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Research paper

Association of guidelines and clinical practice in early Parkinson's disease

T. Keränen [a,b,*], L.J. Virta [c]

[a] National Institute for Health and Welfare, Helsinki, Finland
[b] Science Service Center, Kuopio University Social Insurance Institution of Finland, Hospital, Kuopio, Finland
[c] Research Department, the Turku, Finland

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ABSTRACT

Background: There are limited data on the impact of the published guidelines of Parkinson's diseases (PD) on clinical practice.
Objective: Our aim was to evaluate the impact of clinical guidelines regarding PD by comparing the choice of first anti-Parkinson drug (APD) treatment in PD in two different years.
Methods: Two cohorts of PD incident outpatients, diagnosed during 2005 (n = 1436) and 2012 (n = 1607), were identified from a Finnish nationwide register of special reimbursements for medication costs. Data on their APD drug purchases (ATC codes N04) were obtained from the national prescription register.
Results: Overall, levodopa (LD) monotherapy was the most common initial drug in PD and it was started in more than 80% of the cases aged $\geq$ 75 years. Dopamine agonists (DAs) and monoamine oxidase–B (MAO-B) inhibitors predominated in patients aged $<$ 60 years and the frequency of both drug classes decreased with advancing age. Significant changes in the prescription pattern occurred after the guidelines were issued, from the year 2005 to 2012 (P = 0.002). The use of MAO-B inhibitors increased in patients aged less than 75 years. The use of LD decreased in patients aged 64–74 years while that of DAs increased.
Conclusions: The choice of first APD drug in PD shows significant age- and time-period-related variation. The prescription patterns for the first APD drug in PD in Finland seem to be in accordance with the principles of the national and international guidelines.

1. Introduction

Since the early 2000s, several clinical practice guidelines regarding Parkinson's disease (PD) have been published [1–3]. To date, there are limited data on the impact of the guidelines on clinical practice, for example, on the choice of initial drug treatment in PD. Studies form France and Germany, however, suggest that neurologists are well aware of PD guidelines and that initial drug choices are at least moderately in adherence with the recommendations of the guidelines [4–6]. Evaluation of prescription patterns in early PD in Europe have shown that levodopa (LD) and dopamine agonists (DAs) are the most favored anti-parkinson drugs (APD, followed by amantadine and monoamine oxidase–B (MAO-B) inhibitors, and that drug preferences are influenced by the age of the patient [5–7]. Fayard et al. [6] also reported that there were time-related changes in the prescription pattern: During the 2000s the popularity of DAs increased over LD compared with practices before the year 2000.

The aim of our study was to evaluate the association of a national guideline of PD, published in 2006, and the choice of first APD in community-dwelling PD patients in two different years, 2005 and 2012. We also evaluated whether the 2010 update of the guideline had an impact on treatment choices.

2. Material and methods

2.1. Data sources

Individual-level data were derived from two national drug registers maintained by the Social Insurance Institution of Finland (SII). *The Drug Reimbursement Register* includes patients who have been entitled to reimbursement for outpatient medication costs for certain severe chronic diseases. In the case of PD, patients are allowed a special full reimbursement for APD after they have

* Corresponding author at: National Institute for Health and Welfare, Mannerheimintie 166, 00270, Helsinki, Finland. Tel.: +358 40 866 9883.
E-mail address: tapani.keranen@thl.fi (T. Keränen).

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undergone evaluation by the SII. *The Drug Prescription Register* includes information on drug class (Anatomical Therapeutic Chemical (ATC) Classification system) and dispensing date of the prescriptions delivered from pharmacies and reimbursed by the SII. Thanks to the general sickness insurance that covers all Finnish citizens, the register has good coverage of outpatient purchases of medications that need a prescription [8]. Data from these two registers were linked by the unique personal identity number for each participant, which includes date of birth and gender.

2.2. Identification of incident Parkinson's disease patients

After the diagnosis of PD, an examination-based medical certificate issued from a hospital department of Neurology or Geriatrics, or by a private neurologist or geriatrician, is sent to the SII as an enclosure of the application for the special reimbursement. The certificate must describe the current status of the patient, the relevant diagnostic procedures, and a treatment plan. It also includes the ICD-10 code G20. The certificates are checked by a medical examiner, physician or pharmacist at the regional office of the SII. The administrative process for decision-making by the SII takes only a couple of weeks. Thus, the date-of-entitlement decision was used as the index date for the diagnosis of PD. Almost every Finnish PD patient with APD receives the reimbursement, since it considerably decreases medication expenses. On the rare occasions when the reimbursement has not been applied for, pharmacists generally encourage their patients to request it. The coverage of the prescriptions register for APD is good. According to the annual wholesale statistical database compiled by the Finnish Medicines Agency, Fimea, in 2003 the register of the SII included data from 94% of all outpatient consumption of APD in Finland.

