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Pharmacological treatment of palliative care patients with Parkinson's disease

Abstract

Parkinson's disease is the commonest neurodegenerative condition, which can be eased for a long while, however, it inevitably leads to patients' death. Dying with Parkinson's disease can be problematic as the clinical situation may change dynamically and necessitate frequent drug dose changes and the introduction of new, preferably injectable, drugs may be necessary. Current treatment of Parkinson's disease aims to increase the brain's dopamine focusing mainly on the motor symptoms. The patients suffer frequently from sudden "on" and "off" fluctuations of muscle rigidity accompanied by extreme pain. Classic dopaminergic treatments wear off and become ineffective. The new drug safinamide has been introduced recently with a promising effect on motor and non-motor symptoms including pain. If unavailable, opioids or cannabinoids to relax muscles are the second-best choice. Also, non-motor symptoms like depression, delirium and psychosis may dominate in dying which necessitates antipsychotic treatment with clozapine or quetiapine even if these drugs may hasten deterioration and result in death.

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Key words: Parkinson's disease, motor symptoms, muscle rigidity, pain, safinamide, opioids, clozapine, quetiapine, apomorphine

Introduction

Parkinson's disease is the most common neurodegenerative disease, with the most established specific treatment. Some other related diseases like multisystem atrophy and progressive supranuclear palsy are much less common. Their symptoms are treated in the same way as Parkinson's disease, but these diseases, sometimes called Parkinson's disease +, do not respond as good as pure Parkinson's disease and will not be discussed here. The pharmacological treatment of patients with Parkinson's disease is rather complicated among others because of a plethora of preparations being available on the market and a continuous trade-off process where improvement of the non-motoric symptoms like psychosis happens at the cost of motoric deterioration. Although the best place to die for a patient with Parkinson's disease is at home, care can be extremely challenging and demanding. Displacement from home to a hospital

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or hospice environment may accelerate symptoms of confusion and delirium. Many patients will need the input of a multidisciplinary team, either in a hospital or in hospice or nursing homes. Hospices and general practitioners should increase their knowledge on the treatment of Parkinson's disease and when needed connect with the regional specialist neurologist on call and this is exactly the aim of this article.

Epidemiology

The overall worldwide prevalence of Parkinson's disease is 315 per 100,000 for ages 40 and older. Not surprisingly, the prevalence increases rapidly with age, starting with 41 per 100,000 in the 40–49-year-old age group and increasing over fortyfold to 1,903 per 100,000 for the 80+ years group [1]. Seven and a half million persons worldwide have Parkinson's disease at any time, this is nearly 20% higher than the previous global estimate of 6.3 million in 2004 [2]. In all age groups, there are more males than females [3]. The mortality ratio is estimated at 1.4 (95% CI = 1.28–1.55) [4]. A substantial proportion of deaths from Parkinson's disease occurs in hospitals, although this may not be the most optimal place for palliative care and death [5].

What causes Parkinson's disease?

The hallmark of Parkinson's disease is degeneration of the dopaminergic neurons in the substantia nigra of the brain [6]. The remaining cells of this area accumulate Lewy bodies (i.e. eosinophilic intracytoplasmic inclusions). However, Parkinson's disease patients suffer not only from dopamine shortage, as the dopamine replacement therapy can palliate only some but certainly not all symptoms. The process of neurodegeneration characterized by slowness of movements (bradykinesia), tremor and muscle rigidity begin many years before the first clinical symptoms. Anosmia and REM sleep disturbances are occasionally noticed 20 years before diagnosis [7]. The symptoms become clinically obvious when the patient's number of dopaminergic neurons drops down to 30% and steadily progresses in the course of the disease [8]. Patients with Parkinson's disease have, consequently a very limited and diminishing dopaminergic reserve.

Prognosis, when is the patient with Parkinson's disease dying?

