-2016); (2) different study locations (UK vs. Wales); (3) different inclusion criteria (the minimum age in the CPRD study was 30 years compared to 40 years in the current study, which may have increased the chance of prescribing more DAs in this age group; and (4), perhaps the most important reason, overlap between the location and the actual years covered in the two studies. However, this final assumption cannot be confirmed since there was no stratification by age, gender, years of prescribing, comorbidities, or other patient characteristics in the CPRD study, which raised concerns about its quality (392). In general, the current study found that the tendency to prefer L-dopa as a first line therapy continued, especially after the publication of the PD-MED study in 2014 (236), which showed that early initiation of L-dopa resulted in a better QoL in the long term than initiating DAs and MAO-B inhibitors (236). Also, in 2014, some studies found that L-dopa motor complications are not associated with the exposure time to L-dopa therapy *per se*, but rather with the duration of PD progression itself and the dose of L-dopa (393): therefore, there is no reason to withhold L-dopa therapy in attempting to delay the L-dopa motor complications. Unless there is a breakthrough in disease-modifying agents in PD, the preference for L-dopa over DAs in the early stages of PD is expected to remain, given that a new clinical trial

(the LEAP trial) has confirmed that L-dopa does not cause neurotoxicity side effects, but unfortunately is without neuroprotective properties (89).

Regarding the prescription of ergot DAs, it can be seen from the results that the cardiotoxicity issues of pergolide (208) had a huge impact on its rate of prescription. In accordance with these safety issues, there was no single ergot DA prescribed as a first line treatment to any PD patient in the period of 2012-2016. A shift away from pergolide and other ergot DAs was noted in other countries, including England and Japan (238, 241); however, this was not consistent. For example, in New Zealand, pergolide prescriptions rose slightly between 2006 and 2011, which could be due to prescribers' lack of awareness of these side effects (233). In terms of MAO-B inhibitors, the findings suggest that, following the approval of rasagiline in 2006, the general prescription rate of MAO-B inhibitors increased significantly in Wales. This trend was seen previously in the USA, Finland, and other countries in Europe (227, 231, 238, 245). This study also shows that there was no significant increase in MAO-B inhibitors in 2012-2016 compared to 2006-2011. This could be for two reasons: First, the fact that the purported neuroprotective properties suggested by a range of clinical trials (TEMPO (193), ADAGIO (125)) is unsupported by guidelines (194); and, second, the results of the PD-MED study, which affirmed the inferiority of MAO-B inhibitors to L-dopa in terms of QoL in the long term when treating early symptoms of PD (236). In accordance with 2006 and 2017 NICE guidelines (31, 136), anticholinergics prescribed as a first line option declined significantly in the years covered by this study. A similar trend was seen in some western countries and Australia (238, 242). In contrast, anticholinergic prescription rates were found to be generally high in some Asian studies. Reasons given were anticholinergics' low price, affordability, and old guidelines that had not been updated (223, 224, 234). Anticholinergics were routinely used in PD management before the discovery of L-dopa; however, due to their troublesome

side effects, their use is limited at present to managing severe tremors in younger patients who do not suffer from cognitive problems.

Although in this study L-dopa was the most predominantly prescribed drug in all Parkinson's patients regardless of age, among all study predictors age was a significant predictor of prescription type in all of the study models. In general, younger patients (40-60 years) were more likely to be prescribed DAs, MAO-B inhibitors, and anticholinergics. Older patients (60-80 and >80 years), in contrast, were more likely to be prescribed L-dopa. The tendency to prescribe L-dopa to older people and refrain from prescribing DAs was also seen in other studies (227, 243, 248). This finding was in line with several guidelines that recommend refraining from prescribing DAs and anticholinergics to older people and sticking with L-dopa due to its benign side effects when compared to the complicated side effects of DAs and anticholinergics, especially the cognitive side effects (113, 280, 295). Regarding MAO-B inhibitors, the low prescription rate in elderly patients could be explained by the general preference for L-dopa prescriptions in this group, given that there is no evidence that MAO-B inhibitors are less safe for older people (394, 395).

This study found no significant effect in the prescription of L-dopa compared to DAs based on sex. This was previously reported in several studies (231, 232, 244, 246, 249). One study found that women had lower odds of being prescribed L-dopa (219). This difference might be due to the pharmacokinetic profile of L-dopa, since some studies have suggested that women are more likely than men to develop dyskinesia after taking L-dopa (396). However, this explanation cannot be used in this study, since all patients were *de novo* and none had taken L-dopa before the PD diagnosis; therefore, theoretically, they did not have dyskinesia at the time of the first prescription. Regarding other types of PD medications, no previous studies have examined the effect of sex on prescription

rates. However, in this study, an interesting observation was made regarding the effect of sex on prescription. In the univariate model, females were significantly more likely to be prescribed anticholinergics and less likely to be prescribed MAO-B inhibitors. The significant difference was also noted in the multivariate model of anticholinergics, unlike the MAO-B inhibitor model. With regard to anticholinergics, since this category in this study included only four types of anticholinergics (i.e. benztropine, orphenadrine, procyclidine, and trihexyphenidyl), there are no symptoms mentioned in the literature that would be more common in females than males or vice versa to explain these interesting differences. Therefore, additional investigation is warranted to examine the effects of sex on anticholinergics prescriptions in PwP. Regarding MAO-B inhibitors, as there was a significant effect relating to sex in the univariate model, the absence of significance in the multivariate model could be explained by the confounding effect of one of the other factors in the model. The most appropriate explanation is that the MAO-B inhibitors interact with the antidepressants. In general, there is a risk of interaction between MAO-B and certain antidepressants that can result in serotonin syndrome (386). At the same time, previous studies have suggested a higher level of antidepressant use by women than men (397), which does not explain the lower use of MAO-B inhibitors in women in the univariate model but not in the multivariate model, which took into account the previous use of antidepressants.

The study results also yielded an interesting association between the social deprivation score and the prescription of L-dopa and MAO-B inhibitors. No previous studies in the UK have measured or found such an association; however, in the USA, some studies found that more expensive drugs, such as some DAs and MAO-B inhibitors, were more commonly prescribed to patients with higher socioeconomic status (229). However, in Wales, prescriptions have been free since 2007, so patients' economic status should not be an issue (this

has been confirmed by conducting two sensitivity analyses that excluded prescriptions made in or before 2007 which yielded the same results: see Appendix 10). A possible interpretation of this finding is the significant delay in PD diagnosis in some minority groups (374), as indicated by some reports outside the UK. Given that MAO-B inhibitors are often used as a mild starter drug, people with a lower socioeconomic status may be diagnosed at a slightly later disease stage, in which case the decision may be made to start off with more effective therapy (L-dopa) and therefore skip the MAO-B inhibitors step. Since there is no evidence in Wales to support this explanation, it is worth exploring this issue further (i.e. the effect of social deprivation score on delaying diagnosis of PD) in future research.

Another novel finding of this study was the positive association between diabetes and L-dopa prescription. This is also accompanied by a negative association between diabetes and DAs and MAO-B inhibitors prescription. It has been reported in some studies that newly diagnosed PwP who had diabetes before their diagnosis tended to have more severe motor symptoms and were more prone to developing cognitive decline symptoms (398, 399). It might be claimed that the higher likelihood of prescribing L-dopa to this group of patients was possibly due to their more severe motor symptoms. In this study, this claim cannot be confirmed, since no data were available regarding severity of symptoms; however, it is recommended that future studies that have access to severity scales of PD motor symptoms be carried out to confirm or reject this claim. Dementia patients in this study were also significantly associated with higher L-dopa prescription rates and fewer prescriptions of DAs. This finding is in line with the literature that recommends avoiding prescribing DAs in patients with dementia due to the risk of exacerbating dementia symptoms and increasing confusion (400). In contrast to the literature that recommends avoiding giving anticholinergics to dementia patients (401), this study found an

increase in the prescription of anticholinergics to PwP who had dementia before PD diagnosis. This phenomenon is of concern and was also found in a previous study carried out in the USA, but the finding was not statistically significant (248). It could be argued that there is some evidence that the use of anticholinergics might be linked to future dementia, which could lead to this phenomenon, and which would have biased the results (402); however, this bias was minimised in this study by excluding all patients who had used anticholinergics within one year before their first PD diagnosis.

6.5.2 Strengths and weaknesses

This study provides a large and representative sample of newly diagnosed PwP in Wales, which makes it possible to generalise the findings to the Welsh population. The SAIL databank offers a huge benefit in describing patterns and trends of medications prescribed in real practice, albeit with the risk of some data biases. Efforts have been made in this study to validate the diagnosis and prescriptions data in the SAIL databank (see Chapters 4 and 5). To ensure that a newly diagnosed cohort was truly identified, several robust exclusion criteria were applied (such as excluding possible drug-induced parkinsonism cases and possible prevalence cases, as discussed in Chapter 5). Additionally, sensitivity analyses were conducted and they showed a high degree of robustness in the study results. Although there were no available data regarding the severity of PD, this bias has been minimised by limiting the study to newly diagnosed PwP. This study, however, is not without limitations. The date of the first diagnosis was defined as the first diagnostic code of PD in SAIL, but this may not show the true date of diagnosis. Another limitation is that the profiles of comorbidities extracted by the SAIL analyst from hospital data were extracted up to two years before the date of diagnosis instead of the date of first prescription. It is possible that some comorbidities might have arisen between the date of diagnosis and the date of the first prescription. However, the time interval between these two

dates was very short (less than one year in the entire study cohort), which could minimize the possibility of having new comorbidities during this interval. Another limitation is that some regression models were poorly fitting and failed some model diagnostic tests. This might be due to the presence of unmeasured predicting variables; however, all possible predicting factors available in the SAIL data were used in the models, and future research that considers the PD severity scales as predictors is warranted.

6.5.3 Conclusion

Overall, the results suggest a reasonable level of awareness of efficacy and safety concerns that evolved over the last 17 years. First line therapy in PD between 2000 and 2016 in Wales underwent a significant switch towards L-dopa in all Parkinson's patients regardless of age. However, age was a major determinant of prescription choice, which aligns with our understanding of the use of dopamine agonists in cognitive impairment and also recent literature showing that delaying levodopa therapy in younger patients does not result in a better quality of life in the long term. The findings suggest that social deprivation status and the presence of some comorbidities, such as diabetes and dementia, were associated with prescriptions of some categories of PD medications. Disease severity might confound some of these effects, and this necessitates future research to consider disease severity as a predictor of prescription choice.

CHAPTER 7: L-dopa and Risk of Ischemic Heart Disease

7.1 Introduction

Various types of cardiovascular diseases have been reported in PwP, more frequently than in non-PwP (403). In particular, it has been suggested that ischemic heart disease (IHD) is more prevalent in PwP, especially when other traditional risk factors are present, such as hyperlipidemia, diabetes mellitus, smoking, or arterial hypertension (404). Even without other cardiovascular risk factors, some studies have suggested that the prevalence of IHD is more common in PwP compared to non-PwP (403). In the UK, a Scottish study that examined the GP data of 510,502 patients found that PwP were 22% more likely to develop IHD compared to non-PwP after standardization by age, gender, and social deprivation score (405). This association was not found in a recent systematic review that failed to find a difference in IHD prevalence between PD and non-PwP; however, another cardiovascular disease was found to be more prevalent in PwP, namely stroke (406).

Another problem that may add to the burden of cardiovascular diseases in PwP is the cardiovascular side effects that are caused by some PD medications, particularly ergot DAs (208) and non-ergot DAs (204). On the other hand, there has been some controversy about the cardiac safety of L-dopa. Several studies have suggested a link between L-dopa and IHD from a toxicological point of view, since L-dopa could increase the level of homocysteine, which in turn may cause an increase in aortic stiffness and defective diastolic function, possibly leading eventually to IHD (164, 407). However, despite these studies, additional clinical studies are required before extrapolating this observation to the clinical field.

From clinical and pharmacovigilance standpoints, the PD-MED study found no significant difference in the hospitalization rate between L-dopa, non-ergot DAs and MAO-B inhibitors during the seven years of the study; however, the study did not mention the type of hospitalization or reasons for the hospital admission

(cardiovascular vs. respiratory vs other reasons) (101). Therefore, based on the PD-MED study, it is difficult to reach a conclusion regarding the cardiovascular safety of L-dopa, especially given that a newly published case study found a direct association between L-dopa and IHD in PwP, particularly those with a previous history of cardiovascular events (163).

Nevertheless, real observational clinical data regarding the association between L-dopa and IHD is still scarce. Hence, this chapter examines the association between L-dopa and the one-year risk of IHD hospitalization in newly diagnosed PwP using the SAIL databank.

7.2 Objectives of the study

The main objective of this chapter is to investigate associations of IHD hospitalization risk, all-cardiovascular events (including (1) hospitalization due to arrhythmia, heart failure, IHD, or stroke, and (2) mortality due to cardiovascular causes), and all-cause mortality among users of L-dopa and non-ergot DAs compared with users of MAO-B inhibitors among individuals with newly diagnosed PD.

7.3 Methods

7.3.1 The SAIL databases used, the study cohort, and the primary and secondary endpoints

The study is a retrospective cohort study using the SAIL Databank. The WLGP database was used to identify the PD diagnostic codes, PD medications, and other medications used by PwP that might affect the study outcomes (which will be listed later). For example, some drugs, such as angiotensin-converting enzyme (ACE) inhibitors, are highly effective in reducing IHD risk (408), while other drugs

could increase the risk of IHD, such as tricyclic antidepressants (TCA) (409): therefore, use of these kinds of drugs were taken into account when conducting any analysis in this study. The WDS database was used to obtain the demographic data of PwP. PEDW data were used to identify the comorbidities in PwP (Charlson index components) and the first hospitalization event (IHD and other cardiovascular events). The Annual District Death Extract (ADDE) was used to identify the date and cause of death to account for data censoring and to examine cardiovascular and all-cause mortality. The study cohort for this chapter was the 9,142 patients who were newly diagnosed with PD in the SAIL databank and who had been started on any of the PD medications between 1 January 2000 and 30 September 2016 (as previously explained in Chapter 6). The end date of the study was set at 30 September 2016 to allow for one year of follow-up until the last date of accessing the SAIL data in this project (which was 30 September 2017). In order to control for the effects of previous cardiovascular events before using PD medications, the study cohort were classified into two groups: the group of PwP without previous cardiovascular events and the group of PwP with previous cardiovascular events. The study cohorts of these two groups were restricted to patients who had been prescribed a monotherapy of L-dopa (without entacapone), non-ergot DAs, or MAO-B inhibitors after the first PD diagnosis (therefore, patients prescribed any polytherapy, L-dopa/carbidopa/entacapone combinations, ergot DAs, COMT inhibitors, or anticholinergics were excluded from the analysis). L-dopa/carbidopa/entacapone and COMT inhibitors were excluded to eliminate the possible cardiotoxic effect of entacapone that has been suggested in some previous studies (213). Ergot DAs were excluded due to their low prescribing rates and their confirmed cardiotoxicity (208).

The index date in both study groups (i.e. with previous cardiovascular events and without previous cardiovascular events) was the date of the first PD prescription

in the newly diagnosed PwP. Patients were followed up until the outcome of interest occurred. Person time at risk was measured in days. The primary outcome of this study was the first event of IHD hospitalization (model 1) since the index date. The secondary outcomes were the first event of all cardiovascular events (model 2) and all-cause mortality (model 3) since the index date. Details of these three models, including the time of data censoring, can be seen in Table 7-1. Table 7-2 shows the ICD-10 clinical codes used to identify IHD and other cardiovascular diseases in the hospital data (PEDW).

The one-year follow-up period was chosen to examine the effect of L-dopa on the risk of the outcomes while minimizing the possible confounding effects of the progression of PD motor symptoms (410), since no data on PD progression were available in the SAIL databank. Additionally, the goal of this study was to examine the immediate effect of L-dopa on the study outcomes, and the one-year period seemed to be a reasonable duration to reach this goal. Furthermore, a published case study found a direct and immediate association (within hours after initial use of L-dopa) between L-dopa and IHD in PwP (163), which could also justify the use of a one-year period in the current study.

	Model 1 (ischemic heart disease (IHD))	Model 2 (all cardiovascular events including cardio mortality)	Model 3 (all-cause mortality)
Event (Status)	First diagnostic code of IHD in the hospital data (PEDW) within 365 days after the first prescription of PD medication.	First diagnostic code of all cardiovascular events (IHD, arrhythmia, stroke, or heart failure) in the hospital data (PEDW) or the first cardio mortality in the mortality data (ADDE) within 365 days after the first prescription of PD medication.	The first record of all-cause mortality, including cardio mortality, within 365 days after the first prescription of PD medication.
Index date	The date of the first PD prescription in the newly diagnosed PwP		
Censoring (if any of the following happened before the event)	1. If death occurred. 2. If the PD medication was stopped or changed (if there were more than two months without a prescription of the same initial PD medication, the case would be censored (after adding one month to the date of the last prescription to allow the final presumed dispensed prescription to be utilized by the patient. Additionally, if a new PD medication was added to the patient, the case was censored. 3. If any other cardio event other than IHD happened (i.e., arrhythmia, stroke, or heart failure). 4. The date of patient transfer out from SAIL. 5. Completion of the study duration (i.e. 365 days).	1. If death happened (other than cardio mortality). 2. If the PD medication was stopped or changed (if there were more than two months without a prescription of the same initial PD medication) the case was censored (after adding one month to the date of the last prescription to allow the final presumed dispensed prescription to be utilized by the patient. Additionally, if a new PD medication was added to the patient, the case was censored. 3. The date of patient transfer out from SAIL. 4. Completion of the study duration (i.e., 365 days).	1. If the PD medication was stopped or changed (if there were more than two months without a prescription of the same initial PD medication) the case was censored (after adding one month to the date of the last prescription to allow the final presumed dispensed prescription to be utilized by the patient. Additionally, if a new PD medication was added to the patient, the case was censored. 2. The date of patient transfer out from SAIL. 3. Completion of the study duration (i.e., 365 days).

Table 7-1- Details of the three models used in this study

Outcome	ICD-10 diagnostic codes
Arrhythmia	I45, I47, I48, I49
Heart failure	I50
Ischemic heart disease	I20, I21, I22, I23, I24
Stroke	I60, I61, I62, I63, I64, I65, I66

Table 7-2- ICD-10 codes used to identify study outcomes

7.3.2 Primary variable of interest in the models

The primary variable of interest in all models was the type of PD medication prescribed to newly diagnosed PwP (L-dopa and non-ergot DAs vs. MAO-B inhibitors). Although non-ergot DAs were not the focus of this study, for the sake of completion and to verify the findings of some previous studies that did not find a link between non-ergot DAs and IHD in PwP (204), non-ergot DA users were considered in this study. On the other hand, the PwP who had been prescribed MAO-B inhibitors (selegiline and rasagiline) constituted the reference group. The rationale behind that was that rasagiline is well known for its cardiovascular safety (411, 412). There were some reports in the late 1990s that suggested that selegiline could cause severe orthostatic hypotension (413); however, none of the large-scale clinical trials of selegiline (124, 190, 414) found such a risk or any other significant cardiovascular side effects. Therefore, MAO-B inhibitors (both selegiline and rasagiline) were chosen to be the reference group in this study.

7.3.3 Covariates

As was explained in Chapter 6, the covariates included age, sex, social deprivation status, health board, year of prescribing, and comorbidities. However, unlike the categorical nature of the age variable in Chapter 7, age was treated in this study as a continuous variable to allow more control for the confounding effect of age on the study outcome. Furthermore, and unlike in Chapter 6, the confounding effect of the previous use of several classes of medications that might have had an impact on the IHD risk was considered in this study. These medications comprised diuretics, alpha blockers, beta blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), lipid lowering agents, anti-arrhythmia agents, anti-diabetics (415), antiplatelets, anticoagulants (416), tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), other types of antidepressant (417), nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (418).

Another covariate was added to the group of PwP with previous cardiovascular events. This covariate was the duration between the last cardiovascular event before the index date in PEDW and the first PD prescription. Then, it was categorized into five categories: i.e., one year, two years, three years, four years, or five years and more. This was done to control for long-term cardiovascular disease progression, which might increase with time following IHD or other cardiovascular diseases (419).

7.3.4 Statistical test

7.3.4.1 PwP without previous cardiovascular events group

Patients' characteristics were tabulated and summarized by the type of PD medication. The Cox regression (proportional hazards regression) was used to examine the association between the first PD prescription and the outcome of interest. The first step in building the final regression model was to determine which independent variables to include in the model. The weighted Wald test was conducted to determine whether the overall effect of each independent variable was significant in the model. A particular variable was included in the multivariate model if the p-value of the Wald test was $\leq$ 0.20 (390). Some covariates (*a priori* variables) were included in the multivariable model even though they had a p-value greater than 0.20 because they had theoretical reasons for inclusion. For example, in model (1), in patients without previous cardiovascular events, the type of PD medication variable resulted in a p-value of 0.298; however, it was included in the model, since it was the primary variable of interest. Consequently, and based on the outcomes of the univariate analysis, a multivariate Cox regression that included the candidate variables was built. Before conducting the analysis, the proportional hazard (PH) assumption was assured by conducting the Schoenfeld test. The results of the Schoenfeld test revealed no violations, and hence, the covariates were independent of time. Therefore, the Cox regression model was conducted for all three models. The main explanatory covariate was the type of first PD medication (L-dopa vs. MAO-B inhibitors, and non-ergot DAs vs. MAO-B inhibitors). The final equation of the Cox regression as it appeared in the R 3.5.0 software was as follows:

coxph(Surv(time.to.endpoint, endpoint) ~ type.of.PD.medication + other covariates

In addition to the previous analysis, propensity score methods that control the effect of confounding by treatment type were utilized (420). The propensity score in this case was the probability of being prescribed a particular PD medication at the index date. This was done to maximize the chance that the distribution of observed baseline covariates was similar between treatment group (L-dopa or non-ergot DAs) and reference group (MAO-B inhibitors). Two statisticians were consulted to verify the appropriateness of this method. For every model (IHD, cardiovascular event, etc.), two logistic regression tests were conducted. The dependent variable in the first logistic regression test was being prescribed L-dopa vs. MAO-B inhibitors. On the other hand, being prescribed non-ergot DAs vs. MAO-B inhibitors was the dependent variable in the second logistic regression test. The propensity scores were obtained from these logistic regression models by including the candidate covariates (based on the previous Wald tests or theoretical reasons) as independent variables and the type of medication as dependent variables. To avoid the possibility of violating the linearity assumption of propensity scores, they were categorized into five quintiles (i.e. 0-0.2, 0.21-0.4, 0.41-0.6, 0.61-0.8, and 0.81-1). The propensity score was then added to the Cox regression model as a covariate instead of all of the aforementioned candidate covariates. The main explanatory covariate, which was the type of first PD medication, was also added to the model. The final equation of the Cox regression as it appeared in the R 3.5.0 software was as follows:

coxph(Surv(time.to.endpoint, endpoint) ~ type.of.PD.medication + Propensity.score

The hazard ratio (HR) and confidence intervals were obtained, and the significance level was set at 0.05. Any variable that had fewer than five patients in any group was excluded from the analysis, as recommended by the SAIL

ethical rules. Additionally, some variables (especially in the group of PwP with previous cardiovascular events), although the number of patients was greater than five, were excluded following the SAIL team's recommendation to minimize the risk of any future disclosure of patients' identities. The analysis was carried out using R version 3.5.0 and SPSS version 24.

7.3.4.2 PwP with previous cardiovascular events group

The previous statistical steps were also followed in this group of patients, except for three points. The first point was that a new variable was added to the candidate variables: specifically, the duration between the last cardiovascular event before the index date and the first PD prescription. The second point was that the *a priori* variables were included in the multivariable model. The *a priori* variables in this case were those variables that were chosen in the previous group (i.e., PwP without previous cardiovascular events). The *a priori* variables were also used in the propensity score calculation. The third point was that in this group, only the propensity score method that controlled the effect of confounding by treatment type was utilized.

7.4 Results

Figure 7-1 shows the process of selection of the final sample in both study groups. Appendix 11 shows a detailed description of the total number of patients and whether they developed the study outcomes or not.

7.4.1 PwP without previous cardiovascular events group

In total and out of the 9,142 patients who were newly diagnosed with PD in the SAIL databank (see Chapter 6), 6,487 PwP met the inclusion criteria for this

group. Table 7-3 describes the characteristics of this cohort. Of the group sample, 79.2%, 13.14%, and 7.6% were prescribed L-dopa, non-ergot DAs, and MAO-B inhibitors respectively. In total and within one year after the first PD prescription, 1.75% (n = 114) of patients were hospitalized due to IHD, 3.9% (n = 257) of patients were hospitalized due to all cardiovascular events, and 4.7% (n = 297) of patients had died.

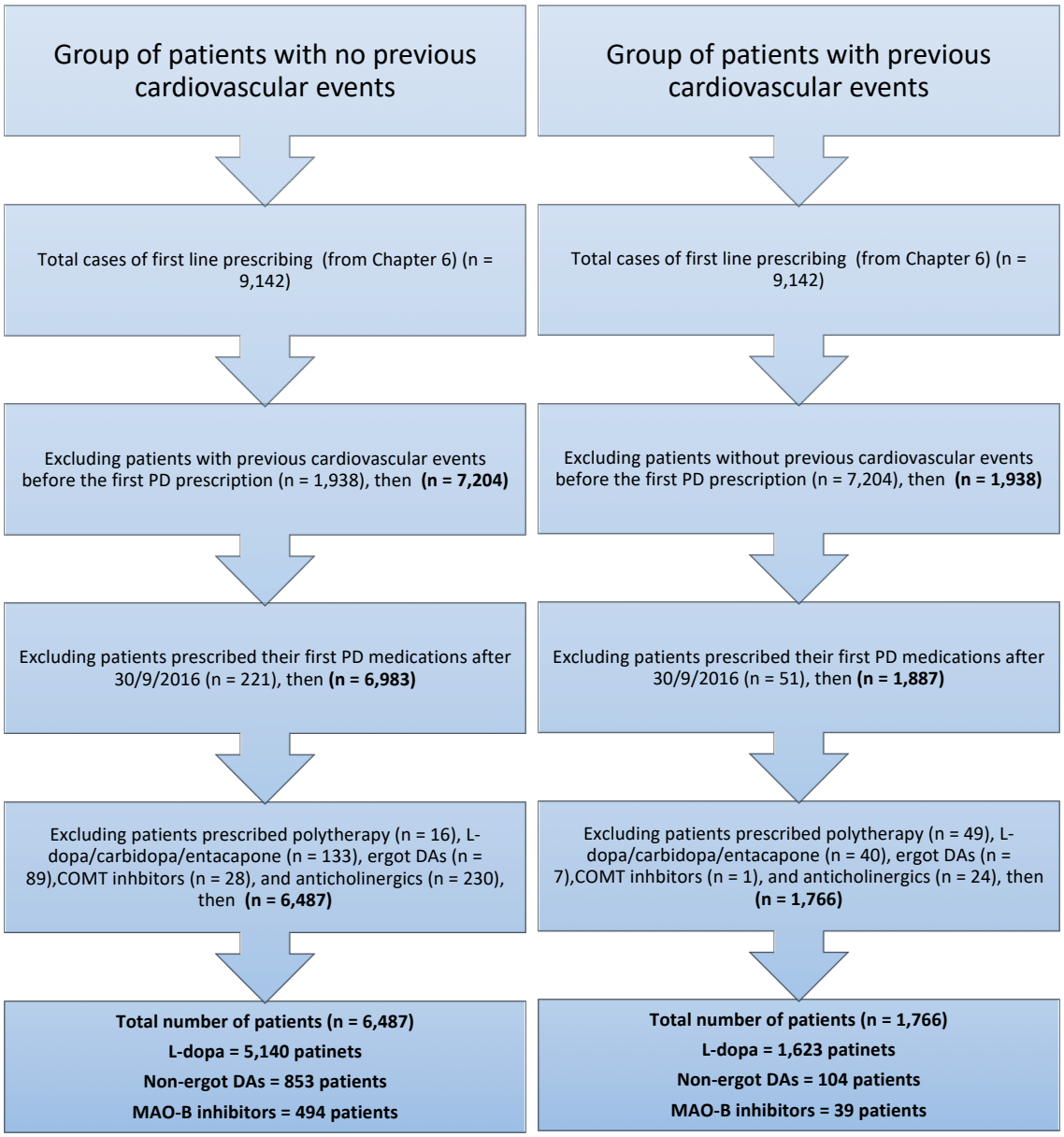


Figure 7-1- Sample selection process

Patients' characteristics	L-dopa therapy (n = 5,140)	Non-ergot DAs (n = 853)	MAO-B inhibitors (n = 494)
Age at the time of prescription	75.57 (95% CI 75.32-75.82)	65.30 (95% CI 64.70-65.91)	67.22 (95% CI 66.37-68.08)
Male	2,919 (56.8 %)	521 (61.1 %)	320 (64.8 %)
Social deprivation score (WIMD)			
WIMD 1 (most deprived)	818 (15.9 %)	133 (15.6 %)	46 (9.3 %)
WIMD 2	920 (17.9 %)	147 (17.2 %)	83 (16.8 %)
WIMD 3	1172 (22.8 %)	207 (24.3 %)	106 (21.5 %)
WIMD 4	1012 (19.7 %)	178 (20.9 %)	106 (21.5 %)
WIMD 5 (least deprived)	1218 (23.7 %)	188(22.0 %)	153 (31.0 %)
Year of prescribing categories			
2000-2005	1557 (30.3 %)	298 (34.9 %)	72 (14.6 %)
2006-2011	1737 (33.8 %)	416 (48.8 %)	233 (47.2 %)
2012-2016	1846 (36 %)	139 (16.3 %)	189 (38.3 %)
Health board			
Abertawe Bro Morgannwg	1264 (24.6 %)	211 (24.7 %)	44 (8.9 %)
Aneurin Bevan	745 (14.5 %)	146 (17.2 %)	60 (12.1 %)
Betsi Cadwaladr	1105 (21.5 %)	171 (20.0 %)	167 (33.8 %)
Cardiff & Vale	704 (13.7 %)	105 (12.2 %)	122 (24.7 %)
Cwm Taf	462 (9 %)	94 (10.9 %)	24 (4.9 %)
Hywel Dda	673 (13.1 %)	83 (9.8 %)	69 (14 %)
Powys	190 (3.7 %)	43 (5.0 %)	8 (1.6 %)
Co-morbidities and medications			
Hypertension	2046 (39.8 %)	240 (28.1 %)	168 (34 %)
Diabetes	277 (5.4 %)	11 (1.3 %)	12 (2.4 %)
Pulmonary disease	216 (4.2 %)	21 (2.5 %)	12 (2.4 %)
Dementia	123 (2.4 %)	n less than 5	n less than 5
Renal disease	56 (1.1 %)	n less than 5	n less than 5
Cancer	61 (1.2 %)	9 (1.1 %)	n less than 5
Connective tissue disorder	46 (0.9 %)	5 (0.6 %)	n less than 5
Peptic ulcer	20 (0.4 %)	n less than 5	n less than 5
Metastatic cancer	20 (0.4 %)	n less than 5	n less than 5
Diuretics before first PD prescription	1459 (28.4 %)	150 (17.6 %)	68 (13.8 %)
Alpha blocker	175 (3.4 %)	19 (2.3 %)	16 (3.2 %)
Beta blocker	971 (18.9 %)	172 (20.2 %)	94 (19 %)
Calcium channel blocker	961 (18.7 %)	122 (14.3 %)	77 (15.6 %)
ACE inhibitors	987 (19.2 %)	123 (14.4 %)	85 (17.2 %)
ARB inhibitors	334 (6.5 %)	47 (5.6 %)	22 (4.5 %)
Lipid lowering agents	1388 (27 %)	196 (23 %)	134 (27.1 %)
Antiplatelet	1449 (28.2 %)	178 (20.9 %)	92 (18.6 %)
Anticoagulants	236 (4.6 %)	21 (2.5 %)	16 (3.2 %)
Antidiabetics	447 (8.7 %)	44 (5.2 %)	30 (6.1 %)
Tri cyclic antidepressants	483 (9.4 %)	74 (8.7 %)	22 (4.5 %)
SSRI antidepressants	843 (16.4 %)	128 (15 %)	39 (7.9 %)
Other antidepressants	246 (4.8 %)	21 (2.5 %)	10 (2 %)
Anti-arrhythmia agents	133 (2.6 %)	10 (1.2 %)	11 (2.2 %)
NSAIDs or COX 2 inhibitors	1023 (19.9 %)	220 (25.8 %)	109 (22.1 %)

