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Chapter 12

Pharmacotherapeutic Challenges in Parkinson's Disease Inpatients

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http://dx.doi.org/10.5772/62561

Abstract

During the natural history of Parkinson's disease (PD), many patients require hospital admission for medical or surgical problems other than the motor features of PD. Therefore, they are often admitted to non-neurological wards where the staff is unfamiliar with PD management. Among the issues related to hospitalization in patients with PD, drug-related problems such as inappropriate levodopa timing of administration, the use of contraindicated, centrally acting antidopaminergic drugs and anticholinergic burden remain among the most troublesome.

Keywords: Parkinson's disease, antidopaminergic, levodopa, inappropriate prescription, antipsychotic

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease known to occur primarily from middle age to later in life [1]. The frequency of PD varies depending on the diagnostic criteria, study population, and is estimated to be 0.3% of the entire population, about 1–2% in people over 60–65 years [1] and 3–5% in people 85 years and older [2, 3]. It is a common progressive and disabling neurological disorder characterized by the degeneration of several different neuronal populations that lead to the cardinal features of PD, which are tremor, bradykinesia, rigidity and postural instability [4].

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During the natural history of the disease, many patients require hospital admission for medical or surgical problems other than the motor features of PD. As a consequence, they are often admitted to non-neurological wards where staff is unfamiliar with PD management, as it is generally managed in the outpatient setting [5, 6]. The problems and complications faced by PD patients while in hospital have urged specialists to develop specific guidelines [7]. Among the issues related to hospitalization in PD patients, drug-related problems remain amongst the most troublesome [8, 9]. In this chapter we will review some of them, such as inappropriate levodopa timing administration, centrally acting antidopaminergic drug administration and anticholinergic burden.

2. Inappropriate inpatient levodopa administration

Management of medication regimens increases in complexity as PD progresses, frequently leading to prescriptions taken six or more times per day. Besides, dosing intervals are specific to each individual patient. Although adequate anti-PD medication management is essential during hospital admissions (regarding drugs, dosages and specific dosage schedules), its management is frequently described as suboptimal, leading to adverse clinical sequelae.

One of the first studies about the problem came from a retrospective study of patients with PD hospitalized in the United Kingdom [10]. In that report, an alarming percentage of patients admitted to the hospital had critical medications stopped or omitted. Even more worryingly, of these around 60% experienced significant adverse effects, including the need to transfer a patient to the intensive care unit. In another study carried out in surgical wards of a Scottish hospital, three out of four hospitalized patients with PD did not receive their medications on time or had had doses entirely omitted [11]. In the same line, in a small study we conducted in Alto Deba hospital (in the Basque Country, Spain) we found that chronic anti-PD prescription was omitted in 12/73 admissions [12].

In a survey of National Parkinson Foundation Center, the majority of the participating centers were not confident that medication schedules were adhered to during hospital stays, perhaps because the importance of medication timing in PD was not well understood by hospital staff [13]. Again, from a patient perspective, a survey carried out by a Dutch team showed that incorrect medication distribution contributed to intrahospital deterioration [14].

The same Dutch team published a prospective study that showed that medication error was the most important risk factor for deterioration [15]. More recently, a cross-sectional chart review carried out in 339 consecutive hospital encounters from 212 PD subjects in Florida has shown that patients who had delayed administration or missed at least one dose stayed longer [16].

Skelly et al. [17], in a study carried out in the Royal Derby Hospital in the United Kingdom (National Parkinson Foundation Centre of Excellence for Parkinson's Disease), reported that 2.5% of all doses were not administered because the drug was not available on time. It has to be remarked that this happened in a ward specially designed to treat patients with PD, with

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an enhanced stock of anti-PD medications [17]. We consider that this problem is likely to be aggravated in other non-specialized wards and especially in smaller hospitals.