How may doctors and nurses guess that a patient with Parkinson's disease is in the last phase of his/her illness? First of all, progressive cachexia (with a BMI below 18) associated with poor food consumption and/or dysphagia may be seen as an important prognostic factor. Cachexia associated with problems in prescribing (when dopaminergic drugs are ineffective and cause frequently fluctuating adverse effects), may signal appropriate timing for hospice referral [9]. Frequent infections, especially aspiration pneumonia further herald a poor prognosis. In Parkinson's disease, a "palliative phase" has been proposed, lasting on average for 2.2 years before death, defined by a waning response to dopaminergic treatments and cognitive decline [10, 11]. Delirium and psychosis unaccompanied by other symptoms are treatable and are not per se signs of a nearing end.

Table 1. Top 10 symptoms "dominating the day" (n = 123)

Symptom frequency	(%)
Immobility	28.5
Pain	20.3
Slowness of movement	17.1
Insomnia	15.4
Stiffness	8.9
Urine urgency	8.9
Urine incontinence	8.9
Anxiety	8.9
Urine frequency	8.1
Drowsiness	7.3

Symptoms that trouble patients with advanced Parkinson's disease

There are a couple of symptoms that bother patients with Parkinson's disease most. The most comprehensive was data on this subject by Lee et al. [12] (adapted) using Palliative Care Assessment Tool (Table 1).

Another study by Higginson et al. [13] (adapted) presented a similar but not identical list (Table 2).

The symptom frequency is not related to the burden the patients experience.

From the pharmacological point of view, it is important to divide the symptoms into those related to motor and non-motor functions. Non-motor related symptoms contribute more to the disease burden compared to motor symptoms [14]. The motor-related symptoms do respond to dopaminergic therapy, although the efficacy of these drugs may

Table 2. Symptoms reported in over 50% of patients

Symptom frequency	(%)
Problems using legs	80.0
Fatigue/lack of energy	84.0
Feeling sleepy	86.0
Pain	86.0
Mouth problems	70.0
Problems using arms	64.0
Difficulty communicating	58.0
Spasms	60.0
Constipation	54.0
Difficulty sleeping	58.0
Difficulty controlling urine	52.0
Problems in swallowing	40.0
Shortness of breath	54.0

steadily decrease in the course of the disease. The non-motor related symptoms tend not to respond to dopaminergic therapy and their intensity, and thus burden, tend to increase after using higher doses of dopaminergic drugs. Palliative care professionals may encounter in the advanced stages of the disease the situations where dopaminergic therapies are less well tolerated, principally due to neuropsychiatric side effects (hallucinations, delirium and psychosis) and motor complications may increase (dyskinesia, motor fluctuations).

Pain in Parkinson's disease

Pain is an important symptom adding to the suffering of Parkinson's disease patients. It is frequently aggravated by depression and may seem to the patient as an insolvable problem. In an all-stages population of Parkinson's disease patients, 76% of them suffered from pain [15]. The most common was muscle pain (41%), followed by radicular pain (27%), central neuropathic pain (22%), dystonic pain (17%) and other pains (24%). Among the latter visceral pain and constipation scored quite high [15]. All pains are more prevalent in the advanced stages of the disease. The brain damage modifies the top-down processing of pain, making patients with Parkinson's disease more sensitive to peripheral pain stimulation [16]. Most of the pain symptoms are related to the motor symptoms of the disease but show different responses to dopaminergic replacement [17]. A new drug safinamide, a monoamine oxidase type B inhibitor and also an inhibitor of glutamate release, showed the greatest reduction in pain intensity assessed by Numerical Rating Scale in several clinical trials (standardized mean difference = –4.83, 95% CI [–5.07 to –4.59], $p < 0.0001$). This drug shortened considerably the "off" periods, especially troubling the patients with the wearing-off effects of dopamine agonists. Interestingly this drug improves also the non-motor symptoms [18]. Two other classes of drugs: opioids and cannabinoids are also efficacious. In the contrast, in a meta-analysis, no analgesic effect whatsoever was found for dopaminergic agonists [19]. Some new concepts about pain in Parkinson's disease and its treatment were summarized recently.

Projecting all these data to the practice of palliative care, oral treatment with safinamide can have its limitation in patients who cease to swallow. Switching to injectable opioids or cannabinoids may be necessary. If safinamide is so efficacious against the pain, its discontinuation in a patient who cannot swallow can have severe consequences and can cause pain rebound, although the half-life is long, and it is administered once daily only.

