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## More than a Century of Apomorphine: The New Faces of an Old Therapy in Parkinson's Disease

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Set of decoupage crafts made by Parkinson's patients from Chulalongkorn Centre of Excellence for Parkinson's Disease & Related Disorders in Thailand.

**Supplement:**

# More than a Century of Apomorphine: The New Faces of an Old Therapy in Parkinson's Disease

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Editorial

# Foreword

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Apomorphine has a long and chequered history in medical therapeutics. It was synthesised from opium (morphine) in the nineteenth century and first used to treat behavioural vices in domesticated animals before entering clinical practice as an emetic, sedative and treatment for erectile impotence. Related aporphine alkaloids are found in many plants including the tubers of some water lily species but there is no known natural source of apomorphine.

The Greek suffix apo meaning away from or distant from, has not prevented apomorphine being associated with the narcotic properties of its parent compound. Despite substantial evidence to the contrary up until 2010 apomorphine was classed as a Schedule 2 drug in California, defined by the United States Controlled Substances Act as a medicine with a high potential for abuse that leads to severe psychological or physical dependence.

More than twenty-five years after it was reintroduced into the British Pharmacopoeia as an efficacious treatment for advanced Parkinson's disease it still remains unavailable to many patients especially in the Americas. It is hard to imagine a similar appalling state of affairs occurring in other areas of medicine such as AIDS or cancer. I would go as far to say it is a global scandal that implicates neurologists and governments even more than the pharmaceutical industry.

The fact that the most effective route of administration for long-term treatment in Parkinson's disease continues to be by subcutaneous injection has certainly been a factor slowing its dissemination but it is far safer and less invasive than its competitors, deep brain stimulation of the subthalamic nucleus or the insertion of a gastro-jejunostomy for enteral dopa administration.

The fact that the drug is more than one hundred and fifty years old ('a mature product' without patent) and can be manufactured cheaply has so far proved to be a regrettable if understandable disincentive to Pharma. What to me is much more surprising is that so little work has been done to develop more powerful orally active aporphines.

Apomorphine is the prototype dopamine agonist and has been extensively used by pharmacologists and neurochemists to study the dopamine pathways of the animal brain. It more closely resembles L-DOPA than any of the currently available orally active dopamine agonists such as ropinirole, pramipexole and rotigotine. It is also the only known dopaminergic agent that has pharmacological effects quantitatively and qualitatively comparable to L-DOPA. At low doses it stimulates the dopamine autoreceptor and may act as a 'dopamine stabiliser' making it of potential interest as a therapy for chorea, schizophrenia and stimulant and opioid dependence.

The Editors are to be congratulated in putting together a supplement that I hope will herald a new era of enlightenment in the therapeutics of Parkinson's disease. Continuous waking day administration of apomorphine by ambulatory mini-pump offers the possibility of transforming the lives of thousands more patients with Parkinson's disease by minimising some of the late complications of treatment such as off period immobility, dyskinesias and impulse control disorders. I hope that it will also stimulate a new 'golden age' of aporphine research that will lead to potent long acting orally active 'apomorphine-like' drugs and novel modes of administration.

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# Unmet needs in Parkinson's disease: New horizons in a changing landscape

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ABSTRACT

The success of levodopa and other classes of drugs have meant that most people with Parkinson's disease enjoy a good quality of life for many years. However, despite the availability of several drugs and formulations that can be used as monotherapy and in combination, there are a number of disease features that the current therapies are unable to address. The disease continues to progress despite treatment, patients suffer from a myriad of motor and non-motor symptoms, and a neuroprotective therapy is urgently required. To move forward with medical and surgical management, it is important to consider new insights that recent research offers and in this review we examine how a better understanding of the disease pathology and progression might improve and enrich our daily clinical practice. It is also timely to consider the service provision changes that will increasingly be needed to effectively manage the needs of the aging population.



## 1. Introduction

Parkinson's disease (PD) is among the most common neurodegenerative disorders, the prevalence of which increases with advancing age. With today's rapidly ageing society it is predicted that the PD patient population will at least double by 2030 [1], and the associated increase in medical costs will be considerable [2]. The success of levodopa and other drug classes has meant that most patients can enjoy a good quality of life for many years [3,4]. However, despite the availability of several drugs and formulations that can be used as monotherapy and in combination, there are a number of disease features that the current therapies are unable to address.

Key medical unmet needs in PD include the need for better animal models replicating the parkinsonian process, slowing of disease progression/neuroprotection, improved biomarkers (imaging, genetic, clinical or other modality), improved 24-h control of motor fluctuations in moderate to advanced disease and more effective treatment of non-motor symptoms (NMS). Nocturnal symptoms as well as early morning fluctuations (motor and NMS) remain neglected [5]. To move forward with medical management, it is important to consider new insights that recent research offers and in this review we examine how a better understanding of the disease pathology and progression might inform our daily clinical practice.

## 2. Research challenge

### 2.1. Animal models of disease pathology

As past research focused on dopaminergic replacement therapy for motor symptoms, the traditional dopamine lesion models (i.e. the 6-hydroxydopamine rat model and MPTP-treated monkey models) formed an important basis for drug development. Indeed, these models were generally helpful in predicting symptomatic motor responses to dopaminergic therapy [6]. However, these have been of limited value in predicting the results of potential neuroprotective therapies, and this is fundamentally because they do not reflect the true complex etiopathogenesis of PD, neither do they

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show progression or Lewy body formation [7]. Additional preclinical models have been developed and these are summarized in Table 1. However, no current preclinical model is able to adequately mirror the tremendous complexity of PD itself.

Indeed, there have been significant advances in understanding the pathophysiology of PD over the past decades and it is now better understood that the disease follows a defined clinical pattern, with a range of NMS defining the pre-motor phase [8]. In the prodromal stage, the most common NMS manifestations are olfactory impairment and raid eye movement behavior disorder while other features such as constipation, somnolence, apathy, fatigue may also be present [9]. The development of many of these symptoms is consistent with the Braak pathology staging in which Lewy bodies first develop in the dorsal motor nucleus of the vagus nerve, the olfactory bulb, enteric nervous system and the submandibular gland, and then later spread to the substantia nigra, areas of the midbrain and basal forebrain, and finally reach areas of the neocortex [10]. Indeed, recent research has implicated the vagus nerve and the gut-brain axis as a potential generator of the pathological process in PD [11]. Added to this complexity, many cellular mechanisms such as protein degradation, oxidative stress, mitochondrial defects, proteolytic stress, neuroinflammation, an impaired ubiquitin protesomal system and autophagy have been suggested to play a role in PD [12]. None of the currently used models of disease, and certainly none of the toxin-induced lesion models, reliably reflect this complex neuropathology – representing a key unmet scientific need in PD [13].

