Saudi Pharmaceutical Journal 29 (2021) 206–212

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Factors affecting the choice of first-line therapy in Parkinson's disease patients in Wales: A population-based study

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ARTICLE INFO

Article history:
Received 23 October 2020
Accepted 14 January 2021
Available online 28 January 2021

Keywords:
Parkinson's disease
Prescribing factors
Social deprivation
L-dopa

ABSTRACT

First line treatment for Parkinson's disease (PD) is typically either L-dopa or a non-ergot dopamine agonist (DA). However, the options for the treatment of motor symptoms in PD patients have increased in the last thirty years, which have seen several new classes of PD medications introduced onto the market. The purpose of this study is to examine the changes in first line therapy of newly diagnosed Parkinson's patients between 2000 and 2016 in Wales.

A population-based study evaluated data from the Secure Anonymised Information Linkage (SAIL) Databank of residents in Wales, aged 40 years or older, newly treated with PD medications between 2000 and 2016. The data was compared across three intervals: 2000–2005, 2006–2011 and 2012–2016. Patients were classified by age at diagnosis into young: 40–60 years; mid, 61–80 years; and older >80 years. Logistic regression was undertaken to determine the predictors of PD medication prescribing.

For the whole study period, the profiles of 9142 newly diagnosed PD patients were analysed. L-dopa was the most common first line therapy (80.6%), followed by non-ergot DAs (12.9%) and monoamine oxidase B (MAO-B) inhibitors (7.9%). Odds of L-dopa prescribing were greater in patients >80 years (OR = 20.46 95%CI: 16.25–25.76) and in the period 2012–2016 (OR = 1.98 95% CI: 1.70–2.29). Prescribing of non-ergot DAs significantly declined in 2012–2016 (OR = 0.42 95% CI: 0.35–0.49). Additional factors influencing first line therapy were deprivation, presence of diabetes and prior use of antidepressants. For example, PD patients residing in the least deprived area were less likely to be prescribed L-dopa compared to patients residing in the most deprived area (OR = 0.77 95% CI: 0.65–0.93).

First line therapy in PD in Wales has undergone a significant switch towards L-dopa over the last 16 years. The data indicates reasonable compliance with guidelines on efficacy and safety issues related to Parkinson's medications.

1. Introduction

Whilst the symptomatic treatment of the neurodegenerative disorder Parkinson's disease (PD) used to be restricted to the dopamine precursor L-dopa and anticholinergics, the number and type of pharmacological agents has increased significantly in the last thirty years with the introduction of several new classes of PD medications. These include non-ergot dopamine agonists (DAs), monoamine oxidase-B (MAO-B) inhibitors and Catechol-O-methyl transferase (COMT) inhibitors. Knowledge on the efficacy and safety of each of these has developed through their prescribing and via post marketing surveillance. For example, the conclusions of a robust review by the American Academy of Neurology (AAN) in 2006 surmised that DAs, MAO-B inhibitors and L-dopa do not provide any disease modifying properties (Suchowersky et al., 2006). DAs were introduced to the practice with the hope of avoiding the dyskinesia 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 (Zhang and Tan, 2016). These trials led to guidelines recommending starting ther-

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2021.01.004
1319-0164/

apy with DAs and not using L-dopa unless the DAs failed to manage the motor symptoms (Miyasaki et al., 2002). However, the effect of dyskinesia and/or the motor fluctuations caused by L-dopa on quality of life (QOL) was unknown until 2014, when the PD-MED study showed that the early use of L-dopa in PD patients led to a better QoL compared to DAs and MAO-B inhibitors in the long term (Gray et al., 2014).

Whilst such findings should influence clinical prescribing and decision making, they have fuelled the ongoing debate on the most appropriate first line therapy for patients newly diagnosed with PD (Gray et al., 2014). This debate has focussed particularly on the initiation of L-dopa versus DAs. For individuals whose motor symptoms impact on their quality of life (QoL), recent guidance from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) recommends commencing L-dopa treatment. In contrast, for individuals whose QoL is not affected by motor symptoms, L-dopa, MAO-B inhibitors and DAs are recommended (Institute, 2017).