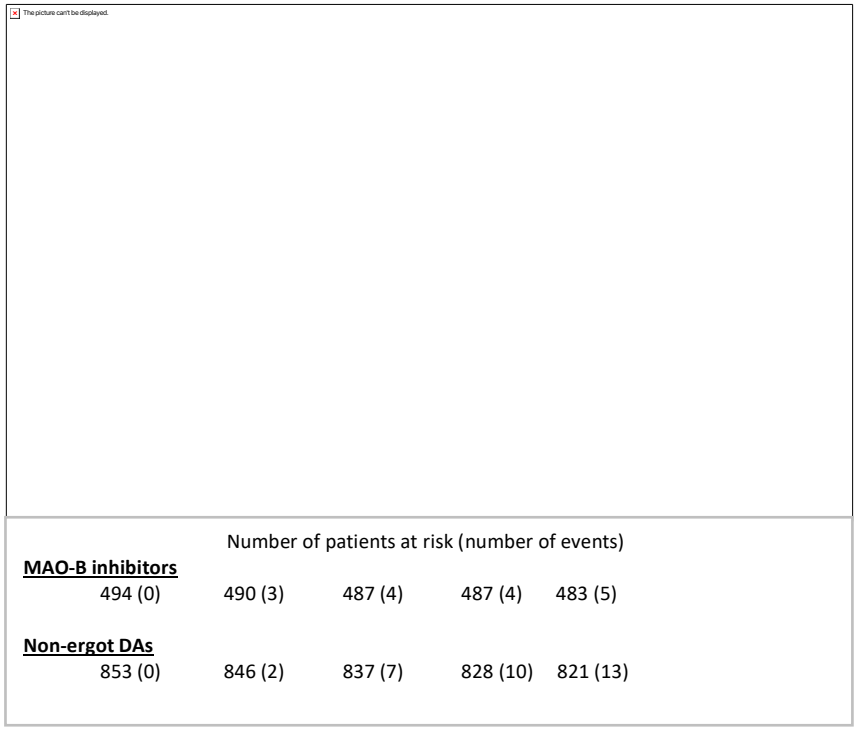
Table 7-3- Cohort characteristics (PwP without previous cardiovascular events)

7.4.1.1 Ischemic heart disease

Using multivariate Cox models – adjusting for covariates and propensity score – no statistically significant difference was found between L-dopa and MAO-B inhibitors with respect to the primary outcome in this study: i.e., IHD. Table 7-4 shows that this lack of difference was also seen in the unadjusted model and in the age-adjusted model. Figure 7-2 presents the Cox regression curves comparing IHD hospitalization over time (365 days) for PwP prescribed L-dopa vs. patients prescribed MAO-B inhibitors. There was no significant difference in risk of IHD hospitalization between the two medications in the propensity-score-adjusted model (p-value = 0.409). Table 7-4 and Figure 7-2 show also that non-ergot DAs were not associated with IHD in all models.

Model	L-dopa prescribing HR (95% CI)	L-dopa prescribing p-value	Non-ergot DAs HR (95% CI)	Non-ergot DAs p-value
Unadjusted model	1.905 (0.775-4.681)	0.160	1.515 (0.540-4.249)	0.430
Model adjusted for age only	1.462(0.586-3.651)	0.416	1.632 (0.581-4.585)	0.352
Model adjusted for all covariates (*a priori* variables and those with Wald test p-values of < 0.20).	1.306 (0.521 -3.271)	0.570	1.319 (0.462 -3.733)	0.603
Model adjusted for the propensity score covariate	1.475 (0.586 -3.711)	0.409	1.386 (0.464-4.128)	0.561

Table 7-4-Multivariable Cox regression analysis of the association between L-dopa and non-ergot DAs prescribing and IHD in PwP without previous cardiovascular events. (MAO-B inhibitors are used as the reference group).



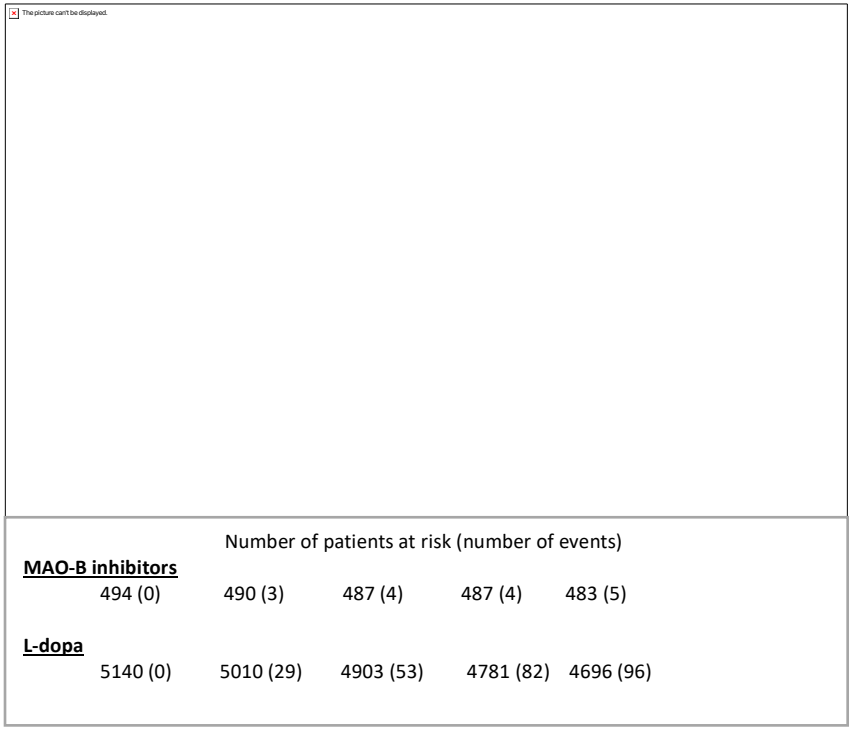


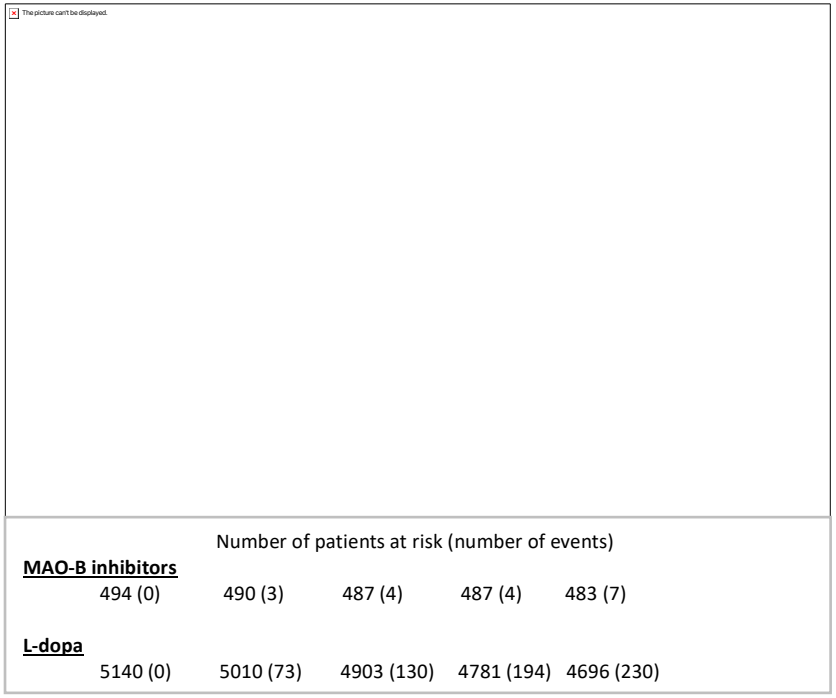
Figure 7-2- Propensity score adjusted Cox regression survival curve of the association between L-dopa and non-ergot DAs prescribing and IHD in PwP (**p-value of L-dopa =0.409 and p-value of non-ergot Das = 0.561**)

7.4.1.1 All cardiovascular events

Table 7-5 shows that in the unadjusted model, L-dopa was associated with a significantly increased risk for all cardiovascular events (HR = 3.258, 95% CI: 1.536-6.910, p-value = 0.002). This significant association disappeared after adjustment for age, other covariates, or propensity score. Figure 7-3 presents the Cox regression curves comparing all cardiovascular events over time (365 days) for PwP prescribed L-dopa vs. MAO-B inhibitors. There was no significant difference in the risk of all cardiovascular events between the two medications in the propensity score adjusted model (p-value = 0.070). Table 7-5 and Figure 7-3 show also that non-ergot DAs were not associated with all cardiovascular events in all models.

Model	L-dopa prescribing HR (95% CI)	L-dopa prescribing p-value	Non-ergot DAs HR (95% CI)	Non-ergot DAs p-value
Unadjusted model	3.258 (1.536-6.910)	0.002	1.664 (0.704-3.936)	0.246
Model adjusted for age only	2.030 (0.949-4.343)	0.068	1.992 (0.812-4.550)	0.137
Model adjusted for all covariates (*a priori* variables and those with Wald test p-values of < 0.20).	1.829 (0.852 -3.927)	0.121	1.744 (0.734 -4.146)	0.208
Model adjusted for the propensity score covariate	2.030 (0.944 -4.356)	0.070	1.747 (0.699-4.366)	0.233

Table 7-5- Multivariable Cox regression analysis of the association between L-dopa and non-ergot DAs prescribing and all cardiovascular events in PwP without previous cardiovascular events. (MAO-B inhibitors are used as the reference group).



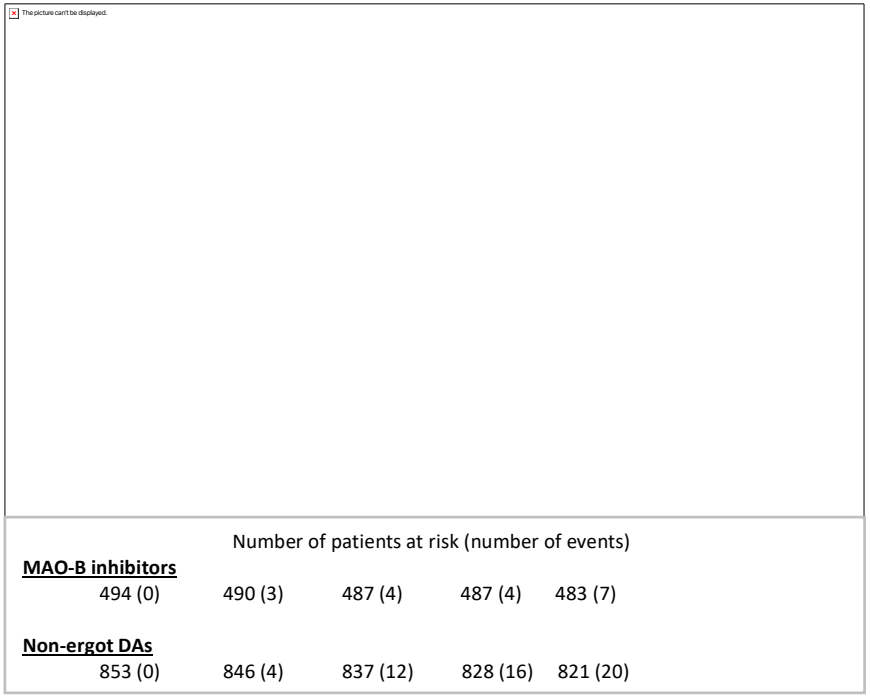


Figure 7-3- Propensity score adjusted Cox regression survival curve of the association between L-dopa and non-ergot DAs prescribing and all cardiovascular events in PwP (**p-value of L-dopa = 0.070 and p-value of non-ergot DAs = 0.233**)

7.4.1.2 All-cause mortality

The multivariate Cox models – adjusted for covariates and propensity score – show no statistically difference between L-dopa and MAO-B inhibitors in all-cause mortality. Table 7-6 shows that there was a difference in the unadjusted model and in the age adjusted model. Figure 7-4 presents the Cox regression curves comparing all-cause mortality over time (365 days) for PwP prescribed L-dopa vs. patients prescribed MAO-B inhibitors. There was no significant difference in the risk of all-cause mortality between the two medications in the propensity-score-adjusted model (p-value = 0.116). Table 7-6 and Figure 7-4 show also that non-ergot DAs were not associated with all-cause mortality in all models.

Model	L-dopa prescribing HR (95% CI)	L-dopa prescribing p-value	Non-ergot DAs HR (95% CI)	Non-ergot DAs p-value
Unadjusted model	5.441 (2.247-13.176)	<0.0001	1.742 (0.633-4.792)	0.283
Model adjusted for age only	2.492 (1.023-6.073)	0.044	2.227 (0.809-6.133)	0.121
Model adjusted for all covariates (*a priori* variables and those with Wald test p-values of < 0.20).	2.036 (0.831 -4.986)	0.120	1.727 (0.624 -4.78)	0.293
Model adjusted for the propensity score covariate	2.044 (0.838-4.987)	0.116	1.987 (0.579-5.001)	0.334

Table 7-6- Multivariable Cox regression analysis of the association between L-dopa and non-ergot DAs prescribing and all-cause mortality in PwP without previous cardiovascular events (MAO-B inhibitors are used as the reference group).

Figure 7-4- Propensity score adjusted Cox regression survival curve of the association between L-dopa and non-ergot DAs prescribing and all-cause mortality in PwP (**p-value of L-dopa = 0.116 and p-value of non-ergot DAs = 0.334).**

7.4.1 PwP with previous cardiovascular events group

A total of 1,766 PwP met the inclusion criteria in this group. Table 7-7 describes this cohort's characteristics. All Cox models (unadjusted and adjusted for age and propensity score) show no difference between L-dopa and MAO-B inhibitors in the study outcomes (Table 7-8).

Patient characteristics	L-dopa therapy (n = 1623)	Non-ergot DAs (n = 104)	MAO-B inhibitors (n = 39)
Age at the time of prescription	79.03 (95% CI 78.76-79.40)	71.19 (95% CI 69.54-72.83)	70.12 (95% CI 67.69-72.55)
Male	1,000 (61.6%)	62 (59.6 %)	30 (76.9 %)
Social deprivation score (WIMD)			
WIMD 1 (most deprived)	308 (19%)	20 (19.2%)	n less than 5
WIMD 2	343 (21.1 %)	23 (22.1%)	6 (15.4%)
WIMD 3	351 (21.6 %)	24 (23.1%)	11 (28.2%)
WIMD 4	308 (19%)	15 (14.4 %)	n less than 5
WIMD 5	313 (19.3 %)	22 (21.2%)	14 (35.9%)
Year of prescribing categories			
2000-2005	374 (23 %)	20 (19.2 %)	5 (12.8%)
2006-2011	600 (36.9 %)	53 (51 %)	20 (51.3 %)
2012-2016	649 (40 %)	31 (29.8 %)	14 (35.9 %)
Health board			
Abertawe Bro Morgannwg	398 (24.5 %)	21 (20.2 %)	n less than 5
Aneurin Bevan	251 (15.5 %)	26 (25 %)	6 (15.4 %)
Betsi Cadwaladr	350 (21.6 %)	20 (19.2 %)	12 (30.8 %)
Cardiff & Vale	204 (12.6 %)	14 (13.5 %)	12 (30.8 %)
Cwm Taf	172 (10.6 %)	13 (12.5 %)	n less than 5
Hywel Dda	187 (11.5%)	n less than 10 (due to the possibility of future disclosure)	n less than 10 (due to the possibility of future disclosure)
Powys	60 (3.7%)	n less than 10 (due to the possibility of future disclosure)	n less than 10 (due to the possibility of future disclosure)
Duration since the first cardiovascular event in PEDW			
One year	230 (14.2%)	13 (12.5%)	n less than 5
Two years	321 (19.8%)	17 (16.3%)	11 (28.2%)
Three years	143 (8.8%)	9 (8.7%)	n less than 5
Four years	132 (8.1%)	12 (11.5%)	n less than 5
Five years and more	797 (49.1%)	53 (51%)	19 (48.7%)
Co-morbidities and medications			
Hypertension	826 (50.9%)	53 (51 %)	28 (71.8 %)
Acute myocardial infarction	225 (13.9%)	16 (15.4%)	n less than 5
Congestive heart failure	170 (10.5%)	6 (5.8%)	n less than 5
Peripheral vascular disease	89 (5.5%)	6 (5.8%)	n less than 5
Cerebral vascular accidents	295 (18.2%)	12 (11.5%)	n less than 5
Diabetes	287 (17.7%)	22 (21.2%)	8 (20.5 %)
Pulmonary disease	201 (12.4%)	15 (14.4%)	n less than 5
Dementia	101 (6.2%)	5 (4.8 %)	n less than 5
Renal disease	88 (5.4%)	n less than 5	n less than 5
Cancer	70 (4.3%)	n less than 5	n less than 5
Connective tissue disorder	32 (2 %)	n less than 5	n less than 5
Peptic ulcer	13 (0.8 %)	n less than 5	n less than 5
Metastatic cancer	8 (0.5 %)	n less than 5	n less than 5
Diuretics before first PD prescription	746 (46%)	41 (39.4 %)	11 (28.2 %)
Alpha blocker	63 (3.9 %)	6 (5.8 %)	n less than 5
Beta blocker	649 (40%)	53 (51 %)	18 (46.2%)
Calcium channel blocker	441 (27.2 %)	28 (26.9 %)	12 (30.8 %)
ACE inhibitors	652 (40.2 %)	42 (40.4 %)	17 (43.6 %)
ARB inhibitors	174 (10.7%)	14 (13.5 %)	6 (15.4 %)
Lipid lowering agents	980 (60.4 %)	76 (73.1 %)	26 (66.7 %)
Antiplatelet	1058 (65.2 %)	69 (66.3 %)	28 (71.8 %)
Anticoagulants	251 (15.5 %)	13 (12.5 %)	n less than 5
Antidiabetics	277 (17.1 %)	23 (22.1 %)	7 (17.9 %)
Tri cyclic antidepressants	167 (10.3 %)	13 (12.5 %)	n less than 5
SSRI antidepressants	333 (20.5 %)	25 (24 %)	n less than 5
Other antidepressants	83 (5.1 %)	6 (5.8 %)	n less than 5
Anti-arrhythmia agents	157 (9.7 %)	5 (4.8 %)	n less than 5
NSAIDs or COX 2 inhibitors	256 (15.8 %)	22 (21.2 %)	6 (15.4 %)

Table 7-7- Cohort characteristics (PwP with previous cardiovascular events)

Model	L-dopa prescribing HR (95% CI)	L-dopa prescribing p-value	Non-ergot DAs HR (95% CI)	Non-ergot DAs p-value
Ischemic heart disease (IHD)				
Unadjusted model	1.820 (0.253-13.079)	0.552	1.538 (0.172-13.758)	0.700
Model adjusted for age only	1.699 (0.232-12.464)	0.602	1.177 (0.127-10.914)	0.886
Model adjusted for the propensity score covariate	1.317 (0.183- 9.475)	0.785	1.346 (0.126-14.395)	0.806
All cardiovascular events				
Unadjusted model	1.315 (0.420-4.123)	0.638	0.913 (0.236-3.530)	0.895
Model adjusted for age only	1.082 (0.340-3.447)	0.894	0.638 (0.159-2.560)	0.526
Model adjusted for the propensity score covariate	1.138 (0.354- 3.661)	0.828	1.622 (0.306-8.587)	0.570
All-cause mortality				
Unadjusted model	1.954 (0.626-6.102)	0.249	1.320 (0.795-2.189)	0.283
Model adjusted for age only	1.011 (0.320-3.197)	0.985	0.893 (0.231-3.455)	0.870
Model adjusted for the propensity score covariate	1.638 (0.516- 5.200)	0.403	0.326 (0.076-1.405)	0.133

Table 7-8- Multivariable Cox regression analysis of the association between L-dopa and non-ergot DAs prescribing and all study outcomes in PwP with previous cardiovascular events. (MAO-B inhibitors are used as the reference group).

7.5 Discussion

7.5.1 L-dopa and risk of ischemic heart disease

This study examined the association between being prescribed L-dopa and the subsequent risk of IHD, all cardiovascular events, and all-cause mortality in a large cohort of newly diagnosed PwP, while considering a broad range of other covariates. This study examined two groups of patients: i.e., patients with and without previous cardiovascular events. In both groups, and within one year of the first prescription, there were no statistically significant associations between levodopa monotherapy and increased risk of ischemic heart disease, other cardiovascular events, or all-cause mortality in models adjusted for all covariates and adjusted for the propensity score. However, the small sample size in the reference group (MAO-B inhibitors) can limit the interpretation, and caution should be exercised in interpreting the finding.

Previous research on L-dopa cardiovascular safety has been sparse and inconclusive. The current study findings were consistent with evidence from previous L-dopa clinical trials (89, 271), indicating that there were no differences in cardiovascular events and particularly IHD between L-dopa and placebo. For example, Verschuur and colleagues (89) randomly assigned patients with early Parkinson's disease to L-dopa or placebo with a follow-up period of 80 weeks, and found no significant difference in the risk of IHD between the two groups. Furthermore, the current findings were similar to those in the PD MED study (101), which found no significant difference in the risk of entering hospitals or institutional care between L-dopa and L-dopa-sparing therapy (MAO-B inhibitors and DAs) during the seven years of the study ($p = 0.4$). The PD MED study, however, did not pay particular attention to cardiovascular hospitalization, and it considered both DAs and MAO-B inhibitors as one comparative arm, which, in terms of cardiovascular risk, could introduce bias into the results because of the

possible risk of heart failure associated with non-ergot DAs (204). The current study, however, looked particularly at IHD and all cardiovascular risk, and restricted the comparative arm (control group) to MAO-B inhibitors only, and it reached the same conclusion as the PD MED study: that is, that L-dopa was not less safe than other PD medications in terms of hospitalization rate (101).

There have been 2 previous studies which did raise concerns, suggesting a link between L-dopa and an increase in the level of homocysteine, which could lead to IHD in PwP (163, 407). Roger and colleagues (407) found that an increase in the homocysteine level in L-dopa users was associated with an increasing risk of cardiovascular diseases (IHD and others); however, there was no control for a broad range of possible covariates that might affect the risk of cardiovascular disease, such as comorbidities and previous medications use. Less persuasively was a case study (163) in which Ng and colleagues reported a case study of a 77-year-old male with no history of previous cardiovascular diseases, who developed myocardial infarction following levodopa initiation. Our study did not find such an association even in patients with previous cardiovascular events in whom the risk of such events was already greatly increased. This would suggest that despite the toxicological reports that revealed an association between L-dopa and the increase in the level of homocysteine and hence an increase in the risk of IHD and other cardiovascular diseases (164, 407), this association could not be found in the real clinical settings. A possible reason for this is the complexity of the pharmacological role of L-dopa, especially its possible role in reducing vascular risk factors, such as hypertriglyceridemia and blood glucose, which might counterbalance the effect of the higher homocysteine level (421). Another possible reason is that the cardiovascular risks caused by high homocysteine levels were not severe enough to cause cardiovascular hospitalization in the study sample. Unfortunately, our current study did not have data available regarding either L-dopa dose or blood homocysteine levels. It

was therefore not possible to determine any direct relationship between L-dopa dose and the homocysteine level, any subsequent effect on the risk of cardiovascular hospitalization. Furthermore, no data were available regarding some over-the-counter (OTC) medicines or commercial products that might reduce the level of homocysteine, such as vitamins B6 and B12 and folic acid (422). Although our results report important exploratory findings, they have low power to detect clinically important differences in cardiovascular risk in L-dopa users due to the small sample size. Future studies using larger population-based datasets are needed to confirm the current findings.

Similar to the results of the PD MED study (204), the current study found no association between L-dopa and an increased mortality rate. The PD MED study compared the rate of mortality between L-dopa and L-dopa spring therapy (both MAO-B inhibitors and DAs) and found no difference in the mortality rate between the two arms of the trial ($p = 0.2$). The current study confirmed such a pattern, but particularly in the L-dopa users against MAO-B inhibitors users only ($p = 0.11$). This is an important difference between the current study and the PD-MED study, since the PD MED study considered all the DAs in the control group (regardless of whether they were non-ergots or ergots), and both of those two types were associated with some type of cardiovascular toxicity, which could theoretically contribute to the rise in the mortality rate (204, 208, 423). However, according to the current findings, the lack of association between L-dopa and the mortality rate was also seen when considering MAO-B inhibitors only as a reference group.

7.5.2 Strengths and weaknesses

This study had several strengths. The SAIL databank makes it possible to link GP files to hospital and death data, and given that SAIL covers almost 80% of all GP

files in Wales (305), the generalizability of the results can be increased, and the reflection of real clinical practice can be maximized. Additionally, the analysis was conducted in two different groups (i.e., with and without previous cardiovascular events), therefore enabling a valid conclusion to be drawn in those two groups.

Although multiple adjustments have been made to the study models, residual confounding is still a threat to this type of observational studies. Specifically, the PD clinical data were not available in the SAIL databank. The shorter duration of follow-up (one year), could be determined as a limitation but this was intentional to as the goal of the study was to examine the immediate and early effects of L-dopa initiation. The relatively lower number of patients in the reference group (MAO-B inhibitors) compared to the L-dopa and non-ergot DAs groups could be problematic in some types of analysis, such as propensity score matching (PSM), in which pairs of treated and untreated patients are formed, such that matched patients have similar propensity score values (420). PSM requires a pool of potential controls that is much larger than the number of treated subjects (420). This obviously does not occur with the current data. Therefore, and based on advice from a statistician, Cox regression was used to model the risk of developing the study outcomes while keeping the group indicator (type of PD medication) as the primary variable of interest and adjusting the model for other relevant patient characteristics. But despite all this, the study had low power to detect clinically important differences in cardiovascular risk due to the small sample size in the reference group. However, it provides an exploratory work that acts as a starting point for further study. Another limitation was the lack of data on some important factors that might contribute to the study outcomes, such as smoking and exercise status. Finally, although propensity score adjustment was carried out in this study, it is difficult to completely rule out the possibility of confounding by indication.

7.6 Conclusion

In summary, this study has shown that, statistically, L-dopa is not associated with increased risk of IHD, cardiovascular risk, or all-cause mortality in the newly diagnosed PD patient within one year after the initiation of therapy. However, the small sample size precludes a definite conclusion being drawn. Future research with a larger sample size and a longer follow-up period, and with access to PD clinical data and homocysteine levels could add further clarity and build on the current work.

CHAPTER 8: Discussion and Conclusion

8.1 Summary of findings

This thesis investigated the incidence and prevalence of PD (epidemiology), the prescribing pattern of first line therapy in PwP (pharmacoepidemiology), and the association between L-dopa and the risk of IHD (pharmacovigilance) in primary care settings in Wales, employing anonymized healthcare data obtained from the SAIL databank. The four main objectives of the thesis were as follows: (1) To validate the completeness of the GP records in the SAIL databank for all prescriptions, particularly PD prescriptions; (2) To validate the accuracy of PD diagnoses in the SAIL databank by comparing the estimates of the incidence and prevalence of PD in SAIL with previous studies conducted in the UK; (3) To examine the changes in first line therapy for newly diagnosed Parkinson's patients between 2000 and 2016 in Wales with respect to several factors, including age, gender, social deprivation status, and co-morbidities; (4) To investigate the association between L-dopa therapy and the risk of IHD in newly diagnosed PwP.