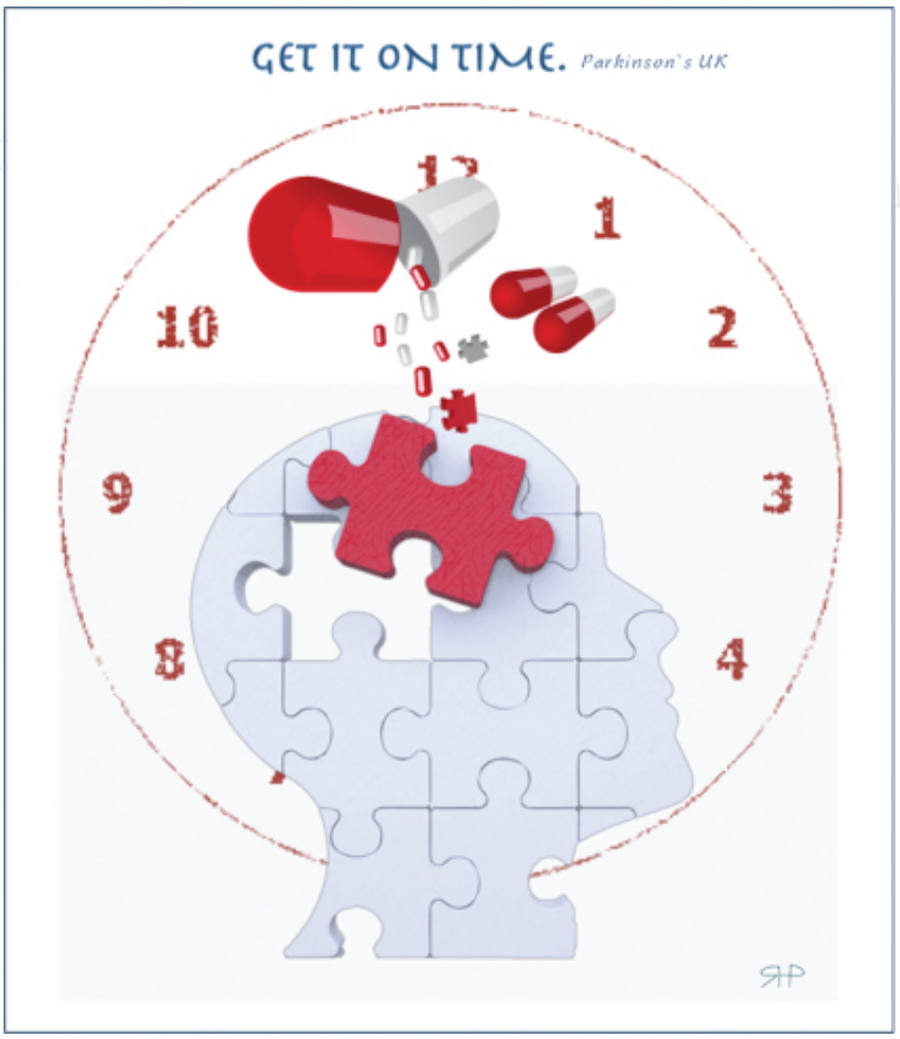


Figure 1. The importance of on-time levodopa administration.

To counteract this difficulty, Parkinson's United Kingdom "**Get it on time campaign**" [18], (**Figure 1**) among others [19], advices that all commercially available antiparkinsonian drugs should be timely available in all hospital wards. Given the data described previously, we find this unfeasible, especially in small hospitals where the availability of all the anti-PD drugs would certainly result in the expiration of many of these drugs before they could be used. May be a reasonable solution can be found in Skelly et al.'s own final considerations: *"The available stock was not used as flexibly as we had hoped: e.g. doses of modified release medications were omitted rather than a temporary switch to available standard release drugs."*

The Institute for Safe Medication Practices (ISMP) has recently issued a generic recommendation that, whereas undoubtedly helpful, will result insufficient. Their recommendation specifically states "*avoiding non-formulary delays ensuring that your formulary provides common*

PD medications and doses so that drug administration is not delayed while the pharmacy obtains non-formulary medications" [20]. Based on the available data, we have recently proposed an algorithm to prevent drug omissions and delays [21] using the equivalent dosages proposed by Tomlinson et al. [22] (**Table 1**).