Notwithstanding these guidelines, there is a paucity of literature on the prescribing and use of PD medications within the UK, particularly with reference to Wales. A recent study used the UK Clinical Practice Research Datalink (CPRD) and found a low rate of L-dopa prescribing, when it was used as an initial therapy (29%), across the UK between 2004 and 2015 (Kalilani et al., 2019). This study did not stratify patients by age, sex, years of prescribing, comorbidities, or other patient characteristics. As a consequence, it has not been possible to understand the current landscape of prescribing in PD and whether this aligns to the evidence base.

In this study, we examined the trends in first line therapy, as well as the impact of age, sex, social deprivation status, and comorbidities, for PD in Wales, over the period 2000–2016.

2. Method

2.1. Data source and study cohort

We conducted a retrospective cohort study using the Secure Anonymised Information Linkage (SAIL) Databank that includes General Practice (GP) prescribing data for approximately 80% of the patient population in Wales (Jones et al., 2017). The SAIL Databank links GP prescribing data to a variety of other health and social care data sources including (but not limited to) patient demographics, hospital episodes and Welsh Index of Multiple Deprivation (WIMD) scores (Jones et al., 2017). All studies using SAIL data need independent Information Governance Review Panel (IGRP) approval. This study obtained IGRP approval (ref 0507). The Research Ethics Service has previously confirmed that SAIL projects using anonymised routinely collected data do not require specific research ethics committee approval.

Data from the SAIL Databank were retrieved for the Welsh population between 2000 and 2016. PD patients were identified if they were (1) diagnosed for first time with PD (Read code, 2nd Revision, Definition 'F12…', 'F120.', 'F12z.', and '147F.') and (2) receiving medication indicated for the treatment of motor symptoms of Parkinson's disease after the date of diagnosis (Read code, 'dq…'). We defined 2000 as the initial study year because of increased quality and consistency of coding and quality of standard electronic health record (EHR) data after 2000. Exclusion criteria were: patients with a PD diagnosis prior to 1/1/2000, patients who were diagnosed under the age of 40, patients diagnosed within 6-months of their SAIL registration date (to ensure that incident cases only were included), patients prescribed any PD medication before the diagnosis date, and patients who were receiving antipsychotics up to one year before PD diagnosis as antipsychotics are known to cause extrapyramidal symptoms which could be erroneously diagnosed as PD (Pringsheim and Barnes, 2018).

2.2. Identify individual PD medications

Read codes for PD medications in GP data were identified and classified into six main categories (supplementary data, Appendix (1)).

First line therapy was defined as the first PD medication(s) prescribed in the 30 days following initial PD diagnosis. Age, sex, social deprivation status, health board, year of prescribing, comorbidities, and previous use of antidepressants were also recorded as covariates (Aboukarr and Giudice, 2018). (Appendix (2), Supplementary Data).

2.3. Statistical analysis

A series of multilevel logistic regressions were undertaken to determine the predictors of PD medication prescribing (Sommet and Morselli, 2017; Lee, 2000). Data were analysed using SPSS v.24.0, and R-software v3.5.0.

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 the PD medications mentioned were tested, except for COMT inhibitors and amantadine since their role in the de novo PD patients is limited (Institute, 2017). 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. 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. An empty regression model was run in R 3.5.0 software for every medication category. This model included the GP data for the practice nested within the health board as a random effect and the intraclass correlation (ICC) was calculated for each model based on the results (Sommet and Morselli, 2017). If the ICC values were less than 10%, a single level logistic regression was run without considering the random effects of GP data at practice and health board levels (Lee, 2000). In line with best practice, 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 and, therefore, the single level logistic regression was applied.

The first step in building the final regression model was to determine which independent variables to include in the multivariate model. A particular variable was included in the multivariate model if the p value of the Wald test in the univariate model was ≤ 0.20. Based on the outcomes of the univariate analysis, a multivariate logistic regression, that 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 $p < 0.05$. Any variable that had less than 5 patients in any group was excluded from the analysis as per SAIL policy.

2.4. Sensitivity analysis

To assess the robustness of the study outcomes, a sensitivity analysis that excluded patients with a history of dementia was conducted. The rationale behind excluding these patients in the

sensitivity analysis was to exclude potentially false PD cases, such as dementia with Lewy body (DLB).

