RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2025, Volume 59, no. 1, pages: 62–69
DOI: 10.5603/pjnns.103168

ISSN: 0028-3843, e-ISSN: 1897-4260

Levodopa and dopamine agonist phobia in Parkinson's Disease — does it really matter? A survey on treatment patterns in Polish tertiary centres

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ABSTRACT

Aim of study. To investigate the treatment strategies of Parkinson's Disease (PD) among movement disorder specialists in tertiary centres in Poland, and how literature warnings (levodopa and dopamine agonist phobia) have influenced their practice.

Material and methods. The survey was conducted between 30 November, 2020 and 18 October, 2021, in four Polish tertiary referral centres for PD (two in Gdansk, one in Sosnowiec, and one in Warsaw). Movement disorder specialists collected information on the treatment of 494 consecutive patients diagnosed with PD. The questionnaire included information on the age of the patient, the duration of PD, the Hoehn&Yahr (H&Y) stage, comorbidities, pharmacotherapy, and advanced PD therapies i.e. deep brain stimulation (DBS), levodopa/carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusions (CSAI).

Results. Levodopa was the most prescribed medication (n = 465/494), followed by dopamine agonists (n = 292/494). The mean dose of levodopa was 810.58 ± 473.11 mg, and it did not exceed 2,000 mg/d in 98.5% of patients. The mean doses of dopamine agonists used were relatively low (ropinirole 8.64 ± 3.94 mg, pramipexole base 1.76 ± 0.65mg). Amantadine (n = 197/494) and MAO-B inhibitors (n = 202/494) were prescribed less frequently. Catechol-o-methyltransferase (COMT) inhibitors (n = 7/494) and anticholinergics (n = 4/494) were rarely used in the studied population. Complex polytherapy with three or more PD medications was the most often used treatment strategy (n = 223/494).

Conclusions and clinical implications. Levodopa remains the gold standard in PD treatment in tertiary movement disorder centres in Poland. Dopamine agonists formed the second most frequently prescribed group of medications; however, the observed low dosages of both levodopa and dopamine agonists may suggest a cautious approach by clinicians. Amantadine and MAO-B inhibitors (mainly rasagiline) constituted important elements of PD pharmacotherapy. The high prevalence of complex polytherapy underlines the complexity of PD management, the cautious use of single medication at high doses, and the need for personalised therapeutic strategies.

Keywords: Parkinson's Disease, levodopa phobia, dopamine agonist phobia, prescription patterns

(*Neurol Neurochir Pol 2025; 59 (1): 62–69*)

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Submitted: 22.10.2024 Accepted: 20.01.2025 Early publication date: 26.02.2025

Introducion

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterised by motor and non-motor symptoms [1]. Pharmacotherapy plays a critical role in managing PD, significantly enhancing both the quality and length of a patient's life [2]. Currently available treatments have only symptomatic effects, with most therapeutic strategies focusing on improving motor symptoms. Historical shifts in treatment approaches, driven by concerns over levodopa-related complications raised two decades ago (known as 'levodopa phobia') and the more recent 'dopamine agonist phobia', may influence current practice [3, 4]. Motor symptom management, such as bradykinesia, tremor, rigidity and gait impairment, is mostly based on dopaminergic medications, such as levodopa (LD) with a dopa decarboxylase inhibitor and non-ergot dopamine agonists (DA) such as ropinirole, pramipexole, piribedil, apomorphine, and rotigotine. Additionally, MAO-B inhibitors (rasagiline, selegiline), COMT inhibitors (entacapone being the only one available in Poland), amantadine and anticholinergics (biperiden, pridinol and trihexyphenidyl) contribute to the therapeutic landscape [5–11]. Advanced therapies, which are specialised treatment options for patients whose symptoms cannot be effectively managed with oral medications, include deep brain stimulation (DBS), levodopa/carbidopa intestinal gel (LCIG), continuous subcutaneous apomorphine (CSAI), and recently continuous subcutaneous levodopa-carbidopa infusions. These therapies are available and fully reimbursed in Poland, although the last-named one was introduced only after the completion of data collection for our study. The complexity of PD management is further compounded by the multitude of available therapeutic options, their adverse effects and interactions, along with inevitable progression of the disease. Furthermore, the availability and reimbursement of PD medications vary in Poland, with some medications being not licensed (e.g. opicapone, safinamide, trihexyphenidyl, istradefylline) or being licenced but not reimbursed (e.g. rasagiline, rotigotine, entacapone). This study aimed to investigate the treatment strategies of PD among movement disorder specialists in tertiary centres in Poland.