### 2.2. Biomarkers of disease progression

New MDS diagnostic criteria for PD have moved away from an approach wholly based on motor symptoms to a combination of central core motor and non-motor features [14]. In this respect, clinical, genetic and imaging biomarkers are emerging as strong predictors of diagnosis and progression – although much work still needs to be done to exactly define the specificity and sensitivity of such tests [15]. The availability of a biomarker battery or package would enable accurate and early diagnosis based on objective evidence allowing for improved individualized therapy as well as for monitoring progression. Indeed, a good biomarker or biomarkers could be used to confirm diagnosis, assess disease progression, and even identify individuals who are in the prodromal stages of the disease [16–18].

Biomarkers can be categorized as '*trait*' (biomarkers which are stable over time), '*state*' (biomarkers which change with disease progression or treatment), and '*pharmacodynamic*' (sometimes referred to as mechanism of action markers). Several potential biomarkers have been pursued, ranging from neuroimaging to possible markers in the blood [19], CSF [20], and even the colon [21]. Specifically, molecular pathways related to α-synuclein, tau and β-amyloid peptides have received considerable attention. Such advances have been extensively reviewed elsewhere [22–25]. Although there are several promising candidates under evaluation, there is increasing consensus that no single candidate will provide full utility in isolation. A combinatorial approach, using a variety of approaches that take into account the multifactorial pathogenesis of PD will likely be necessary. Recent evidence also suggests that sleep and imaging measures, and to some extent NMS (assessed using appropriate NMS scales) may be more helpful than currently available CSF biomarkers and cognitive scales in quantifying progression [15].

### 2.3. Understanding PD phenotype and disease progression

It is well established that rates of disease progression in PD can be variable, and the motor subtype divisions of 'tremor dominant' versus 'postural instability/gait difficulty' (PIGD) parkinsonism have been broadly accepted and used in a variety of clinical studies [26–29]. Although definitions and methodologies have varied, studies generally have reported a worse prognosis in terms of disability, quality of life, disease progression and risk of dementia for patients with the PIGD phenotype as compared with the tremor dominant phenotype [30–33]. However, accumulating evidence is bringing the longitudinal stability of these phenotypes into question [34]. The Parkinson's Progression Markers Initiative (PPMI) has published one-year analysis data from patients who were untreated at the time of enrollment. The study found substantial instability of motor subtype; almost a third (29%) of patients originally classified as having PIGD dominant disease shifted to a tremor dominant phenotype during the first year of diagnosed disease [35]. This instability of motor phenotypes, and the recognition that PD subtypes are largely characterized by the severity of non-dopaminergic features has led to evaluation of non-motor symptoms as an alternative scheme.

According to the concept of NMS subtyping, the predominant NMS symptoms experienced will depend on which non-dopaminergic nuclei (in the limbic and brainstem areas) are most affected by the underlying disease neuropathology and spread. In one recent proposal, Sauerbier et al. suggested at least seven distinct NMS dominant subtypes of PD: Cognitive dominant, apathy dominant, depression/anxiety dominant, sleep dominant, pain dominant, fatigue dominant and autonomic dominant [8]. Within this scheme, sleep-dominant and autonomic-dominant subtypes are grouped into a 'brainstem phenotype,' where the underlying pathology is thought to involve the brainstem and olfactory route. Likewise, the cognitive dominant subtype is thought to reflect late-onset disease where cortical pathology predominates and the depression, fatigue and pain dominant subtypes are grouped under a 'limbic phenotype' where the olfactory route predominates [8]. The stability of non-motor subtypes has not been studied and it is probable that non-motor subtypes will also change throughout the disease course. Nevertheless, this form of NMS PD subtyping allows for future PD research to be more focused, by utilizing a subset of specific patients and working to improve their quality of life.

## 3. Treatment challenges

### 3.1. Neuroprotection

The prime unmet clinical need in PD is a 'neuroprotective' and/or 'disease-modifying' treatment that can halt or at least slow the progression of this progressive disease. While there have been many promising candidate agents in preclinical studies, no drug or treatment strategy has proven to be neuroprotective or disease-modifying in PD. Some of the key barriers to development of such an agent have already been described above. The lack of a robust model (or models) of disease with a prolonged prodromal period, severely impairs our ability to screen and test new products. Without validated biomarkers of disease, it is virtually impossible to prove an effect on the underlying disease progression. Recent experience with the rasagiline ADAGIO trial [36] showed us that it can be very hard to interpret clinical data, no matter how sophisticated the trial design is [37,38], and the availability of a biomarker is now considered a pre-requisite for the development of new disease-modifying treatment strategies for PD [39,40]. Moreover, since patients already have undergone significant neurodegeneration before they develop overt motor symptoms, treatment at diagnosis may already be too late for a neuroprotective agent. The only way would be to accurately identify pre-motor patients, and this would require a reliable biomarker [41].

**Table 1**
Examples of current preclinical models for Parkinson's disease.

- Pharmacologic models
  - Reserpine treated rodents
  - Haloperidol treated rodents
- Neurotoxin and dopamine depletion based
  - MPTP lesioned monkeys
  - MPTP treated mice
  - 6-OHDA lesioned rats (full and partial lesions)
- Pesticide-induced models
  - Rotenone rodent model
  - Paraquat and Maneb models
- Proteasomal inhibitor models
- Glial activation models
- Synuclein deposition based
  - Transgenics
  - Viral vectors
  - Prion like propagation based
- Genetic model system based
  - PINK1
  - Parkin
  - DJ1
  - LRRK2
- Induced pluripotent cells
- Minipig models

Moreover, it is only possible to demonstrate that drug slows the rate of progression, when one has an understanding of the benchmark rate. Finally, given the heterogeneity of disease, it is entirely likely that not all medications will be suitable for all patients and an understanding of disease types will be essential.

### 3.2. Management of motor complications

In the absence of a neuroprotective agent, we must rely on the effective management of symptoms (motor and non-motor). At present, levodopa remains unchallenged as the most efficacious and best tolerated antiparkinsonian drug, albeit one that is often limited by the development of response fluctuations and dyskinesia [42,43]. Motor fluctuations are almost invariably associated with often disabling non motor fluctuations [44]. Patient surveys consistently highlight the negative impact that being 'OFF' has on the patient [45,46], and other studies show the significant impact of motor fluctuations on patient quality of life [3,47]. In particular, the early morning OFF state is associated with significant and distressing NMS as shown in a recent multicenter survey [48] and management of this common problem remains a key unmet need. Recent studies using apomorphine injections for first dose of the day or for dose failures in PD are therefore timely [49].