3. Results

During the study period (2000–2016) and after applying the exclusion criteria, there were 9142 newly diagnosed PD patients who had been initiated on PD therapy (Appendix 3). The mean age is 73.4 years. 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 1). A very low prescription rate for medications from the ergot DAs category was seen throughout the study (no more than 3.96%). For other characteristics of the study cohort among different treatment groups, see Table 1.

Table 1
Characteristics of the study cohort.

	Number of patients (total n = 9142)
Initial PD medication*	
Anticholinergics	325 (3.60%)
Dopamine Agonists (DAs)	1291 (14.10%)
Levodopa	7366 (80.60%)
levodopa plus carbidopa or benserazide	7287 (79.70%)
levodopa plus carbidopa plus entacapone	79 (0.86%)
MAO-B inhibitors	719 (7.90%)
Number of patients on combination therapy	963 (10.53%)
Age, mean (years)	73.4 years
40–60 years	845 (9.24%)
61–80 years	5670 (62.02%)
>80 years	2627 (28.74%)
Sex	
Male	5358 (58.61%)
Female	3784 (41.39%)
Welsh Index of Multiple deprivation (WIMD) quintile	
1 (most deprived areas)	1517 (16.59%)
2	1685 (18.43%)
3	2060 (22.53%)
4	1794 (19.62%)
5 (least deprived areas)	2086 (22.82%)
Health board	
Swansea Bay University Health	2128 (23.28%)
Aneurin Bevan	1408 (15.40%)
Betsi Cadwaladr	2005 (21.93%)
Cardiff & Vale	1275 (13.95%)
Cwm Taf	845 (9.24%)
Hywel Dda	1158 (12.67%)
Powys**	323 (3.53%)
Year of first prescribing	
2000–2005	2602 (28.46%)
2006–2011	3228 (35.31%)
2012–2016	3312 (36.23%)
Comorbidities	
Diabetes	656 (7.18%)
Pulmonary disease	510 (5.58%)
Cerebral vascular accident	338 (3.70%)
Acute myocardial infarction	321 (3.51%)
Dementia	255 (2.79%)
Congestive heart failure	192 (2.10%)
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	2076 (22.70%)

* The total percentage exceeds 100% because patients can be on more than one medication.
** Powys is unusual in that there are no acute hospitals there and that many patients would go to England for treatment.

3.1. Logistic regression to identify factors that correlate with prescribing of first line therapy

- **Anticholinergics model**

As shown in Table 2, 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-val ue < 0.0001) (see Fig. 2). The odds of prescription of anticholinergics had significantly declined in the 2012–2016 period compared to the 2000–2005 period (p-value < 0.0001) (Fig. 1). Patients with dementia had higher odds of being prescribed anticholinergics (p-value = 0.001) (Table 2).

- **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) (Fig. 1). 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 2). Patients who used antidepressants within one year before PD diagnosis were 15.9% less likely to be prescribed DAs (p-value = 0.029).

- **Ergots DAs model**

Table 2 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 2).

- **Non-ergots DAs**

Table 2 shows that the outcomes of this model were largely similar to those reported in the DAs model. 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% (Fig. 1). The other difference was that there were no significant effects of dementia and previous use of antidepressants in this model (Table 2).

- **L-dopa model**

Table 2 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 around 3 and 19 times 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

Table 2
- A series of multivariate logistic regression to predict prescribing of PD medications in the newly diagnosed PD patients.