Material and methods

The survey was conducted between 30 November, 2020 and 18 October, 2021 in four Polish tertiary referral centres for PD (two in Gdansk, one in Sosnowiec, and one in Warsaw). Movement disorder specialists collected information on the treatment of 494 consecutive patients diagnosed with PD either according to UK Brain Bank Criteria [12] for patients diagnosed before 2015, or Movement Disorders Society criteria [13] for those diagnosed after 2015. The material was collected during the COVID-19 pandemic and the aim of our previous study was to assess the role of amantadine as a preventive SARS-CoV-2 medication [14]. The questionnaire included information on the age of the patient, the duration of PD, the Hoehn&Yahr (H-Y) stage, comorbidities, pharmacotherapy, and advanced PD therapies i.e. DBS, LCIG, and CSAI. Patients were divided into groups based on age (< 50, 50–59, 60–69, ≥ 70 years), H&Y stage (I–V), and disease duration (0–5, 6–10, > 10 years). The mean doses of the most often prescribed medications with standard deviation were calculated in groups depending on age, H&Y stage score, and disease duration. Rasagiline was excluded from these calculations due to its fixed dosing.

The collected data is part of routine history taking and did not include any additional interventions nor influence medical decisions, and therefore Bioethical Committee approval was not required.

Results

Basic demographic data

Movement disorder specialists collected data from 494 patients (301 males, 60.93%). The mean age of the patients was 64.75 years (SD ± 10.62, range: 27-89). The mean H&Y score was 2.45 (SD ± 0.68, range: 1–5), and the mean duration of PD was 9.54 years (SD ± 5.80, range 1–30). 270/494 (54.66%) patients had at least one comorbidity. Full data concerning comorbidities can be found in the Supplementary Material.

Mono and polytherapy

A total of 119 patients (24.09%) were on monotherapy only, with 104 on LD, 14 on DA (pramipexole n = 7, ropinirole n = 7), and one on rasagiline. A further 152 patients (30.77%) were treated with two medications, and 151 (30.57%) and 72 (14.57%) with three and four medications respectively. The distribution of pharmacotherapy in the study population is set out in Figure 1.

Age

The number of individuals with specific medications in groups related to patient age (< 50, 50–59, 60–69, ≥ 70 years) is set out in Figure 2A.

Hoehn&Yahr stage

The number of patients with specific medications at different stages of PD according to Hoehn&Yahr stage (I–IV) is set out in Figure 2B.

Duration of disease

The number of patients with specific medications in groups related to disease duration (0–5, 6–10 years, > 10 years) is set out in Figure 2C.