We now better understand that the dose and pulsatile pharmacokinetics of levodopa are closely associated with the development of motor complications [50–52] and, together with the development of a broad armamentarium of adjunctive therapies (i.e. dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine), we are now better equipped to design better treatment strategies for our patients with motor fluctuations. However, it is also clear that, despite all these advances, current standards of therapy do not completely abolish motor fluctuations. This is one area where a greater understanding of the full impact of disease – beyond the central nervous system – may help. For example, widespread involvement of the GI system is common in PD, with alpha synuclein and Lewy bodies demonstrated throughout the enteric nervous system, including within myenteric neurons [53] (Table 2). Indeed, it is now estimated that >70% PD patients have GI disorders, including gastric dysmotility (gastroparesis) and bacterial overgrowth [54]. Very importantly, these GI problems can occur early on in the course of PD, and should no longer be considered a feature of advanced disease [54,55]. Since levodopa and many other orally administered PD drugs are absorbed in small intestine, it is thought that these problems might be a key contributor to motor fluctuations in some patients [54]. If the drug is not absorbed, it cannot be expected to exert its therapeutic action.

The relevance of drug absorption cannot be underestimated, and has led to a reappraisal of how we view OFF episodes. Whereas, we once very much focused on 'end-of-dose wearing-off', we now increasingly consider the time taken to ON, which is related to drug absorption and has been reported to be more than twice the duration of wearing-off [56]. Nocturnal hypokinesia and early morning off is often the longest OFF period in the daily treatment cycle [5,57], and delays to ON time and dose failures have been reported to account for >60% of daily OFF time [58]. As such, this provides a rationale for using non-oral therapies such as apomorphine injections or infusion which do not rely on GI absorption to manage motor fluctuations in patients where oral treatments do not provide sufficient control. Significant advances in continuous non-oral levodopa delivery are also being made at an ever increasing rate [59].

### 3.3. Management of non-motor complications

As discussed above, NMS are now considered a key component of PD that are explained by the widespread pathology of the disease, and which may represent a clinical biomarker of its premotor phase [60]. The burden of non-motor symptoms can define a patient's health-related quality of life [61], and is a major contributor to increased healthcare costs [62]. However, clinicians often regard the management of NMS as being secondary to motor symptom control. This may, in part, be because clinicians do not feel as able to deal with NMS as they do with motor symptoms. Although some evidence supports the efficacy of certain treatments for depression, dementia, psychosis, constipation, orthostatic hypotension and sialorrhea, there is insufficient evidence for efficacious treatments for other important non-motor symptoms that certainly contribute to poor quality of life, such as neurogenic bladder disturbance, erectile dysfunction, fatigue, insomnia, apathy, anxiety and excessive daytime sleepiness [60,63]. The emergence of recent controlled trials concentrated on key non-motor issues such as Parkinson associated pain [64] or sleep [65] is highly encouraging. Nevertheless, the broad spectrum of NMS in PD clearly highlight the need for developing non-dopaminergic therapies that target the non-dopaminergic degeneration in PD.

It is also important to note that some NMS are dopa responsive. Levodopa response fluctuations are not limited to motor symptoms, and most patients with motor fluctuations also experience NMS fluctuations (NMS which worsen in OFF episodes) [66]. Recently, the EuroInf study clearly demonstrated that improvements in dopaminergic responsive NMS (with levodopa and apomorphine infusion) lead to robust improvements in quality of life [67].

**Table 2**
GI abnormalities prevalent in PD which may hamper oral drug absorption.

- Dysphagia
- Drooling
- Gastritis/H Pyori related
- Peptic ulcer/H Pylori
- Delayed Gastric emptying
- Small intestinal bacterial overgrowth (SIBO)
- Intestinal microbiota alteration

### 3.4. Multidisciplinary service provision

To manage the complex needs of people with PD, it is increasingly accepted that a multidisciplinary team (MDT) approach should be developed to provide professional care in all motor and non-motor aspects of PD throughout the course of the disease. Healthcare providers are tasked not only to care for the patients but also to offer assistance to their caregivers who play a vital role along the illness trajectory. The MDT approach uses experts in PD from different health care professions as needed. Members can include a neurologist, a specialist Parkinson's nurse, a speech and language therapist, a physiotherapist, a social worker, a psychiatrist, an occupational therapist, a sexologist, and a dietician [68,69]. There are different models of multidisciplinary teams: inpatient facility, community rehabilitation facility, and synchronized multidisciplinary treatment in the community.

However, despite this understanding, national and international surveys constantly identify problems with service implementation [70–72]. One way to tackle this is to provide good evidence to payers and service providers that the approach provides opportunities for efficiencies. From the nursing perspective, there is ample evidence that Parkinson's nurses, improve patients sense of well-being, save money and improve care [73,74]. Parkinson's nurses can provide a range invaluable services, from nurse prescribing, to support of infusion therapies (levodopa and apomorphine), timely referral to other services, not to mention patient and caregiver education and emotional support [69]. From the perspective of the allied therapy services, one of the main barriers has been to demonstrate consistent efficacy and cost benefits [75]. While most physiotherapy trials have shown short-term benefits, most of the observed differences between treatments have been small and the studies have not been of high quality [76]. Nevertheless, systematic reviews have found that physiotherapy interventions such as balance training combined with muscle strengthening, range of movement and walking training exercise, are effective in improving balance in patients with Parkinson's disease and more effective than balance exercises alone [77]. Complementary physical therapies such as dancing, hydrotherapy and robotic gait training also appear to be of therapeutic benefit, increasing mobility and quality of life in some people living with PD [78].

In terms of randomized controlled trials, the evidence base is relatively small. Sturkenboom et al. conducted a randomized controlled trial to evaluate the efficacy of occupational therapy for PD. In this study, home-based, individualized occupational therapy led to an improvement in self-perceived performance in daily activities in PD patients vs. control therapy [79]. More recently, Monticone et al. reported a randomized controlled trial that demonstrated a 25-point difference in MDS-UPDRS scores as well as quality of life in favor of inpatient multidisciplinary rehabilitation versus nursing care plus 'standard' physiotherapy (both groups received the same duration of PT intervention) [80]. The question remains which types of physical and occupational therapies provide the most benefit, and how the cost of these interventions balance against the costs of hospitalization and institutionalization. This area of research deserves urgent attention.

### 3.5. Nursing home and end of life/palliative

In the final stages of PD, it is now vital to consider that our patients are now living longer with their disease and co-morbidities. A growing body of evidence highlights a high burden of difficult-to-manage and highly debilitating non-motor symptoms (e.g. constipation, loss of bladder control, swallowing difficulties, drooling, breathlessness, sleep problems and pain) [81,82], significant caregiver distress [83,84], and a high utilization of medical services especially in the last year of life [85]. At this stage, many patients move into nursing homes for their care, where the majority of patients require support in performing activities of daily living [86]. However, neurologists and PD nurses often lose track of these patients and continuity of medical care can be difficult for these patients to access. In the US, one study of large Medicare patients found that only a third (33%) of nursing home residents with PD had outpatient neurologist care [85]. In a qualitative study conducted in the Netherlands, patients reported a similar lack of access, as well as a lack of emotional support and insufficient staff knowledge on PD-related issues (e.g. motor fluctuations and the need for adherence to medication timing) [87].