		Anticholinergics		DAs		Ergot DAs		Non-ergot DAs		Levodopa		MAO-B inhibitors	
Independent variable		OR**	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age categories	40–60 years (Ref)												
	61–80 years	**0.61**	**0.44–0.84**	**0.28**	**0.24–0.33**	**0.50**	**0.31–0.80**	**0.28**	**0.24–0.33**	**4.00**	**3.43–4.66**	**0.48**	**0.39–0.59**
	> 80 years	**0.29**	**0.19–0.44**	**0.06**	**0.05–0.08**	**0.13**	**0.06–0.28**	**0.06**	**0.05–0.08**	**19.17**	**15.72–24.72**	**0.14**	**0.11–0.20**
Sex	Males (Ref)												
	Females	**1.32**	**1.05–1.65**	–	–	–	–	–	–	0.94	0.84–1.06	0.85	0.72–1.01
Social deprivation score (WIMD)	1 (most deprived areas) (Ref)												
	2	**0.63**	**0.45–0.88**	–	–	–	–	–	–	0.93	0.77–1.13	**1.35**	**1.00–1.83**
	3	**0.47**	**0.33–0.66**	–	–	–	–	–	–	0.88	0.73–1.06	**1.40**	**1.05–1.87**
	4	**0.53**	**0.37–0.76**	–	–	–	–	–	–	**0.80**	**0.66–0.97**	**1.69**	**1.26–2.25**
	5 (least deprived areas)	**0.55**	**0.39–0.76**	–	–	–	–	–	–	**0.77**	**0.65–0.93**	**1.98**	**1.51–2.61**
Year of prescribing categories	2000–2005 (Ref)												
	2006–2011	**0.37**	**0.28–0.49**	0.99	0.86–1.14	–	–	**1.35**	**1.16–1.57**	**0.87**	**0.76–0.99**	**2.26**	**1.80–2.83**
	2012–2016	**0.32**	**0.24–0.43**	**0.43**	**0.36–0.50**	–	–	**0.59**	**0.50–0.71**	**1.91**	**1.65–2.21**	**2.44**	**1.95–3.06**
Diabetes		–	–	**0.53**	**0.38–0.75**	–	–	**0.56**	**0.40–0.79**	**1.37**	**1.04–1.82**	**0.51**	**0.32–0.80**
Pulmonary disease		–	–	0.89	0.64–1.23	–	–	0.90	0.64–1.25	1.05	0.79–1.40	**0.60**	**0.37–0.97**
Cerebral vascular accident		0.56	0.25–1.22	0.67	0.41–1.09	–	–	0.68	0.41–1.13	1.45	0.89–2.33	–	–
Acute myocardial infarction		–	–	0.90	0.58–1.41	–	–	0.97	0.62–1.51	1.22	0.82–1.82	0.58	0.30–1.12
Dementia		**2.45**	**1.44–4.16**	**0.48**	**0.26–0.90**	–	–	0.55	0.29–1.03	1.43	0.88–2.31	–	–
Congestive heart failure		–	–	0.68	0.34–1.32	–	–	0.65	0.32–1.32	**2.06**	**1.06–3.99**	0.76	0.33–1.76
Renal disease		–	–	1.01	0.51–2.00	–	–	0.91	0.44–1.87	1.68	0.82–3.43	–	–
Cancer		–	–	0.85	0.46–1.59	–	–	0.84	0.44–1.61	0.84	0.50–1.40	0.60	0.24–1.48
Peripheral vascular disease		–	–	0.98	0.45–2.11	–	–	1.03	0.48–2.22	1.15	0.57–2.33	–	–
Connective tissue disorder		–	–	–	–	–	–	–	–	1.99	0.84–4.71	–	–
Paraplegia		–	–	–	–	–	–	–	–	**10.06**	**1.31–77.22**	–	–
Diabetes complications		–	–	–	–	–	–	–	–	3.23	0.76–13.67	–	–
Metastatic cancer		–	–	–	–	–	–	–	–	1.90	0.53–6.75	–	–
Previous use of antidepressants		1.14	0.88–1.48	**0.84**	**0.72–0.98**	**0.56**	**0.33–0.96**	0.86	0.74–1.01	**1.33**	**1.15–1.53**	**0.40**	**0.31–0.52**

DAs, Dopamine Agonists; MAO-B, Monoamine Oxidase B; OR, Odd ratio; CI, Confidence interval; Ref, Reference; WIMD, Welsh Index of Multiple Deprivation.
**The significant OR is in bold.
* Not applicable (this variable was not included in the multivariable analysis because it had a P-value > 0.20 in the univariate analysis.