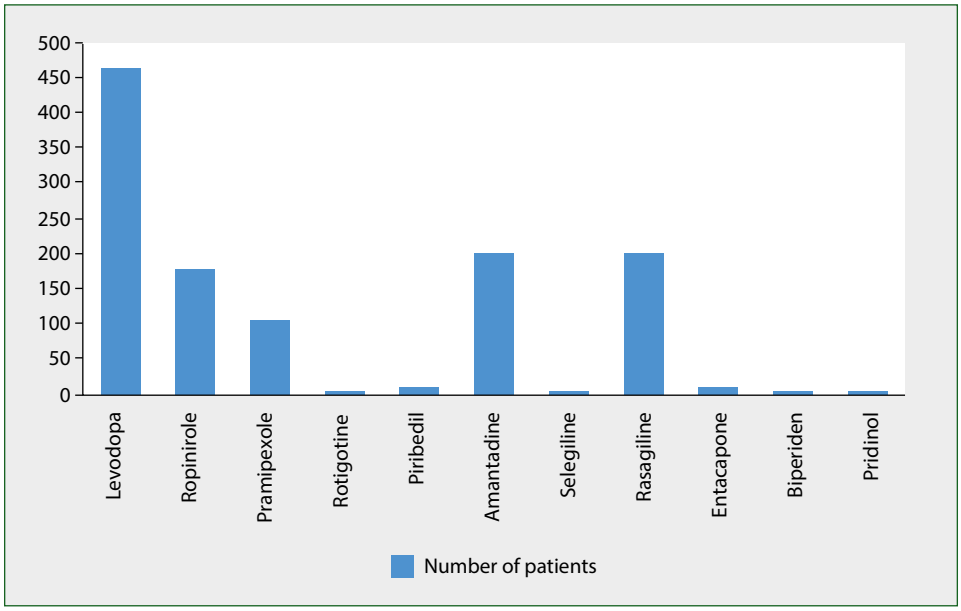

Figure 1. Number of patients treated with each medication

Mode of therapy

In the studied group, 394/494 patients (79.76%) received oral pharmacotherapy exclusively, whereas 84 (17%) were treated with DBS, 12 patients (2.43%) were on LCIG, and four patients (0.81%) were on CSAI. In the DBS group, 80 (95.25%) patients were on levodopa, 51 (60.71%) on DA (ropinirole 43, pramipexole seven, piribedil one), 41 (48.81%) on amantadine, 20 (23.81%) on MAO-B inhibitors (all on rasagiline), one (1.19%) on entacapone, and one (1.19%) on anticholinergics (i.e. biperiden).

Mean doses

The mean dose of each selected medication across the whole study population was as follows: LD 810.58 mg (SD ± 473.11), ropinirole 8.64 mg (SD ± 3.94), pramipexole (base) 1.76 mg (SD ± 0.65), and amantadine 254.57 mg (SD ± 78.11). Mean doses of patients treated with DBS were slightly different: levodopa 892.5 mg (SD ± 550.05), ropinirole 8.47 mg (SD ± 4.11), pramipexole (base) 1.65 mg (SD ± 0.82), and amantadine 285.36 mg (SD ± 85.33). The doses adjusted to age, H&Y, and disease duration are set out in Table 1. LD dose distribution is set out in Table 2. All ropinirole or pramipexole medications were prescribed in extended release preparations.

Discussion

'LD phobia', which emerged at the start of the 21st century, was driven by unproven hypotheses of LD toxicity and studies suggesting that DA might delay the onset of motor complications [3]. Consequently, clinical guidelines in the early 2000s recommended the use of DA as initial therapy. 'DA phobia' is a more recent phenomenon that has potentially led to reduced use of this group of medications by clinicians [4]. The concern primarily stems from warnings about side effects associated with DA treatment, including excessive daytime sleepiness, sleep attacks, postural hypotension with the associated risk of falls and injuries, peripheral oedema, and above all neuropsychiatric symptoms such as the increased risk of impulse control disorder [15, 16].

According to data collected by the Polish National Health Fund, there were 99,471 patients diagnosed with PD who were provided with health services in 2021 in Poland. A substantial amount (494) of patients took part in our study, which makes our cohort a representative sample of the population (0.50%).

Our results show that LD was the most frequently prescribed medication across all patient groups, regardless of age, H&Y scale score, disease duration, or type of therapy. Specifically, LD was used by 361 patients (96.27%) on polytherapy and 104 patients (87.40%) on monotherapy. The lowest but predominant use of LD was observed among patients under 50 and those who also had an H&Y scale score of 1 (Fig. 2). The overall prescription rate of LD in our cohort (94.12%) was higher than reported in studies from Japan in 2023 (85.4% [17] and 74% [18]), international cohorts in 2023 (79.5% [19]), India in 2017 (92.2% [20]), and the United States in 2016 (90% [21]).