Syndromes in patients with advanced Parkinson's disease

Rigidity and lack of dopaminergic effect

Rigidity and increased pain due to lack of dopaminergic effect is the main concern of many, but not all patients with advanced Parkinson's disease. This may be due to problems with swallowing and absorption of the drug, problems with the equivalency of different formulations or conscient discontinuation of the treatment by patients wishing to "end the misery" and wishing to die earlier. Increased rigidity is frequently associated with tremor and pain. The pain may be felt spontaneously at rest but will be more accentuated as tenderness on palpation and movement. Also, rigid muscles may entrap nerves causing localized neuropathy which is particularly insensitive to classical analgesics [20–22]. In some cases, injections of local anaesthetics and steroids may bring instant relief [20]. In this scenario, the respiratory muscles may also become rigid, which may be responsible for hypopnea, breathlessness and anxiety.

In the late stages of Parkinson's disease patients obtain response fluctuations to dopaminergic treatment. They fluctuate between "on" and "off". Sudden rigidity can occur at any moment. Injections of apomorphine (a dopamine agonist) can help these patients within minutes [23]. Although dose reduction is needed frequently for patients with Parkinson's disease (see later), abrupt discontinuation of the dopaminergic drugs should be avoided at any time. Discontinuation of dopamine agonists may result in

an acute Dopamine Agonist Withdrawal Syndrome characterized by troublesome anxiety, panic attacks, depression, dysphoria and insomnia [24, 25]. This condition can be prevented by slow dose reduction.

Delirium and psychosis

Patients with delirium do not suffer a deficiency of dopaminergic drugs. They are also not rigid and the "cogwheel phenomenon" is usually absent. Instead, the non-motor related symptoms may be in the foreground. In the later stages of the disease levodopa and dopamine agonists are responsible for several psychiatric complications, including hallucinations and psychosis [26]. These symptoms are often triggered by an infection (for example aspiration pneumonia or urinary tract infection). Also, the excessive fixation on the motor-related symptoms and overdoses of the dopaminergic drugs may be the culprit. Delirium and psychosis when treated with classical antipsychotics, because of their anti-dopaminergic effects may further complicate the picture. Also, pain treatment with morphine may induce delirium and psychosis. If opioid dose reduction is impossible, treatment with atypical antipsychotics like clozapine or quetiapine is indicated [27].

Treatments strategies for Parkinson's disease

The treatment strategy in case of a lack of dopamine in the brain is either to provide a precursor for dopamine synthesis (levodopa) or to activate directly dopaminergic receptors (dopaminergic agonists like ropinirole or rotigotine) or slow the metabolism of existing dopamine (entacapone or rasagiline). Combinations of these drugs are frequently used. In the course of the disease, the patient is usually responding initially to the treatment with the levodopa, which is seen as a diagnosis of Parkinson's disease. However. In the course of the disease, because of further degeneration of dopaminergic neurons, levodopa acts shorter and the patient experiences symptoms at intervals. Slow-release formulations help a bit but do not solve this problem. The patients need to take drugs more often and some of them start to experience adverse effects at the peak-plasma level of the drugs. These drug-induced adverse effects may be dyskinesias (strange movements and motor fluctuations) [28].

Although the motor-related symptoms respond as a rule to levodopa, the non-motor symptoms, like delirium or psychosis may become worse. The managing physician should make a trade-off by looking at what is the most troublesome symptom for the patient. The dose of levodopa should not be increased further and if possible, decreased. Usually, improvement of delirium and psychosis can be obtained with clozapine or quetiapine, even at the cost of deterioration of motor function and rigidity.

Alternative methods of administering anti-Parkinsonian medication

When the patient cannot swallow tablets or capsules, but still can take fluids, the physician can prescribe a dispersible levodopa formulation. The fluids can be thickened before consumption and applied with a spoon. The conversion rate from slow-release to dispersible formulations can be settled as 1:1. If the patient chalks with the spoon administration one can consider using a nasogastric tube. The introduction of a new nasogastric tube can be very stressful for dying patients. Also, this can be maintained only for a short time. Enteral food can interfere with the absorption of the drug in the gut. The levodopa should be administered 30 minutes before or two hours after the enteral food.