The lack of understanding of PD-related issues is also of key concern when considering perioperative periods. People with advanced PD often have a wide range of comorbidities and surgery (particularly urological, ophthalmological and orthopedic procedures) is common. Retrospective database studies have shown that compared with age-matched controls, PD patients undergoing surgery have longer hospital stays, more perioperative complications and higher in-hospital mortality [88–90]. This is because, when hospitalized, patients with PD face some unique challenges related to medication management, mental status changes, infections, and emergence of psychiatric symptoms, and there is a lack of awareness of simple solutions such as parenteral administration of dopaminergic medication during long surgeries [91]. It is therefore very important to recognize problems that may arise upon hospitalization of a patient with PD and provide education to health care professionals involved in the inpatient care of patients with PD.

In the very end stages, the complexity of patient needs may require specialist palliative care involvement that aims to deliver physical, psychological, emotional and spiritual care for patients and their caregivers. However, current medical systems have yet to adequately respond to this need through the provision of palliative care services to both PD patients and to affected families [92, 93]. For example, most people prefer to receive end-of-life care in familiar surroundings rather than in hospital, and hospitals are rarely set up to provide such services. Nevertheless, an international survey of 11 countries found that a substantial proportion (up to 75% in some countries) of PD deaths occurred in the hospital setting [94]. A key barrier to the development of palliative care pathways is the lack of evidence-based knowledge on how to build a service that integrates neurological and palliative care [95, 96]. Uncertainty about the timing of palliative care means that often it is not considered until a patient reaches crisis point, despite the recognized need for early planning due to increased prevalence of dementia [97]. More work also is needed to prevent inappropriate hospital transfers near death – for example by providing training and education regarding the needs of people living with very advanced PD.

## 4. Summary and conclusions

In recent years, there has been tremendous progress in our understanding of the underlying pathology of PD, together with an increasing recognition that PD is more than a motor disorder caused by dopamine degeneration. However, as might be expected, there has been a time lag in drug development with few novel therapies coming to market in recent years [98, 99]. For PD research to move forward, we need to consider the impact of the numerous recent insights on the development of new drugs and tailored strategies. For many years, our focus has been on developing new oral medications, but it is increasingly apparent that problems with the GI system appear early in PD and can affect how oral medications are absorbed. This supports the recent surge in interest in

non-oral therapies which bypass the GI system.

It also is timely to consider the projected increases in PD prevalence. Service provision plans for our aging population should consider how a multidisciplinary team can increase efficiencies, and treatment plans should consider the full patient journey – from early diagnosis through to end of life care.

## Conflict of interest

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# Apomorphine and levodopa in Parkinson's disease: Two revolutionary drugs from the 1950's

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ABSTRACT

This article reviews the history of apomorphine and levodopa, which were both discovered in the 1950's and have revolutionized treatment paradigms of Parkinson's disease. Although the discovery of levodopa is a prime example of successful translation of basic neuroscience into clinical routine, the history of apomorphine was based on less solid evidence.

Despite this, both drugs are, more than 6 decades after the first clinical experiments, still the two most efficacious medications to treat patients with Parkinson's disease. New and promising delivery strategies for both levodopa and apomorphine are currently under investigation to further improve clinical responses.



## 1. Introduction

After more than 50 years of clinical use levodopa still remains the gold-standard of symptomatic efficacy in the treatment of Parkinson's disease (PD) [1]. None of the later drugs developed to treat the motor symptoms of PD has shown equivalent effects on the Unified Parkinson Disease Rating Scale or other outcome measures in comparative clinical trials and most, if not all, PD patients eventually require levodopa. The only exception to this is the dopamine agonist apomorphine, which matches levodopa in terms of the magnitude of effect on the cardinal motor features. It is fascinating to note that both drugs were first used in PD patients in a revolutionary period of PD drug discovery in the 1950's – in the case of apomorphine even before the role of striatal dopamine depletion in PD had become apparent.

## 2. The history of apomorphine

Apomorphine can be traced back to ancient civilizations, like that of the Maya who used extracts of the bulbs and roots of the water lily species (Nymphaea ampla, Nymphaea caerulea) containing apomorphine for religious rites more than 2000 years BC - likely because of its aphrodisiac and hallucinogenic properties [2].

The conscious medical use of apomorphine, however, only began thousands of years later after Matthiessen and Wright had noted in 1869 that a new compound was created when morphine was dehydrated with hydrochloric acid and called this new substance apomorphine [3]. Soon after this discovery the strong emetic properties of apomorphine were recognized and Thumas speculated in 1891 that emesis was induced by stimulation of the vomiting centre on the floor of the IV ventricle [4]. Apomorphine was then given as an emetic to remove foreign bodies from the esophagus or to treat poisoning [5].

## 3. Apomorphine and movement disorders

The different central nervous system effects of apomorphine began to unfold in the late 19th century when several authors noticed the sedative and hypnotic effects of apomorphine, when used in lower non-emetic doses. In 1891 Gee found that apomorphine could trigger stereotypies in dogs, rodents and other animals who are incapable of vomiting [4] and at the end of the 19th century apomorphine became a useful drug for a variety of psychiatric disorders such as delirium tremens in alcohol addiction, schizophrenia, mania, depression and sleeplessness [3]. During the trials in alcohol dependence, another interesting observation was made: spontaneous erections were reported in 30–55% of individuals [6] which eventually led to a temporary market introduction of Uprima as a therapy for erectile dysfunction in 2001 [7].

The potential effects of apomorphine on motor behavior was also noted already in the 19th century with studies by Harnack,

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**Table 1**
Table adapted from Tolosa et al. [11].

| | |
|---|---|
| 1884 | Apomorphine first suggested for treatment of parkinsonism |
| 1951 | Apomorphine injections cause marked improvement in PD patients |
| 1960 | Striatal dopamine deficiency in PD patients described |
| 1961 | Levodopa first tried for parkinsonism |
| 1965 | Apomorphine noted to be structurally similar to dopamine |
| 1967 | Oral levodopa's effectiveness demonstrated in patients with parkinsonism |
| 1970 | Similarities between apomorphine and L-dopa |
| 1972 | Beneficial effects of apomorphine for PD patients rediscovered |

who performed the first detailed pharmacological experiments of apomorphine in mammals and frogs in 1874 and concluded that apomorphine acts on different brain centres involving wilful behavior, respiratory and cardiovascular control [2]. In 1870, Pierce reported a reduction in chorea after injection of apomorphine in a patient with rheumatic fever and already in 1884 Weil in Lyon used apomorphine regularly in patients with chorea, jacksonian epilepsy and hiccoughs and even speculated that apomorphine may be useful for patients with PD [8] (Table 1).