Drug	Conversion Factor
Immediate release levodopa	1
Controlled release levodopa	0.75
Entacapone*	LD 0.33
Tolcapone*	LD 0.5
Duodopa®	1.11
Pramipexole	100
Ropirinole	20
Rotigotine	30
Selegiline	10
Rasagiline	100
Amantadine	1
Apomorphine	10
Bromocriptine	10

*To calculate the total LED for COMT inhibitors (entacapone and tolcapone), the total levodopa (including controlled release levodopa if COMT inhibitor is given simultaneously) amount should be calculated and then multiplied by the appropriate value. For Stalevo®, the levodopa and COMT inhibitor should be split and calculated separately.

Table 1. Conversion factors to calculate levodopa equivalent dose (LED) adapted from ref [22].

In **Figure 2**, we provide an example for how the algorithm could be applied to prevent an omission.

Nevertheless, if a PD patient must be kept *Nil per Os (NPO)*, thus interfering with the patient's unique schedule of medication administration, a neurologist or Neurology team should oversee the medication regimen change to avoid complications, using alternatives such as intradermal rotigotin or subcutaneous apomorphine [23]. In the same study mentioned above, 88% of admissions (227/257) were some dosage was not administered because of "oral intolerance" or NPO status, no alternative drug was used. In four hospitals, no patient received an alternative drug.

http://dx.doi.org/10.5772/62561

Paraphrasing Magdalinou "*PD medications should be regarded as important as insulin is for diabetics*" [10]. We completely agree. It is about time we take the appropriate measures to minimize the problem.

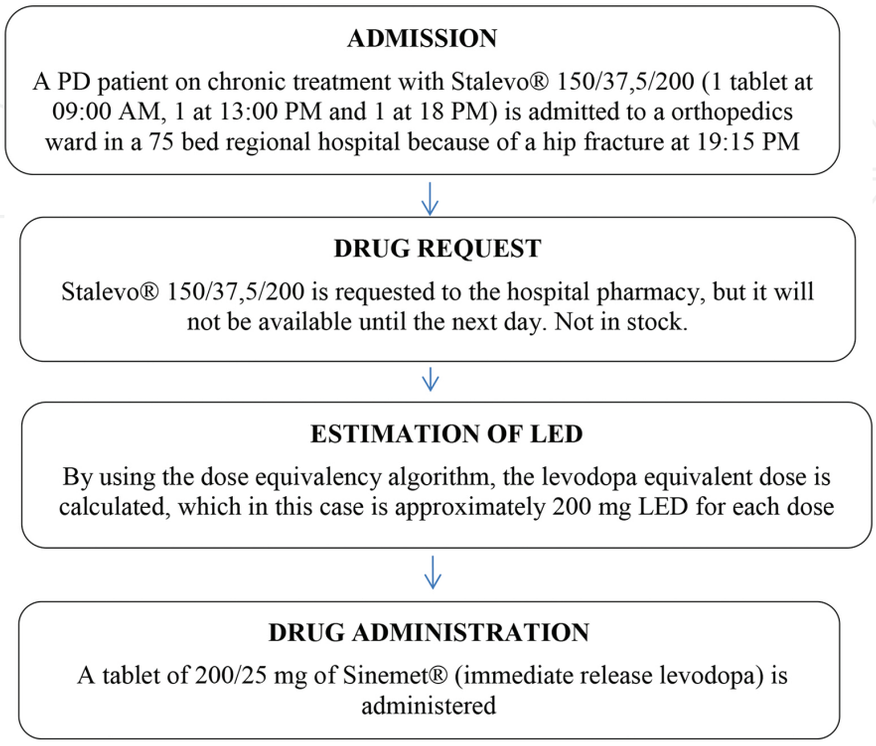


Figure 2. Theoretical example of the algorithm application.