We identified all patients with a diagnosis of PD (ICD-10 code G20) who had received the special reimbursement for the cost of APD between both 1st January–31st December 2005 and 1st January–31st December 2012. In 2005, the cohort included 1436 incident cases and in 2012 the cohort included 1607 incident cases that met the criteria in the whole country and were therefore included to the study (Table 1).

2.3. Analysis of Anti-Parkinson Drug initiation

To evaluate the use of APD, we extracted from the Prescription register information on all APD purchases, both with the special full reimbursement (100%) and with the basic reimbursement (42%) of purchases, of the incident patient, three years preceding and one year after the diagnosis of PD. According to the first APD purchase the patients were categorized into monotherapy and polytherapy groups. The monotherapy initiations comprised the following four groups:

- anticholinergic agents, tertiary amines (ATC code N04AA) or amantadine (N04BB);
- MAO B inhibitors (N04BD);
- DAs (N04BC);
- and LD preparations, including LD with dopadecarboxylase inhibitors and LD with carbidopa and entacapone (N04BA).

The polytherapy group comprised of patients whose first APD purchases included two or more different drugs at the same date.

2.4. Finnish current care guideline for the management of Parkinson's disease

A working group, appointed by the Finnish Neurological Society and the Finnish Medical Society Duodecim, published the first clinical guideline in PD in 2006 and an updated version in 2010 [9]. In comparison with the 2006 guideline, the 2010 update favored more strongly levodopa sparing strategies in early PD. In the 2010 guideline, the use of MAO-B-inhibitors, even prior to the development of any functional deficit, is recommended. Furthermore, for patients with a functional deficit who are younger (usually under 75 years of age) and otherwise in good condition, the guideline advocates to start the treatment with a DA or MAO-B-inhibitor (Fig. 1). In other patients (patients aged $\geq$ 75 years or with significant disability), initial treatment with LD is recommended.

2.5. Statistical analysis

Descriptive results were expressed as percentages and means. Patients were divided into three groups according to age at treatment initiation. The Cochran-Mantel-Haenszel Chi^2 test for trend was used to determine changes in the choice of initial therapies between 2005 and 2012. The statistical analyses were performed with SAS version 9.2.

3. Results

Overall, LD was the most common first APD drug prescribed in PD (57% of all monotherapy cases, followed by DAs [23%], and MAO-B inhibitors [12%] during both of the two study years) (Table 1).

There was a significant variation in the choice of the first drug according to the age group of patients. The use of DAs and MAO-B inhibitors predominated in patients aged < 60 years and the frequency of both drug classes decreased with advancing age of the patients. LD was started in more than 80% of the cases in patients aged $\geq$ 75 years at the onset of drug treatment.

Table 1
The choice of initial anti-Parkinson drug in patients with Parkinson's disease, by age at treatment initiation and by study year.

	Age 36–60 years		Age 60–74 years		Age ≥ 75 years		In total	
	2005 (*n* = 216)	2012 (*n* = 179)	2005 (*n* = 638)	2012 (*n* = 774)	2005 (*n* = 582)	2012 (*n* = 654)	2005 (*n* = 1436)	2012 (*n* = 1607)
Male gender (%)	65	63	57	63	50	54	55	59
Median age (years)	56	55	69	69	79	80	73	73
Monotherapy initiation (%)								
Biperiden or amantadine	2.8	2.8	2.7	2.1	2.9	1.5	2.8	1.9
MAO-B inhibitors	18.5	33.5	11.9	17.0	4.5	5.4	9.9	14.1
Dopamine agonists	46.7	38.0	26.5	34.1	7.4	8.0	21.7	23.9
Levodopa[a]	24.1	18.4	50.5	40.2	81.3	83.3	59.0	55.3
Polytherapy initiation (%)	7.9	7.3	8.4	6.6	3.9	1.8	6.6	4.7
Total (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
P-values for year difference in initiations	0.0212		0.0002		0.94		0.0017	

[a] Figures for levodopa comprise all levodopa formulations, i.e. levodopa + carbidopa, levodopa + benserazide, levodopa + carbidopa + entacapone.