Much later and based on previous research which showed that apomorphine improved rigidity in decerebrate animals, Lettvin, Amador and Schwab used subemetic doses of apomorphine (0.6–0.9 mg subcutaneously) in PD in 1951. They noticed mild and transient nausea followed by improvement in rigidity, muscle weakness and tremor lasting for up to three hours. Furthermore, patients also reported improvement in wellbeing [9]. Based on their observation they advised home injections of apomorphine with the assistance of a nurse or carer. However, Schwab et al. also recognized the limitations and the short lasting effects of subcutaneous apomorphine injections and tried to produce a prolonged release formulation as well as an oral formulation mixed in fruit juice. However, the effects after oral indigestion of apomorphine (initially with belladonna) were modest. Struppler and Uexkuell in Germany also noted the effects of subcutaneous apomorphine on PD tremor [10].

However, due to its peripheral adverse effects at higher doses (particularly nausea and orthostatic hypotension), apomorphine was hardly used in clinical practice to treat parkinsonism.

It took almost another 20 years until Cotzias treated 15 PD patients, who were either drug naïve or had already responded to levodopa, with subcutaneous apomorphine and observed potent antiparkinson effects [12]. However, given its short lasting effects, he developed oral apomorphine and used it in doses between 150 and 1440 mg. At higher doses, Cotzias observed azotemia and more adverse effects than levodopa, which hindered its use as a therapeutic agent [13]. N-propylnorapomorphine, another oral apomorphine analogue, was prescribed at lower doses to avoid nephrotoxicity, but was too weak to alleviate motor symptoms [14].

Cotzias noted that the clinical effects of apomorphine and levodopa were additive and that the adverse effects of apomorphine were less severe in those who had received levodopa therapy previously. Levodopa-induced nausea also was thought to be somehow counteracted by previous administration of apomorphine [4].

The report by Corsini et al., published in 1979, showed that domperidone, a peripheral dopamine antagonist that does not penetrate the blood-brain barrier, blocks the unwanted adverse effects of apomorphine, facilitated further research [15]. Lees and Stern finally demonstrated in the mid 1980s that administration of apomorphine, either as a bolus or given subcutaneously, significantly reduced OFF periods in PD by 50% using a novel mode of drug delivery via a battery powered portable pump system, which significantly increased the drug's half-life [16]. Over the following 30 years, multiple studies have consistently confirmed the short- and long-term efficacy of either subcutaneous intermittent injections or continuous infusions of apomorphine in reducing OFF time in PD patients with levodopa related motor fluctuations (for review see Ref. [17]). Continuous subcutaneous infusions of apomorphine also reduce pre-existing levodopa-induced dyskinesia, supporting the concept of continuous dopaminergic drug delivery as a means of treating and possibly preventing the development of drug-induced involuntary movements in PD [18]. A double-blind randomized placebo-controlled trial of subcutaneous apomorphine infusions in fluctuating PD has just been completed and results are expected to provide formal evidence of the efficacy of this approach that has already established itself by decades of successful clinical use (TOLEDO trial, ClinicalTrials.gov Identifier: NCT0200612).

Current problems with the use of apomorphine in clinical practice include adverse skin reactions with fibrotic nodules at the needle insertion points, as well as rare instances of eosinophilic panniculitis or Coombs positive haemolytic anaemia. Novel subcutaneous formulations with improved local tolerability as well as attempts to refine pump technology for subcutaneous infusions as well as efforts to develop effective alternative delivery routes are in clinical development.

## 4. The history of levodopa

Before becoming interested in apomorphine, Cotzias had reported in 1967 that high doses of the oral racemic mixture D,L-dopa (D,L-3,4-dihydroxyphenylalanine) significantly improved motor function in PD [19] and replicated the dramatic effects using pure levodopa in 1969 [20]. At that time Cotzias believed that the loss of neuromelanin in the substantia nigra was the main factor in the pathogenesis of PD.

D,L-dopa was, however, not a new substance. There is a debate whether George Barger and James Ewens from London [21], Mannich and Jacobsohn in Berlin [4], or the Polish expatriate, Funk, a year later in 1911 [22] synthesized levodopa for the first time. In the same year as Funk, the Italian pharmacologist, Torquato Torquati, isolated levodopa from the pods and seeds of the bean “Vicia faba”. Two years later, Guggenheim isolated levodopa following the method of Torquati [23] and administered 1 g of levodopa to rabbits and did not see any unusual adverse effects. However, when he ingested 2.5 g of levodopa in a self-experiment he experienced severe nausea and vomiting. In 1914, Fromherz and Hermanns from the University in Freiburg reported that “ *r-3-4-dioxyphenalanine, whether applied per os or subcutaneously, causes severe emesis in dogs which makes any metabolic experiment impossible … Rabbits, who do not possess a vomiting reflex, exhibited a state of excitement similar to that of apomorphine toxicity, which manifests itself in restless wandering and continuous gnawing*” [4].

The breakthrough of levodopa in PD was, however, facilitated by research with reserpine. Reserpine, an alkaloid extract from the root of the plant *Rauwolfia serpentina*, was first used to reduce sympathetic function and blood pressure. In 1945, Indian researchers already had noted that high doses of reserpine caused

parkinsonism and two years after its introduction to Western clinics, parkinsonism was reported in up to 60% of patients following administration of reserpine [4].