As expected, there was a gradual increase in the mean LD dose with advancing age, higher H&Y scale score, and longer disease duration (Tab. 1). In most patients, the prescribed doses of LD were below 1,000 mg, with doses exceeding 2,000 mg in only seven (1.50%) cases (Tab. 2). The mean LD dose in our study (810.58 ± 473.11 mg) was higher than that reported in 2021 in a study from the United Kingdom

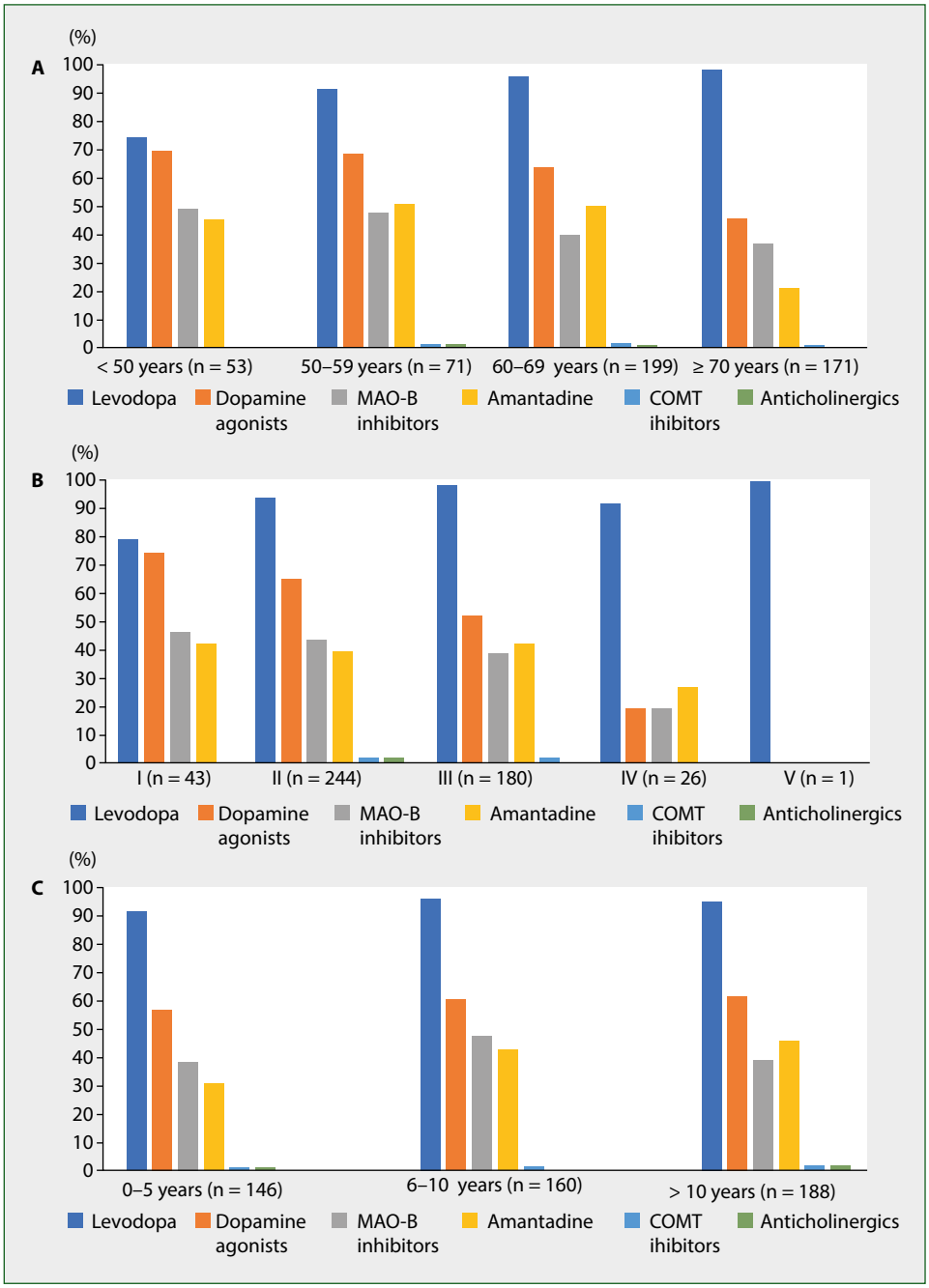

Figure 2. Medications used regarding age distribution (**A**), H&Y staging (**B**), and disease duration (**C**)

and the United States (658.57 ± 503.55 mg) [22], and in earlier studies from the United States in 2012 (two groups: 684.0 ± 412.8 and 559.7 ± 310.6 mg) [23], and Poland in 2011 (801.11 ± 430.58 mg) [24].