An elegant method for a dying patient is to administer dopamine agonist rotigotine in a transdermal patch. This drug, however, may cause unacceptable sedation. This may be often desirable, but occasionally it may impede patients' communication with the family. The patches come as 2, 4, 6 and 8 mg/24 hours. They need to be renewed every day and the maximal dose is 16 mg/24 hours. The equivalent dose is calculated by multiplying the levodopa dose $\times$ 0.033 [29]. Never cut the patch but use the (lower) approximation. It takes time before the drug will work, so you may end up with a dying patient who will not benefit from the drug yet as he/she will die before the effect will be established. When the patient used previously a combination of levodopa, carbidopa and entacapone (Stalevo®) calculate the rotigotine dose by multiplying the levodopa dose by 0.043 [29]. The dose of previously used ropinirole is multiplied by 0.66 and pramipexole by 3.3 [29]. If the patient is agitated and hallucinates the reduction of the calculated dose of rotigotine is indicated. However, when the patient is rigid and receives a much too low dose of levodopa, the dose of rotigotine may be increased in comparison to the dose of previously used dopaminergic drugs.

Another useful and cheap drug is apomorphine, which is a potent dopamine agonist [23]. The effects begin after 10–20 minutes and last for 100 minutes. Therapeutic doses vary between 2–6 mg every 8 hours and are frequently used to smooth the ON-OFF periods. But the drug can also be administered continuously by an SC pump. Approximately 20% of patients will experience nausea, which is easily treatable with domperidone [30].

Table 3. Drugs to avoid in patients with Parkinson's disease, modified from [8]

Avoid	Consider instead
Antiemetics	
Prochlorperazine	Domperidone
Chlorpromazine	Ondansetron (not to be used with apomorphine)
Metoclopramide	Cyclizine
Cinnarizine	
Nabilone	
Hyoscine hydrobromide	
Antipsychotics	
Amisulpride	Lorazepam and diazepam
Chlorpromazine	Sertraline
Fluphenazine	Quetiapine
Haloperidol	Mirtazapine

Drugs to avoid in patients with Parkinson's Disease (Table 3)

The drugs in the left-hand column may worsen the symptoms of Parkinson's disease and increase the risk of the neuroleptic malignant-like syndrome because they block dopamine receptors. The drugs in the right-hand column are safer alternatives. When there is a need for an antipsychotic drug, one should choose drugs with a minimum of extrapyramidal adverse effects; quetiapine. Sedation can be best achieved by an antihistamine preparation; for example, promethazine or meclizine.

Palliative sedation

It is not infrequently that dying patients with Parkinson's disease are agitated and need to be sedated to avoid damaging themselves and their surroundings. Classical sedation with midazolam may be insufficient and drugs with strong antihistamine effects (promethazine or meclizine) may be added. Also, the addition of low doses of levomepromazine may help. Insomnia can be best treated with sedating tricyclic antidepressant amitriptyline. Occasionally propofol may be used to obtain sedation although Parkinson's disease patients may be more sensitive to this drug than the general population of the same age [31].

Conclusions

Patients with advanced Parkinson's disease are a special challenge to palliative care units and hospices. Not infrequently these units should seek contact by telephone with neurologists. Some patients may die peacefully without much intervention. Few will suffer a shortage of dopaminergic effects and will need substitution till the end (either orally, trans-dermally or SC). A different and much more common appearance is troublesome delirium and psychosis which needs to be treated with slow levodopa dose reduction and careful antipsychotic treatment and, when necessary, sedation. Pain can be problematic and needs a careful assessment and specific treatment. It should be noted that in Poland Parkinson's disease is not put on the list of National Health Found that allows qualified patients for specialist palliative care, although some patients with Parkinson's disease can be qualified for specialist palliative care only on the ground of another diagnosis, e.g., pressure sores.

Declaration of conflict of interests

The authors declares that there is no conflict of interest.

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