The Swedish pharmacologist, Carlsson, also was interested in the effects of reserpine on catecholamines and hypothesized that parkinsonism was caused not by release of dopamine but rather a depletion of the transmitter triggered by reserpine. He suggested that dopamine may play a major role in motor disorders and went on to show that 200 mg per kg intravenous levodopa could alleviate reserpine-induced parkinsonism in rabbits within 10–15 min [24]. These experiments were published in 1957 and later complemented by work from Rosgren and Bertler, two students of Carlsson, which demonstrated that dopamine concentration in dog brain was highest in the striatum [25]. Carlsson's seminal discoveries eventually earned him the Nobel Prize in Medicine and Physiology in 2000. His views were confirmed in 1959 by the Japanese neurologist, Sano, who extended the work of Carlsson, Rosgren and Bertler and for the first time investigated the distribution of dopamine and its precursor, dopa, in three human brains [26]. The breakthrough discovery, however, of selective depletion of striatal dopamine in PD brains came from the Viennese pharmacologist, Oleh Hornykiewicz. On advice from his mentor, Blaschko, Hornykiewicz had become interested in the work by Carlsson and also that of Frowein and Degwitz, who studied the effects of levodopa on reserpine-induced parkinsonism in psychiatric patients [4]. Together with Ehringer, he found severe striatal and nigral dopamine loss only in PD brains but not in the brains of patients with Huntington's disease or controls [27]. Based on these findings, Hornykiewicz convinced Birkmayer to administer 50 mg of levodopa intravenously to a PD patient "L.S." The dramatic improvement of parkinsonism was captured on film and was presented to the Viennese College of Physicians in 1961. Birkmayer published their observations on the effects of levodopa on parkinsonian akinesia in the same year [28]. The Japanese neurologist, Sano, had reported transient improvement of rigidity and tremor in a PD patient after 200 mg of intravenous D,L-dopa a year earlier, but because the effects lasted only for a few minutes he had concluded that "*Dopa had no practical therapeutic value*" [29].

Subsequent studies of the effects of levodopa on PD motor symptoms by groups in Germany, Sweden, Italy, Canada, USA and Finland yielded rather unspectacular results, including the first report with orally administered levodopa by McGeer and Zeldowicz in 1964 [30]. In short, levodopa did not have its breakthrough as a new treatment for PD for several years [31]. It was only after Cotzias' publication of the effects of large oral doses of racemic D,L-dopa in 1967 that the dramatic efficacy of levodopa in PD became widely appreciated. Cotzias later confessed that his successful trials with levodopa were due to his ignorance of the previous levodopa studies, since they may have dissuaded him from his own attempts [4].

Melvin Yahr, despite initially being skeptical, performed the first double-blind, placebo-controlled study, administering levodopa to 56 PD patients, 3 patients with postencephaltic parkinsonism and 1 patient with progressive supranuclear gaze palsy. He reported significant improvement in parkinsonism in the majority of the patients and, similarly to Cotzias, also observed adverse effects such as dyskinesia and gastrointestinal problems [32]. With the development of the peripheral dopa decarboxylase inhibitors, carbidopa and benserazide, a 4-fold increase in the bio-availability of levodopa was achieved and, at the same time, peripheral adverse effects such as nausea or hypotension were markedly attenuated. This reduction in dopaminergic adverse effects even prompted the choice of a brand name - Sinemet ("sine emesis") - which was the first levodopa/carbidopa combination pill marketed in the USA [33].

## 5. Conclusions

Despite their limitations levodopa, the gold standard therapy for all stages of PD [34], and apomorphine are both still the most potent drugs to alleviate parkinsonism. No other currently available drug can match their efficacy. Ironically, both are salutary examples of drugs that were initially met with considerable scepticism regarding their efficacy and usefulness. While levodopa was used on the basis of emerging understanding of the role of striatal dopamine depletion in the parkinsonian brain and its introduction into therapy can rightly be considered a textbook example of the concept of translational medicine, apomorphine 's history is marked by a mixture of serendipity and the persistence of extraordinary researchers. Although more than 60 years have elapsed since the early days of apomorphine and levodopa, both drugs continue to be at the forefront of clinical research, with several phase 2 and phase 3 programs under way to improve their safety and efficacy via alternative formulations and innovative delivery routes, including novel extended release formulations as well as transdermal and intrapulmonary application of levodopa and sublingual film strips of apomorphine [34–37].

Although drug development programs in the pharmaceutical industry now follow the dogma of target validation through understanding the mode of action of a drug and demonstration of 'target engagement', the history of levodopa and apomorphine in particular reminds us that the alternative path, where chance meets an observant and prepared mind, can lead to the discovery of highly efficacious agents.

## Conflict of interest

AD received travel grants from Medtronic to attend the Movement Disorders Congress in 2017. Otherwise none within the past 12 months. WP reports personal fees from AbbVie, Allergan, AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Britannia, GlaxoSmithKline, Ipsen, Lundbeck, Medtronic, MSD, Merck-Serono, Merz Pharmaceuticals, Novartis, Orion Pharma, Teva, UCB and Zambon (consultancy and lecture fees in relation to clinical drug development programmes for PD). Royalties: Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press.

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# Apomorphine - pharmacological properties and clinical trials in Parkinson's disease

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ABSTRACT

Apomorphine is often considered an archetypal dopamine agonist used in the treatment of Parkinson's disease (PD). However, it can be clearly differentiated from most other commonly used dopamine agonists on the basis of its pharmacology and on its unique clinical profile. Like levodopa and dopamine, apomorphine acts as a potent, direct and broad spectrum dopamine agonist activating all dopamine receptor subtypes. It also has affinity for serotonin receptors, and α-adrenergic receptors. Apomorphine is usually titrated to a dose that provides an equivalent antiparkinsonian response to that provided by levodopa, and its subcutaneous delivery allows a rapid onset of action, usually within 7–10 min. The mode of apomorphine delivery impacts on its clinical profile so as to provide two very different approaches to therapy in PD. When administered as an acute subcutaneous injection, it induces reliable and rapid relief from OFF periods underscoring its utility as a rescue medication. When given as a subcutaneous infusion, it significantly improves overall daily OFF time and there is also evidence to suggest that, in those patients who replace most or all of their oral drugs with apomorphine infusion, dyskinesia may also improve. In this paper, we review the rich pharmacology of apomorphine and review its efficacy in PD based on data from clinical trials.



## 1. Introduction

Apomorphine as a natural product has been used over many centuries as an emetic, sedative, anticonvulsant, antipsychotic, as well as for alcohol dependence and for sexual dysfunction [1]. It was first suggested as a treatment of Parkinson's disease (PD) by Weil in 1844, but its utility in the treatment of parkinsonian disorders was not reported until the work of Schwab in 1951. This was based on the ability of apomorphine to relieve rigidity in experimental animals [2] and it was not until 1967, that its strong structural similarity to dopamine was noted [1,3,4]. However, the widespread use of apomorphine in PD was impeded by its poor oral bioavailability and initial side-effect profile. The peripheral adverse effects of apomorphine, notably nausea, reflect its dopamine agonist activity and became easier to manage with the introduction of peripherally acting dopamine antagonists such as domperidone in Europe and trimethobenzamide in the USA [5].