However, previous studies from the United Kingdom published in 2003 [25] and Poland in 2004 [26] documented comparatively higher mean doses of LD, of 955.8 ± 540.4 mg and 871 ± 446 mg, respectively. The compared studies examined slightly younger [25], similar [24], and older populations [22, 23, 26] in terms of mean age, whereas mean duration of disease was slightly shorter in two studies [22, 24], longer in two [25, 26], and no information was provided in one [23].

The high prescription rates suggest that there is no reluctance to use LD in tertiary centres in Poland. However, results reported in the abovementioned studies suggest that the paradigm of LD treatment might have changed over the past 20 years, as today's mean doses of LD might be lower than those of two decades ago.

DAs constituted the second most important component of the PD treatment strategy in the studied population. They

Table 1. Mean doses of selected medications regarding age, H&Y staging, and duration of disease

Drug	Age			
	< 50 years	50–59	60–69	≥ 70
Levodopa	723.44 mg (± 558.43)	714.23 mg (± 471.74)	781.17 mg (± 414.12)	902.23 mg (± 502.78)
Ropinirole	8.77 mg (± 3.95)	8.75 mg (± 3.76)	8.65 mg (± 4.19)	8.47 mg (± 3.70)
Pramipexole (base)	1.57 mg (± 0.70)	1.89 mg (± 0.79)	1.79 mg (± 0.61)	1.77 mg (± 0.59)
Amantadine	262.50 mg (± 96.96)	261.11 mg (± 54.91)	243.00 mg (± 79.46)	274.32 mg (± 77.84)
Drug	**H&Y stage**			
	I	II	III	IV
Levodopa	397.06 mg (± 263.98)	772.09 mg (± 458.42)	879.40 mg (± 424.64)	1,250 mg (± 669.52)
Ropinirole	6.29 mg (± 3.91)	8.41 mg (± 3.65)	9.57 mg (± 4 .20)	–
Pramipexole (base)	1.49 mg (± 0.58)	1.83 mg (± 0.65)	1.86 mg (± 0.64)	1.31 mg (± 0.53)
Amantadine	233.33 mg (± 76.70)	244.79 mg (± 79.30)	266.45 mg (± 74.56)	314.29 mg (± 69.01)
Drug	**Disease duration**			
	0–5 years	6–10 years	> 10 years	
Levodopa	598.50 mg (± 328.91)	778.22 mg (± 397.09)	997.05 mg (± 547.84)	
Ropinirole	7.42 mg (± 4.21)	9.00 mg (± 3.40)	9.09 mg (± 4.03)	
Pramipexole (base)	1.50 mg (± 0.50)	1.90 mg (± 0.61)	1.88 mg (± 0.75)	
Amantadine	221.59 mg (±5 7.46)	247.76 mg (± 78.54)	276.74 mg (± 80.69)	

Table 2. Distribution of levodopa doses

Levodopa dose (mg)	≤ 500	> 500 to 1,000	> 1,000 to 1,500	> 1,500 to 2,000	> 2,000
Number of patients	161 (34.62%)	189 (40.65%)	75 (16.13%)	33 (7.10%)	7 (1.50%)

were used by 278 patients (74.13%) on PD polytherapy and 14 patients (11.76%) on monotherapy, totalling 59.11% of the whole cohort. Their prescription rate was higher than those reported in recent studies from Japan (30.4% [17] and 52.8% [18]), the international cohort (57.4% [19]), India (22.9% [20]), and the United States (29–31% [21] and 24–27% [27] in 2021).