Before conducting the studies that addressed these objectives, a thorough systematic literature review (Chapter 2) was conducted, with the purpose of defining the main changes that have occurred in the safety and efficacy profiles of PD medications since the discovery of L-dopa. The review assessed the extant studies regarding the prescribing patterns and determinants of PD medications worldwide. In total, 44 studies were identified concerning prescribing patterns, and/or prescribing determinants, across 17 countries. Unsurprisingly, L-dopa was the most commonly prescribed medication in all studies, accounting for between 46.50% and 100% of all prescriptions for PD. In several studies, the prescribing rate of ergot DAs decreased over time, concordant with guidance. In contrast, the prescribing rates of non-ergot DAs was found to have increased over the last 10 years (2007 to 2017) in the majority of studies. With regard to the prescribing factors, two major categories were present: patient factors and prescriber

factors, with the patients' age being the most common factor affecting the prescription in the majority of the studies. The review revealed a paucity of literature regarding the use of PD medications in the UK, particularly with specific reference to Wales. Therefore, there was a clear rationale for exploring this issue further using anonymized population-level data.

Big data is increasingly employed to understand UK prescribing patterns and pharmacoepidemiology. One such prescribing dataset is the GP data in SAIL. However, it is important to ensure that this data is valid and complete prior to conducting any research concerning prescribed medications. Therefore, Chapter 4 assessed whether the GP records for all prescriptions, particularly PD prescriptions, in SAIL were complete, and whether they could be employed to evaluate the prescribing trends and patterns of PD medications in Wales. This was achieved by comparing the prescription records in SAIL with the national reference, the General Practice Prescribing Data Extract (GP Data Extract), released by the NHS Wales Shared Services Partnership every month. This contains all the prescriptions administered in all the GP practices in Wales. The prescribing rates for PD medications were found to be highly comparable between SAIL and the GP Data Extract, as there was a difference of just one prescription per 100,000 for dopaminergic PD medications when comparing the two sources of information. It was therefore determined that the SAIL data was appropriate for use in monitoring the prescribing trends for PD in Wales. In turn, this information could be used to evaluate the impact of new treatment guidelines on prescribing trends for PD. However, an additional validation step to the GP recording in SAIL was required, namely the accuracy of the PD diagnosis.

Chapter 5 sought to validate the accuracy of the PD diagnosis by conducting an epidemiological study of the residents of Wales, UK, aged 40 years or older, between 2000 and 2017. The chapter revealed that the prevalence of PD

increased in the period concerned, with a relatively stable incidence rate that may be due to the aging population. After analysing 16,693,205 single person-years during the period 2000 to 2016, the incidence rate was found to range from 54.74 to 68.04 per 100,000 person years, across the study period. The incidence rate did not differ significantly between the reference year (the calendar year of 2000) and the majority of the years of the study period (in 2016, the IRR was 1.05 95% CI 0.93–1.18). However, the overall prevalence rate increased from 319.40 to 370.05 per 100,000 population between 2000 and 2016, and it differed significantly between the reference year and the subsequent years (in 2016, the PRR was 1.16 95% CI 1.11–1.21). The chapter found that social deprivation status may play a role in the PD incidence rate, since, for the whole study period, the incidence of PD was significantly lower in the most deprived areas (quintile 1), compared with the least deprived areas (quintile 5). One explanation for this may be the presence of a greater number of PD preventive factors in the population living in the most deprived areas, such as higher rates of physical activity and a higher smoking rate (355). Another explanation may be that people who live in deprived areas are more prone to have a delay in PD diagnosis (374). The latter explanation was deemed to be reasonable, and was cited in Chapter 6, in the discussion of the present study's findings. Overall, the incidence rate of PD in the population assessed in this study was found to be comparable to the incidence rates determined in previous studies conducted in the UK, which may be an indicator of the data's validity.

Having confirmed the validity and completeness of the GP records in SAIL in Chapters 4 and 5, the next step was to examine the prescribing trend of PD medications, using the electronic data in SAIL (Chapter 6). Profiles of 9,142 newly diagnosed PwP were analysed in this chapter, and L-dopa was found to be the most common first line therapy (80.6%), followed by non-ergot DAs (12.9%), and MAO-B inhibitors (7.9%). The results of a multivariate logistic regression revealed

that the odds of L-dopa being prescribed were greater in older patients of more than 80 years of age, compared to those of 40 to 60 years of age (OR = 19.71 95%CI: 15.72-24.72), and in the period 2012 to 2016, compared with 2000 to 2005 (OR = 1.91 95% CI: 1.65-2.21). In contrast, the prescribing of non-ergot DAs was found to have declined significantly in the period 2012 to 2016 (OR = 0.59 95% CI: 0.50-0.71). This chapter therefore demonstrated that the first line therapy for PwP in Wales between 2000 and 2016 underwent a significant shift in favour of L-dopa, regardless of the patients' age. This correlated temporally with the demonstration that delaying L-dopa therapy in younger patients by using DAs did not result in improved QOL in the long term (101). Furthermore, other variables influencing first line therapy choice were found to include gender, dementia, diabetes, social deprivation score, and previous use of antidepressants. The chapter then discussed the impact of the social deprivation score on prescribing, and the results revealed that patients who lived in the least deprived areas were 22.1% less likely to be prescribed L-dopa, compared with patients from the most deprived areas (p-value = 0.007). Unlike L-dopa, patients who lived in the least deprived areas were found to be 98.8% more likely to be prescribed MAO-B inhibitors than those living in the most deprived areas (p-value <0.0001). This association was not discovered by any of the extant UK studies; however, in the US, studies have reported that patients with higher socioeconomic status are more commonly prescribed expensive drugs, such as MAO-B inhibitors (229). Nevertheless, since prescriptions have been free in Wales since 2007, patients' economic status should not be an issue. A possible interpretation of this finding is the significant delay in PD diagnosis in some minority groups (374), as indicated by certain reports conducted outside the UK. Given that MAO-B inhibitors are often used as a mild starter drug, people with lower socioeconomic status may be diagnosed at a slightly later disease stage, in which case the decision may be made to commence with more effective therapy (L-dopa), and to skip the MAO-B inhibitors step. This interpretation is consistent with the findings of Chapter 5, which indicated that the rate of PD was

significantly lower in the most deprived areas, which may be due to delayed diagnosis (see Section 8.1.1). Future research exploring this interpretation more thoroughly is warranted

The final part of this thesis consisted of a short study investigating the associations of IHD hospitalization risk, all-cardiovascular hospital events, and all-cause mortality among users of L-dopa, compared with users of MAO-B inhibitors, in newly diagnosed PwP. The study cohort concerned was classified into two groups: PwP without previous cardiovascular events (6,487 PwP), and PwP with previous cardiovascular events (1,766 PwP). In both groups, and within one year of the first prescription, it was found that, statistically, L-dopa is not associated with increased risk of IHD, cardiovascular risk, or all-cause mortality. The lack of association between L-dopa and all the study outcomes in the current study was consistent in the models adjusted for all covariates and for the propensity score. The study findings, therefore, concurred with the findings of several previous L-dopa clinical trials (89, 271). However, the findings did not concur with those of other previous studies that suggested a link between L-dopa and an increase in homocysteine levels, which caused IHD in PwP (163, 407). Nevertheless, this result should be interpreted with caution because of the small sample size and low power to detect clinically important differences. More research with a longer duration and larger sample size is required to confirm the short- and long-term cardiac safety profile of L-dopa.

8.1.1 Social deprivation and early diagnosis of PD in the UK

The availability of health care to all UK citizen irrespective of their ability to pay, was a principle that guided the founding of the NHS more than seventy years ago. Its aim was to provide a universal health care system that reduced very apparent inequalities in health care primarily driven through socioeconomic

class. However, a nationalised system is also well placed to review the data on health (in)equality and governmental reports starting from as early as the 1980s have in fact evidenced that health inequalities were widening in England and Wales (424). The "Black Report" published by the UK Department of Health and Social Security in August 1980 was the first of its kind that showed how health outcomes (death and ill-health) were unequally distributed among people in the UK (425). Subsequent reports in the following years reinforced the Black Reports' findings and suggested that inequalities existed in all health care aspects (426, 427).

Julian Tudor Hart's Inverse Care Law in 1971 captured a key aspect of health care provision, stating that "the availability of good medical care tends to vary inversely with the need for it in the population served" (428). The law is still relevant nowadays (429, 430), and a quick search on the term "Inverse Care Law" and Hart's original paper (Google Scholar) for 2019 found about 400 and 200 citations respectively. Although we are making an assumption at the current time, one legitimate hypothesis would be that there is a delay in PD diagnosis in the most deprived areas where the high-need individuals receive less than optimal medical care, and this can be illustrated in the following two ways:

a. Hart noted that doctors who graduated from prestigious medical schools (e.g. Oxford, Cambridge, etc..) are more likely to serve patients in middle class areas than working class areas (428) which raised concerns about the quality of care and the ability to detect early symptoms of PD in deprived areas that served by probably less qualified doctors. Although Hart's observation seems out-dated, there is still evidence suggesting that medical students with a high socioeconomic status have less interest in serving in most deprived areas after graduation (431, 432). Furthermore, UK data has shown that students from more deprived areas are less likely to apply and

less likely to be accepted in medical schools in the UK compared to their peers who graduated from private or grammar schools (433), although this gap has decreased slightly in the last few years with affirmative recruitment strategies (434). This noted that majority of medical students are from less deprived areas, and hence, have no interest in working in the most deprived areas after graduation, reaffirming Hart's original observation (433). Moreover, there is evidence that there is an "inverse training law" by which there are more training opportunities to new GP trainees in less deprived areas compared to the most deprived areas (435). This may be driven by the vicious cycle of chronic lack of facilities, small sizes of practises and high workload in deprived areas making it harder for practises to meet training requirements and take on trainees, those that do experience those environments may then feel hesitant to work in these practises (435).

b. Although the whole UK population has the right to access to NHS services, this does not necessarily reflect an equal health care. People living in the most deprived areas are more likely to have more chronic health issues and a greater number of psychological diseases (373). This leads to more time required to discuss their issues with their GPs, but this commonly not available because of over-stretched clinics (373). It is therefore likely that, GPs who encounter people in the most deprived areas (who present with chronic and psychosocial problems and may also have unrecognized early symptoms of PD), will probably focus on the more serious, pressing conditions and leave the less obvious ones (i.e. symptoms of PD) due to time constraints (429). Importantly, it is not uncommon now for practises to institute a "one problem per consultation" policy in which patients are discouraged from raising multiple concerns in a single GP consultation (436). In a complex disorder such as Parkinson's disease, early diagnosis is challenging and is often made on presentation of a plethora of symptoms which makes it harder for deprived patients to discuss all their serious

conditions with the GP because of the one-time policy, let alone the less obvious conditions such as early symptoms of PD.

It must be recognized that, the problems that the inverse care law highlights are not confined to some diseases or medical conditions such as delaying the diagnosis of diseases, not giving the patient enough time for consultation, or the fact that medical trainees are hesitant to practice in the most deprived areas. It is a reality that this law appears to be more rooted in the health system in the UK, which requires solutions to be both more comprehensive and realistic at the same time. Recommendations and potential solutions to address the inverse care law in the context of this thesis are discussed in Section 8.2.2.

8.2 Reflection on the combined framework of the thesis

As discussed in Chapter 1, the theoretical framework underpinning this thesis concerned the concept of linking pharmacoepidemiology with improving 'population health' (Figure 8-1). It merged the definition of pharmacoepidemiology and drug utilization research into two well-known frameworks, namely the Eisenberg Framework of Clinical Decision-Making and Judgment and the Integrated Framework for Risk Management and Population Health (146, 147).

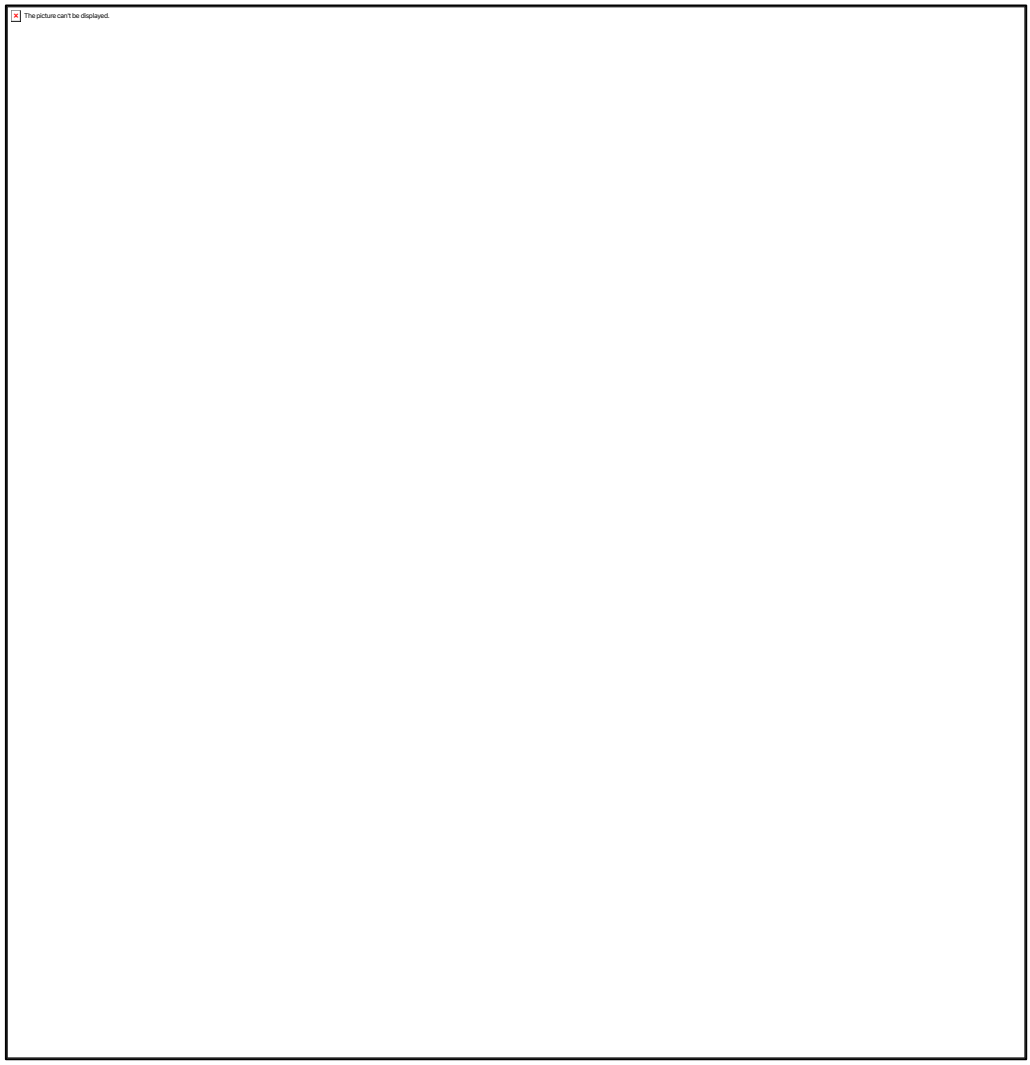


Figure 8-1-The combined framework employed for the thesis.

8.2.1 Eisenberg Framework of Clinical Decision-Making and Judgment

The argument employed by Eisenberg in his framework is that a complex interplay between patients, physicians, patient-physician interactions, and health-system characteristics is responsible for physicians' clinical decisions (146). Due to the lack of data in SAIL, it was not possible to explore the physicians' impact on prescribing PD medications in the present study: therefore, the impact of patient-physician interactions requires a qualitative examination that could not be undertaken for this thesis due to time and resource constraints. However, the impact of patient factors and health-system characteristics was examined in this thesis (Figure 8-2).

Figure 8-2- Factors affecting PD medication prescribing according to the Eisenberg Framework of Clinical Decision-Making and Judgment.

8.2.2 Integrated Framework for Risk Management and Population Health

This framework defines the health determinants as the factors associated with either improving the population's health or exposing the population to health

risks by employing both qualitative and quantitative methods. Using the SAIL databank, this thesis had access to large datasets from multiple data sources and utilized advanced analytical methods, such as regression models and the propensity score technique, to examine two major health risks in the PD field: the inappropriate prescribing of antiparkinsonian agents and the association between PD medications and some side effects, concerning L-dopa and IHD in particular. As noted previously, the findings of this thesis serve as a benchmark for implementing multiple interventions, in terms of regulatory, economic, advisory, community, and technological interventions, which will improve the health of patients with PD.

8.2.3 Regulatory interventions

In the UK, most PwP are managed by Care of the Elderly (COTE) physicians, or neurologists and PD Nurse Specialists (PDNS), who in turn provide GPs with recommendations regarding initiating, titrating, or changing PD medication regimens. Since NICE guidelines in 2017 recommended that all suspected cases of PD should be referred immediately, with no treatment, to a specialist (31), and due to an increase in the prevalence in PD over time, the impact of the workload on COTE, neurology, and PDNS services should be considered. Although the results of the 2017 UK Parkinson's audit revealed that the majority of PwP had access to PDNS (≈ 98%) (437), the quality of the services and the adequacy of time per visit remain under question. For example, in 2006, a national survey of PDNS in England and Wales revealed that the majority of nurses had a high workload, and approximately 35% lacked the time necessary to deliver the appropriate services to PwP (438). The same phenomenon was reported in neurology services in some parts of the UK, where a mismatch between need and the provision of services was observed (439). Therefore, a

national strategy to increase the number of COTE physicians, neurologists, and PDNS should be implemented, with the aim of extending the time devoted to PD services and reducing average waiting times, which in turn will improve the service provided to PwP as a whole.

Another regulatory aspect for policymakers and stakeholders to consider is the suggested effect of social deprivation on delaying PD diagnoses as a real manifestation of health inequality (see the Inverse Care Law). In 2017, NHS Wales published a report that included a delivery plan targeting the health improvement of patients with neurological disorders by ensuring access to high quality services and reducing health inequalities (440). The plan included raising patients' awareness, developing the education framework for both staff and patients, and facilitating GPs' timely access to advice from specialists (440). A more comprehensive approach involving both GPs and the community is required to ensure that this plan is delivered to patients living in the most deprived areas, since these patients are already expected to be less educated and to have difficulties accessing GP services (316). Additionally, and to reverse the inverse care law, there should be an investment from the government in creating more new GPs and retain the current ones in the whole country and especially in GPs served the most deprived areas where the number of patients per GP is 15% higher than other areas (441). This will provide the GPs with the time they need to make a productive consultation that includes detecting less obvious medical issues such as the early symptoms of PD (in the context of this thesis). Time is the "real currency of the GP" (442), and if pressures of short time and high demands are not addressed properly, not only the quality of care will be affected, but, the GPs themselves may leave, or have the intention to leave, their jobs due to unbearable work intensity (443).

Another intervention that should be considered to address the inverse care law, is to widen participation in medical schools by student from most deprived areas who are currently under-represented (434). This may help in providing practices in deprived areas with more qualified GPs who share the same backgrounds and may understand more clearly the social and medical issues in the population of these areas. Although the annual report on widening participation in medical schools, released in November 2018 by the Medical Schools Council's, concluded that there is a very good progress in attaining equality between genders and among different ethnicity backgrounds in the UK, the report highlighted that more progress is needed to approach equality in variables other than gender and race such as social deprivation (444). Several strategies can be used to tackle this issue including encouragement and advice from schools, parental and family expectation, and outreach programs by universities that approach the deprived students in their schools and show students the opportunity and the possibility of attaining medical schools for all backgrounds (445).

8.2.4 Economic interventions

This thesis revealed that there is poor recording of important PD clinical data in SAIL: for example, finding that there was no information in the GPs' data for 44.2% of the study cohort regarding the patients' smoking status. Other important PD clinical data that were also found to be absent in SAIL were dose instructions; scales of motor symptoms severity, such as the Hoehn and Yahr scales; and the diagnostic subtype of PD. Therefore, NHS Wales should encourage GPs to record this type of data consistently. The current Quality and Outcomes Framework (QOF) for GPs in Wales does not include PD, or other movement disorders, in its scheme for financial incentives (446). The QOF is a voluntary system that encourages good practice in GPs by providing financial incentives using an annual quality improvement cycle (446). Given the long-term

nature of PD, and its progressive pattern, including PD in the QOF scheme may provide an opportunity to improve the recording of PD data in GP systems. Such recording could be used by policymakers and researchers to examine the effectiveness of the current PD management plan and its impact on the clinical outcomes of PwP.

As previously noted, this thesis revealed a significant shift to a higher rate of L-dopa prescribing in recent years. This may represent an adherence to what some experts have suggested is the abandonment of the widespread use of more expensive drugs, such as rasagline and pramipexole, and a reversion to a cheaper and more effective option, L-dopa, as this may save £84 million annually in England alone (238). As Parkinson's management is enormously complex, and the strategies involved are highly affected by individual differences, it is difficult to assume the correctness of this hypothesis. It was widely accepted that younger PwP should postpone L-dopa as much as possible, and start DAs or MAO-B inhibitors in order to delay L-dopa induced dyskinesia (113). However, new emerging evidence suggests that this approach may not be appropriate for the following reasons: (1) the idea that DAs reduced risk of L-dopa induced dyskinesia appears to be unfounded, and starting with DAs will not significantly delay dyskinesia onset when L-dopa is introduced later (447), (2) initiating L-dopa is supported by the extant evidence of the notorious side effects of DAs such as ICDs which are more common in younger PwP and may be more serious than dyskinesia (447), and (3) PwP with non-troublesome dyskinesia (that did not cause functional disability and/or meaningful discomfort) may prefer to have dyskinesias rather being rigid and slow because of motor symptoms of PD (93). Notwithstanding, it is the best option to personalise the treatment and every patient should be looked at and managed individually based on impact of dyskinesia on QOL, motor and non-motor symptoms of PD. Given that the LEAP

study found that L-dopa did not slow the progression of PD, the option of prescribing MAO-B inhibitors or DAs is still possible (447).

8.2.5 Advisory interventions

Some of the extant studies suggested that GPs should be aware of the prodromal symptoms of PD, such as constipation and sleep disorders, and their strong association with the future development of PD (448). Therefore, it is important for NHS Wales to advise and train GPs on how to detect the early symptoms of PD efficiently, and especially these prodromal symptoms. Special consideration should be given to those who, according to the present study's findings, are claimed to have a late diagnosis of PD, such as patients who live in deprived areas, or who have diabetes. Also, it is important to provide GPs in deprived areas with adequate support and enough facilities that enable them to reverse the apparent inverse training law and train more medical students and GP trainees (435). There are multiple initiatives in the UK aimed to train GPs to work in deprived areas, and help practises in these areas in offering medical students the required training and teaching (435). In Wales, the Welsh Government and Cardiff University launched the Academic Fellows' Scheme in 2001 that provide support to GPs in deprived areas of South East Wales and make them appropriate places for teaching and training (449). The scheme provides two-year academic fellowships for novice GPs and allows them to practise in deprived areas, teach undergraduate students, and conduct research (449). Thompson and colleagues found that until 2015, the scheme has recruited 28 fellows in 32 practises and resulted in mutual benefits both for the practises and fellows (449). The majority of fellows (61%) continue to work in practises that are located in deprived area after completing their fellowships (449). Although promising, this data is out-dated and should be updated regularly to see if there

is any improvement in the number of fellows and practises participating in the scheme.

GPs have a role that should not be underestimated, especially with regard to the discovery of the early and prodromal symptoms of PD. They should not expect their patients to mention these symptoms: rather, the patients should be questioned about them, since there may be symptoms that they fail to mention, such as depression and sleep disorders, because they believe they are unrelated to PD. The immediate referral of suspected cases to a specialist, with no treatment, is another important aspect of the role that should be played by the GPs, as recommended by NICE 2017 guidelines (31). A further important role for GPs is to be vigilant for the possible side effects of PD medications during their regular patient visits, such as signs of ICDs caused by DAs or the cardiovascular side effects of L-dopa. It is important to note that the current thesis examined the cardiovascular effects of L-dopa for only one year following L-dopa initiation. Therefore, continuous vigilance of GPs, and prompt referral to a specialist when these side effects are observed, is required.

Meanwhile, the role of pharmacists should be seen as that of a liaison between patients and prescribers, by improving the processes of PD medication use, which in turn will improve the clinical outcomes of PwP (450). As a result of their expertise, pharmacists may contribute to solving therapeutic issues and disseminating knowledge about PD and the proper use of PD medications among patients (451). The Medication Utilisation Review (MUR) represents an opportunity for community pharmacists to discuss matters with patients, and to counsel them on use of medicines (452). Although evidence of the efficacy of MUR for general patients is limited (452), some positive initiatives highlighted the importance of MUR in the PD field (453). A previous small-scale study examined the PwP satisfaction with PD-specific MURs services provided in eight

pharmacies in North West London (453). The study reported that of 32 PwP, 96% were satisfied with the services, and 86% reported an improvement in their understanding of their medications (453). PwP feedbacks highlighted the following issues with their medicines: confusion whether the medicine should be taken before or after food, frequency of doses, and what is the right time for the right dose (453). The participants were happy to talk to the pharmacist and hoped that this service can be again offered (453). Further studies employing a larger sample size and greater geographical representativeness are recommended to confirm the results of the North West London study.

Several roles can be performed by community pharmacists with regard to MUR. Pharmacists should check all drug-related issues in PwP, such as the timing and dose of medications and their possible side effects, particularly the ICDs symptoms that might be caused by DAs. Additionally, and as recommended by NICE 2017 guidelines, the pharmacist should discuss with the patient the use of over-the-counter (OTC) dietary supplements, since a high protein supplement may delay the absorption of some medications, such as L-dopa (31). Pharmacists can also identify PwP who do not attend the pharmacy themselves to pick up their medications, and can then invite them, with or without their carers, to attend the MUR service to check the appropriateness of their medication use and to inform the prescribers about any issues discovered.

8.2.6 Community interventions

In concurrence with some of the suggestions made in the present thesis, evidence from studies conducted outside the UK demonstrated that lower economic status is associated with a misunderstanding of PD, and with later detection of its symptoms (454, 455). Therefore, raising community awareness of the early symptoms of PD in the most deprived areas of Wales is an important

role that should be considered by PD research and charity groups, such as Parkinson's UK. Furthermore, community programmes and campaigns should aim to raise awareness of the risks and benefits of PD medications, in order to facilitate the involvement of PwP in making decisions about their own care.

8.2.7 Technological interventions

This thesis revealed a number of issues that could be addressed through the current revolution in technology. One such technological improvement is to link the GP data in SAIL to the PD clinical data held in secondary clinics, which will provide researchers with additional information to facilitate the examination of the impact of PD clinical data on the epidemiology and pharmacoepidemiology of PD and other diseases.

Moreover, the data employed for the purpose of this thesis did not provide a concrete assurance that the prescriptions provided by GPs are dispensed to the patients. Hence, linking the prescription data in SAIL to pharmacy dispensing data is another issue that should be considered. Adherence to PD medications is a matter of concern (348); however, it was not possible to address this as part of the present thesis, due to the lack of access to the dispensing data.

8.3 Strengths and weaknesses

The strengths and weaknesses of thesis were discussed previously; however, this section illustrates in general terms the advantages and disadvantages of using SAIL data for conducting pharmacoepidemiological studies in PwP.

The fact that the SAIL data employed for this study covered approximately 80% of the GP data in Wales (305), and spanned more than 15 years, may be

considered the most important strength of this thesis, as it provided more generalizable results than studies with smaller sample sizes and shorter duration. Furthermore, the ability to link the GP data to the multiple data resources of demographics, social deprivation, hospital, and mortality data assisted in the obtainment of as many variables as possible in the multivariable models that were conducted for this thesis. Another strength was that older patients constituted the majority of the study cohort for this thesis, which was of particular importance, since this group are usually unrepresented in randomized clinical trials (456). Finally, the thesis contributed to the validity of SAIL data by providing evidence of complete prescriptions recording and accurate diagnosis of PD. However, further studies are important to validate the prescribing rates of other types of medications and diagnosis of other diseases.

In contrast, there were a number of limitations involved in this study, including a lack of PD clinical data; a lack of dispensing data; and the presence of unmeasured confounders, such as patients' QOL, patient and physician preferences, and the subtype and severity of the PD. These limitations could be threats to internal validity whereby unmeasured confounders may lead to a wrong assumption of causal relationship in observational studies (457). Additionally, due to data access difficulties and quality issues, co-morbidities (Charlson comorbidity index components) were only extracted from the hospital data (PEDW) rather than being combined with the GP data (WLGP), which may increase the risk of misclassification; therefore, caution should be exercised when interpreting results related to comorbidities. Selection bias and confounding by indication were identified as potential threats to internal validity of the thesis findings. They occur when the study outcome (e.g. IHD in Chapter 7) is caused by differences in the study groups characteristics, rather than a real effect of the treatment (e.g. L-dopa vs MAO-B inhibitors) (457). Although not fully removed, this threat was minimized by applying propensity score technique

that maximizes the chance that the distribution of observed baseline covariates was similar between study groups. Additionally, PwP were only included if there was less than six months between the date of registration in SAIL GP data and the index date. Also, there should not be a previous history of PD medications (up to one year before the index date) in PwP prescriptions files. These steps were made to ensure that only incidence cases were included and minimize the selection bias would result from inclusion of prevalence cases.