Even so, the use of apomorphine to treat PD remained limited as levodopa had become established as the cornerstone of PD treatment, and other dopamine agonists that could be orally administered were introduced. The focus on using levodopa and dopamine agonists as monotherapy or in combination took attention away from apomorphine, and its clinical use was limited to a small group of neurologists who championed its use by acute subcutaneous injection and continuous infusion for many years, most notably Andrew Lees in London, UK [6–9]. They were proved to be right, and with the demonstration of the limitations of oral levodopa and dopamine agonist therapy in the later stages of PD, there is increasing recognition of the value of the use of apomorphine in the treatment of sudden OFF periods and 'wearing-off' where oral medication does not provide adequate clinical efficacy. Yet, even today, apomorphine is an underused drug in PD, mainly employed in specialist tertiary referral centers because its potent clinical effectiveness often is not fully appreciated by general neurologists

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[10–12]. Questions are frequently raised about the comparative efficacy of apomorphine compared with oral levodopa or dopamine agonist therapy and other therapies for treating advanced disease (levodopa infusion and deep brain stimulation [DBS]). There is also apprehension about employing a therapy that requires the use of delivery devices.

However, apomorphine can be clearly differentiated from most other commonly used dopamine agonists on the basis of its pharmacology and its unique clinical profile, and the objective of this short review is to emphasize that differentiation. The safety of apomorphine has been extensively reviewed by Bhidayasiri and colleagues elsewhere in this supplement [13] and so, will not be covered here.

### 1.1. Receptor pharmacology of apomorphine

Apomorphine is an aporphine derivative of the dibenzoquinoline class, which has a molecular structure that in simple terms looks like a 'rigid' form of dopamine (Fig. 1). This structural similarity gives apomorphine its dopaminergic activity and it is why it acts as a potent direct and broad spectrum dopamine agonist drug activating all dopamine D1-like (D1, D5) and D2-like (D2, D3, D4) receptors [14]. Its high potency and affinity for dopamine receptors together with its reliability and rapid onset of action after subcutaneous administration has led to apomorphine becoming a key 'tool' compound in countless laboratory investigations of experimental models of PD. In normal rodents, it induces stereotyped behavior in rats and climbing behavior in mice. It reverses motor deficits in reserpine or haloperidol treated rodents, 6-OHDA lesioned rats, and MPTP treated primates [15], all reflecting its central dopamine agonist actions.

The commonly held view is that apomorphine is the archetypal dopamine agonist, but this is not correct when looking at its wealth of actions on dopamine receptors and other receptor sites relevant to PD. In fact, apomorphine is a molecule with a diverse range of pharmacological effects (Table 1). Even when considering its interactions with dopamine receptors, it differs from oral dopamine agonists in common use. For example, whereas the actions of pramipexole and ropinirole are limited to D2-like receptors (D2 and D3), apomorphine interacts with both the D1 and D2 receptor classes and with all major subtypes (D1, D2, D3, D4, D5) [14–17], which may have important functional consequences as outlined below.

The restricted interaction of oral dopamine agonists with dopamine receptor subtypes is often cited as a key reason why compounds like ropinirole and pramipexole do not appear to have equivalent antiparkinsonian efficacy to levodopa as assessed in monotherapy studies [18]. Through its conversion to dopamine, levodopa acts at all types of dopamine receptor (as does the endogenous neurotransmitter) in the normal brain. In contrast, oral dopamine agonists have a restricted interaction with dopamine receptors, with less activation of D1 receptors, which has been cited as a reason why they produce less dyskinesia than levodopa. The D1 receptor (notably its trafficking and signaling pathways associated with the direct striatal output pathway) has been blamed for initiating dyskinesia [19,20], but in reality this has never been proven. In preclinical studies, the administration of D1 agonists does not lead to a greater degree of dyskinesia induction or expression than seen with D2 agonist drugs. Rather, there looks to be an advantage in stimulating D1 receptors as this is known to reverse motor deficits in animal models of PD and in humans [21,22]. D1 receptor activity also may be of benefit in treating a non-motor symptom of PD: There is an association between the D1 receptor activity and improvement in bladder hyperreflexia, which has been demonstrated in both experimental models of PD and in clinical studies [23,24]. Apomorphine, which also has D1 receptor activity, has been shown to improve bladder function in a biphasic manner in rodent studies [25], and this has been reflected in clinical investigations [26,27].

Dopamine receptors are located in many parts of the brain other than the basal ganglia. Areas include cortical and limbic regions and the actions of dopamine agonists at these sites are associated with some adverse effects of dopamine replacement therapy in PD including impulse control disorders (ICDs) and visual hallucinations. So, a broad dopamine-like action of apomorphine might be seen as a disadvantage. For example, it has been suggested that ICDs may be due to activity at D3 receptors in limbic regions [28]. Indeed, the relatively high proportions of patients with ICDs on pramipexole, ropinirole and rotigotine has been shown to be linearly correlated with their D3 receptor selectivity relative to D2 receptors [28]. Apomorphine has a lower D3:D2 ratio than pramipexole and ropinirole [17] and this may be of clinical relevance although it is currently unknown whether the incidence of ICDs is actually lower when administering apomorphine, compared with other dopamine agonists.

Replacement of dopamine through levodopa may not be the only reason why levodopa is so highly effective in PD. Some of the dopamine produced from levodopa is, in turn, converted to noradrenaline (which is also deficient in PD). In addition, dopamine derived from levodopa accumulates in serotonergic neurons and can displace 5-HT. In this respect, apomorphine also has a rich pharmacology in that it has affinity for serotonin receptors (5HT1A, 5HT2A, 5HT2B, and 5HT2C), and α-adrenergic receptors (α1B, α1D, α2A, α2B, and α2C) [14]. This is not the case for the most commonly used oral agonists, ropinirole and pramipexole, which have a generally more restricted pharmacological profile.

Almost all drugs show selectivity for one particular receptor that mediates their major pharmacological and clinical activity. However, very few are specific in their receptor interactions with the majority showing off target activities that are a potential cause of undesirable side effects. In the past, when an off target pharmacologic action occurred at therapeutic doses, a drug with multiple pharmacological actions was not considered multimodal for its rich pharmacology but rather a "dirty" drug. This was certainly the case for the ergot derivatives (bromocriptine, pergolide and cabergoline) which were all held to be highly effective drugs for the treatment of PD, but which largely went out of use due to the rare but serious occurrence of pulmonary fibrosis and cardiac fibrotic valvulopathies, which were attributed to their potent effects at 5-HT2B receptors [29,30]. It was a major reason why the non-ergots, such as ropinirole and pramipexole, were developed and why their activities were purposefully designed to be limited to dopamine receptors and only some dopamine receptor subtypes.