3. Central-acting antidopaminergic administration

Not only anti-PD drugs like levodopa should be taken into account when patients are admitted to hospital. Some drugs are considered inappropriate in PD, since in the same way as dopaminergic drug omissions, they can worsen motor functioning. This is the case with central-acting dopamine antagonists.

While PD has traditionally been considered a motor system disorder, it is nowadays recognized to be a complex condition with diverse clinical features that include neuropsychiatric and many other non-motor symptoms. Researchers are increasingly attending to and characterizing the non-motor symptoms of the disease such as depression, apathy, dementia and psychosis.

3.1. Psychosis

Although patients with both parkinsonism and dementia commonly experience spontaneous visual hallucinations, delusions and paranoia even in the absence of medications for the motor dysfunction, the introduction of dopaminergic therapies frequently triggers or exacer-

bates the underlying propensity to psychosis in patients who have PD dementia. Correctable infectious, toxic and metabolic etiologies (delirium) must be ruled out. If symptoms persist, antiparkinsonian drugs should be slowly reduced, which usually results in a worsening of the parkinsonian features that may be poorly tolerated. When these measures fail, therapy with antipsychotic drugs might be needed [24–26].

Almost all antipsychotic drugs are known to produce PD exacerbation. Clozapine is the only antipsychotic that has level I evidence to support its use in these patients [26]. Nevertheless, quetiapine is frequently considered the first-line choice for treating psychotic symptoms in PD (e.g., by the American Academy of Neurology), and it is usually reported as the most frequently used [27]. The rest of antipsychotic agents, especially high potency drugs such as haloperidol, are considered inappropriate in PD. In the same line, and as PD disease usually affects old people (aged >65 years), the most frequently used tools employing explicit criteria to detect potentially inappropriate prescriptions in older patients (Beers and STOPP-START) criteria consider inappropriate all antipsychotics other than clozapine or quetiapine [28, 29]. We were surprised to find aripiprazole included as one of the least-problematic antipsychotic therapies for PD psychosis, at the same level as quetiapine and clozapine in the last version of the Beers criteria. Despite its promising receptorial profile, preliminary experience with aripiprazole shows a discouraging safety and efficacy profile in individuals with PD, who represent the most stringent test of a drug's potential for inducing parkinsonism. In this sense, severe worsening of motor function has been reported, with one individual requiring parenteral fluid substitution and another requiring nasogastric tube feeding [30]. In light of the evidence mentioned above and considering the widespread use of the Beers criteria, we believe including aripiprazole in the same category as clozapine and quetiapine for the treatment of PD psychosis could do more harm than good [31].

Delirium, or acute confusional state, has been reported as very prevalent in PD inpatients, and being involved in as many as a quarter of admissions [32, 33]. Dementia, which mainly affects patients with advanced disease, constitutes a known risk factor for delirium. As pointed out before, correctable infectious, toxic and metabolic etiologies should be ruled out before considering antipsychotic treatment. Sadly, many times haloperidol is prescribed in our setting to treat "agitation" in patients, either with PD or not.

3.2. Nausea and vomiting

Nausea and vomiting, which are common adverse effects of anti-PD medications (levodopa and dopamine agonists), might require treatment with antiemetic drugs. Metoclopramide and other centrally acting antiemetics are contraindicated in PD patients because they block dopaminergic receptors in the nigrostriatal area, generating deleterious motor effects [26]. Some cases of metoclopramide-associated encephalopathy have even been reported [34, 35].

On the other side, domperidone has traditionally been considered as the gold standard, since it does not readily cross the blood-brain barrier [26]. Nevertheless, its cardiac safety has been put into question recently [36, 37].

http://dx.doi.org/10.5772/62561

3.3. Hiccups

Hiccups are starting to be considered one more "non-motor" symptom of PD [38]. A study evaluated the presence of hiccups in 90 PD patients and 100 age-matched controls, finding that hiccups were more frequent in PD patients than in healthy controls. Interestingly, chlorpromazine (a "typical" antipsychotic formally contraindicated in PD) is usually used to treat incoercible hiccups.