8.4 Future research

The findings of the systematic literature review in Chapter 2, which examined the extant pharmacoepidemiological studies in PD, revealed heterogeneity in their study design, duration, and data sources. This is understandable, due to the lack of quality assessment tools in the pharmacoepidemiology files (217): therefore, future studies should focus on developing a quality assessment tool that would help researchers in drug utilization research to make appropriate decisions. This thesis contributed to the validity of the SAIL Databank in terms of PD diagnosis and prescriptions, evidencing the fact that the Databank can be employed to examine PD incidence and prevalence, and to monitor the prescribing trends of PD medications at population level in Wales. Future researchers might add to the evidence of SAIL's validity by examining other diseases and other types of medications, and by utilizing other methods of validity, such as linking GP data to secondary clinic data, in order to compare the two types of dataset. Furthermore, examining the external validity of current findings by repeating the same research in other countries in the UK would be an area of future research. Due to the unavailability of the data, the factors that affect prescribing in PwP were limited in this thesis to patient factors and healthcare characteristics; however, these factors cannot be alone in affecting the prescribing in PwP. Physician factors, in particular, should be investigated in future studies, as several extant studies in different fields have demonstrated

the presence of different prescribing behaviour among different types of prescribers, such as movement disorder specialists versus neurologists versus GPs (242, 248, 251). Therefore, future qualitative research should focus on the impact of type, preferences, and years of experience of prescribers in prescribing PD medications in Wales.

Finally, the findings of this thesis explored the cardiovascular safety of L-dopa and demonstrated that it was not statistically associated with increased risk of IHD, cardiovascular risk, or all-cause mortality in the newly diagnosed PwP in the study, within one year following the initiation of therapy. However, the sample size is relatively small; therefore, future research with a larger sample size is required to confirm the cardiovascular safety of L-dopa.

8.5 Final conclusion

The findings of this thesis advanced the knowledge of three scientific areas of PD in Wales: epidemiology, pharmacoepidemiology, and pharmacovigilance. The estimated prevalence of PD is increasing. Therefore, measures to encounter this trend by increasing the number of PD healthcare professionals are important.

This thesis has contributed to safety evidence around the utilisation of L-dopa, which is critical with the evidence of its increasing use. However, given that UK wide there is a political focus on the equality of access to healthcare, evidence of the socioeconomic gradient impacting on care in PD is highlighted by two areas of this thesis, making it a key focus for cooperation between all sectors to further research, awareness raising, and clinical resourcing.

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Appendices

Appendix 1- Search methods for identification of prescribing pattern studies for antiparkinsonian agents (EMBASE, MEDLINE and PsycINFO)

#	Key word(s)	Results
1	Drug utilization.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	44,235
2	Prescribing pattern.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	1,323
3	Pharmacoepidemiology.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	15,532
4	Prescribing trend.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	94
5	Inappropriate prescribing.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	6,825
6	Prescribing factors.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	30
7	Prescribing determinants.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	5
8	Prescribing behavior.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	1,196
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	65,945
10	Parkinson's disease.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	200,952
11	Idiopathic Parkinson's disease.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	7,278
12	Primary Parkinsonism.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	44
13	Paralysis agitans.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	1,768
14	Antiparkinson drugs.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	470
15	Antiparkinsonians.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	124
16	Antiparkinsonian Agents.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	517
17	Levodopa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	74,814
18	L-Dopa.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	29,406
19	Dopamine agonists.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	20,956
20	apomorphine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	35,382
21	Cabergoline.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	6,943
22	lisuride.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	4,157
23	pergolide.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	6,318
24	pramipexole.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	8,423
25	ropinirole.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	5,928
26	rotigotine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	2,736
27	Amantadine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	21,704
28	Catechol O-Methyltransferase Inhibitors.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	1,167
29	entacapone.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	3,795
30	tolcapone.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	2,188
31	Monoamine Oxidase Inhibitors.mp.[mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	15,585
32	selegiline.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	12,833
33	rasagiline.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	3,191
34	Anticholinergics.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tc, id, tm]	7,064
35	orphenadrine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	2,835
36	procyclidine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	1,819
37	trihexyphenidyl.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh]	7,959
38	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	344,736
39	9 and 38	813
40	limit 39 to English language	733
41	limit 40 to humans [Limit not valid in PsycINFO; records were retained]	682

Appendix 2- Studies that examined PD medications prescribing patterns between 16 March 2018 and 15 December 2019

Study	Country	Type of study	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings	Quality score (out of 10)
Kalilani et al. (1)	USA and UK	Retrospective study using data from the US IBM MarketScan database and the UK Clinical Practice Research Datalink (CPRD	USA (2012-2017) and UK (2004-2015).	Inpatient and outpatient settings	11,280 patients in USA and 7,775 patients in UK	Percentage of patients prescribed each drug/drug class	Country	L-dopa was the most commonly prescribed first-line medication in both countries (USA=70.1% and UK=29%)	5
Dubaz et al. (2)	USA	Retrospective study using data from the Parkinson's Foundation Quality Improvement Initiative registry	2010/2017 comparison	Community	2,717 patients	Percentage of patients prescribed each drug/drug class	Age, sex, comorbidities, year of prescribing, and Hoehn and Yahr PD stage	DAs and L-dopa prescribing has not changed between 2010 and 2017. MAO-B inhibitors prescribing has increased by 52% in 2017 compared to 2010.	7
Houghton et al. (3)	USA	Retrospective study using data from the Truven Health MarketScan® Commercial Claims and Medicare Supplemental databases	2008-2016 No comparison	Inpatient and outpatient settings	84,104 patients	Percentage of patients prescribed each drug/drug class	Age, sex, comorbidities	L-dopa is the most prescribed medication in all age and gender groups, followed by DAs and then MAO-B inhibitors.	8
Nan et al (4)	China	Retrospective cross-sectional study using data from two hospitals in Beijing	2007/2010 comparison	Inpatient setting	136 patients	Percentage of patients prescribed each drug/drug class	Age, hospital type	DAs prescribing has increased significantly in younger patients following publication of the guidelines	5
Szasz et al. (5)	Romania	Retrospective cross-sectional study using data in the Neurological Clinics in Târgu Mureș,	2003-2017 No comparison	Inpatient setting	2,379 patients	Percentage of patients prescribed each drug/drug class	Age, sex, and disease duration	L-dopa is the most prescribed medication in all age and gender groups followed by DAs and then, MAO-B inhibitors.	6
Kasamo et al. (6)	Japan	Retrospective cross-sectional study using the large Japanese medical claims database	2005-2016 No comparison	Community	131 young-onset PwP	Percentage of patients prescribed each drug/drug class	Age, sex, and comorbidities,	The study is limited to young-onset PwP. DAs are the most prescribed medications in this group of patients, followed by anticholinergics and then levodopa.	7
Machado-Alba et al. (7)	Colombia	Retrospective cross-sectional study using systematized database in the Colombian health system.	2015	Community	2,898 patients	Percentage of patients prescribed each drug/drug class	Age, sex, and city of residence	Most patients were on monotherapy (69.4%). Among monotherapy patients, anticholinergics were the most commonly prescribed, followed by L-dopa, and them non-ergot DAs.	6
M George et al. (8)	India	Prospective observational study	NA	Inpatient	60 patients	Percentage of patients prescribed each drug/drug class	Age, sex, and disease duration	L-dopa is the most prescribed medication in all age and gender groups, followed by DAs, and then anticholinergics.	5

PD medications prescription rates

Country	Year	L-dopa only	L-dopa combination	COMT inhibitors	Ergot DAs	Non-ergot DAs	All DAs	MAO-B inhibitors	Amantadine	Anticholinergics
USA/UK (1)	(2012-2017)-(2004-2015)[a]	70.1/29	—/46.5	—	—/10	10.8/34.7	10.8/44.7	8.2	2.2	—/4.4
USA (2)	2010-2017	—	86.2-86.1[b]	17.5-11.5	—	—	43.2-39.4	22.4-30	17.7-15.1	4.8-3.6
USA (3)	2008-2016[c]	—	70.3	—	—	—	15.5	8.3	3.1	—
China (4)	2007-2010[c]	66.9	—	—	—	8.1	8.1	10.30	17.60	18.40
Romania (5)	2003-2017	42.1	—	—	—	—	9.7	1.5	—	—
Japan (6)	2005-2016[d]	19.7	—	—	9	40.2	49.2	0.8[e]	1.6	23.8
Colombia (7)	2015[f]	25.9	—	—	13.2	18.5	31.7	3	10.24	29
India (8)	NA	45.96	48.11	—	—	20.13	20.13	5.03	7.91	18.7

a. This study examined the initial prescription (first line therapy) in the USA (from 2012-2017) and the UK (from 2004-2015)

b. Prescribing rates for 2010 and 2017 respectively.

c. This study examined the initial prescription (first line therapy).

d. This study examined the initial prescription (first line therapy) for young onset PwP.

e. This percentage is for selegiline only. Rasagiline was not included because it was approved in Japan in 2018 (after the study time frame).

f. All percentages presented in this table for this study are for patients on monotherapy.

Quality appraisal checklist using the Joanna Briggs Institute Critical Appraisal Tool

Study[a]	Representative sample	Appropriate recruitment	Adequate sample size	Reporting of study subjects and setting	Data coverage of the identified sample is adequate	Objective, standard criteria used for measurement of the condition	The condition was measured reliably and objectively	Appropriate statistical analysis	Ensuring confounding factors/subgroups/ differences are identified and accounted for.	Subpopulations identified using objective criteria	Quality score
Kalilani et al. (1)	Y	UC	Y	Y	Y	Y	N	N	N	N	5
Dubaz et al. (2)	N	UC	N	Y	Y	Y	Y	Y	Y	Y	7
Houghton et al. (3)	Y	UC	Y	Y	Y	Y	UC	Y	Y	Y	8
Nan et al. (4)	N	N	N	Y	Y	Y	Y	Y	N	N	5
Szasz et al. (5)	N	UC	N	Y	Y	Y	Y	N	Y	Y	6
Kasamo et al. (6)	N	UC	Y	Y	Y	Y	UC	Y	Y	Y	7
Machado-Alba et al. (7)	Y	UC	Y	Y	Y	N	N	Y	N	Y	6
M George et al. (8)	N	UC	N	Y	Y	Y	Y	Y	N	N	5

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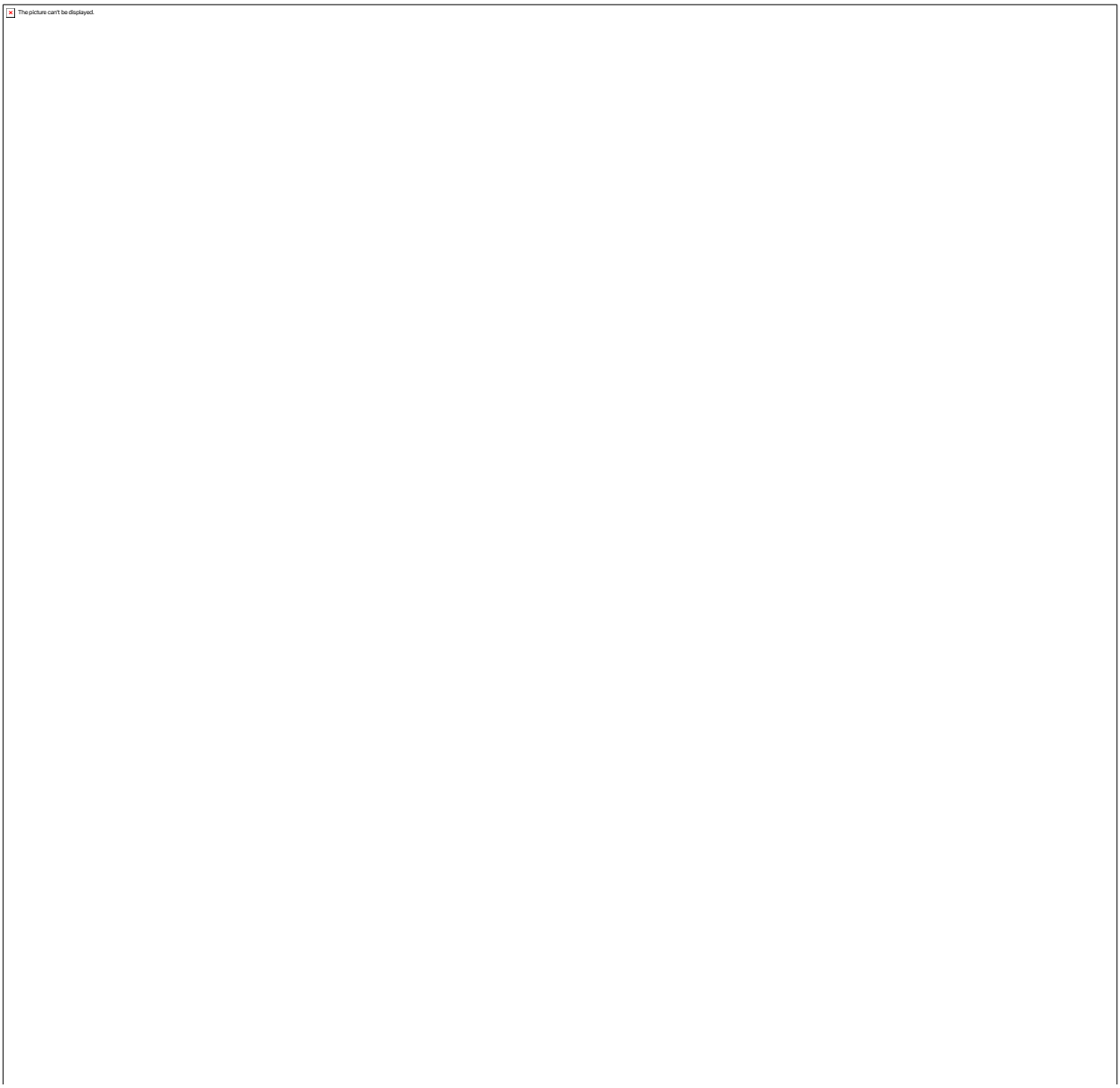
8. George. M, Joseph. L, Mathew. M, Ann. J, Thomas. T. Prescribing Trends in Parkinson's Disease and risk factors involved with Levodopa-induced motor complication in a tertiary care hospital. WJPR. 2018;7(16):875-61. doi: 10.20959/wjpr201816-1311

Appendix 3- PRISMA flow chart for systematic research of prescribing patterns and determinants in non-English studies



Study	Country	Type of study	Source of data	Year	Setting	Number of patients and/or prescriptions	Unit of analysis	Prescribing determinants	Comments/ Main findings
Xiau-hua et al. [1]	China	Retrospective repeated cross-sectional	Hospital data (34 hospitals in Nanjing)	2012/2014 comparison	Hospital	N/A	Defined daily doses (DDD) per 1000 inhabitants per day	N/A	General increase in use of L-dopa and DAs.
Fritze [2]	Germany	Retrospective cross-sectional	German drug registry.	2012	Community	N/A	Defined daily doses (DDD) per 1000 inhabitants per day	N/A	General increase in use of all PD medications General increase in use of non-ergot DAs.
Fritze [3]	Germany	Retrospective cross-sectional	German drug registry.	2011	Community	N/A	Defined daily doses (DDD) per 1000 inhabitants per day	N/A	The most commonly prescribed medication is L-dopa (90.27%) followed by DAs (40.66%).
Montane et al [4]	Spain	Retrospective repeated cross-sectional	Prescription registry (ECOM database of the Ministry of Health)	1989/1998	Community	N/A	Defined daily doses (DDD) per 1000 inhabitants per day	N/A	General increase in use of selegiline, pergolide, and levodopa.

Appendix 4- Studies that examined prescribing patterns of PD medications in non-English studies

References:

[1] L. Xiao-hua, Z. Z-Young-hong. Analysis of anti-parkinson disease drugs used in 34 hospitals in Nanjing during 2012—2014. Chinese Journal of New Drugs. 2016;352(12):1431-1435.

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Appendix 5- Joanna Briggs Institute Critical Appraisal Tool for Use in Prevalence Studies

(The following tool was adapted entirely from *Z Munn et al).*

The ten criteria used to assess the methodological quality of studies reporting prevalence data and an explanation for each are described below. These questions can be answered either with a yes, no, unclear, or not applicable.

1. Was the sample representative of the target population?

This question relies upon knowledge of the broader characteristics of the population of interest. If the study is of women with breast cancer, knowledge of at least the characteristics, demographics, and medical history is needed. The term "target population" should not be taken to infer every individual from everywhere or with similar disease or exposure characteristics. Instead, give consideration to specific population characteristics in the study, including age range, gender, morbidities, medications, and other potentially influential factors. For example, a sample may not be representative of the target population if a certain group has been used (such as those working for one organisation, or one profession) and the results then inferred to the target population (i.e. working adults).

2. Were study participants recruited in an appropriate way?

Recruitment is the calling or advertising strategy for gaining interest in the study, and is not the same as sampling. Studies may report random sampling from a population, and the methods section should report how sampling was performed. What source of data were study participants recruited from? Was the sampling frame appropriate? For example, census data is a good example of appropriate recruitment, as a good census will identify everybody. Was everybody included who should have been included? Were any groups of persons excluded? Was the whole population of interest surveyed? If not, was random sampling from a defined subset of the population employed? Was stratified random sampling with eligibility criteria used to ensure the sample was representative of the population to which the researchers were generalizing?

3. Was the sample size adequate?

An adequate sample size is important to ensure good precision of the final estimate. Ideally we are looking for evidence that the authors conducted a sample size calculation to determine an adequate sample size. This will estimate how many subjects are needed to produce a reliable

estimate of the measure(s) of interest. For conditions with a low prevalence, a larger sample size is needed. Also consider sample sizes for subgroup (or characteristics) analyses, and whether these are appropriate. Sometimes, the study will be large enough (as in large national surveys) whereby a sample size calculation is not required. In these cases, sample size can be considered adequate.

When there is no sample size calculation and it is not a large national survey, the reviewers may consider conducting their own sample size analysis using the following formula:

Where:
n = sample size
Z= Z statistic for a level of confidence
P= Expected prevalence or proportion (in proportion of one; if 20%, P= 0.2)
d= precision (in proportion of one; if 5%, d= 0.05)

4. Were the study subjects and setting described in detail?

Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. women vs. men, socio-demographic variables between countries). Has the study sample been described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them?

5. Is the data analysis conducted with sufficient coverage of the identified sample?

A large number of dropouts, refusals or “not founds” amongst selected subjects may diminish a study’s validity, as can low response rates for survey studies.
- Did the authors describe the reasons for non-response and compare persons in the study to those not in the study, particularly with regards to their socio-demographic characteristics?
- Could the not-responders have led to an underestimate of prevalence of the disease or condition under investigation?
- If reasons for non-response appear to be unrelated to the outcome measured and the characteristics of non-responders are comparable to those in the study, the researchers may be able to justify a more modest response rate.
- Did the means of assessment or measurement negatively affect the response rate (measurement should be easily accessible, conveniently timed for participants, acceptable in length, and suitable in content).

6. Were objective, standard criteria used for measurement of the condition?

Here we are looking for measurement or classification bias. Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

7. Was the condition measured reliably?

Considerable judgment is required to determine the presence of some health outcomes. Having established the objectivity of the outcome measurement instrument (see item 6 of this scale), it is important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?
- Has the researcher justified the methods chosen?
- Has the researcher made the methods explicit? (For interview method, how were interviews conducted?)

8. Was there appropriate statistical analysis?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify the analytical technique used and how specific variables were measured. Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond. Prevalence rates found in studies only provide estimates of the true prevalence of a problem in the larger population. Since some subgroups are very small, 95% confidence intervals are usually given.

9. Are all important confounding factors/ subgroups/differences identified and accounted for?

Incidence and prevalence studies often draw or report findings regarding the differences between groups. It is important that authors of these studies identify all important confounding factors, subgroups and differences and account for these.

10. Were subpopulations identified using objective criteria? Objective criteria should also be used where possible to identify subgroups (refer to question 6).

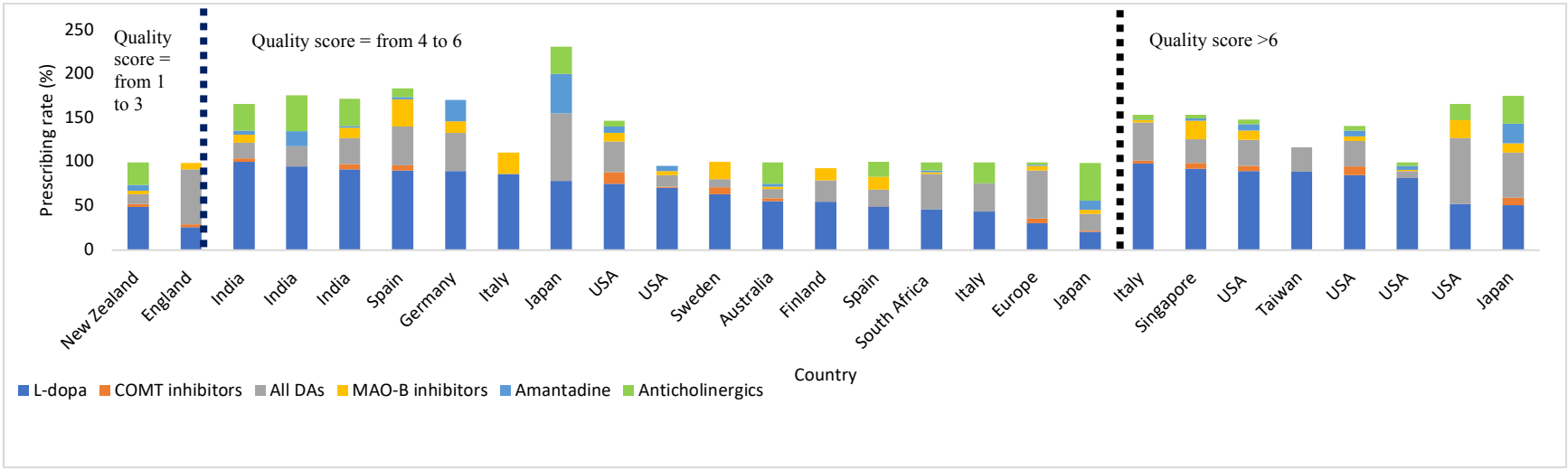
	L-dopa prescribing rate[a]			COMT inhibitors prescribing rate			All DAs prescribing rate			MAO-B inhibitors prescribing rate			Amantadine prescribing rate			Anticholinergics prescribing rate		
	Median	Range	p-value[a]	Median	Range	p-value	Median	Range	p-value	Median	Range	p-value	Median	Range	p-value	Median	Range	p-value
Quality score																		
(1-3)	37.38	26-48.76	0.091	3.58	3.53-3.63	0.245	36.73	11.20-62.26	0.825	5.57	3.88-7.27	0.575	6.71	NA (one study only)	0.895	25.44	NA (one study only)	0.285
(4-6)	70.92	21-100		4.80	0.24-13.31		26.45	9.21-76.92		10.81	2.10-31		5.46	1.10-44.23		5.46	2.91-43	
>6	87.17	51-98.50		6.80	3.10-10.10		28.75	7.63-75		10.50	1.67-21		5.14	0.80-22.10		5.14	3.81-31.40	
Source of data																		
Insurance-claims, prescription registries, or drug sales databases	53.78	21-90	**0.009[b]**	5.61	1-13.31	0.245	29	9.21-75	0.825	9.63	2.10-24.60	0.575	6.58	1.10-22.10	0.895	18.18	2.91-43	0.285
Medical charts and administrative databases	83.60	43.73-94.80		6	0.24-10.10		25	7.63-32.04		8.90	1.67-21		5.10	2-17.20		22.90	3.81-40.40	
Patients' interviews, questionnaires, or surveys	90.40	78.84-100		4	3.10-5.80		43.70	18-76.92		11.08	2.30-31		5	0.80-44.23		19.80	8.50-30.76	

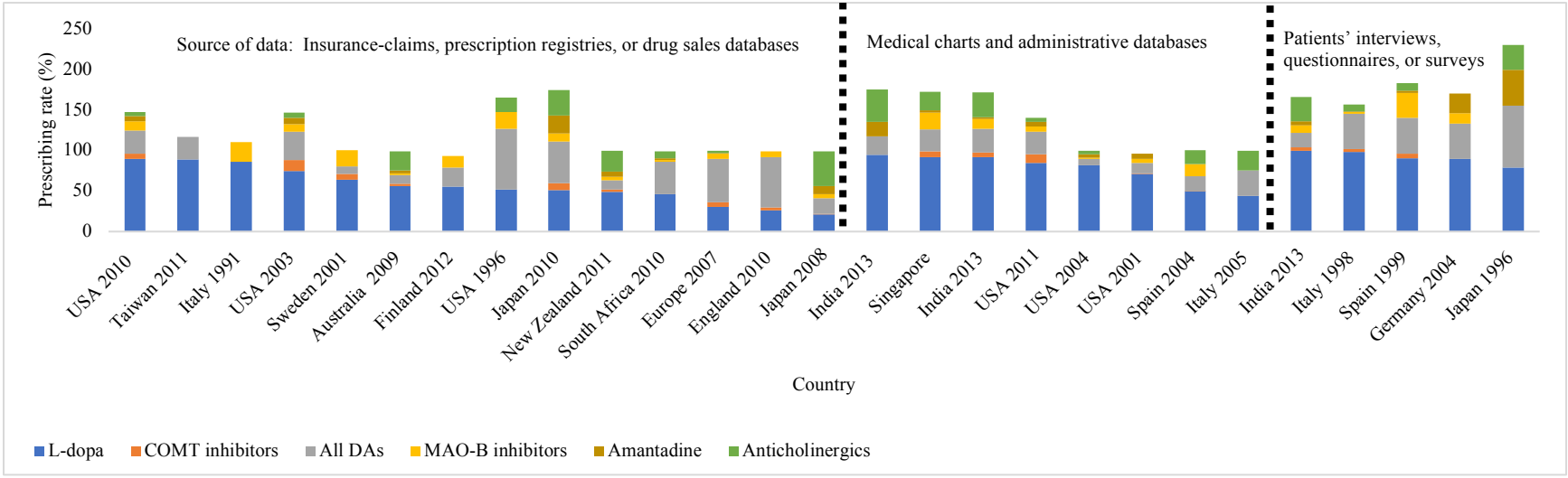
a. Test based on Kruskal-Wallis statistic, significance level at $p < 0.05$.

b. Post-hoc analysis: Insurance-claims, prescription registries, or drug sales databases vs. medical charts and administrative databases p = 0.234. Insurance-claims, prescription registries, or drug sales databases vs. patients' interviews, questionnaires, or surveys p = 0.011. Medical charts and administrative databases vs. patients' interviews, questionnaires, or surveys p = 0.582.

Appendix 6- Results of Kruskal-Wallis test for assessing differences in prescribing rates according to the quality score of the studies and source of data

Appendix 7- Prescribing pattern of PD medications according to quality scores of the studies and source of data




Source of data: Insurance-claims, prescription registries, or drug sales databases
Medical charts and administrative databases
Patients' interviews, questionnaires, or surveys
Prescribing rate (%)
250
200
150
100
50
0
USA 2010
Taiwan 2011
Italy 1991
USA 2003
Sweden 2001
Australia 2009
Finland 2012
USA 1996
Japan 2010
New Zealand 2011
South Africa 2010
Europe 2007
England 2010
Japan 2008
India 2013
Singapore
India 2013
USA 2011
USA 2004
USA 2001
Spain 2004
Italy 2005
India 2013
Italy 1998
Spain 1999
Germany 2004
Japan 1996
Country
L-dopa
COMT inhibitors
All DAs
MAO-B inhibitors
Amantadine
Anticholinergics

Appendix 8- Ethical approval from the Information Governance Revie Panel (IGRP) at SAIL Databank.