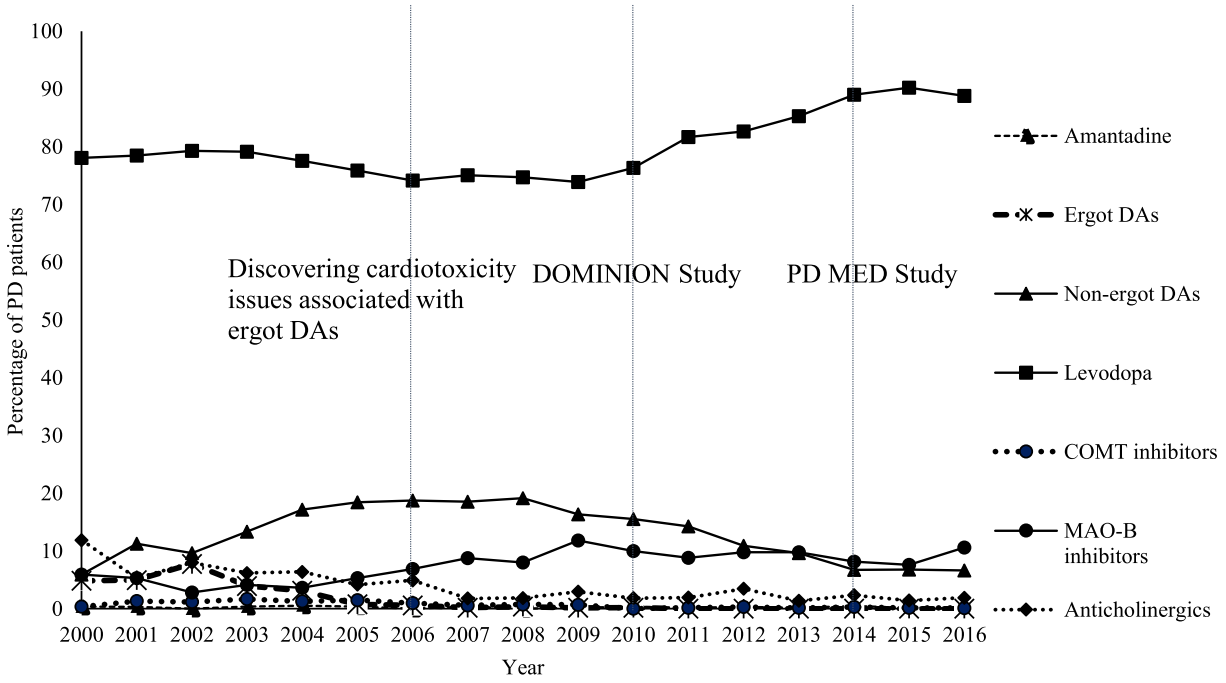

Fig. 1. Changes in the pattern of initial therapy prescribed to PD patients over time (medication categories).