Whatever the reason for they were prescribed, centrally acting antidopaminergic drugs have shown to generate deleterious effects in PD inpatients. The study carried out in Florida, which was mentioned above [16], showed that contraindicated dopamine blocking agent's administration (which occurred in 23% of the cases) was significantly related to an increased length of stay (8,2 vs 3,5 days)(**Figure 3**).

In conclusion, avoiding drugs known to exacerbate motor symptoms should be a priority. Clozapine and quetiapine should be preferred among antipsychotics [9]. Regarding antiemetic use, low dose of domperidone seems reasonable.



Figure 3. Deleterous effects of antidopaminergics in Parkinson's Disease.

4. Anticholinergic burden in PD inpatients

Anticholinergic toxicity is often the consequence of the cumulative burden of multiple medications and metabolites rather than a result of the action of a single drug [39]. Thus, treatment of comorbidities (e.g., bladder control problems, psychosis and depression) with drugs with anticholinergic properties could contribute to aggravate the problem. Indeed, the

most frequently used tools employing explicit criteria to detect potentially inappropriate prescriptions in the elderly dedicate a specific section to anticholinergic drug use [28, 29]. Drugs with anticholinergic activity can lead to adverse reactions in the central nervous system such as cognitive disturbance, especially in elderly people, so extreme caution is required when using them in people with previously known cognitive dysfunction. In this sense, dementia has a prevalence of 80–90% in the most advanced phases of PD [25, 27]. Besides, using anticholinergics in patients on cholinesterase inhibitors (which are the treatment of dementia in PD) could limit their beneficial effect due to a pharmacodynamic interaction [28]. Further, peripheral anticholinergic side effects, including tachycardia, constipation, urinary retention and blurred vision, should also be considered because they may lead to serious morbidity, especially in PD patients who frequently present with autonomic dysfunction.

Anticholinergics like trihexyphenidil, biperiden and benztropine have remained one of the available antiparkinsonian drugs in the antiparkinsonian armamentarium. But considering the potential risks, it is easier to understand why nowadays anticholinergics are hardly used to treat PD, with the exception of severe tremor in younger patients without cognitive dysfunction [40].

In a recent study on PD patients admitted to acute care hospitals in the Basque Health care system, we found that anticholinergic burden was relatively high and arose from drugs prescribed to treat non-motor symptoms and other comorbidities rather than the motor symptoms of the disease [41]. Interestingly, the total number of drugs and cholinesterase drug prescriptions were independently associated with anticholinergic drug use whatever the scale administered (the study was performed using four different scales to measure anticholinergic burden).

As described above, anticholinergic toxicity is often the result of the cumulative burden of multiple medications. For that purpose, many drug lists have been designed to measure the total anticholinergic burden, but they substantially differ both in which drugs are included and in the anticholinergic activity assigned to each compound [42]. Moreover, some drugs with undoubted anticholinergic properties (such as biperiden, solifenacin, trospium and fesoterodine) that were prescribed to some inpatients had to be discarded in this study as these compounds do not appear in any of the published lists [43], including the list providing a systematic review of the literature, which in our opinion is the most complete so far [44]. Thus, developing a credible, consistent, periodically updated screening tool to measure anticholinergic burden should be a priority, in order to avoid confusion in the future [45].

In definitive, potential anticholinergic toxicity should be kept in mind by clinicians, especially in those elderly patients suffering from cognitive dysfunction. Alternative drugs that lack anticholinergic activity should be used when possible.

In conclusion, all professionals involved in healthcare should pay attention to the specific pharmacotherapeutic challenges faced by PD patients in acute care hospitals. Efforts should be made to administer each levodopa dose on time. Drugs with central antidopaminergic activity like haloperidol and metoclopramide should be avoided. And finally, using alternative drugs without antimuscarinic properties when possible seems a reasonable option.

http://dx.doi.org/10.5772/62561

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