Appendix 9- Clinical codes used in the thesis

Coding system	Code	Description	Defined
The initial codes that used to identify patients with Parkinson disease from SAIL databank (The first step).			
Read codes (version 2)	F12..00	Parkinson's disease	Definite diagnosis of Parkinson's
Read codes (version 2)	F120.00	Paralysis agitans	Definite diagnosis of Parkinson's
Read codes (version 2)	F12z.00	Parkinson's disease not otherwise specified	Definite diagnosis of Parkinson's
Read codes (version 2)	147F.00	History of Parkinson's disease	Definite diagnosis of Parkinson's
Read codes (version 2)	2987	On examination: Parkinson flexion posture	Suggestive diagnosis of Parkinson's
Read codes (version 2)	2987.11	On examination: Parkinson posture	Suggestive diagnosis of Parkinson's
Read codes (version 2)	2994	On examination: festination/Parkinson gait	Suggestive diagnosis of Parkinson's
Read codes (version 2)	2994.11	On examination: Parkinson gait	Suggestive diagnosis of Parkinson's
Read codes (version 2)	297A.00	On examination: Parkinsonian tremor	Suggestive diagnosis of Parkinson's
Read codes (version 2)	8T06.00	Referral to Parkinson's service	Suggestive diagnosis of Parkinson's
Read codes (version 2)	8T06000	Referral to community Parkinson's service	Suggestive diagnosis of Parkinson's
Read codes (version 2)	TJ64z00	Adverse Reaction to Anti-Parkinsonism Drugs not otherwise specified	Suggestive diagnosis of Parkinson's
Read codes (version 2)	U606711	[X] Adverse reaction to anti-parkinsonism drug	Suggestive diagnosis of Parkinson's
Read codes (version 2)	U606712	[X] Adverse reaction to amantadine	Suggestive diagnosis of Parkinson's
Read codes (version 2)	U606713	[X] Adverse reaction to levodopa, L-dopa	Suggestive diagnosis of Parkinson's
Read codes (version 2)	U606714	[X] Adverse reaction to trihexyphenidyl	Suggestive diagnosis of Parkinson's
Read codes (version 2)	U606718	[X] Adverse reaction to anti-parkinsonism drugs not otherwise specified	Suggestive diagnosis of Parkinson's
Read codes (version 2)	F1303	Parkinsonism and orthostatic hypotension	Suggestive diagnosis of Parkinson's
Read codes (version 2)	dq…	Dopaminergic drugs	Parkinson's medications
Read codes (version 2)	dq1..	Levodopa	Parkinson's medications
Read codes (version 2)	dq11.	Levodopa 125mg capsule	Parkinson's medications
Read codes (version 2)	dq12.	Levodopa 250mg capsule	Parkinson's medications
Read codes (version 2)	dq13.	Levodopa 500mg capsule	Parkinson's medications
Read codes (version 2)	dq14.	Levodopa 500mg tablet	Parkinson's medications
Read codes (version 2)	dq2..	Levodopa with benserazide / Co-benedopa / Madopar	Parkinson's medications
Read codes (version 2)	dq21.	Madopar 62.5 capsule	Parkinson's medications
Read codes (version 2)	dq22.	Madopar 125 capsule	Parkinson's medications
Read codes (version 2)	dq23.	Madopar 250 capsule	Parkinson's medications
Read codes (version 2)	dq24.	Madopar 62.5 disp tablet	Parkinson's medications
Read codes (version 2)	dq25.	Madopar 125 dispersible tablet	Parkinson's medications
Read codes (version 2)	dq26.	Madopar CR 125 m/r capsule	Parkinson's medications
Read codes (version 2)	dq27.	Co-beneldopa 12.5mg/50mg cap	Parkinson's medications
Read codes (version 2)	dq28.	Co-beneldopa 25mg/100mg cap	Parkinson's medications
Read codes (version 2)	dq29.	Co-beneldopa 50mg/200mg cap	Parkinson's medications
Read codes (version 2)	dq2a.	Co-benel 12.5mg/50mg disp tab	Parkinson's medications
Read codes (version 2)	dq2b.	Co-benel 25mg/100mg m/r cap	Parkinson's medications
Read codes (version 2)	dq2c.	Co-benel 25mg/100mg disp tab	Parkinson's medications
Read codes (version 2)	dq3..	Levodopa with carbidopa/ Co-careldopa / Sinemet	Parkinson's medications
Read codes (version 2)	dq3..	Levodopa with carbidopa	Parkinson's medications
Read codes (version 2)	dq31.	Sinemet-110 tablet	Parkinson's medications
Read codes (version 2)	dq32.	Sinemet-275 tablet	Parkinson's medications
Read codes (version 2)	dq33.	Sinemet-Plus tablet	Parkinson's medications
Read codes (version 2)	dq34.	Sinemet-LS tablet	Parkinson's medications
Read codes (version 2)	dq34.	Sinemet-62.5 tablet	Parkinson's medications
Read codes (version 2)	dq35.	Co-careldopa 12.5mg/50mg tab	Parkinson's medications
Read codes (version 2)	dq36.	Co-careldopa 10mg/100mg tablet	Parkinson's medications
Read codes (version 2)	dq37.	Co-careldopa 25mg/100mg tablet	Parkinson's medications
Read codes (version 2)	dq38.	Co-careldopa 25mg/250mg tablet	Parkinson's medications
Read codes (version 2)	dq39.	Sinemet CR m/r tablet	Parkinson's medications
Read codes (version 2)	dq3A.	Half-Sinemet CR m/r tablet	Parkinson's medications
Read codes (version 2)	dq3a.	Co-careldop 50mg/200mg m/r tab	Parkinson's medications
Read codes (version 2)	dq3B.	Stalevo 50mg/12.5mg/200mg tab	Parkinson's medications
Read codes (version 2)	dq3b.	Co-careldop 25mg/100mg m/r tab	Parkinson's medications
Read codes (version 2)	dq3C.	Stalevo 100mg/25mg/200mg tab	Parkinson's medications
Read codes (version 2)	dq3c.	STANEK 175/43.75/200mg tablets	Parkinson's medications
Read codes (version 2)	dq3D.	Stalevo 150mg/37.5mg/200mg tab	Parkinson's medications

Read codes (version 2)	dq3d.	STANEK 200mg/50mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3E.	Tilolec 100mg/25mg m/r tablet	Parkinson's medications
Read codes (version 2)	dq3F.	Tilolec 200mg/50mg m/r tablet	Parkinson's medications
Read codes (version 2)	dq3G.	Duodopa 5mg/20mg/mL gel 100mL	Parkinson's medications
Read codes (version 2)	dq3H.	CARAMET CR 25mg/100mg m/r tabs	Parkinson's medications
Read codes (version 2)	dq3I.	CARAMET CR 50mg/200mg m/r tabs	Parkinson's medications
Read codes (version 2)	dq3J.	STALEVO 200mg/50mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3K.	STALEVO 125/31.25/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3L.	STALEVO 75/18.75/200mg tablets	Parkinson's medications
Read codes (version 2)	dq3M.	STALEVO 175/43.75/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3N.	SASTRAVI 50/12.5/200mg tablets	Parkinson's medications
Read codes (version 2)	dq3O.	SASTRAVI 75/18.75/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3P.	SASTRAVI 100mg/25mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3Q.	SASTRAVI 125/31.25/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3R.	SASTRAVI 150/37.5/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3S.	SASTRAVI 175/43.75/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3s.	L-DOPA/CARB/ENTAC 418.75mg tab	Parkinson's medications
Read codes (version 2)	dq3T.	SASTRAVI 200mg/50mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3t.	L-DOPA/CARB/ENTAC 293.75mg tab	Parkinson's medications
Read codes (version 2)	dq3U.	STANEK 50mg/12.5mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3u.	L-DOPA/CARB/ENTAC 356.25mg tab	Parkinson's medications
Read codes (version 2)	dq3V.	STANEK 75mg/18.75mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3v.	L-DOPA/CARBI/ENTAC 450mg tabs	Parkinson's medications
Read codes (version 2)	dq3w.	Co-careldo 5/20mg/mL gel 100mL	Parkinson's medications
Read codes (version 2)	dq3w.	Carbi/Levodo 5/20mg/mL 100mL	Parkinson's medications
Read codes (version 2)	dq3X.	STANEK 100mg/25mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3x.	L-dopa/carbi/entac 387.5mg tab	Parkinson's medications
Read codes (version 2)	dq3Y.	STANEK 125/31.25/200mg tablets	Parkinson's medications
Read codes (version 2)	dq3y.	L-dopa/carbi/entac 325mg tab	Parkinson's medications
Read codes (version 2)	dq3Z.	STANEK 150mg/37.5mg/200mg tabs	Parkinson's medications
Read codes (version 2)	dq3z.	L-dopa/carbi/entac 262.5mg tab	Parkinson's medications
Read codes (version 2)	dq4..	Amantadine	Parkinson's medications
Read codes (version 2)	dq41.	Symmetrel [park] 100mg capsule	Parkinson's medications
Read codes (version 2)	dq42.	Symmetrel [park] 50mg/5ml syr	Parkinson's medications
Read codes (version 2)	dq43.	Mantadine 100mg capsule	Parkinson's medications
Read codes (version 2)	dq44.	Amantadine HCl 50mg/5mL syrup	Parkinson's medications
Read codes (version 2)	dq4z.	Amantadine HCl 100mg capsule	Parkinson's medications
Read codes (version 2)	dq5..	Bromocriptine	Parkinson's medications
Read codes (version 2)	dq5..	Bromocriptine [parkinsons]	Parkinson's medications
Read codes (version 2)	dq51.	Parlodel [park] 1mg tablets	Parkinson's medications
Read codes (version 2)	dq52.	Parlodel [park] 2.5mg tablets	Parkinson's medications
Read codes (version 2)	dq53.	Parlodel [park] 5mg capsule	Parkinson's medications
Read codes (version 2)	dq54.	Parlodel [park] 10mg capsules	Parkinson's medications
Read codes (version 2)	dq55.	Parlodel starter	Parkinson's medications
Read codes (version 2)	dq56.	Bromocriptine [park] 1mg tabs	Parkinson's medications
Read codes (version 2)	dq57.	Bromocriptine [park] 5mg caps	Parkinson's medications
Read codes (version 2)	dq5y.	Bromocriptine 2.5mg tablet	Parkinson's medications
Read codes (version 2)	dq5z.	Bromocriptine 10mg capsule	Parkinson's medications
Read codes (version 2)	dq6..	Selegiline	Parkinson's medications
Read codes (version 2)	dq61.	Eldepryl 5mg tablet	Parkinson's medications
Read codes (version 2)	dq62.	Eldepryl 10mg tablet	Parkinson's medications
Read codes (version 2)	dq63.	Eldepryl 10mg/5mL syrup	Parkinson's medications
Read codes (version 2)	dq64.	Vivapryl 5mg tablet	Parkinson's medications
Read codes (version 2)	dq65.	Vivapryl 10mg tablet	Parkinson's medications
Read codes (version 2)	dq66.	Stilline 5mg tablet	Parkinson's medications
Read codes (version 2)	dq67.	Stilline 10mg tablet	Parkinson's medications
Read codes (version 2)	dq68.	Centrapryl 5 tablet	Parkinson's medications
Read codes (version 2)	dq69.	Centrapryl 10 tablet	Parkinson's medications
Read codes (version 2)	dq6A.	Zelapar 1.25mg tablet	Parkinson's medications
Read codes (version 2)	dq6w.	Selegiline HCl 1.25mg tablet	Parkinson's medications
Read codes (version 2)	dq6x.	Selegiline HCl 10mg/5mL syrup	Parkinson's medications
Read codes (version 2)	dq6y.	Selegiline HCl 10mg tablet	Parkinson's medications
Read codes (version 2)	dq6z.	Selegiline HCl 5mg tablet	Parkinson's medications
Read codes (version 2)	dq7..	Lisuride maleate	Parkinson's medications
Read codes (version 2)	dq71.	Lisuride maleate 200mcg tablet	Parkinson's medications
Read codes (version 2)	dq72.	Revanil 200micrograms tablet	Parkinson's medications

Read codes (version 2)	dq8..	Pergolide mesylate	Parkinson's medications
Read codes (version 2)	dq81.	Pergolide 50micrograms tablet	Parkinson's medications
Read codes (version 2)	dq82.	Pergolide 250micrograms tablet	Parkinson's medications
Read codes (version 2)	dq83.	Pergolide 1mg tablet	Parkinson's medications
Read codes (version 2)	dq84.	Celance 50micrograms tablet	Parkinson's medications
Read codes (version 2)	dq85.	Celance 250micrograms tablet	Parkinson's medications
Read codes (version 2)	dq86.	Celance 1mg tablet	Parkinson's medications
Read codes (version 2)	dq87.	Celance 50mcg starter pack	Parkinson's medications
Read codes (version 2)	dq88.	Pergolide 50mcg starter pack	Parkinson's medications
Read codes (version 2)	dq89.	Pergolide 50+250mcg start pack	Parkinson's medications
Read codes (version 2)	dq8A.	Celance 50+250mcg starter pack	Parkinson's medications
Read codes (version 2)	dq9..	Apomorphine hydrochloride	Parkinson's medications
Read codes (version 2)	dq91.	Britaject 20mg/2mL injection	Parkinson's medications
Read codes (version 2)	dq92.	Apomorphine HCl 20mg/2mL inj	Parkinson's medications
Read codes (version 2)	dq93.	Britaject 50mg/5mL injection	Parkinson's medications
Read codes (version 2)	dq94.	Apomorphine HCl 50mg/5mL inj	Parkinson's medications
Read codes (version 2)	dq95.	Apomorphine HCl 30mg/3mL pen	Parkinson's medications
Read codes (version 2)	dq96.	Britaject 30mg/3mL pen	Parkinson's medications
Read codes (version 2)	dq97.	APO-go 20mg/2mL injection	Parkinson's medications
Read codes (version 2)	dq98.	APO-go 50mg/5mL injection	Parkinson's medications
Read codes (version 2)	dq99.	APO-go 30mg/3mL prefilled pen	Parkinson's medications
Read codes (version 2)	dq9A.	APO-go PFS 50mg/10mL inj soln	Parkinson's medications
Read codes (version 2)	dq9z.	Apomorphine HCl 50mg/10mL pfs	Parkinson's medications
Read codes (version 2)	dqA..	Ropinirole hydrochloride	Parkinson's medications
Read codes (version 2)	dqA1.	Ropinirole 0.25mg tablet	Parkinson's medications
Read codes (version 2)	dqA2.	Ropinirole 1mg tablet	Parkinson's medications
Read codes (version 2)	dqA3.	Ropinirole 2mg tablet	Parkinson's medications
Read codes (version 2)	dqA4.	Ropinirole 5mg tablet	Parkinson's medications
Read codes (version 2)	dqA5.	ReQuip 0.25mg tablet	Parkinson's medications
Read codes (version 2)	dqA6.	ReQuip 1mg tablet	Parkinson's medications
Read codes (version 2)	dqA7.	ReQuip 2mg tablet	Parkinson's medications
Read codes (version 2)	dqA8.	ReQuip 5mg tablet	Parkinson's medications
Read codes (version 2)	dqA9.	Ropinirole 250+500+1000mcg pck	Parkinson's medications
Read codes (version 2)	dqAA.	EPPINIX XL 3mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAa.	Ropinirole 0.5mg+1mg+2mg pack	Parkinson's medications
Read codes (version 2)	dqAB.	EPPINIX XL 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAb.	ReQuip tablet starter pack	Parkinson's medications
Read codes (version 2)	dqAC.	EPPINIX XL 6mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAc.	ReQuip tablet follow-on pack	Parkinson's medications
Read codes (version 2)	dqAD.	EPPINIX XL 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAd.	ADARTREL 2mg tablets	Parkinson's medications
Read codes (version 2)	dqAe.	ROPINIROLE 500mcg tablets	Parkinson's medications
Read codes (version 2)	dqAf.	ADARTREL 500micrograms tablets	Parkinson's medications
Read codes (version 2)	dqAg.	REQUIP XL 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAh.	REQUIP XL 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAi.	REQUIP XL 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAj.	ROPINIROLE 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAk.	ROPINIROLE 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAl.	ROPINIROLE 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAm.	REPINEX XL 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAn.	REPINEX XL 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAo.	REPINEX XL 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAp.	RAPONER XL 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAq.	RAPONER XL 3mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAr.	ROPINIROLE 3mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAs.	RAPONER XL 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAt.	RAPONER XL 6mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAu.	ROPINIROLE 6mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAv.	RAPONER XL 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAw.	AIMPART XL 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAx.	AIMPART XL 4mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAy.	AIMPART XL 8mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqAz.	EPPINIX XL 2mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqB..	Cabergoline	Parkinson's medications
Read codes (version 2)	dqB1.	Cabergoline 1mg tablet	Parkinson's medications
Read codes (version 2)	dqB2.	Cabergoline 2mg tablet	Parkinson's medications

Read codes (version 2)	dqB3.	Cabergoline 4mg tablet	Parkinson's medications
Read codes (version 2)	dqB4.	Cabaser 1mg tablet	Parkinson's medications
Read codes (version 2)	dqB5.	Cabaser 2mg tablet	Parkinson's medications
Read codes (version 2)	dqB6.	Cabaser 4mg tablet	Parkinson's medications
Read codes (version 2)	dqC..	Tolcapone	Parkinson's medications
Read codes (version 2)	dqC1.	Tolcapone 100mg tablet	Parkinson's medications
Read codes (version 2)	dqC2.	Tolcapone 200mg tablet	Parkinson's medications
Read codes (version 2)	dqC3.	Tasmar 100mg tablet	Parkinson's medications
Read codes (version 2)	dqC4.	Tasmar 200mg tablet	Parkinson's medications
Read codes (version 2)	dqD..	Entacapone	Parkinson's medications
Read codes (version 2)	dqD1.	Entacapone 200mg tablet	Parkinson's medications
Read codes (version 2)	dqD2.	Comtess 200mg tablet	Parkinson's medications
Read codes (version 2)	dqE..	Pramipexole	Parkinson's medications
Read codes (version 2)	dqE1.	Mirapexin 0.088mg tablet	Parkinson's medications
Read codes (version 2)	dqE2.	Mirapexin 0.18mg tablet	Parkinson's medications
Read codes (version 2)	dqE3.	Mirapexin 0.7mg tablet	Parkinson's medications
Read codes (version 2)	dqE4.	MIRAPEXIN 350mcg tablets	Parkinson's medications
Read codes (version 2)	dqE5.	MIRAPEXIN 260mcg m/r tablets	Parkinson's medications
Read codes (version 2)	dqE6.	MIRAPEXIN 520mcg m/r tablets	Parkinson's medications
Read codes (version 2)	dqE7.	MIRAPEXIN 1.05mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqE8.	MIRAPEXIN 2.1mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqE9.	MIRAPEXIN 3.15mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEA.	MIRAPEXIN 1.57mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEB.	MIRAPEXIN 2.62mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEo.	PRAMIPEXOLE 1.1mg tablets	Parkinson's medications
Read codes (version 2)	dqEp.	PRAMIPEXOLE 2.62mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEq.	PRAMIPEXOLE 1.57mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEr.	PRAMIPEXOLE 3.15mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEs.	PRAMIPEXOLE 2.1mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEt.	PRAMIPEXOLE 1.05mg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEu.	PRAMIPEXOLE 520mcg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEv.	PRAMIPEXOLE 260mcg m/r tablets	Parkinson's medications
Read codes (version 2)	dqEw.	PRAMIPEXOLE 350mcg tablets	Parkinson's medications
Read codes (version 2)	dqEx.	Pramipexole 0.088mg tablet	Parkinson's medications
Read codes (version 2)	dqEx.	Pramipexole HCl 0.125mg tablet	Parkinson's medications
Read codes (version 2)	dqEy.	Pramipexole 0.18mg tablet	Parkinson's medications
Read codes (version 2)	dqEy.	Pramipexole HCl 0.25mg tablet	Parkinson's medications
Read codes (version 2)	dqEz.	Pramipexole 0.7mg tablet	Parkinson's medications
Read codes (version 2)	dqEz.	Pramipexole HCl 1mg tablet	Parkinson's medications
Read codes (version 2)	dqF..	Rasagiline	Parkinson's medications
Read codes (version 2)	dqFz.	Rasagiline 1mg tablet	Parkinson's medications
Read codes (version 2)	dqG..	Rotigotine	Parkinson's medications
Read codes (version 2)	dqGt.	ROTIGOTINE 3mg/24hours patches	Parkinson's medications
Read codes (version 2)	dqGu.	ROTIGOTINE 1mg/24hours patches	Parkinson's medications
Read codes (version 2)	dqGv.	Rotigotine 2+4+6+8mg pack	Parkinson's medications
Read codes (version 2)	dqGw.	Rotigotine 8mg/24hours patch	Parkinson's medications
Read codes (version 2)	dqGx.	Rotigotine 6mg/24hours patch	Parkinson's medications
Read codes (version 2)	dqGy.	Rotigotine 4mg/24hours patch	Parkinson's medications
Read codes (version 2)	dqGz.	Rotigotine 2mg/24hours patch	Parkinson's medications
Read codes (version 2)	dr...	Anticholinergics	Parkinson's medications
Read codes (version 2)	dr1..	Trihexyphenidyl hydrochloride	Parkinson's medications
Read codes (version 2)	dr1w.	Trihexyphenidyl HCl 2mg tablet	Parkinson's medications
Read codes (version 2)	dr1x.	Trihexyphenidyl HCl 5mg tablet	Parkinson's medications
Read codes (version 2)	dr2..	Orphenadrine hydrochloride	Parkinson's medications
Read codes (version 2)	dr2w.	Orphenadrine HCl 50mg/5mL syr	Parkinson's medications
Read codes (version 2)	dr2x.	Orphenadrine HCl 25mg/5mL liq	Parkinson's medications
Read codes (version 2)	dr2y.	Orphenadrine HCl 50mg tablet	Parkinson's medications
Read codes (version 2)	dr3..	Benztropine mesylate	Parkinson's medications
Read codes (version 2)	dr3y.	Benztropine mesylate 2mg tab	Parkinson's medications
Read codes (version 2)	dr6..	Procyclidine hydrochloride	Parkinson's medications
Read codes (version 2)	dr6w.	Procyclidine 2.5mg/5mL syrup	Parkinson's medications
Read codes (version 2)	dr6x.	Procyclidine 5mg/5mL s/f syrup	Parkinson's medications
Read codes (version 2)	dr6y.	Procyclidine HCl 5mg tablet	Parkinson's medications
Read codes (version 2)	dr6z.	Procyclidine HCl 10mg/2mL inj	Parkinson's medications
Codes used to exclude patients with secondary Parkinsonism or Parkinson-plus syndrome (applied after the initial extraction of PD cases in the first step.			
Read codes (version 2)	F124.	Vascular parkinsonism	Exclusion criteria (secondary

			Parkinsonism)
Read codes (version 2)	A94y1	Syphilitic parkinsonism	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F121.	Drug induced parkinsonism	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F123.	Postencephalitic parkinsonism	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F12W.	Secondary parkinsonism due to other external agents	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F12X.	Secondary parkinsonism, unspecified	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	Fyu2200	[X]Parkinsonism in disease classified elsewhere	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	Fyu2900	[X]Secondary parkinsonism, unspecified	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	Fyu2100	[X]Other secondary parkinsonism	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F122.00	Malignant neuroleptic syndrome	Exclusion criteria (secondary Parkinsonism)
Read codes (version 2)	F1304	Progressive supranuclear palsy	Exclusion criteria (Parkinson-plus syndrom)
Read codes (version 2)	F24y0	Progressive supranuclear palsy	Exclusion criteria (Parkinson-plus syndrom)
Read codes (version 2)	F174.	Multiple system atrophy	Exclusion criteria (Parkinson-plus syndrom)
Read codes (version 2)	F1740	Multpl sstm atrphy, cerblr var	Exclusion criteria (Parkinson-plus syndrom)
Read codes (version 2)	F1741	Multpl sstm atroph, Parksn var	Exclusion criteria (Parkinson-plus syndrom)
Read codes (version 2)	F11y2	Corticobasal degeneration	Exclusion criteria (Parkinson-plus syndrom)
Codes used to identify PwP with psychosis or/and on antipsychotics (applied after the initial extraction of PD cases in the first step.			
Read codes (version 2)	1464 .	H/O: schizophrenia	Psychosis codes
Read codes (version 2)	E10..	Schizophrenic disorders	Psychosis codes
Read codes (version 2)	E100.	Simple schizophrenia	Psychosis codes
Read codes (version 2)	E1000	Unspecified schizophrenia	Psychosis codes
Read codes (version 2)	E1001	Subchronic schizophrenia	Psychosis codes
Read codes (version 2)	E1002	Chronic schizophrenic	Psychosis codes
Read codes (version 2)	E1003	Acute exacerbation of subchronic schizophrenia	Psychosis codes
Read codes (version 2)	E1004	Acute exacerbation of chronic schizophrenia	Psychosis codes
Read codes (version 2)	E1005	Schizophrenia in remission	Psychosis codes
Read codes (version 2)	E100z	Simple schizophrenia NOS	Psychosis codes
Read codes (version 2)	E101.	Hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1010	Unspecified hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1011	Subchronic hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1012	Chronic hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1013	Acute exacerbation of subchronic hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1014	Acute exacerbation of chronic hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	E1015	Hebephrenic schizophrenia in remission	Psychosis codes
Read codes (version 2)	E101z	Hebephrenic schizophrenia NOS	Psychosis codes
Read codes (version 2)	E102.	Catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1020	Unspecified catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1021	Subchronic catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1022	Chronic catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1023	Acute exacerbation of subchronic catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1024	Acute exacerbation of chronic catatonic schizophrenia	Psychosis codes
Read codes (version 2)	E1025	Catatonic schizophrenia in remission	Psychosis codes
Read codes (version 2)	E102z	Catatonic schizophrenia NOS	Psychosis codes
Read codes (version 2)	E103.	Paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1030	Unspecified paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1031	Subchronic paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1032	Chronic paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1033	Acute exacerbation of subchronic paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1034	Acute exacerbation of chronic paranoid schizophrenia	Psychosis codes
Read codes (version 2)	E1035	Paranoid schizophrenia in remission	Psychosis codes
Read codes (version 2)	E103z	Paranoid schizophrenia NOS	Psychosis codes
Read codes (version 2)	E104.	Acute schizophrenic episode	Psychosis codes
Read codes (version 2)	E105.	Latent schizophrenia	Psychosis codes

Read codes (version 2)	E1050	Unspecified latent schizophrenia	Psychosis codes
Read codes (version 2)	E1051	Subchronic latent schizophrenia	Psychosis codes
Read codes (version 2)	E1052	Chronic latent schizophrenia	Psychosis codes
Read codes (version 2)	E1053	Acute exacerbation of subchronic latent schizophrenia	Psychosis codes
Read codes (version 2)	E1054	Acute exacerbation of chronic latent schizophrenia	Psychosis codes
Read codes (version 2)	E1055	Latent schizophrenia in remission	Psychosis codes
Read codes (version 2)	E105z	Latent schizophrenia NOS	Psychosis codes
Read codes (version 2)	E106.	Residual schizophrenia	Psychosis codes
Read codes (version 2)	E107.	Schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1070	Unspecified schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1071	Subchronic schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1072	Chronic schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1073	Acute exacerbation of subchronic schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1074	Acute exacerbation of chronic schizo-affective schizophrenia	Psychosis codes
Read codes (version 2)	E1075	Schizo-affective schizophrenia in remission	Psychosis codes
Read codes (version 2)	E107z	Schizo-affective schizophrenia NOS	Psychosis codes
Read codes (version 2)	E10y.	Other schizophrenia	Psychosis codes
Read codes (version 2)	E10y0	Atypical schizophrenia	Psychosis codes
Read codes (version 2)	E10y1	Coenesthopathic schizophrenia	Psychosis codes
Read codes (version 2)	E10yz	other schizophrenia	Psychosis codes
Read codes (version 2)	E10z.	Schizophrenia NOS	Psychosis codes
Read codes (version 2)	ZV110	[V]Personal history of schizophrenia	Psychosis codes
Read codes (version 2)	Eu2..	[X]Schizophrenia, schizotypal and delusional disorders	Psychosis codes
Read codes (version 2)	Eu20.	[X]Schizophrenia	Psychosis codes
Read codes (version 2)	Eu200	[X]Paranoid schizophrenia	Psychosis codes
Read codes (version 2)	Eu201	[X]Hebephrenic schizophrenia	Psychosis codes
Read codes (version 2)	Eu202	[X]Catatonic schizophrenia	Psychosis codes
Read codes (version 2)	Eu203	[X]Undifferentiated schizophrenia	Psychosis codes
Read codes (version 2)	Eu204	[X]Post-schizophrenic depression	Psychosis codes
Read codes (version 2)	Eu205	[X]Residual schizophrenia	Psychosis codes
Read codes (version 2)	Eu206	[X]Simple schizophrenia	Psychosis codes
Read codes (version 2)	Eu20y	[X]Other schizophrenia	Psychosis codes
Read codes (version 2)	Eu20z	[X]Schizophrenia, unspecified	Psychosis codes
Read codes (version 2)	Eu22.	[X]Persistent delusional disorders	Psychosis codes
Read codes (version 2)	Eu220	[X]Delusional disorder	Psychosis codes
Read codes (version 2)	Eu221	[X]Delusional misidentification syndrome	Psychosis codes
Read codes (version 2)	Eu222	[X]Cotard syndrome	Psychosis codes
Read codes (version 2)	Eu22y	[X]Other persistent delusional disorders	Psychosis codes
Read codes (version 2)	Eu22z	[X]Persistent delusional disorder, unspecified	Psychosis codes
Read codes (version 2)	Eu25.	[X]Schizoaffective disorders	Psychosis codes
Read codes (version 2)	Eu250	[X]Schizoaffective disorder, manic type	Psychosis codes
Read codes (version 2)	Eu251	[X]Schizoaffective disorder, depressive type	Psychosis codes
Read codes (version 2)	Eu252	[X]Schizoaffective disorder, mixed type	Psychosis codes
Read codes (version 2)	Eu25y	[X]Other schizoaffective disorders	Psychosis codes
Read codes (version 2)	Eu25z	[X]Schizoaffective disorder, unspecified	Psychosis codes
Read codes (version 2)	E11..	Bipolar psychoses	Psychosis codes
Read codes (version 2)	E114.	Bipolar affective disorder, currently manic	Psychosis codes
Read codes (version 2)	E1140	Bipolar affective disorder, currently manic, unspecified	Psychosis codes
Read codes (version 2)	E1141	Bipolar affective disorder, currently manic, mild	Psychosis codes
Read codes (version 2)	E1142	Bipolar affective disorder, currently manic, moderate	Psychosis codes
Read codes (version 2)	E1143	Bipolar affective disorder, currently manic, severe, without mention of psychosis	Psychosis codes
Read codes (version 2)	E1144	Bipolar affective disorder, currently manic, severe, with psychosis	Psychosis codes
Read codes (version 2)	E1145	Bipolar affective disorder, currently manic, in partial or unspecified remission	Psychosis codes
Read codes (version 2)	E1146	Bipolar affective disorder, currently manic, in full remission	Psychosis codes
Read codes (version 2)	E114z	Bipolar affective disorder, currently manic, NOS	Psychosis codes
Read codes (version 2)	E115.	Bipolar affective disorder, currently depressed	Psychosis codes
Read codes (version 2)	E1150	Bipolar affective disorder, currently depressed, unspecified	Psychosis codes
Read codes (version 2)	E1151	Bipolar affective disorder, currently depressed, mild	Psychosis codes
Read codes (version 2)	E1152	Bipolar affective disorder, currently depressed, moderate	Psychosis codes
Read codes (version 2)	E1153	Bipolar affective disorder, currently depressed, severe, without mention of psychosis	Psychosis codes
Read codes (version 2)	E1154	Bipolar affective disorder, currently depressed, severe, with psychosis	Psychosis codes