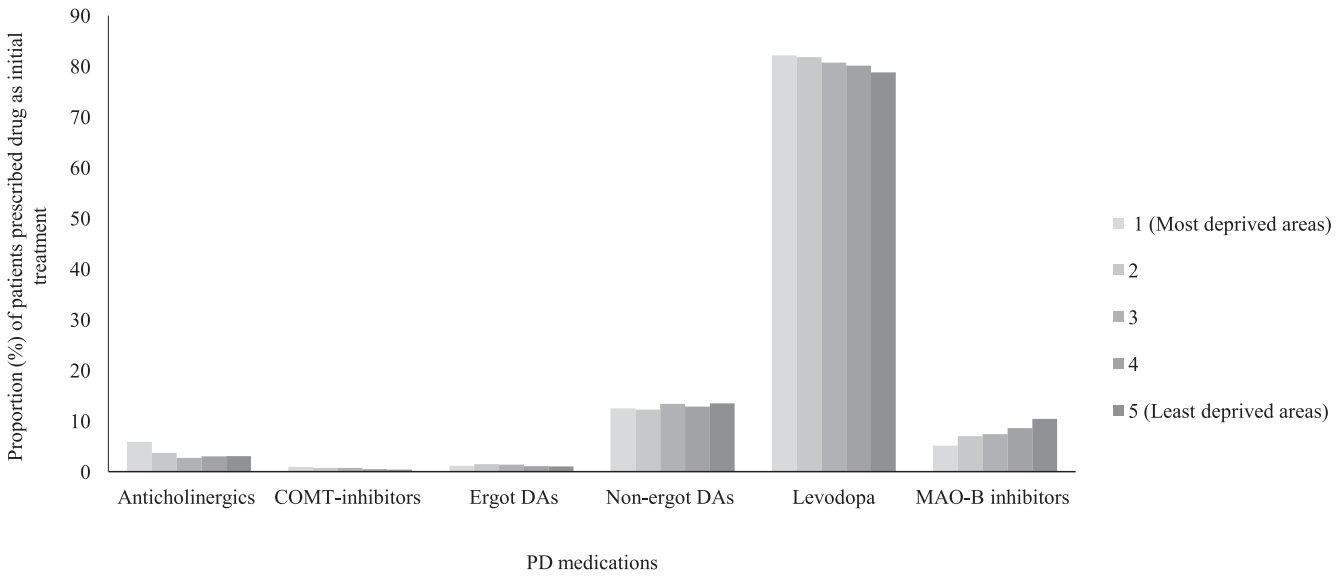

Fig. 2. Prescribing percentage of PD medications stratified by social deprivation (WIMD quintile). WIMD, Welsh Index of Multiple Deprivation; COMT, Catechol-O-methyltransferase; DAs, Dopamine Agonists; MAO-B, Monoamine Oxidase-B.

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 PD patients in the 2012–2016 period were 91.3% more likely to be prescribed L-dopa compared to newly diagnosed PD patients in the 2000–2005 period (p-value < 0.0001) (Fig. 1). 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 2).

- **MAO-B inhibitors model**

Table 2 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) . PD patients were around 1.4 times 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). No apparent

increase in MAO-B inhibitors in 2012–2016 compared to 2006–2011 was seen (Fig. 1). 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 2).

3.2. The sensitivity analysis

The outcomes of the sensitivity analysis were consistent after excluding dementia patients (Appendix (4) in Supplementary Data).

4. Discussion

This purpose of this study is to examine the trends in first line therapy for PD patients in Wales, over the period 2000–2016. The analysis examined 9142 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 therapy prescribed (80.6% of patients); a similar pattern is reported in other countries such as the USA, Japan, and Taiwan (Huse et al., 2006; Swarztrauber et al., 2006; Guo et al., 2014; Nakaoka et al., 2014). A previous UK study showed a lower rate of L-dopa prescribing when used as an initial therapy, either as monotherapy or in combination (46.5%) (Kalilani et al., 2019). There was no obvious reason that explained this huge difference in L-dopa prescribing rate. However, the method of identifying PD patients and medications in the CPRD study may be not the same as ours (Kalilani et al., 2019). Nevertheless, this assumption cannot be confirmed since the exact method of identifying patient and medications in CPRD study was not clear. Additionally, there was no stratification by patient characteristics in the CPRD study (Institute, 2017).

Over the study period (2000–2016), the trends in first therapy underwent a significant switch towards L-dopa (particularly after 2010) in all PD patients, irrespective of age at presentation. Whilst there have been no reported studies after 2010 that have examined the trend of prescribing L-dopa as a first therapy across years, several studies have shown a general increase in L-dopa prescribing prior to 2010 for all stages of PD, i.e. both as an initiation therapy and after progression of PD (Hollingworth et al., 2011; Pitcher et al., 2014). It is well documented in some studies that many PD patients who were initiated on DAs or MAO-B inhibitors were augmented with or switched to L-dopa after 5 years from the original therapy (Olanow et al., 2001).

In contrast to other studies, this study has demonstrated a significant move away from prescribing non-ergot DAs, starting in 2010 in Wales. Of note, this was the year of publication of the results of the DOMINION study which found that impulse control disorders (ICDs) are significantly associated with DA usage (Weintraub et al., 2010). Furthermore, other safety concerns related to DAs were identified around 2010, including the risk of heart failure that is associated with pramipexole usage (Mokhles et al., 2012). This might go some way to explain the shift from prescribing of DAs as first therapy to prescribing L-dopa which is more effective and has less significant side effects (Olanow and Stocchi, 2017). 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 trend was for all PD patients, regardless of whether or not they were newly diagnosed (Crispo et al., 2015). This current study also found that the tendency to prefer L-dopa as a first line therapy continued after the publication of the PD-MED study in 2014 (Guo et al., 2014) which showed that early initiation of L-dopa resulted in better long term QoL compared to DAs and MAO-B inhibitors. With respect to the prescribing of ergot DAs, it may be inferred from the results of this study that the cardiotoxicity issues associated with pergolide (Yamamoto et al., 2006) had a significant impact on its rate of prescribing (Fig. 1). In accordance with these safety issues, no single ergot DA was prescribed as a first line therapy in the period 2012–2016. Although Kalilani et al. reported a 10% of ergot DAs use as a first line therapy in UK between 2004 and 2015, they did not stratify by year of prescribing (Kalilani et al., 2019); and therefore, it is not possible to examine the effect of ergot DA safety literature on prescribing in their study.