In our study, we observed a relatively higher use of DA among younger patients (< 50) and those in the early stages of the disease (Fig. 2). Their use declined with advancing age and disease progression (Fig. 2). Ropinirole was prescribed nearly twice as often as pramipexole (Fig. 1), despite reports of comparable efficacy and tolerability between the two [28]. This may be influenced by the prescriber's routine, as ropinirole was the first new generation (non-ergotamine) DA licenced and reimbursed in Poland, while pramipexole entered the market several years later. The mean doses of ropinirole in patients with an H&Y scale score of I and disease duration of less than 5 years were lower than the suggested clinically meaningful dose of 8 mg [29, 30]. We observed a gradual increase in ropinirole dosing with disease progression and higher H&Y scale scores. Mean doses of pramipexole exceeded reported minimal effective dose of 1.05 mg (1.50 mg of salt) [31, 32], although were relatively low compared to a maximum daily dose of 3.15 mg (4.50 mg of salt). Piribedil was used only by eight patients, most likely due to its burdensome dosing regimen, which requires intake several (3–5) times a day [33]. The prescription rate for rotigotine transdermal patch was very low, despite evidence of its effectiveness, tolerability, and ease of use [34], probably because it is not reimbursed in Poland.

Overall, the mean doses of DA in our cohort were relatively low compared to maximum range of ropinirole (24 mg/d) and pramipexole (3.15 mg/d of base). However, there is a scarcity of studies on DA dosing in real-world populations for direct comparison. The lower prescription rate of DAs compared to LD may reflect, to some extent, the influence of DA phobia. On the other hand, these medications were more frequently prescribed in Poland (in terms of the number of treated patients).

MAO-B inhibitors were frequently prescribed in our study population, regardless of age, H&Y stage, and disease duration. Specifically, 201 patients received MAO-B inhibitors as a part of polytherapy and one patient as monotherapy, totalling 40.69% of the studied cohort. This prescription rate was higher than those reported in previous studies from Japan (21.1% [17] and 12.3% [18]), international cohorts (37.9% [19]), India (3.3% [20]), and the United States (9–11% [21] and 28–30% [27]). Despite similar costs and evidence of the effectiveness of selegiline and rasagiline [7, 8], the use of the former was considerably lower (Fig. 1). This disparity may be attributable to the numerous side effects and drug interactions associated with selegiline treatment [35] and more recent and

extended clinical trials with rasagiline showing its safety and good profile for the treatment of tremor.

Amantadine was prescribed to 197 patients (39.88%), a usage higher than those reported in recent studies from Japan (10% [17] and 13.4% [18]), international cohorts (21% [19]), India (16.6% [20]), and the United States (7–8% [21]). In our study, we observed an increase in the prescription rate of amantadine with progression of disease and with age (in groups < 50, 50–59, and 60–69 years), followed by a decrease after the age of 70 (Fig. 2). This trend was probably due to its cardiovascular contraindications and potential side effects in older patients [8]. However, an increase of amantadine use with duration of the disease (Fig. 2), and of its mean doses with duration of the disease and H&Y scale score, was observed (Tab. 1), presumably due to the growing need for its anti-dyskinetic properties as the disease progresses [9, 36]. The minimal effective dose of amantadine in the treatment of PD has not been clearly defined [36], and to the best of our knowledge data concerning mean doses of amantadine in real-world populations for direct comparison is limited. Nevertheless, amantadine was used from early disease stages, and nowadays due to reports of its possibly preventive anti-dyskinetic effect, such treatment (i.e. polytherapy from the very beginning) seems to be the rational approach [37]. The amantadine extended release preparation is unavailable in Poland.

COMT inhibitors were rarely used in the studied population. Entacapone was only prescribed to seven patients (1.42%), despite its good safety profile and proven effectiveness in combination with LD [38, 39]. This prescription rate was much lower compared to reported usage of COMT inhibitors in studies from Japan (17.6% [17] and 20.9% [18]), international cohorts (49.7% [19]), India (3.3% [20]), and the United States (6–8% [21] and 7–18% [27]). The relatively high monthly therapy cost and lack of reimbursement for entacapone in Poland were presumably the reasons for its low usage. However, since our data collection period ended, the price of entacapone has fallen, which has increased its prescription rate.