Read codes (version 2)	E1155	Bipolar affective disorder, currently depressed, in partial or unspecified remission	Psychosis codes
Read codes (version 2)	E1156	Bipolar affective disorder, currently depressed, in full remission	Psychosis codes
Read codes (version 2)	E115z	Bipolar affective disorder, currently depressed, NOS	Psychosis codes
Read codes (version 2)	E116.	Mixed bipolar affective disorder	Psychosis codes
Read codes (version 2)	E1160	Mixed bipolar affective disorder, unspecified	Psychosis codes
Read codes (version 2)	E1161	Mixed bipolar affective disorder, mild	Psychosis codes
Read codes (version 2)	E1162	Mixed bipolar affective disorder, moderate	Psychosis codes
Read codes (version 2)	E1163	Mixed bipolar affective disorder, severe, without mention of psychosis	Psychosis codes
Read codes (version 2)	E1164	Mixed bipolar affective disorder, severe, with psychosis	Psychosis codes
Read codes (version 2)	E1165	Mixed bipolar affective disorder, in partial or unspecified remission	Psychosis codes
Read codes (version 2)	E1166	Mixed bipolar affective disorder, in full remission	Psychosis codes
Read codes (version 2)	E116z	Mixed bipolar affective disorder, NOS	Psychosis codes
Read codes (version 2)	E117.	Unspecified bipolar affective disorder	Psychosis codes
Read codes (version 2)	E1170	Unspecified bipolar affective disorder, unspecified	Psychosis codes
Read codes (version 2)	E1171	Unspecified bipolar affective disorder, mild	Psychosis codes
Read codes (version 2)	E1172	Unspecified bipolar affective disorder, moderate	Psychosis codes
Read codes (version 2)	E1173	Unspecified bipolar affective disorder, severe, without mention of psychosis	Psychosis codes
Read codes (version 2)	E1174	Unspecified bipolar affective disorder, severe, with psychosis	Psychosis codes
Read codes (version 2)	E1175	Unspecified bipolar affective disorder, in partial or unspecified remission	Psychosis codes
Read codes (version 2)	E1176	Unspecified bipolar affective disorder, in full remission	Psychosis codes
Read codes (version 2)	E117z	Unspecified bipolar affective disorder, NOS	Psychosis codes
Read codes (version 2)	E11y.	Other and unspecified manic-depressive psychoses	Psychosis codes
Read codes (version 2)	E11y0	Unspecified manic-depressive psychoses	Psychosis codes
Read codes (version 2)	E11y1	Atypical manic disorder	Psychosis codes
Read codes (version 2)	E11y3	Other mixed manic-depressive psychoses	Psychosis codes
Read codes (version 2)	E11yz	Other and unspecified manic-depressive psychoses NOS	Psychosis codes
Read codes (version 2)	Eu31.	[X]Bipolar affective disorder	Psychosis codes
Read codes (version 2)	Eu310	[X]Bipolar affective disorder, current episode hypomanic	Psychosis codes
Read codes (version 2)	Eu311	[X]Bipolar affective disorder, current episode manic without psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu312	[X]Bipolar affective disorder, current episode manic with psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu313	[X]Bipolar affective disorder, current episode mild or moderate depression	Psychosis codes
Read codes (version 2)	Eu314	[X]Bipolar affective disorder, current episode severe depression without psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu315	[X]Bipolar affective disorder, current episode severe depression with psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu316	[X]Bipolar affective disorder, current episode mixed	Psychosis codes
Read codes (version 2)	Eu317	[X]Bipolar affective disorder, currently in remission	Psychosis codes
Read codes (version 2)	Eu31y	[X]Other bipolar affective disorders	Psychosis codes
Read codes (version 2)	Eu31z	[X]Bipolar affective disorder, unspecified	Psychosis codes
Read codes (version 2)	212V.	Bipolar affective disorder resolved	Psychosis codes
Read codes (version 2)	Eu30.	[X]Bipolar disorder, single manic episode	Psychosis codes
Read codes (version 2)	Eu300	[X]Hypomania	Psychosis codes
Read codes (version 2)	Eu301	[X]Mania without psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu302	[X]Mania with psychotic symptoms	Psychosis codes
Read codes (version 2)	Eu30y	[X]Other manic episodes	Psychosis codes
Read codes (version 2)	Eu30z	[X]Manic episode, unspecified	Psychosis codes
Read codes (version 2)	212T.	Psychosis, schizophrenia and bipolar affective disorder resolved	Psychosis codes
Read codes (version 2)	d4...	All antipsychotic drugs	Antipsychotic drugs
Read codes (version 2)	d4f..	SULPIRIDE	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f1.	DOLMATIL 200mg tablets	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f2.	*SULPITIL 200mg tablets x28CP	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f3.	*SULPITIL 200mg tablets x112CP	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f4.	*SULPAREX 200mg tablets	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f5.	DOLMATIL 400mg tablets	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4f6.	SULPOR 200mg/5mL oral solution	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4fw.	SULPIRIDE 200mg/5mL oral solution	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4fx.	SULPIRIDE 400mg tablets	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d4fy.	SULPIRIDE 200mg/5mL sugar free solution	Antipsychotic drugs (Sulpiride)

Read codes (version 2)	d4fz.	SULPIRIDE 200mg tablets	Antipsychotic drugs (Sulpiride)
Read codes (version 2)	d41..	CHLORPROMAZINE HYDROCHLORIDE	Typical antipsychotic drugs
Read codes (version 2)	d411.	CHLORPROMAZINE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d412.	CHLORPROMAZINE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d413.	CHLORPROMAZINE 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d414.	CHLORPROMAZINE 100mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d415.	CHLORPROMAZINE 25mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d416.	CHLORACTIL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d417.	CHLORACTIL 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d418.	CHLORACTIL 100mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d419.	*DOZINE 25mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d41A.	CHLORPROMAZINE 25mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d41B.	CHLORPROMAZINE 100mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d41a.	*LARGACTIL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d41b.	*LARGACTIL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d41c.	*LARGACTIL 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d41d.	*LARGACTIL 100mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d41e.	*LARGACTIL 25mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d41f.	LARGACTIL FORTE 100mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d41g.	*LARGACTIL 25mg/mL injection	Typical antipsychotic drugs
Read codes (version 2)	d41h.	LARGACTIL [CNS] 50mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d41i.	*LARGACTIL 100mg suppositories	Typical antipsychotic drugs
Read codes (version 2)	d41j.	CHLORPROMAZINE 100mg/5mL sugar free suspension	Typical antipsychotic drugs
Read codes (version 2)	d41k.	CHLORPROMAZINE 100mg suppositories	Typical antipsychotic drugs
Read codes (version 2)	d41l.	CHLORPROMAZINE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d41m.	CHLORPROMAZINE 50mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d41o.	CHLORPROMAZINE 100mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d42..	BENPERIDOL	Typical antipsychotic drugs
Read codes (version 2)	d421.	ANQUIL 250micrograms tablets	Typical antipsychotic drugs
Read codes (version 2)	d422.	*BENQUIL 250micrograms tablets	Typical antipsychotic drugs
Read codes (version 2)	d42z.	BENPERIDOL 250microgram tablets	Typical antipsychotic drugs
Read codes (version 2)	d43..	*CHLORPROTHIXENE	Typical antipsychotic drugs
Read codes (version 2)	d431.	*TARACTAN 15mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d432.	*TARACTAN 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d43y.	*CHLORPROTHIXENE 15mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d43z.	*CHLORPROTHIXENE 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d44..	DROPERIDOL [CENTRAL NERVOUS SYSTEM USE]	Typical antipsychotic drugs
Read codes (version 2)	d441.	*DROLEPTAN 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d442.	*DROLEPTAN 1mg/mL oral liquid	Typical antipsychotic drugs
Read codes (version 2)	d443.	*DROLEPTAN 10mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d444.	XOMOLIX 2.5mg/1mL solution for injection	Typical antipsychotic drugs
Read codes (version 2)	d44w.	DROPERIDOL 2.5mg/1mL solution for injection	Typical antipsychotic drugs
Read codes (version 2)	d44x.	*DROPERIDOL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d44y.	*DROPERIDOL 1mg/mL oral liquid	Typical antipsychotic drugs
Read codes (version 2)	d44z.	*DROPERIDOL 10mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d45..	FLUPENTIXOL [ANTIPSYCHOTIC]	Typical antipsychotic drugs
Read codes (version 2)	d451.	DEPIXOL 3mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d45z.	FLUPENTIXOL 3mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d46..	FLUPHENAZINE HYDROCHLORIDE	Typical antipsychotic drugs
Read codes (version 2)	d461.	*MODITEN 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d462.	*MODITEN 2.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d463.	*MODITEN 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d46x.	FLUPHENAZINE HYDROCHLORIDE 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d46y.	FLUPHENAZINE HYDROCHLORIDE 2.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d46z.	FLUPHENAZINE HYDROCHLORIDE 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47..	HALOPERIDOL [ANTIPSYCHOTIC]	Typical antipsychotic drugs
Read codes (version 2)	d471.	HALOPERIDOL 1.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d472.	HALOPERIDOL 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d473.	HALOPERIDOL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d474.	HALOPERIDOL 20mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d475.	HALOPERIDOL 2mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d476.	DOZIC 1mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d477.	*DOZIC 2mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d478.	FORTUNAN 500micrograms tablets	Typical antipsychotic drugs
Read codes (version 2)	d479.	*FORTUNAN 1.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47A.	HALOPERIDOL 2mg/5mL sugar free solution	Typical antipsychotic drugs

Read codes (version 2)	d47B.	HALOPERIDOL 1mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d47C.	KENTACE 1.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47D.	KENTACE 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47E.	KENTACE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47F.	KENTACE 20mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47a.	*FORTUNAN 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47b.	*FORTUNAN 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47c.	*FORTUNAN 20mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47d.	HALDOL 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47e.	HALDOL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47f.	HALDOL 2mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d47g.	*HALDOL 10mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d47h.	HALDOL 5mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47i.	*HALDOL 10mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47j.	SERENACE 500micrograms capsules	Typical antipsychotic drugs
Read codes (version 2)	d47k.	SERENACE 1.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47l.	SERENACE 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47m.	SERENACE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47n.	SERENACE 20mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d47o.	SERENACE 2mg/mL liquid 100mL	Typical antipsychotic drugs
Read codes (version 2)	d47p.	SERENACE 5mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47q.	SERENACE 20mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47r.	HALOPERIDOL 500microgram capsules	Typical antipsychotic drugs
Read codes (version 2)	d47s.	SERENACE 2mg/mL liquid 500mL	Typical antipsychotic drugs
Read codes (version 2)	d47t.	HALOPERIDOL 1mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d47u.	HALOPERIDOL 500micrograms tablets	Typical antipsychotic drugs
Read codes (version 2)	d47v.	HALOPERIDOL 5mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47w.	HALOPERIDOL 10mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47x.	HALOPERIDOL 20mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d47y.	HALOPERIDOL 10mg/mL oral solution	Typical antipsychotic drugs
Read codes (version 2)	d48..	LEVOMEPROMAZINE	Typical antipsychotic drugs
Read codes (version 2)	d481.	NOZINAN 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d482.	*VERACTIL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d483.	NOZINAN 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d48y.	LEVOMEPROMAZINE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d48z.	LEVOMEPROMAZINE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d49..	OXYPERTINE	Typical antipsychotic drugs
Read codes (version 2)	d491.	*INTEGRIN 10mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d492.	*INTEGRIN 40mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d49y.	*OXYPERTINE 10mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d49z.	*OXYPERTINE 40mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4a..	PERICYAZINE	Typical antipsychotic drugs
Read codes (version 2)	d4a1.	*NEULACTIL 2.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4a2.	*NEULACTIL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4a3.	*NEULACTIL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4a4.	*NEULACTIL FORTE 10mg/5mL syrp	Typical antipsychotic drugs
Read codes (version 2)	d4aw.	PERICYAZINE 2.5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4ax.	PERICYAZINE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4ay.	*PERICYAZINE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4az.	PERICYAZINE 10mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4b..	PERPHENAZINE [CENTRAL NERVOUS SYSTEM USE]	Typical antipsychotic drugs
Read codes (version 2)	d4b1.	FENTAZIN 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4b2.	FENTAZIN 4mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4b3.	*FENTAZIN 8mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4b4.	*FENTAZIN 5mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4b5.	PERPHENAZINE 2mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d4b6.	PERPHENAZINE 4mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d4bx.	PERPHENAZINE 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4by.	PERPHENAZINE 4mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4bz.	*PERPHENAZINE 8mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4c..	PIMOZIDE	Typical antipsychotic drugs
Read codes (version 2)	d4c1.	*ORAP 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4c2.	ORAP 4mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4c3.	*ORAP 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4cx.	*PIMOZIDE 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4cy.	PIMOZIDE 4mg tablets	Typical antipsychotic drugs

Read codes (version 2)	d4cz.	*PIMOZIDE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4d..	PROCHLORPERAZINE [antipsych] [see dhe..]	Typical antipsychotic drugs
Read codes (version 2)	d4e..	PROMAZINE HYDROCHLORIDE	Typical antipsychotic drugs
Read codes (version 2)	d4e1.	*SPARINE 50mg/5mL suspension	Typical antipsychotic drugs
Read codes (version 2)	d4e2.	*SPARINE 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4e3.	*SPARINE 100mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4e4.	PROMAZINE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4e5.	PROMAZINE 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4ev.	PROMAZINE 25mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4ew.	PROMAZINE 50mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4ex.	*PROMAZINE 50mg/5mL suspension	Typical antipsychotic drugs
Read codes (version 2)	d4ey.	PROMAZINE 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4ez.	*PROMAZINE 100mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4g..	THIORIDAZINE	Typical antipsychotic drugs
Read codes (version 2)	d4g1.	*MELLERIL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4g2.	*MELLERIL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4g3.	*MELLERIL 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4g4.	*MELLERIL 100mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4g5.	*MELLERIL 25mg/5mL suspension	Typical antipsychotic drugs
Read codes (version 2)	d4g6.	MELLERIL 100mg/5mL oral suspension	Typical antipsychotic drugs
Read codes (version 2)	d4g7.	MELLERIL 25mg/5mL orange syrup	Typical antipsychotic drugs
Read codes (version 2)	d4gp.	THIORIDAZINE 10mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4gq.	THIORIDAZINE 25mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d4gr.	THIORIDAZINE 50mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d4gs.	THIORIDAZINE 100mg/5mL sugar free solution	Typical antipsychotic drugs
Read codes (version 2)	d4gt.	*THIORIDAZINE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4gu.	THIORIDAZINE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4gv.	THIORIDAZINE 50mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4gw.	THIORIDAZINE 100mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4gx.	THIORIDAZINE 25mg/5mL suspension	Typical antipsychotic drugs
Read codes (version 2)	d4gy.	THIORIDAZINE 100mg/5mL oral suspension	Typical antipsychotic drugs
Read codes (version 2)	d4gz.	*THIORIDAZINE 25mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4h..	TRIFLUOPERAZINE [ANTIPSYCHOTIC]	Typical antipsychotic drugs
Read codes (version 2)	d4h1.	STELAZINE 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4h2.	STELAZINE 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4h3.	*STELAZINE 2mg m/r capsules	Typical antipsychotic drugs
Read codes (version 2)	d4h4.	*STELAZINE 10mg m/r capsules	Typical antipsychotic drugs
Read codes (version 2)	d4h5.	*STELAZINE 15mg m/r capsules	Typical antipsychotic drugs
Read codes (version 2)	d4h6.	STELAZINE 1mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4h7.	STELAZINE CONCENTRATE 10mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d4h8.	*STELAZINE 1mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4h9.	TRIFLUOPERAZINE 5mg/5mL sugar free syrup	Typical antipsychotic drugs
Read codes (version 2)	d4hA.	STELAZINE FORTE 5mg/5mL sugar free oral suspension	Typical antipsychotic drugs
Read codes (version 2)	d4hr.	TRIFLUOPERAZINE 5mg/5mL sugar free oral suspension	Typical antipsychotic drugs
Read codes (version 2)	d4hs.	TRIFLUOPERAZINE 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4ht.	TRIFLUOPERAZINE 5mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4hu.	*TRIFLUOPERAZINE 2mg m/r caps	Typical antipsychotic drugs
Read codes (version 2)	d4hv.	*TRIFLUOPERAZINE 10mg m/r caps	Typical antipsychotic drugs
Read codes (version 2)	d4hw.	*TRIFLUOPERAZINE 15mg m/r caps	Typical antipsychotic drugs
Read codes (version 2)	d4hx.	TRIFLUOPERAZINE 1mg/5mL syrup	Typical antipsychotic drugs
Read codes (version 2)	d4hy.	TRIFLUOPERAZINE 10mg/mL liquid	Typical antipsychotic drugs
Read codes (version 2)	d4hz.	TRIFLUOPERAZINE 1mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4i1.	TRIFLUPERIDOL	Typical antipsychotic drugs
Read codes (version 2)	d4i2.	TRIPERIDOL 500micrograms tablets	Typical antipsychotic drugs
Read codes (version 2)	d4iy.	*TRIPERIDOL 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4iz.	TRIFLUPERIDOL 500microgram tablets	Typical antipsychotic drugs
Read codes (version 2)	d4l..	*TRIFLUPERIDOL 1mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4j..	ZUCLOPENTHIXOL DIHYDROCHLORIDE	Typical antipsychotic drugs
Read codes (version 2)	d4j1.	CLOPIXOL 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4j2.	CLOPIXOL 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4j3.	CLOPIXOL 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4jx.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 2mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4jy.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 10mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4jz.	ZUCLOPENTHIXOL DIHYDROCHLORIDE 25mg tablets	Typical antipsychotic drugs
Read codes (version 2)	d4k..	LOXAPINE SUCCINATE	Typical antipsychotic drugs
Read codes (version 2)	d4k1.	*LOXAPINE 10mg capsules	Typical antipsychotic drugs

Read codes (version 2)	d4k2.	*LOXAPINE 25mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d4k3.	*LOXAPINE 50mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d4k4.	*LOXAPAC 10mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d4k5.	*LOXAPAC 25mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d4k6.	*LOXAPAC 50mg capsules	Typical antipsychotic drugs
Read codes (version 2)	d4n..	ZUCLOPENTHIXOL ACETATE	Typical antipsychotic drugs
Read codes (version 2)	d4n1.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d4n2.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d4n3.	ZUCLOPENTHIXOL ACETATE 50mg/1mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d4n4.	ZUCLOPENTHIXOL ACETATE 100mg/2mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d5...	ANTIPSYCHOTIC DEPOT INJECTIONS	Typical antipsychotic drugs
Read codes (version 2)	d51..	FLUPENTIXOL DECANOATE	Typical antipsychotic drugs
Read codes (version 2)	d511.	DEPIXOL 20mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d512.	*DEPIXOL 20mg/1mL syringe	Typical antipsychotic drugs
Read codes (version 2)	d513.	DEPIXOL 40mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d514.	*DEPIXOL 40mg/2mL syringe	Typical antipsychotic drugs
Read codes (version 2)	d515.	*DEPIXOL 200mg/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d516.	DEPIXOL CONC. 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d517.	DEPIXOL CONC. 500mg/5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d518.	DEPIXOL CONC. 50mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d519.	FLUPENTIXOL 50mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d51a.	DEPIXOL LOW VOLUME 200mg/1mL intramuscular injection	Typical antipsychotic drugs
Read codes (version 2)	d51s.	FLUPENTHIXOL DECANOATE 20mg/1mL prefilled syringe	Typical antipsychotic drugs
Read codes (version 2)	d51t.	FLUPENTHIXOL DECANOATE 40mg/2mL prefilled syringe	Typical antipsychotic drugs
Read codes (version 2)	d51u.	FLUPENTIXOL DECANOATE 200mg/1mL intramuscular injection	Typical antipsychotic drugs
Read codes (version 2)	d51v.	FLUPENTIXOL DECANOATE 20mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d51w.	FLUPENTIXOL DECANOATE 40mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d51x.	FLUPENTHIXOL DECANOATE 200mg/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d51y.	FLUPENTIXOL DECANOATE 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d51z.	FLUPENTHIXOL DECANOATE 500mg/5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52..	FLUPHENAZINE DECANOATE	Typical antipsychotic drugs
Read codes (version 2)	d521.	MODECATE 12.5mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d522.	MODECATE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d523.	*MODECATE 25mg/1mL syringe	Typical antipsychotic drugs
Read codes (version 2)	d524.	MODECATE 50mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d525.	*MODECATE 50mg/2mL syringe	Typical antipsychotic drugs
Read codes (version 2)	d526.	*MODECATE 250mg/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d527.	MODECATE CONCENTRATE 50mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d528.	MODECATE CONCENTRATE 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d529.	FLUPHENAZINE DECANOATE 50mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52A.	*DECAZATE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52B.	*DECAZATE 50mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52C.	*DECAZATE 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52a.	FLUPHENAZINE DECANOATE 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52s.	FLUPHENAZINE DECANOATE 25mg/1mL prefilled syringe	Typical antipsychotic drugs
Read codes (version 2)	d52t.	FLUPHENAZINE DECANOATE 50mg/2mL prefilled syringe	Typical antipsychotic drugs
Read codes (version 2)	d52u.	FLUPHENAZINE DECANOATE 12.5mg/0.5mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52v.	FLUPHENAZINE DECANOATE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52w.	FLUPHENAZINE DECANOATE 50mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d52x.	FLUPHENAZINE DECANOATE 250mg/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d53..	*FLUPHENAZINE ENANTHATE	Typical antipsychotic drugs
Read codes (version 2)	d531.	MODITEN ENANTHATE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d532.	FLUPHENAZINE ENANTHATE 25mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d54..	FLUSPIRILENE	Typical antipsychotic drugs
Read codes (version 2)	d541.	*REDEPTIN 2mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d542.	*REDEPTIN 6mg/3mL injection	Typical antipsychotic drugs
Read codes (version 2)	d543.	*REDEPTIN 12mg/6mL injection	Typical antipsychotic drugs
Read codes (version 2)	d544.	FLUSPIRILENE 2mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d545.	FLUSPIRILENE 6mg/3mL injection	Typical antipsychotic drugs
Read codes (version 2)	d546.	FLUSPIRILENE 12mg/6mL injection	Typical antipsychotic drugs
Read codes (version 2)	d55..	HALOPERIDOL DECANOATE	Typical antipsychotic drugs
Read codes (version 2)	d551.	HALDOL DECANOATE 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d552.	HALDOL DECANOATE 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d553.	HALOPERIDOL 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d554.	HALOPERIDOL 100mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d56..	PIPOTIAZINE PALMITATE	Typical antipsychotic drugs

Read codes (version 2)	d561.	PIPORTIL DEPOT 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d562.	PIPORTIL DEPOT 100mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d563.	PIPOTIAZINE 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d564.	PIPOTIAZINE 100mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d57..	ZUCLOPENTHIXOL DECANOATE	Typical antipsychotic drugs
Read codes (version 2)	d571.	CLOPIXOL 200mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d572.	*CLOPIXOL 2g/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d573.	CLOPIXOL CONC. 500mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d574.	CLOPIXOL ACUPHASE 50mg/1mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d575.	CLOPIXOL ACUPHASE 100mg/2mL injection (oily)	Typical antipsychotic drugs
Read codes (version 2)	d576.	ZUCLOPENTHIXOL DECANOATE 200mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d577.	ZUCLOPENTHIXOL DECANOATE 50mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d578.	ZUCLOPENTHIXOL DECANOATE 100mg/2mL injection	Typical antipsychotic drugs
Read codes (version 2)	d57y.	ZUCLOPENTHIXOL DECANOATE 2g/10mL injection	Typical antipsychotic drugs
Read codes (version 2)	d57z.	ZUCLOPENTHIXOL DECANOATE 500mg/1mL injection	Typical antipsychotic drugs
Read codes (version 2)	d4l..	CLOZAPINE	Atypical antipsychotic drugs
Read codes (version 2)	d4l1.	CLOZAPINE 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4l2.	CLOZAPINE 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4l3.	CLOZARIL 25mg tablets x84CP	Atypical antipsychotic drugs
Read codes (version 2)	d4l4.	CLOZARIL 100mg tablets x84CP	Atypical antipsychotic drugs
Read codes (version 2)	d4l5.	CLOZARIL COMMUNITY PACK 25mg tablets x28CP	Atypical antipsychotic drugs
Read codes (version 2)	d4l6.	CLOZARIL COMMUNITY PACK 100mg tablets x28CP	Atypical antipsychotic drugs
Read codes (version 2)	d4l7.	DENZAPINE 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4l8.	DENZAPINE 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4l9.	ZAPONEX 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4lA.	ZAPONEX 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4lB.	DENZAPINE 50mg/mL oral suspension 100mL	Atypical antipsychotic drugs
Read codes (version 2)	d4lC.	CLOZAPINE 50mg/mL oral suspension	Atypical antipsychotic drugs
Read codes (version 2)	d4lD.	DENZAPINE 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4lE.	CLOZAPINE 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4lF.	DENZAPINE 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4lG.	CLOZAPINE 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4m..	REMOXIPRIDE	Atypical antipsychotic drugs
Read codes (version 2)	d4m1.	REMOXIPRIDE 150mg m/r capsules	Atypical antipsychotic drugs
Read codes (version 2)	d4m2.	REMOXIPRIDE 300mg m/r capsules	Atypical antipsychotic drugs
Read codes (version 2)	d4m3.	*ROXIAM 150mg m/r capsules	Atypical antipsychotic drugs
Read codes (version 2)	d4m4.	*ROXIAM 300mg m/r capsules	Atypical antipsychotic drugs
Read codes (version 2)	d4p..	RISPERIDONE	Atypical antipsychotic drugs
Read codes (version 2)	d4p1.	RISPERIDONE 1mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p2.	RISPERIDONE 2mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p3.	RISPERIDONE 3mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p4.	RISPERIDONE 4mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p5.	RISPERDAL 1mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p6.	RISPERDAL 2mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p7.	RISPERDAL 3mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p8.	RISPERDAL 4mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4p9.	RISPERIDONE 1mg/mL liquid	Atypical antipsychotic drugs
Read codes (version 2)	d4pA.	RISPERDAL 1mg/mL liquid	Atypical antipsychotic drugs
Read codes (version 2)	d4pB.	RISPERIDONE 6mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pC.	RISPERDAL 6mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pD.	RISPERDAL 0.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pE.	RISPERDAL CONSTA 25mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4pF.	RISPERDAL CONSTA 37.5mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4pG.	RISPERDAL CONSTA 50mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4pH.	RISPERIDONE 1mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pJ.	RISPERIDONE 2mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pK.	RISPERDAL QUICKLET 1mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pL.	RISPERDAL QUICKLET 2mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pM.	RISPERIDONE 0.5mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pN.	RISPERDAL QUICKLET 0.5mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pO.	RISPERDAL QUICKLET 3mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pP.	RISPERDAL QUICKLET 4mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pQ.	RISPERIDONE 3mg oro-dispersible tablets	Atypical antipsychotic drugs

Read codes (version 2)	d4pR.	RISPERIDONE 4mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4pw.	RISPERIDONE 50mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4px.	RISPERIDONE 37.5mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4py.	RISPERIDONE 25mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4pz.	RISPERIDONE 0.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q..	SERTINDOLE	Atypical antipsychotic drugs
Read codes (version 2)	d4q1.	SERTINDOLE 4mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q2.	SERTINDOLE 12mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q3.	SERTINDOLE 16mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q4.	SERTINDOLE 20mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q5.	SERDOLECT 4mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q6.	SERDOLECT 12mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q7.	SERDOLECT 16mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4q8.	SERDOLECT 20mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r..	OLANZAPINE	Atypical antipsychotic drugs
Read codes (version 2)	d4r1.	OLANZAPINE 5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r2.	OLANZAPINE 7.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r3.	OLANZAPINE 10mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r4.	ZYPREXA 5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r5.	ZYPREXA 7.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r6.	ZYPREXA 10mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r7.	OLANZAPINE 2.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r8.	ZYPREXA 2.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4r9.	ZYPREXA VELOTAB 5mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rA.	ZYPREXA VELOTAB 10mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rB.	ZYPREXA 15mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rC.	ZYPREXA VELOTAB 15mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rD.	ZYPREXA 10mg injection (pdr for recon)	Atypical antipsychotic drugs
Read codes (version 2)	d4rE.	ZYPREXA VELOTAB 20mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rF.	ZYPREXA 20mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rG.	ZALASTA 2.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rH.	ZALASTA 5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rI.	ZALASTA 7.5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rJ.	ZALASTA 15mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rK.	ZALASTA 20mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rL.	ZALASTA 5mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rM.	ZALASTA 10mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rN.	ZALASTA 15mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rO.	ZALASTA 20mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rP.	ZALASTA 10mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rt.	OLANZAPINE 20mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4ru.	OLANZAPINE 20mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rv.	OLANZAPINE 10mg injection (pdr for recon)	Atypical antipsychotic drugs
Read codes (version 2)	d4rw.	OLANZAPINE 15mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rx.	OLANZAPINE 15mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4ry.	OLANZAPINE 5mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4rz.	OLANZAPINE 10mg dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s..	QUETIAPINE	Atypical antipsychotic drugs
Read codes (version 2)	d4s1.	QUETIAPINE 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s2.	QUETIAPINE 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s3.	QUETIAPINE 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s4.	QUETIAPINE 25mg+100mg tablets starter pack	Atypical antipsychotic drugs
Read codes (version 2)	d4s5.	SEROQUEL 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s6.	SEROQUEL 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s7.	SEROQUEL 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4s8.	SEROQUEL 25mg+100mg tablets starter pack	Atypical antipsychotic drugs
Read codes (version 2)	d4s9.	SEROQUEL 150mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sA.	SEROQUEL 25mg+100mg+150mg tablets starter pack	Atypical antipsychotic drugs
Read codes (version 2)	d4sB.	SEROQUEL 300mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sC.	SEROQUEL XL 50mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sD.	SEROQUEL XL 200mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sE.	SEROQUEL XL 300mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sF.	SEROQUEL XL 400mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sG.	SEROQUEL XL 150mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4ss.	QUETIAPINE 150mg m/r tablets	Atypical antipsychotic drugs