The general prescribing rate of MAO-B inhibitors increased significantly in Wales, following the approval of rasagiline in 2006. This trend has also been described in the USA and Finland (Crispo et al., 2015; Keränen and Virta, 2016). There was no apparent increase in MAO-B inhibitors in 2012–2016 compared to 2006–2011 (Fig. 1). This could be for two reasons. Firstly, the fact that the neuroprotective properties suggested by a range of clinical trials such as TEMPO trial (Hauser et al., 2009), is negated by some guidelines (Schapira, 2011); and, second, the results of the PD-MED study that confirmed the inferiority of MAO-B inhibitors to L-dopa in terms of long term QoL when treating early symptoms of PD (Guo et al., 2014).

L-dopa was the predominant first drug prescribed in all Parkinson's patients regardless of age. However, age was a significant predictor of the first prescribed agent 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 adults (60–80 and >80 years), in contrast, were more likely to be prescribed L-dopa. The tendency to prescribe L-dopa to older adults and refrain from prescribing DAs has been similarly reported in other studies (Swarztrauber et al., 2006; Keränen and Virta, 2016; Fayard et al., 2011) and is in line with a variety of guidelines that recommend refraining from prescribing DAs and anticholinergics to older adults due to the risk of medicines related harm (particularly cognitive side effects) (Olanow et al., 2001).

There is an interesting association between social deprivation score and the prescribing of L-dopa and MAO-B inhibitors. No previous UK studies have measured or found such an association; however, in the USA, some studies have found that more expensive drugs, such as some DAs and MAO-B inhibitors, were more commonly prescribed to patients with a higher socioeconomic status (Goudreau et al., 2016; Orayj and Lane, 2019). In Wales, prescriptions have been free of charge since 2007, so the economic status of the patients should not be an issue. A possible interpretation of this finding is the significant delay in PD diagnosis in some minority groups which has been reported outside the UK (Dahodwala et al., 2011). Given that MAO-B inhibitors are often used as a starter drug, individuals with a lower socioeconomic status may be diagnosed at a later disease stage, in which case the decision may be made to commence with L-dopa as the more effective therapy and therefore skip the MAO-B inhibitors step.

The positive association between diabetes and L-dopa prescribing identified in this study is strengthened by a negative association between diabetes and DA and MAO-B inhibitor prescribing. This may be multifactorial. Some studies report that newly diagnosed PD patients who have diabetes prior to the PD diagnosis tend to have more severe motor symptoms (Cereda et al., 2012). Given that as diabetes rates are linked to social deprivation indices this could explain the association, but more work should be done to determine exactly what this relationship is.

This was the first study to present a detailed description of the factors associated with the prescription trends of antiparkinsonian

medications in newly diagnosed PD patients in Wales. Moreover, it was the first study to examine changes in first line therapy in PD patients following the publication of the PD-MED study in 2014. To ensure that a newly diagnosed cohort was identified, several robust exclusion criteria were applied (such as excluding possible drug-induced Parkinsonism cases and possible prevalent cases). Sensitivity analyses 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 PD patients.

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. Other limitations in this study are lack of PD clinical data; 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.

To conclude, this study provides a large and representative sample of newly diagnosed PD patients in Wales, generalisable across the UK due to highly comparative practise. The results indicate a reasonable level of awareness of efficacy and safety concerns related to PD medications that have evolved over the last 17 years and alignment with contemporary guidance. Importantly, there is evidence here of differences in prescribing, based not only on age, but on social deprivation indices and comorbidities which require further interrogation.

Funding

This research received an external funding from King Khalid University (KKU) in Saudi Arabia supporting KO to undertake a PhD at Cardiff University, UK.

Acknowledgements

We appreciate the assistance provided by the Secure Anonymised Information Linkage (SAIL) Databank team, Swansea University, Swansea, UK.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2021.01.004.

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