We observed a very low use of anticholinergics in the studied population, as they were prescribed to only four patients (0.81%). This prescription rate was lower than in recent studies from Japan (12.7% [17] and 1% [18]), international cohorts (1.5% [19]), and the United States (5–6% [21] and 2% [27]). The difference was even more pronounced compared to a study based on data from India (38.6% [20]), in which the high prescription rate of anticholinergics presumably resulted from their affordability. Low usage of anticholinergics in our cohort probably stemmed from contraindications and possible side effects associated with treatment with this group of medications, in particular a deterioration of cognitive functions and higher risk of psychotic events, as well as the risk of constipation [40, 41].

Most patients (79.76%) in the studied group were treated only with oral pharmacotherapy. However, a relatively high number of patients (17%) were treated with DBS, underlining the importance of this method in tertiary centres in Poland. LCIG and CSAI therapies are reimbursed through a special medication programme in Poland, which requires one-day inpatient visits. As the predominant part of our data collection took place in outpatient settings, many of these patients did not participate in this study and are thus underrepresented. The assessment of therapy in patients treated with advanced methods requires further, extended research.

Our results show a significantly lower share of PD monotherapy than in studies from Japan [17, 18, 42], India [20], China [43], and the US [27] published between 2017 and 2023. A substantial group of patients in our study (45.14%) were treated with three or more medications (Fig. 2), in contrast to the 18% [42] reported in a recent Japanese study. Complex polytherapy with at least two drugs, and often three or more, constitutes a leading strategy in tertiary centres in Poland. This reflects a nuanced approach to PD treatment, allowing for personalised pharmacotherapy tailored to the specific needs of each patient, especially those experiencing motor fluctuations, dyskinesias, LD resistant tremor and the need to decrease the possible side effects when using more medications.

Clinical implications and future directions

LD remains the gold standard in PD treatment, with its widespread use dispelling concerns about LD phobia. However, the overall doses are lower than 20 or 30 years ago. While DAs constitute the second most frequently prescribed group of medications, their relatively low doses may suggest a cautious approach, possibly reflecting lingering 'DA phobia'. Other medications, particularly MAO-B inhibitors and amantadine, also play important roles in PD management and are more commonly used in Poland. The high prevalence of complex polytherapy, whereby nearly half of patients are treated with three or more medications, underlines the complexity of PD management and the need for personalised therapeutic strategies.

Future studies, particularly in non-tertiary care settings involving general neurologists, are essential to provide a more comprehensive understanding of PD treatment patterns in Poland. Conducting interviews with providers about their approach to pharmacotherapy could provide valuable additional insights. Continued monitoring of these trends will inform best practice and optimise patient outcomes.

The main limitation of this study is that the analysis of movement disorder specialists' practices may not fully represent the general pharmacotherapy landscape for PD in Poland. Tertiary care settings typically involve patients with more advanced stages of the disease, which could influence prescription patterns. Clinical practices at the time of publication may have changed since our data collection took place in 2020 and 2021. The influence of published data and congress

discussions on possible side effects of PD medications and real-world clinical practice is difficult to assess. Such assessment should take a long term perspective that takes into account local limitations e.g. availability, reimbursement.

Article information

Conflicts of interest: *The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*
Funding: *This publication was prepared without any external source of funding.*
Data availability statement: *The original contributions presented in this study are included in the article and as the Supplementary Material. Further inquiries can be directed to the corresponding author.*
Ethics statement: *The collected data is part of routine history taking and did not include any additional interventions nor influence medical decisions. Therefore, Bioethical Committee approval was not required.*
Authors' contributions: *JK — data management, calculations, compilation of study findings, writing of manuscript; JD — clinical patient management, data collection, manuscript revision; FP — clinical patient management, data collection and management; DK, MK-B, WS, AR, KS — clinical patient management, data collection; JS — clinical patient management, data collection, manuscript revision, supervision of study.*
Acknowledgements: *We would like to thank Paweł Przytuła from Appsilon Sp. Z o.o. for his contribution and support in the analysis and management of the source data.*
Supplementary material: *Full data concerning comorbidities.*

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