Read codes (version 2)	d4st.	QUETIAPINE 400mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4su.	QUETIAPINE 300mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sv.	QUETIAPINE 200mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sw.	QUETIAPINE 50mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sx.	QUETIAPINE 300mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4sy.	QUETIAPINE 25mg+100mg+150mg tablets starter pack	Atypical antipsychotic drugs
Read codes (version 2)	d4sz.	QUETIAPINE 150mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t..	AMISULPRIDE	Atypical antipsychotic drugs
Read codes (version 2)	d4t1.	AMISULPRIDE 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t2.	AMISULPRIDE 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t3.	SOLIAN 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t4.	SOLIAN 200mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t5.	SOLIAN 400mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4t6.	SOLIAN 100mg/mL sugar free oral solution	Atypical antipsychotic drugs
Read codes (version 2)	d4t7.	SOLIAN 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4tx.	AMISULPRIDE 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4ty.	AMISULPRIDE 100mg/mL sugar free oral solution	Atypical antipsychotic drugs
Read codes (version 2)	d4tz.	AMISULPRIDE 400mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u..	ZOTEPINE	Atypical antipsychotic drugs
Read codes (version 2)	d4u1.	*ZOTEPINE 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u2.	*ZOTEPINE 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u3.	*ZOTEPINE 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u4.	*ZOLEPTIL 25mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u5.	*ZOLEPTIL 50mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4u6.	*ZOLEPTIL 100mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v..	ARIPIPRAZOLE	Atypical antipsychotic drugs
Read codes (version 2)	d4v1.	ABILIFY 10mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v2.	ABILIFY 15mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v3.	ABILIFY 30mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v4.	ABILIFY 5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v5.	ABILIFY 10mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v6.	ABILIFY 15mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4v7.	ABILIFY 1mg/mL oral solution	Atypical antipsychotic drugs
Read codes (version 2)	d4v8.	ABILIFY 9.75mg/1.3mL solution for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4vs.	ARIPIPRAZOLE 9.75mg/1.3mL solution for injection	Atypical antipsychotic drugs
Read codes (version 2)	d4vt.	ARIPIPRAZOLE 1mg/mL oral solution	Atypical antipsychotic drugs
Read codes (version 2)	d4vu.	ARIPIPRAZOLE 10mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4vv.	ARIPIPRAZOLE 15mg oro-dispersible tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4vw.	ARIPIPRAZOLE 5mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4vx.	ARIPIPRAZOLE 30mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4vy.	ARIPIPRAZOLE 15mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4vz.	ARIPIPRAZOLE 10mg tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4w..	PALIPERIDONE	Atypical antipsychotic drugs
Read codes (version 2)	d4w1.	INVEGA 3mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4w2.	INVEGA 6mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4w3.	INVEGA 9mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4w4.	*INVEGA 12mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4w5.	XEPLION 50mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4w6.	XEPLION 75mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4w7.	XEPLION 100mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4w8.	XEPLION 150mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4ws.	PALIPERIDONE 150mg suspension for injection pfs	Atypical antipsychotic drugs
Read codes (version 2)	d4wt.	PALIPERIDONE 100mg suspension for injection pfs	Atypical antipsychotic drugs
Read codes (version 2)	d4wu.	PALIPERIDONE 75mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4wv.	PALIPERIDONE 50mg suspension for injection prefilled syringe	Atypical antipsychotic drugs
Read codes (version 2)	d4ww.	*PALIPERIDONE 12mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4wx.	PALIPERIDONE 9mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4wy.	PALIPERIDONE 6mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4wz.	PALIPERIDONE 3mg m/r tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4x..	ASENAPINE	Atypical antipsychotic drugs
Read codes (version 2)	d4x1.	SYCREST 5mg sublingual tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4x2.	ASENAPINE 5mg sublingual tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4x3.	SYCREST 10mg sublingual tablets	Atypical antipsychotic drugs
Read codes (version 2)	d4x4.	ASENAPINE 10mg sublingual tablets	Atypical antipsychotic drugs
Read codes (version 2)	d58..	OLANZAPINE PAMOATE	Atypical antipsychotic drugs
Read codes (version 2)	d581.	ZYPADHERA 210mg powder+solvent for suspension for injection	Atypical antipsychotic drugs

Read codes (version 2)	d582.	ZYPADHERA 300mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d583.	ZYPADHERA 405mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d58x.	OLANZAPINE 405mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d58y.	OLANZAPINE 300mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Read codes (version 2)	d58z.	OLANZAPINE 210mg powder+solvent for suspension for injection	Atypical antipsychotic drugs
Codes used to identify PwP with depression or/and on antidepressants (applied after the initial extraction of PD cases in the first step.			
Read codes (version 2)	1B17.00	Depressed	Depression codes
Read codes (version 2)	1B17.11	C/O - feeling depressed	Depression codes
Read codes (version 2)	1B1U.00	Symptoms of depression	Depression codes
Read codes (version 2)	1B1U.11	Depressive symptoms	Depression codes
Read codes (version 2)	1BQ..00	Loss of capacity for enjoyment	Depression codes
Read codes (version 2)	1BT..00	Depressed mood	Depression codes
Read codes (version 2)	1BT..11	Low mood	Depression codes
Read codes (version 2)	1BU..	Loss of hope for the future	Depression codes
Read codes (version 2)	2257.00	O/E - depressed	Depression codes
Read codes (version 2)	8BK0.00	Depression management programme	Depression codes
Read codes (version 2)	8CAa.00	Patient given advice about management of depression	Depression codes
Read codes (version 2)	8HHq.00	Referral for guided self-help for depression	Depression codes
Read codes (version 2)	9H90.00	Depression annual review	Depression codes
Read codes (version 2)	9H91.00	Depression medication review	Depression codes
Read codes (version 2)	9H92.00	Depression interim review	Depression codes
Read codes (version 2)	9HA0.00	On depression register	Depression codes
Read codes (version 2)	9Ov..00	Depression monitoring administration	Depression codes
Read codes (version 2)	9Ov0.00	Depression monitoring first letter	Depression codes
Read codes (version 2)	9Ov1.00	Depression monitoring second letter	Depression codes
Read codes (version 2)	9Ov2.00	Depression monitoring third letter	Depression codes
Read codes (version 2)	9Ov3.00	Depression monitoring verbal invite	Depression codes
Read codes (version 2)	9Ov4.00	Depression monitoring telephone invite	Depression codes
Read codes (version 2)	9kQ..00	On full dose long term treatment for depression	Depression codes
Read codes (version 2)	E11..12	Depressive psychoses	Depression codes
Read codes (version 2)	E112.00	Single major depressive episode	Depression codes
Read codes (version 2)	E112.11	Agitated depression	Depression codes
Read codes (version 2)	d831.	Marplan 10mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d83z.	Isocarboxazid 10mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d84..	tranylcypromine	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d841.	Parnate 10mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d84z.	Tranylcypromine 10mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d85..	moclobemide	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d851.	Manerix 150mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d852.	Moclobemide 150mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d853.	Manerix 300mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	d854.	Moclobemide 300mg tablet	Monoamine-oxidase inhibitors antidepressants
Read codes (version 2)	da2..	tryptophan	Other antidepressants
Read codes (version 2)	da22.	Optimax 500mg tablet	Other antidepressants
Read codes (version 2)	da23.	Optimax 1g/6g powder	Other antidepressants
Read codes (version 2)	da24.	Optimax WV 500mg tablets	Other antidepressants
Read codes (version 2)	da2y.	Pacitron 500mg tablet	Other antidepressants
Read codes (version 2)	da2z.	Tryptophan 500mg tablet	Other antidepressants
Read codes (version 2)	da22.	Tryptophan 1g/6g powder	Other antidepressants
Read codes (version 2)	da7..	venlafaxine	Other antidepressants
Read codes (version 2)	da71.	Venlafaxine 37.5mg tablet	Other antidepressants
Read codes (version 2)	da72.	Venlafaxine 75mg tablet	Other antidepressants
Read codes (version 2)	da73.	Efexor 37.5mg tablet	Other antidepressants

Read codes (version 2)	da74.	Efexor 75mg tablet	Other antidepressants
Read codes (version 2)	da75.	Venlafaxine 50mg tablet	Other antidepressants
Read codes (version 2)	da76.	Efexor 50mg tablet	Other antidepressants
Read codes (version 2)	da77.	Venlafaxine 75mg m/r capsule	Other antidepressants
Read codes (version 2)	da78.	Efexor XL 75mg m/r capsule	Other antidepressants
Read codes (version 2)	da79.	Venlafaxine 150mg m/r capsule	Other antidepressants
Read codes (version 2)	da7A.	Efexor XL 150mg m/r capsule	Other antidepressants
Read codes (version 2)	da7a.	VENAXX XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7B.	RODOMEL XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7b.	VAXALIN XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7C.	RODOMEL XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7c.	VAXALIN XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7D.	WINFEX XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7d.	ALVENTA XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7E.	WINFEX XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7e.	ALVENTA XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7F.	TRIXAT XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7f.	RANFAXINE XL 150mg m/r caps	Other antidepressants
Read codes (version 2)	da7G.	TRIXAT XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7g.	RANFAXINE XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7H.	VIEPAX XL 75mg m/r tablets	Other antidepressants
Read codes (version 2)	da7h.	BONILUX XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7I.	VENLAFAXINE 75mg m/r tablets	Other antidepressants
Read codes (version 2)	da7i.	BONILUX XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7J.	VIEPAX XL 150mg m/r tablets	Other antidepressants
Read codes (version 2)	da7j.	TONPULAR XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7K.	VENLAFAXINE 150mg m/r tablets	Other antidepressants
Read codes (version 2)	da7k.	TONPULAR XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7L.	TARDCAPS XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7l.	FORAVEN XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7M.	TARDCAPS XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7m.	FORAVEN XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7N.	VIEPAX 37.5mg tablets	Other antidepressants
Read codes (version 2)	da7n.	DEPEFEX XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7O.	VIEPAX 75mg tablets	Other antidepressants
Read codes (version 2)	da7o.	DEPEFEX XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7P.	VENSIR XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7p.	VENLALIC XL 37.5mg m/r tablets	Other antidepressants
Read codes (version 2)	da7Q.	VENSIR XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7q.	VENLAFAXINE 37.5mg m/r tablets	Other antidepressants
Read codes (version 2)	da7R.	TIFAXIN XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7r.	SUNVENIZ XL 75mg m/r tablets	Other antidepressants
Read codes (version 2)	da7S.	TIFAXIN XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7s.	SUNVENIZ XL 150mg m/r tablets	Other antidepressants
Read codes (version 2)	da7T.	VEXARIN XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da7t.	VENLADEX XL 75mg m/r tablets	Other antidepressants
Read codes (version 2)	da7U.	VEXARIN XL 150mg m/r capsules	Other antidepressants
Read codes (version 2)	da7u.	VENLADEX XL 150mg m/r tablets	Other antidepressants
Read codes (version 2)	da7V.	VENLALIC XL 75mg m/r tablets	Other antidepressants
Read codes (version 2)	da7v.	EFEXOR XL 225mg m/r capsules	Other antidepressants
Read codes (version 2)	da7W.	VENLALIC XL 150mg m/r tablets	Other antidepressants
Read codes (version 2)	da7w.	VENLAFAXINE 225mg m/r capsules	Other antidepressants
Read codes (version 2)	da7X.	VENLALIC XL 225mg m/r tablets	Other antidepressants
Read codes (version 2)	da7Y.	VENLAFAXINE 225mg m/r tablets	Other antidepressants
Read codes (version 2)	da7Z.	VENAXX XL 75mg m/r capsules	Other antidepressants
Read codes (version 2)	da8.	nefazodone	Other antidepressants
Read codes (version 2)	da81.	Nefazodone HCl 100mg tablet	Other antidepressants
Read codes (version 2)	da82.	Nefazodone HCl 200mg tablet	Other antidepressants
Read codes (version 2)	da83.	Dutonin 100mg tablet	Other antidepressants
Read codes (version 2)	da84.	Dutonin 200mg tablet	Other antidepressants
Read codes (version 2)	da85.	Nefazodone initiation tab pack	Other antidepressants
Read codes (version 2)	da86.	Dutonin initiation tab pack	Other antidepressants
Read codes (version 2)	daA..	reboxetine	Other antidepressants
Read codes (version 2)	daA1.	Reboxetine 4mg tablet	Other antidepressants
Read codes (version 2)	daA2.	Edronax 4mg tablet	Other antidepressants
Read codes (version 2)	daB..	mirtazapine	Other antidepressants

Read codes (version 2)	daB1.	Mirtazapine 30mg tablet	Other antidepressants
Read codes (version 2)	daB2.	Zispin 30mg tablet	Other antidepressants
Read codes (version 2)	daB3.	Mirtazapine 30mg disp tab	Other antidepressants
Read codes (version 2)	daB4.	Zispin SolTab 30mg disp tab	Other antidepressants
Read codes (version 2)	daB5.	Mirtazapine 15mg disp tab	Other antidepressants
Read codes (version 2)	daB6.	Zispin SolTab 15mg disp tab	Other antidepressants
Read codes (version 2)	daB7.	Mirtazapine 45mg disp tab	Other antidepressants
Read codes (version 2)	daB8.	Zispin SolTab 45mg disp tab	Other antidepressants
Read codes (version 2)	daBy.	Mirtazapine 45mg tablet	Other antidepressants
Read codes (version 2)	daBz.	Mirtazapine 15mg tablet	Other antidepressants
Read codes (version 2)	daD..	agomelatine	Other antidepressants
Read codes (version 2)	daD1.	VALDOXAN 25mg tablets	Other antidepressants
Read codes (version 2)	daD2.	AGOMELATINE 25mg tablets	Other antidepressants
Read codes (version 2)	daE.	vortioxetine	Other antidepressants
Read codes (version 2)	daE1.	BRINTELLIX 5mg tablets	Other antidepressants
Read codes (version 2)	daE2.	VORTIOXETINE 5mg tablets	Other antidepressants
Read codes (version 2)	daE3.	BRINTELLIX 10mg tablets	Other antidepressants
Read codes (version 2)	daE4.	VORTIOXETINE 10mg tablets	Other antidepressants
Read codes (version 2)	daE5.	BRINTELLIX 20mg tablets	Other antidepressants
Read codes (version 2)	daE6.	VORTIOXETINE 20mg tablets	Other antidepressants
Read codes (version 2)	gde..	duloxetine	Other antidepressants
Read codes (version 2)	gde1.	Yentreve 20mg g/r capsule	Other antidepressants
Read codes (version 2)	gde2.	Yentreve 40mg g/r capsule	Other antidepressants
Read codes (version 2)	gde3.	Cymbalta 30mg g/r capsule	Other antidepressants
Read codes (version 2)	gde4.	Cymbalta 60mg g/r capsule	Other antidepressants
Read codes (version 2)	gdew.	Duloxetine 60mg g/r capsule	Other antidepressants
Read codes (version 2)	gdex.	Duloxetine 30mg g/r capsule	Other antidepressants
Read codes (version 2)	gdey.	Duloxetine 20mg g/r capsule	Other antidepressants
Read codes (version 2)	gdez.	Duloxetine 40mg g/r capsule	Other antidepressants
Codes used to identify PwP with dementia or/and on antidementia drugs (applied after the initial extraction of PD cases in the first step.			
Read codes (version 2)	1B1A.12	Memory loss symptom	Memory problems
Read codes (version 2)	1B1A.13	Memory disturbance	Memory problems
Read codes (version 2)	1B1Y.00	Poor visual sequential memory	Memory problems
Read codes (version 2)	1B1a.00	Poor auditory sequential memory	Memory problems
Read codes (version 2)	1S21.00	Disturbance of memory for order of events	Memory problems
Read codes (version 2)	28G..00	Forgetful	memory problems
Read codes (version 2)	3A10.00	Memory: own age not known	Memory problems
Read codes (version 2)	3A20.00	Memory: present time not known	Memory problems
Read codes (version 2)	3A30.00	Memory: present place not knwn	Memory problems
Read codes (version 2)	3A40.00	Memory: present year not known	Memory problems
Read codes (version 2)	3A50.00	Memory: own DOB not known	Memory problems
Read codes (version 2)	3A60.00	Memory: present month not knwn	Memory problems
Read codes (version 2)	3A70.00	Memory: important event not kn	Memory problems
Read codes (version 2)	3A80.00	Memory: import.person not knwn	Memory problems
Read codes (version 2)	3A91.00	Memory: count down unsuccess.	Memory problems
Read codes (version 2)	3AA1.00	Memory: address recall unsucc.	Memory problems
Read codes (version 2)	8BIk.00	Patient forgets to take medication	Memory problems
Read codes (version 2)	8HTY.00	Referral to memory clinic	Memory problems
Read codes (version 2)	9Nk1.00	Seen in memory clinic	Memory problems
Read codes (version 2)	E2A1000	Mild memory disturbance	Memory problems
Read codes (version 2)	E2A1100	Organic memory impairment	Memory problems
Read codes (version 2)	R00z011	[D]Memory deficit	Memory problems
Read codes (version 2)	Z7A1300	Memory skills training	Memory problems
Read codes (version 2)	Z7A1500	Memory retraining	Memory problems
Read codes (version 2)	Z7CA100	Isolated memory skills	Memory problems
Read codes (version 2)	Z7CE412	Memory loss symptom	Memory problems
Read codes (version 2)	Z7CE414	Memory disturbance	Memory problems
Read codes (version 2)	Z7CE415	Loss of memory	Memory problems
Read codes (version 2)	Z7CE500	Forgetful	Memory problems
Read codes (version 2)	Z7CE611	Memory loss	Memory problems
Read codes (version 2)	Z7CE612	Memory gone	Memory problems
Read codes (version 2)	Z7CE613	Dysmnesia	Memory problems
Read codes (version 2)	Z7CE615	Loss of memory	Memory problems
Read codes (version 2)	Z7CE616	LOM - Loss of memory	Memory problems
Read codes (version 2)	Z7CEA00	Impairment of registration	Memory problems
Read codes (version 2)	Z7CEA11	Impairment of working memory	Memory problems

Read codes (version 2)	Z7CEA12	Impairment of immediate recall	Memory problems
Read codes (version 2)	Z7CEA13	Impairment of primary memory	Memory problems
Read codes (version 2)	Z7CEB11	Loss of memory for remote events	Memory problems
Read codes (version 2)	Z7CEB12	Poor memory for remote events	Memory problems
Read codes (version 2)	Z7CEC11	Loss of memory for recent events	Memory problems
Read codes (version 2)	Z7CEC12	No memory for recent events	Memory problems
Read codes (version 2)	Z7CEH00	Memory impairment	Memory problems
Read codes (version 2)	Z7CEH11	Memory dysfunction	Memory problems
Read codes (version 2)	Z7CEH12	Memory deficit	Memory problems
Read codes (version 2)	Z7CEH13	Bad memory	Memory problems
Read codes (version 2)	Z7CEH14	Memory problem	Memory problems
Read codes (version 2)	Z7CEH15	Poor memory	Memory problems
Read codes (version 2)	Z7CEI00	Mixes past with present	Memory problems
Read codes (version 2)	Z7CEJ00	Memory lapses	Memory problems
Read codes (version 2)	Z7CEK00	Minor memory lapses	Memory problems
Read codes (version 2)	Z7CEL00	Mild memory disturbance	Memory problems
Read codes (version 2)	Z7CEM00	Distortion of memory	Memory problems
Read codes (version 2)	Z7CEN00	Confabulation	Memory problems
Read codes (version 2)	Z7CEN11	Invents experiences to compensate for loss of memory	Memory problems
Read codes (version 2)	Z7CEO00	Momentary confabulation	Memory problems
Read codes (version 2)	Z7CEP00	Fantastical confabulation	Memory problems
Read codes (version 2)	Z7CF200	Has delayed recall	Memory problems
Read codes (version 2)	Z7CF800	Poor short-term memory	Memory problems
Read codes (version 2)	Z7CF811	Short-term memory loss	Memory problems
Read codes (version 2)	Z7CFA00	Unable to recall random address at five minutes	Memory problems
Read codes (version 2)	Z7CFC00	Unable to recall five-digit number at five minutes	Memory problems
Read codes (version 2)	Z7CFE00	Unable to reproduce geometric figure at five minutes	Memory problems
Read codes (version 2)	Z7CFF00	Forgets what was going to do	Memory problems
Read codes (version 2)	Z7CFG00	Forgets what was going to say	Memory problems
Read codes (version 2)	Z7CFH00	Forgets recent activities	Memory problems
Read codes (version 2)	Z7CFI00	Forgets what has just done	Memory problems
Read codes (version 2)	Z7CFJ00	Forgets what has just said	Memory problems
Read codes (version 2)	Z7CFK00	Forgets what has just read	Memory problems
Read codes (version 2)	Z7CFL00	Forgets what has just seen	Memory problems
Read codes (version 2)	Z7CFM00	Forgets what has just heard	Memory problems
Read codes (version 2)	Z7CFO00	Poor long-term memory	Memory problems
Read codes (version 2)	Z7CFO11	Long-term memory loss	Memory problems
Read codes (version 2)	Z7CFQ00	Unable to remember own date of birth	Memory problems
Read codes (version 2)	Z7CFS00	Unable to remember own age	Memory problems
Read codes (version 2)	Z7CFS11	Cannot remember own age	Memory problems
Read codes (version 2)	Z7CFU00	Unable to remember day of the week	Memory problems
Read codes (version 2)	Z7CFW00	Unable to remember today's date	Memory problems
Read codes (version 2)	Z7CFW11	Cannot remember today's date	Memory problems
Read codes (version 2)	Z7CFY00	Unable to remember month of year	Memory problems
Read codes (version 2)	Z7CFa00	Unable to remember current year	Memory problems
Read codes (version 2)	Z7CFc00	Unable to remember name of reigning monarch	Memory problems
Read codes (version 2)	Z7CFc11	Cannot remember reigning monarch	Memory problems
Read codes (version 2)	Z7CFc12	Unable to remember name of current monarch	Memory problems
Read codes (version 2)	Z7CFe00	Unable to remember name of current prime minister	Memory problems
Read codes (version 2)	Z7CFe11	Cannot remember current prime minister	Memory problems
Read codes (version 2)	Z7CFf00	Cannot remember name of school	Memory problems
Read codes (version 2)	Z7CFg00	Cannot remember names of intimates	Memory problems
Read codes (version 2)	Z7CFh00	Cannot remember birth dates of children	Memory problems
Read codes (version 2)	Z7CFi00	Cannot remember wedding anniversary	Memory problems
Read codes (version 2)	Z7CFk00	Unable to remember objects	Memory problems
Read codes (version 2)	Z7CFm00	Unable to remember faces	Memory problems
Read codes (version 2)	Z7CFo00	Unable to remember sounds	Memory problems
Read codes (version 2)	Z7CFq00	Unable to remember motor skills	Memory problems
Read codes (version 2)	Z7CFs00	Unable to remember new motor skills	Memory problems
Read codes (version 2)	Z7CFu00	Unable to remember old motor skills	Memory problems
Read codes (version 2)	Z7CFw00	Memory aided by use of diary	Memory problems
Read codes (version 2)	Z7CFx00	Memory aided by use of labels	Memory problems
Read codes (version 2)	Z7CFz00	Memory aided by use of lists	Memory problems
Read codes (version 2)	Z7CGP00	Delayed verbal memory	Memory problems
Read codes (version 2)	ZD11300	Auditory memory therapy	Memory problems
Read codes (version 2)	E00..00	Senile and presenile organic psychotic conditions	Possible Alzheimer's disease

Read codes (version 2)	E00..11	Senile dementia	Possible Alzheimer's disease
Read codes (version 2)	E00..12	Senile/presenile dementia	Possible Alzheimer's disease
Read codes (version 2)	E000.00	Uncomplicated senile dementia	Possible Alzheimer's disease
Read codes (version 2)	E001.00	Presenile dementia	Possible Alzheimer's disease
Read codes (version 2)	E001000	Uncomplicated presenile dementia	Possible Alzheimer's disease
Read codes (version 2)	E001100	Presenile dementia with delirium	Possible Alzheimer's disease
Read codes (version 2)	E001200	Presenile dementia with paranoia	Possible Alzheimer's disease
Read codes (version 2)	E001300	Presenile dementia with depression	Possible Alzheimer's disease
Read codes (version 2)	E001z00	Presenile dementia NOS	Possible Alzheimer's disease
Read codes (version 2)	E002.00	Senile dementia with depressive or paranoid features	Possible Alzheimer's disease
Read codes (version 2)	E002000	Senile dementia with paranoia	Possible Alzheimer's disease
Read codes (version 2)	E002100	Senile dementia with depression	Possible Alzheimer's disease
Read codes (version 2)	E002z00	Senile dementia with depressive or paranoid features NOS	Possible Alzheimer's disease
Read codes (version 2)	E003.00	Senile dementia with delirium	Possible Alzheimer's disease
Read codes (version 2)	E00z.00	Senile or presenile psychoses NOS	Possible Alzheimer's disease
Read codes (version 2)	Eu02z11	[X] Presenile dementia NOS	Possible Alzheimer's disease
Read codes (version 2)	Eu02z12	[X] Presenile psychosis NOS	Possible Alzheimer's disease
Read codes (version 2)	Eu02z14	[X] Senile dementia NOS	Possible Alzheimer's disease
Read codes (version 2)	Eu02z15	[X] Senile psychosis NOS	Possible Alzheimer's disease
Read codes (version 2)	Eu02z16	[X] Senile dementia, depressed or paranoid type	Possible Alzheimer's disease
Read codes (version 2)	Eu05700	[X]Mild cognitive disorder	Possible Alzheimer's disease
Read codes (version 2)	F11z.11	Cerebral atrophy	Possible Alzheimer's disease
Read codes (version 2)	Eu00.00	[X]Dementia in Alzheimer's disease	Probable Alzheimer's disease
Read codes (version 2)	Eu00000	[X]Dementia in Alzheimer's disease with early onset	Probable Alzheimer's disease
Read codes (version 2)	Eu00011	[X]Presenile dementia,Alzheimer's type	Probable Alzheimer's disease
Read codes (version 2)	Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset	Probable Alzheimer's disease
Read codes (version 2)	Eu00013	[X]Alzheimer's disease type 2	Probable Alzheimer's disease
Read codes (version 2)	Eu00100	[X]Dementia in Alzheimer's disease with late onset	Probable Alzheimer's disease
Read codes (version 2)	Eu00111	[X]Alzheimer's disease type 1	Probable Alzheimer's disease
Read codes (version 2)	Eu00112	[X]Senile dementia,Alzheimer's type	Probable Alzheimer's disease
Read codes (version 2)	Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset	Probable Alzheimer's disease
Read codes (version 2)	Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type	Probable Alzheimer's disease
Read codes (version 2)	Eu00z00	[X]Dementia in Alzheimer's disease, unspecified	Probable Alzheimer's disease
Read codes (version 2)	Eu00z11	[X]Alzheimer's dementia unspec	Probable Alzheimer's disease
Read codes (version 2)	F110.00	Alzheimer's disease	Probable Alzheimer's disease
Read codes (version 2)	F110000	Alzheimer's disease with early onset	Probable Alzheimer's disease
Read codes (version 2)	F110100	Alzheimer's disease with late onset	Probable Alzheimer's disease
Read codes (version 2)	Fyu3000	[X]Other Alzheimer's disease	Probable Alzheimer's disease
Read codes (version 2)	8BPa.00	Antipsychotic drug therapy for dementia	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E02y100	Drug-induced dementia	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01111	[X]Predominantly cortical dementia	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02000	[X]Dementia in Pick's disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02100	[X]Dementia in Creutzfeldt-Jakob disease	Other dementia (non Alzheimer's disease dementias)
Read codes (version 2)	Eu02200	[X]Dementia in Huntington's disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02300	[X]Dementia in Parkinson's disease	Other dementia (non Alzheimer's disease dementias)
Read codes (version 2)	Eu02400	[X]Dementia in human immunodef virus [HIV] disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02500	[X]Lewy body dementia	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu04100	[X]Delirium superimposed on dementia	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	F111.00	Pick's disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	F116.00	Lewy body disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	F11x200	Cerebral degeneration due to cerebrovascular disease	Other dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004.00	Arteriosclerotic dementia	Vascular dementia (non-Alzheimer's disease dementias)

Read codes (version 2)	E004.11	Multi infarct dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004000	Uncomplicated arteriosclerotic dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004100	Arteriosclerotic dementia with delirium	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004200	Arteriosclerotic dementia with paranoia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004300	Arteriosclerotic dementia with depression	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E004z00	Arteriosclerotic dementia NOS	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01.00	[X]Vascular dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01.11	[X]Arteriosclerotic dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01000	Eu01000 [X]Vascular dementia of acute onset	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01100	[X]Multi-infarct dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01200	[X]Subcortical vascular dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01300	[X]Mixed cortical and subcortical vascular dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01y00	[X]Other vascular dementia	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu01z00	[X]Vascular dementia, unspecified	Vascular dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	6AB..00	Dementia annual review	Non-specific dementia (non Alzheimer's disease dementias)
Read codes (version 2)	9hD0.00	Excepted from dementia quality indicators: Patient unsuitabl	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	9hD1.00	Excepted from dementia quality indicators: Informed dissent	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E00y.00	Other senile and presenile organic psychoses	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	E041.00	Dementia in conditions EC	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02.00	[X]Dementia in other diseases classified elsewhere	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02y00	[X]Dementia in other specified diseases classif elsewhere	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02z00	[X] Unspecified dementia	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	Eu02z13	[X] Primary degenerative dementia NOS	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	F112.00	Senile degeneration of brain	Non-specific dementia (non-Alzheimer's disease dementias)
Read codes (version 2)	dy1..	Donepezil Hydrochloride	Drugs for dementia
Read codes (version 2)	dy11.	Donepezil HCl 5mg tablet	Drugs for dementia
Read codes (version 2)	dy12.	Donepezil HCl 10mg tablet	Drugs for dementia
Read codes (version 2)	dy13.	Aricept 5mg tablet	Drugs for dementia
Read codes (version 2)	dy14.	Aricept 10mg tablet	Drugs for dementia
Read codes (version 2)	dy15.	ARICEPT EVESS 5mg disp tabs	Drugs for dementia
Read codes (version 2)	dy16.	ARICEPT EVESS 10mg disp tabs	Drugs for dementia
Read codes (version 2)	dy1y.	DONEPEZIL HCL 10mg disp tabs	Drugs for dementia
Read codes (version 2)	dy1z.	DONEPEZIL HCL 5mg disp tabs	Drugs for dementia
Read codes (version 2)	dy3..	Galantamine	Drugs for dementia
Read codes (version 2)	dy31.	Reminyl 4mg tablet	Drugs for dementia
Read codes (version 2)	dy32.	Reminyl 8mg tablet	Drugs for dementia
Read codes (version 2)	dy33.	Reminyl 12mg tablet	Drugs for dementia
Read codes (version 2)	dy34.	Reminyl 4mg/mL s/f oral soln	Drugs for dementia
Read codes (version 2)	dy35.	Reminyl XL 8mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy36.	Reminyl XL 16mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy37.	Reminyl XL 24mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy38.	GALSYA XL 8mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy39.	GALSYA XL 16mg m/r capsules	Drugs for dementia

Read codes (version 2)	dy3A.	GALSYA XL 24mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3B.	ACUMOR XL 8mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3C.	ACUMOR XL 16mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3D.	ACUMOR XL 24mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3E.	LOTPROSIN XL 8mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3F.	LOTPROSIN XL 16mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3G.	LOTPROSIN XL 24mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3H.	ELMINO XL 8mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3I.	ELMINO XL 16mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3J.	ELMINO XL 24mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3K.	LUVENTA XL 8mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3L.	LUVENTA XL 16mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3M.	LUVENTA XL 24mg m/r capsules	Drugs for dementia
Read codes (version 2)	dy3t.	Galantamine 8mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy3u.	Galantamine 16mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy3v.	Galantamine 24mg m/r capsule	Drugs for dementia
Read codes (version 2)	dy3w.	Galantamine 4mg/mL s/f soln	Drugs for dementia
Read codes (version 2)	dy3x.	Galantamine 4mg tablet	Drugs for dementia
Read codes (version 2)	dy3y.	Galantamine 8mg tablet	Drugs for dementia
Read codes (version 2)	dy3z.	Galantamine 12mg tablet	Drugs for dementia
Read codes (version 2)	dB1..	Memantine Hydrochloride	Drugs for dementia
Read codes (version 2)	dB11.	Memantine HCl 10mg tablet	Drugs for dementia
Read codes (version 2)	dB12.	Memantine HCl 10mg/g oral dps	Drugs for dementia
Read codes (version 2)	dB13.	Ebixa 10mg tablet	Drugs for dementia
Read codes (version 2)	dB14.	Ebixa 10mg/g oral drops	Drugs for dementia
Read codes (version 2)	dB15.	EBIXA 20mg tablets	Drugs for dementia
Read codes (version 2)	dB16.	MEMANTINE HCL 20mg tablets	Drugs for dementia
Read codes (version 2)	dB17.	EBIXA TREATMENT INIT PACK tabs	Drugs for dementia
Read codes (version 2)	dB18.	NEMDATINE 10mg tablets	Drugs for dementia
Read codes (version 2)	dB19.	NEMDATINE 20mg tablets	Drugs for dementia
Read codes (version 2)	dy2..	Rivastigmine	Drugs for dementia
Read codes (version 2)	dy21.	Rivastigmine 1.5mg capsule	Drugs for dementia
Read codes (version 2)	dy22.	Rivastigmine 3mg capsule	Drugs for dementia
Read codes (version 2)	dy23.	Rivastigmine 4.5mg capsule	Drugs for dementia
Read codes (version 2)	dy24.	Rivastigmine 6mg capsule	Drugs for dementia
Read codes (version 2)	dy25.	Exelon 1.5mg capsule	Drugs for dementia
Read codes (version 2)	dy26.	Exelon 3mg capsule	Drugs for dementia
Read codes (version 2)	dy27.	Exelon 4.5mg capsule	Drugs for dementia
Read codes (version 2)	dy28.	Exelon 6mg capsule	Drugs for dementia
Read codes (version 2)	dy29.	Rivastigmine 2mg/mL oral soln	Drugs for dementia
Read codes (version 2)	dy2A.	Exelon 2mg/mL oral solution	Drugs for dementia
Read codes (version 2)	dy2B.	EXELON 4.6mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2C.	EXELON 9.5mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2D.	RIVASTIGMINE 4.6mg/24h patches	Drugs for dementia
Read codes (version 2)	dy2E.	RIVASTIGMINE 9.5mg/24h patches	Drugs for dementia
Read codes (version 2)	dy2F.	NIMVASTID 1.5mg capsules	Drugs for dementia
Read codes (version 2)	dy2G.	NIMVASTID 3mg capsules	Drugs for dementia
Read codes (version 2)	dy2H.	NIMVASTID 4.5mg capsules	Drugs for dementia
Read codes (version 2)	dy2I.	NIMVASTID 6mg capsules	Drugs for dementia
Read codes (version 2)	dy2J.	EXELON 13.3mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2K.	RIVASTIGMINE 13.3mg/24hr patch	Drugs for dementia
Read codes (version 2)	dy2L.	ALZEST 4.6mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2M.	ALZEST 9.5mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2N.	PROMETAX 4.6mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2O.	PROMETAX 9.5mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2P.	SOMNITON 4.6mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2Q.	SOMNITON 9.5mg/24hrs patches	Drugs for dementia
Read codes (version 2)	dy2R.	VOLEZE 4.6mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2S.	VOLEZE 9.5mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2T.	VOLEZE 13.3mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2U.	ELUDEN 4.6mg/24hours patches	Drugs for dementia
Read codes (version 2)	dy2V.	ELUDEN 9.5mg/24hours patches	Drugs for dementia
Codes used to identify cardiovascular events in hospital data			
ICD-10	I20	Angina pectoris	Ischaemic heart diseases
ICD-10	I20.0	Unstable angina	Ischaemic heart diseases
ICD-10	I20.1	Angina pectoris with documented spasm	Ischaemic heart diseases

ICD-10	I20.8	Other forms of angina pectoris	Ischaemic heart diseases
ICD-10	I20.9	Angina pectoris, unspecified	Ischaemic heart diseases
ICD-10	121	Acute myocardial infarction	Ischaemic heart diseases
ICD-10	I21.0	Acute transmural myocardial infarction of anterior wall	Ischaemic heart diseases
ICD-10	I21.1	Acute transmural myocardial infarction of inferior wall	Ischaemic heart diseases
ICD-10	I21.2	Acute transmural myocardial infarction of other sites	Ischaemic heart diseases
ICD-10	I21.3	Acute transmural myocardial infarction of unspecified site	Ischaemic heart diseases
ICD-10	I21.4	Acute subendocardial myocardial infarction	Ischaemic heart diseases
ICD-10	I21.9	Acute myocardial infarction, unspecified	Ischaemic heart diseases
ICD-10	122	Subsequent myocardial infarction	Ischaemic heart diseases
ICD-10	I22.0	Subsequent myocardial infarction of anterior wall	Ischaemic heart diseases
ICD-10	I22.1	Subsequent myocardial infarction of inferior wall	Ischaemic heart diseases
ICD-10	I22.8	Subsequent myocardial infarction of other sites	Ischaemic heart diseases
ICD-10	I22.9	Subsequent myocardial infarction of unspecified site	Ischaemic heart diseases
ICD-10	I23	Certain current complications following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.0	Haemopericardium as current complication following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.1	Atrial septal defect as current complication following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.2	Ventricular septal defect as current complication following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial	Ischaemic heart diseases
ICD-10	I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction	Ischaemic heart diseases
ICD-10	I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute my	Ischaemic heart diseases
ICD-10	I23.8	Other current complications following acute myocardial infarction	Ischaemic heart diseases
ICD-10	124	Other acute ischaemic heart diseases	Ischaemic heart diseases
ICD-10	I24.0	Coronary thrombosis not resulting in myocardial infarction	Ischaemic heart diseases
ICD-10	I24.1	Dressler syndrome	Ischaemic heart diseases
ICD-10	I24.8	Other forms of acute ischaemic heart disease	Ischaemic heart diseases
ICD-10	I24.9	Acute ischaemic heart disease, unspecified	Ischaemic heart diseases
ICD-10	I45.6	pre-excitation syndrome	Arrhythmia
ICD-10	I47	paroxysmal tachycardia	Arrhythmia
ICD-10	I47.0	re-entry ventricular arrhythmia	Arrhythmia
ICD-10	I47.1	supraventricular tachycardia	Arrhythmia
ICD-10	I47.2	ventricular tachycardia	Arrhythmia
ICD-10	I47.9	"paroxysmal tachycardia, unspecified"	Arrhythmia
ICD-10	I48	atrial fibrillation and flutter	Arrhythmia
ICD-10	I49	other cardiac arrhythmias	Arrhythmia
ICD-10	I49.0	ventricular fibrillation and flutter	Arrhythmia
ICD-10	I49.1	atrial premature depolarization	Arrhythmia
ICD-10	I49.2	junctional premature depolarization	Arrhythmia
ICD-10	I49.3	ventricular premature depolarization	Arrhythmia
ICD-10	I49.4	other and unspecified premature depolarization	Arrhythmia
ICD-10	I49.5	sick sinus syndrome	Arrhythmia
ICD-10	R00.0	"tachycardia, unspecified"	Arrhythmia
ICD-10	150	Heart failure	Heart failure
ICD-10	I50.0	Congestive heart failure	Heart failure
ICD-10	I50.1	Left ventricular failure	Heart failure
ICD-10	I50.9	Heart failure, unspecified	Heart failure
ICD-10	160	Subarachnoid haemorrhage	Stroke
ICD-10	I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation	Stroke
ICD-10	I60.1	Subarachnoid haemorrhage from middle cerebral artery	Stroke
ICD-10	I60.2	Subarachnoid haemorrhage from anterior communicating artery	Stroke
ICD-10	I60.3	Subarachnoid haemorrhage from posterior communicating artery	Stroke
ICD-10	I60.4	Subarachnoid haemorrhage from basilar artery	Stroke
ICD-10	I60.5	Subarachnoid haemorrhage from vertebral artery	Stroke
ICD-10	I60.6	Subarachnoid haemorrhage from other intracranial arteries	Stroke

ICD-10	I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified	Stroke
ICD-10	I60.8	Other subarachnoid haemorrhage	Stroke
ICD-10	I60.9	Subarachnoid haemorrhage, unspecified	Stroke
ICD-10	161	Intracerebral haemorrhage	Stroke
ICD-10	I61.0	Intracerebral haemorrhage in hemisphere, subcortical	Stroke
ICD-10	I61.1	Intracerebral haemorrhage in hemisphere, cortical	Stroke
ICD-10	I61.2	Intracerebral haemorrhage in hemisphere, unspecified	Stroke
ICD-10	I61.3	Intracerebral haemorrhage in brain stem	Stroke
ICD-10	I61.4	Intracerebral haemorrhage in cerebellum	Stroke
ICD-10	I61.5	Intracerebral haemorrhage, intraventricular	Stroke
ICD-10	I61.6	Intracerebral haemorrhage, multiple localized	Stroke
ICD-10	I61.8	Other intracerebral haemorrhage	Stroke
ICD-10	I61.9	Intracerebral haemorrhage, unspecified	Stroke
ICD-10	162	Other nontraumatic intracranial haemorrhage	Stroke
ICD-10	I62.0	Subdural haemorrhage (acute)(nontraumatic)	Stroke
ICD-10	I62.1	Nontraumatic extradural haemorrhage	Stroke
ICD-10	I62.9	Intracranial haemorrhage (nontraumatic), unspecified	Stroke
ICD-10	163	Cerebral infarction	Stroke
ICD-10	I63.0	Cerebral infarction due to thrombosis of precerebral arteries	Stroke
ICD-10	I63.1	Cerebral infarction due to embolism of precerebral arteries	Stroke
ICD-10	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	Stroke
ICD-10	163.3	Cerebral infarction due to thrombosis of cerebral arteries	Stroke
ICD-10	163.4	Cerebral infarction due to embolism of cerebral arteries	Stroke
ICD-10	163.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	Stroke
ICD-10	163.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	Stroke
ICD-10	163.8	Other cerebral infarction	Stroke
ICD-10	163.9	Cerebral infarction, unspecified	Stroke
ICD-10	164	Stroke, not specified as haemorrhage or infarction	Stroke
ICD-10	165	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	Stroke
ICD-10	I65.0	Occlusion and stenosis of vertebral artery	Stroke
ICD-10	I65.1	Occlusion and stenosis of basilar artery	Stroke
ICD-10	I65.2	Occlusion and stenosis of carotid artery	Stroke
ICD-10	I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries	Stroke
ICD-10	I65.8	Occlusion and stenosis of other precerebral artery	Stroke
ICD-10	I65.9	Occlusion and stenosis of unspecified precerebral artery	Stroke
ICD-10	166	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	Stroke
ICD-10	I66.0	Occlusion and stenosis of middle cerebral artery	Stroke
ICD-10	166.1	Occlusion and stenosis of anterior cerebral artery	Stroke
ICD-10	166.2	Occlusion and stenosis of posterior cerebral artery	Stroke
ICD-10	166.3	Occlusion and stenosis of cerebellar arteries	Stroke
ICD-10	166.4	Occlusion and stenosis of multiple and bilateral cerebral arteries	Stroke
ICD-10	166.8	Occlusion and stenosis of other cerebral artery	Stroke
ICD-10	166.9	Occlusion and stenosis of unspecified cerebral artery	Stroke
Codes used to identify the smoking and hypertension status			
Read codes (version 2)	G2...00	Hypertensive disease	Hypertension
Read codes (version 2)	G20..00	Essential hypertension	Hypertension
Read codes (version 2)	G200.00	Malignant essential hypertension	Hypertension
Read codes (version 2)	G201.00	Benign essential hypertension	Hypertension
Read codes (version 2)	G20..11	High blood pressure	Hypertension
Read codes (version 2)	G202.00	Systolic hypertension	Hypertension
Read codes (version 2)	G203.00	Diastolic hypertension	Hypertension
Read codes (version 2)	G20z.00	Essential hypertension NOS	Hypertension
Read codes (version 2)	G20z.11	Hypertension NOS	Hypertension
Read codes (version 2)	G24..00	Secondary hypertension	Hypertension
Read codes (version 2)	G240.00	Secondary malignant hypertension	Hypertension
Read codes (version 2)	G240000	Secondary malignant renovascular hypertension	Hypertension
Read codes (version 2)	G240z00	Secondary malignant hypertension NOS	Hypertension
Read codes (version 2)	G241.00	Secondary benign hypertension	Hypertension
Read codes (version 2)	G241000	Secondary benign renovascular hypertension	Hypertension

Read codes (version 2)	G241z00	Secondary benign hypertension NOS	Hypertension
Read codes (version 2)	G244.00	Hypertension secondary to endocrine disorders	Hypertension
Read codes (version 2)	G24z.00	Secondary hypertension NOS	Hypertension
Read codes (version 2)	G24z000	Secondary renovascular hypertension NOS	Hypertension
Read codes (version 2)	G24z100	Hypertension secondary to drug	Hypertension
Read codes (version 2)	G24zz00	Secondary hypertension NOS	Hypertension
Read codes (version 2)	G2y..00	Other specified hypertensive disease	Hypertension
Read codes (version 2)	G2z..00	Hypertensive disease NOS	Hypertension
Read codes (version 2)	Gyu2.00	[X]Hypertensive diseases	Hypertension
Read codes (version 2)	Gyu2000	[X]Other secondary hypertension	Hypertension
Read codes (version 2)	1371	Never smoked tobacco	Never-smoker
Read codes (version 2)	9kn..	Non-smoker annual review - enhanced services administration	Never-smoker
Read codes (version 2)	137K.	Stopped smoking	Ex-smoker
Read codes (version 2)	137L.	Current non-smoker	Ex-smoker
Read codes (version 2)	137N.	Ex-pipe smoker	Ex-smoker
Read codes (version 2)	137O.	Ex-cigar smoker	Ex-smoker
Read codes (version 2)	137S.	Ex-smoker	Ex-smoker
Read codes (version 2)	137T.	Date ceased smoking	Ex-smoker
Read codes (version 2)	1377	Ex-trivial smoker (< 1 per day)	Ex-smoker
Read codes (version 2)	1378	Ex-light smoker (1 - 9 per day)	Ex-smoker
Read codes (version 2)	1379	Ex-moderate smoker (10 - 19 per day)	Ex-smoker
Read codes (version 2)	137A.	Ex-heavy smoker (20 - 39 per day)	Ex-smoker
Read codes (version 2)	137B.	Ex-very heavy smoker (40 + per day)	Ex-smoker
Read codes (version 2)	137F.	Ex-smoker - amount unknown	Ex-smoker
Read codes (version 2)	137i.	Ex-tobacco chewer	Ex-smoker
Read codes (version 2)	137j.	Ex-cigarette smoker	Ex-smoker
Read codes (version 2)	137K0	Recently stopped smoking	Ex-smoker
Read codes (version 2)	9km..	Ex-smoker annual review - enhanced services administration	Ex-smoker
Read codes (version 2)	13p4.	Smoking free weeks	Ex-smoker
Read codes (version 2)	137l.	Ex roll-up cigarette smoker	Ex-smoker
Read codes (version 2)	745H%	(Various) Smoking cessation therapy	Smoker
Read codes (version 2)	du3%	(Various) Nicotine replacement therapy	Smoker
Read codes (version 2)	du6%	(Various) Bupropion	Smoker
Read codes (version 2)	du7%	(Various) additional nicotine replacement therapy	Smoker
Read codes (version 2)	du8%	(Various) Varenicline	Smoker
Read codes (version 2)	du9%	(Various) Nicotine withdrawal products	Smoker
Read codes (version 2)	E251%	(Various) tobacco dependence	Smoker
Read codes (version 2)	137..	Tobacco consumption	Smoker
Read codes (version 2)	137Z	Tobacco consumption NOS	Smoker
Read codes (version 2)	137X.	Cigarette consumption	Smoker
Read codes (version 2)	137Y.	Cigar consumption	Smoker
Read codes (version 2)	137E.	Tobacco consumption unknown	Smoker
Read codes (version 2)	137g.	Cigarette pack years	Smoker
Read codes (version 2)	1372	Trivial smoker - < 1 per day	Smoker
Read codes (version 2)	1373	Light smoker - 1-9 per day	Smoker
Read codes (version 2)	1374	Moderate smoker - 10-19 per day	Smoker
Read codes (version 2)	1375	Heavy smoker - 20-39 per day	Smoker
Read codes (version 2)	1376	Very heavy smoker - 20-39 per day	Smoker
Read codes (version 2)	137a.	Pipe tobacco consumption	Smoker
Read codes (version 2)	137b.	Ready to stop smoking	Smoker
Read codes (version 2)	137C.	Keeps trying to stop smoking	Smoker
Read codes (version 2)	137c.	Thinking about stopping smoking	Smoker
Read codes (version 2)	137e.	Smoking restarted	Smoker
Read codes (version 2)	137G.	Trying to give up smoking	Smoker
Read codes (version 2)	137H.	Pipe smoker	Smoker
Read codes (version 2)	137J.	Cigar smoker	Smoker
Read codes (version 2)	137M.	Rolls own cigarettes	Smoker
Read codes (version 2)	137P.	Cigarette smoker	Smoker
Read codes (version 2)	137Q.	Smoking started	Smoker
Read codes (version 2)	137R.	Current smoker	Smoker
Read codes (version 2)	137V.	Smoking reduced	Smoker
Read codes (version 2)	137D.	Admitted tobacco cons untrue ?	Smoker
Read codes (version 2)	137d.	Not interested in stopping smoking	Smoker
Read codes (version 2)	137f.	Reason for restarting smoking	Smoker
Read codes (version 2)	137h.	Minutes from waking to first tobacco consumption	Smoker
Read codes (version 2)	6791	Health ed. - smoking	Smoker

Read codes (version 2)	67910	Health education - parental smoking	Smoker
Read codes (version 2)	137m.	Failed attempt to stop smoking	Smoker
Read codes (version 2)	13p..	Smoking cessation milestones	Smoker
Read codes (version 2)	13p0.	Negotiated date for cessation of smoking	Smoker
Read codes (version 2)	13p8.	Lost to smoking cessation follow-up	Smoker
Read codes (version 2)	38DH.	Fagerstrom test for nicotine dependence	Smoker
Read codes (version 2)	67A3.	Pregnancy smoking advice	Smoker
Read codes (version 2)	67H1.	Lifestyle advice regarding smoking	Smoker
Read codes (version 2)	67H6.	Brief cessation for smoking cessation	Smoker
Read codes (version 2)	8B2B.	Nicotine replacement therapy	Smoker
Read codes (version 2)	8B3f.	Nicotine replacement therapy provided free	Smoker
Read codes (version 2)	8B3Y.	Over the counter nicotine replacement therapy	Smoker
Read codes (version 2)	8BP3.	Nicotine replacement therapy provided by community pharmacis	Smoker
Read codes (version 2)	8CAg.	Smoking cessation advice provided by community pharmacist	Smoker
Read codes (version 2)	8CAL.	Smoking cessation advice	Smoker
Read codes (version 2)	8CdB.	Stop smoking service opportunity signposted	Smoker
Read codes (version 2)	8H7i.	Referral to smoking cessation advisor	Smoker
Read codes (version 2)	8HBM.	Stop smoking face to face follow-up	Smoker
Read codes (version 2)	8HkQ.	Referral to NHS stop smoking service	Smoker
Read codes (version 2)	8HTK.	Referral to stop-smoking clinic	Smoker
Read codes (version 2)	8I2I.	Nicotine replacement therapy contraindicated	Smoker
Read codes (version 2)	8I2J.	Bupropion contraindicated	Smoker
Read codes (version 2)	8I39.	Nicotine replacement therapy refused	Smoker
Read codes (version 2)	8I3M.	Bupropion refused	Smoker
Read codes (version 2)	8I6H.	Smoking review not indicated	Smoker
Read codes (version 2)	8IAj.	Smoking cessation advice declined	Smoker
Read codes (version 2)	8IEK.	Smoking cessation program declined	Smoker
Read codes (version 2)	8IEM.	Smoking cessation drug therapy declined	Smoker
Read codes (version 2)	9hG..	Exception reporting: smoking quality indicators	Smoker
Read codes (version 2)	9hG0.	Excepted from smoking quality indicators: Patient unsuitable	Smoker
Read codes (version 2)	9hG1.	Excepted from smoking quality indicators: Informed dissent	Smoker
Read codes (version 2)	9kc..	Smoking cessation - enhanced services administration	Smoker
Read codes (version 2)	9kc0.	Smoking cessation monitor template complet - enhanc serv admin	Smoker
Read codes (version 2)	9ko..	Current smoker annual review - enhanced service admin	Smoker
Read codes (version 2)	9N2k.	Seen by smoking cessation advisor	Smoker
Read codes (version 2)	9N4M.	DNA - did not attend smoking cessation clinic	Smoker
Read codes (version 2)	9Ndg.	Declined consent for follow-up by smoking cessation team	Smoker
Read codes (version 2)	9NdV.	Consent given follow-up after smoking cessation intervention	Smoker
Read codes (version 2)	9NdW.	Consent given for smoking cessation data sharing	Smoker
Read codes (version 2)	9NdY.	Declined consent for follow-up evaluation after smoking cess interven	Smoker
Read codes (version 2)	9NdZ.	Declined consent for smoking cessation data sharing	Smoker
Read codes (version 2)	9NS02	Referral for smoking cessation service offered	Smoker
Read codes (version 2)	9OO..	Attends stop smoking monitor admin	Smoker
Read codes (version 2)	9OO1.	Attends stop smoking monitor	Smoker
Read codes (version 2)	9OO2.	Refuses stop smoking monitor	Smoker
Read codes (version 2)	9OO3.	Stop smoking monitor default	Smoker
Read codes (version 2)	9OO4.	Stop smoking monitor 1st letter	Smoker
Read codes (version 2)	9OO5.	Stop smoking monitor 2nd letter	Smoker
Read codes (version 2)	9OO6.	Stop smoking monitor 3rd letter	Smoker
Read codes (version 2)	9OO7.	Stop smoking monitor verb.inv.	Smoker
Read codes (version 2)	9OO8.	Stop smoking monitor phone inv	Smoker
Read codes (version 2)	9OO9.	Stop smoking monitoring delete	Smoker
Read codes (version 2)	9OOA.	Stop smoking monitor check.done	Smoker
Read codes (version 2)	9OOB.	Stop smoking invitation short message service text message	Smoker
Read codes (version 2)	9OOB0	Stop smoking invitation first SMS text message	Smoker
Read codes (version 2)	9OOB1	Stop smoking invitation second SMS text message	Smoker
Read codes (version 2)	9OOB2	Stop smoking invitation third SMS text message	Smoker
Read codes (version 2)	9OOZ.	Stop smoking monitor admin.NOS	Smoker
Read codes (version 2)	E023.	Nicotine withdrawal	Smoker
Read codes (version 2)	J0364	Tobacco deposit on teeth	Smoker
Read codes (version 2)	SMC..	Toxic effect of tobacco and nicotine	Smoker
Read codes (version 2)	TJHy2	Adverse reaction to nicotine	Smoker
Read codes (version 2)	U6099	[X] Bupropion causing adverse effects in therapeutic use	Smoker

Read codes (version 2)	ZV4K0	[V] Tobacco use	Smoker
Read codes (version 2)	ZV6D8	[V] Tobacco abuse counselling	Smoker
Read codes (version 2)	13p5.	Smoking cessation programme start date	Smoker
Read codes (version 2)	9ko..	Current smoker annual review - enhanced service admin	Smoker
Charlson comorbidity index			
ICD-10	I21.x, I22.x, I25.2	Myocardial infarction	Charlson index
ICD-10	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	Congestive heart failure	Charlson index
ICD-10	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	Peripheral vascular disease	Charlson index
ICD-10	G45.x, G46.x, H34.0, I60.x-I69.x	Cerebrovascular disease	Charlson index
ICD-10	F00.x-F03.x, F05.1, G30.x, G31.1	Dementia	Charlson index
ICD-10	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	Chronic pulmonary disease	Charlson index
ICD-10	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	Rheumatic disease	Charlson index
ICD-10	K25.x-K28.x	Peptic ulcer disease	Charlson index
ICD-10	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	Mild liver disease	Charlson index
ICD-10	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	Diabetes	Charlson index
ICD-10	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	Diabetes with chronic complication	Charlson index
ICD-10	G04.1, G11.4,	Hemiplegia or paraplegia	Charlson index

	G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9		
ICD-10	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	Renal disease	Charlson index
ICD-10	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.	Cancer	Charlson index
ICD-10	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	Moderate or severe liver disease	Charlson index
ICD-10	C77.x-C80.x	Metastatic solid tumor	Charlson index

Appendix 10- Sensitivity analysis results for L-dopa and MAO-B inhibiters that exclude prescriptions made in or before 2007

L-dopa Model

Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	1.339	3.815	3.123 -4.662	<0.0001
	> 80 years	3.066	21.455	15.653-29.408	<0.0001
Sex	Males (ref)				
	Females	-0.077	0.926	0.793 -1.080	0.326
Social deprivation score (WIMD)	1 (most deprived) (ref)				
	2	-0.022	0.978	0.750-1.275	0.868
	3	-0.200	0.819	0.639 -1.049	0.114
	4	-0.293	0.746	0.578 -0.962	0.024
	5 (least deprived)	-0.263	0.769	0.601 -0.984	0.037
Diabetes		0.092	1.096	0.786 -1.528	0.589
Pulmonary disease		0.131	1.140	0.801 -1.621	0.466
Cerebral vascular accident		0.440	1.552	0.839 -2.874	0.162
Acute myocardial infarction		0.187	1.206	0.745 -1.951	0.445
Dementia		0.371	1.449	0.715 -2.937	0.303
Congestive heart failure		0.688	1.990	0.846 -4.680	0.115
Renal disease		0.581	1.787	0.749 -4.267	0.191
Cancer		-0.337	0.714	0.379 -1.344	0.296
Peripheral vascular disease		0.233	1.262	0.517-3.080	0.609
Connective tissue disorder		0.787	2.197	0.665-7.256	0.197
Diabetes complications		0.973	2.646	0.610 -11.480	0.194
Metastatic cancer		1.275	3.578	0.432-29.649	0.237
Previous use of antidepressants		0.251	1.285	1.069 -1.544	0.008

MAO-B inhibitors Model

Independent variable		Coefficient	Odds Ratio (OR)	Confidence Interval of Odds Ratio (CI)	P-value
Age categories	40-60 years (ref)				
	61-80 years	-0.833	0.435	0.340 -0.556	<0.0001
	> 80 years	-2.114	0.121	0.084-0.173	<0.0001
Sex	Males (ref)				
	Females	-0.147	0.863	0.709 -1.050	0.142
Social deprivation score (WIMD)	1 (most deprived) (ref)				
	2	0.263	1.300	0.905-1.868	0.155
	3	0.441	1.554	1.107 -2.179	0.011
	4	0.660	1.935	1.379-2.715	<0.0001
	5 (least deprived)	0.604	1.830	1.315 -2.546	<0.0001
Diabetes		-0.651	0.521	0.314 -0.866	0.012
Pulmonary disease		-0.462	0.630	0.373 -1.063	0.083
Acute myocardial infarction		-0.516	0.597	0.287-1.243	0.168
Congestive heart failure		-0.484	0.616	0.221 -1.716	0.354
Cancer		-0.200	0.819	0.325-2.060	0.671
Previous use of antidepressants		-0.923	0.397	0.299-0.528	<0.0001

Appendix 11- Flow chart of all patients and outcomes of the study (including censoring data)