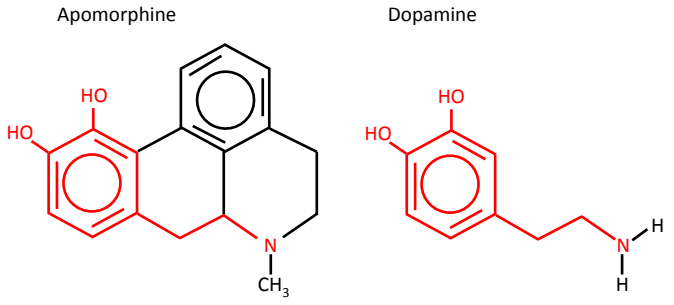


**Fig. 1.** Molecular structure of (a) apomorphine and (b) dopamine.
Red lines denote the common dopaminergic moiety.

**Table 1**
Receptor affinity (mean $pK_i$ values minus log $K_i$ values) of apomorphine, pramipexole and ropinirole at recombinant human monoaminergic receptors.

| | Receptor affinity (mean $pK_i$ values minus log $K_i$ values) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $D_1$ | $D_{2S}$ | $D_{2L}$ | $D_3$ | $D_4$ | $D_5$ | $\alpha_{1A}$ | $\alpha_{1B}$ | $\alpha_{1D}$ | $\alpha_{2A}$ | $\alpha_{2B}$ | $\alpha_{2C}$ | $5HT_{1A}$ | $5HT_{1B}$ | $5HT_{1D}$ | $5HT_{2A}$ | $5HT_{2B}$ | $5HT_{2C}$ |
| Apomorphine | 6.43 | 7.46 | 7.08 | 7.59 | 8.36 | 7.83 | 5.70 | 6.17 | 7.19 | 6.85 | 7.18 | 7.44 | 6.93 | 5.53 | 5.91 | 6.92 | 6.88 | 6.99 |
| Pramipexole | <5 | 6.02 | 5.77 | 7.98 | 6.89 | <5 | <5 | <5 | <5 | 5.77 | 6.20 | <5 | 6.16 | 5.08 | 5.78 | <5 | <5 | <5 |
| Ropinirole | <5 | 6.17 | 6.03 | 7.43 | 6.07 | <5 | <5 | <5 | <5 | 5.73 | 6.12 | 5.92 | 6.54 | <5 | 5.86 | <5 | 5.42 | <5 |

Data from Ref. [14]. Data are log values with higher numbers reflecting higher receptor affinity. For example, the difference between a mean $pK_i$ value of 7 and a mean value of 8 represents one order of magnitude.

However, in considering a multimodal pharmacological profile in a drug, it is the balance between the various pharmacological actions that becomes critical and the degree of interaction with individual receptors that dictates the therapeutic efficacy versus adverse effect profile. This is certainly true in the case of the rich pharmacology of apomorphine. For example, apomorphine also interacts with 5-HT2B receptors but it is about an order of magnitude less potent than the ergot derivatives (at least *in vitro*) [14] and analysis of the FDA adverse event database found no similar safety signal for apomorphine [31]. It has been suggested repeatedly that apomorphine may have a relatively low proclivity to induce visual hallucinations [32–34], and its activity at the 5-HT2 receptors has been proposed as a potential mechanism [33].

### 1.2. Apomorphine – pharmacokinetics, pharmacodynamics and dyskinesia induction

The polycyclic and tertiary amine structures not only confer apomorphine's dopamine-like properties, but also allow rapid transport across the blood-brain barrier [35]. This is a point of differentiation from levodopa which has to bind to a saturable, carrier-mediated transport system [36]. Apomorphine is very lipophilic and when given via the subcutaneous route equilibrates very rapidly between the central and peripheral compartments. Antiparkinsonian efficacy has been shown to be directly linked to the concentration of apomorphine in the cerebrospinal fluid [35]. The oral bioavailability of apomorphine is very poor, due to almost complete first pass hepatic metabolism [37], so all further reference to the pharmacokinetics of apomorphine in this paper refers to its subcutaneous delivery as used clinically in the treatment of PD.

After subcutaneous administration, apomorphine follows a two-compartment pharmacokinetic model with an absorption, distribution, and terminal half-life of 5.8, 4.8, and approximately 30 min, respectively [38]. Early studies showed that drug absorption, volume of distribution, plasma clearance, and half-lives were similar for subcutaneous injection, subcutaneous infusion, and intravenous infusion [38,39]. The peak plasma concentration is achieved after 10–20 min, and the maximal concentration is achieved in the cerebrospinal fluid after 30 min [39]. However, there is high inter-individual variability in Tmax, Cmax, and plasma concentrations, with some studies reporting five-to ten-fold differences in Cmax and AUC [39]. The peripheral pharmacokinetics show linearity with dose across a range of doses (2–8 mg) that cover those most commonly used in PD [40,41].

The pharmacokinetic profile of apomorphine described applies equally to intermittent acute injection and continuous infusion of the drug. However, the mode of delivery has the impact of providing two very different approaches to therapy in PD. The use of intermittent administration through an injection pen as rescue therapy reflects its rapid and reliable efficacy. The speed of onset after intermittent injection (within 7–10 min [42–44]) makes it a practical solution for patients with delayed or unpredictable responses to levodopa who need to reach an ON state quickly and reliably. Apomorphine's short elimination half-life, which parallels its clinical response, lasting some 45–60 min, usually does not interfere with daily oral drug treatment but rather bridges the gaps in motor function in those with frequent or unexpected OFF periods.

In preclinical models of PD, repeated acute 'pulsatile' dosing of dopamine agonists, including apomorphine, has been associated with the priming of basal ganglia for dyskinesia development [45,46] but importantly this occurs to a lesser degree than seen with levodopa [46]. Dyskinesia induction in accordance with the concept of continuous dopaminergic stimulation (CDS) is said to be due to the short half-life of dopaminergic drugs, and apomorphine does have a short half-life. However, this correlation is not correct and comparison in MPTP-treated primates of dopamine agonists of differing half-lives shows that, as a class, dopamine agonists inherently produce less dyskinesia than levodopa [47–50]. So, the risk of priming for dyskinesia with intermittent apomorphine will probably be lower than for pulsatile administration of levodopa. Clinically, all patients using intermittent administration of apomorphine as a rescue therapy will have had levodopa with or without oral dopamine agonist treatment for several years, and will therefore already be primed for dyskinesia expression. As a consequence, it is certainly true that some patients with pre-existing levodopa-induced dyskinesia will exhibit an increase in the duration and intensity of involuntary movements with intermittent apomorphine injection.

In contrast to the ideas encompassed by CDS, there is far more cogent evidence that it is continuous drug delivery (CDD) in the treatment of PD that conveys the lowest risk of induction of dyskinesia irrespective of whether this involves dopamine agonist or levodopa therapy. The evidence for the benefits of providing CDD based on preclinical investigations and clinical experience, has been extensively reviewed elsewhere [51–53]. A CDD based approach provides a more physiological stimulation of striatal dopamine receptors, avoiding the onset of motor complications. The use of continuous subcutaneous apomorphine infusions meets the aims of providing continuous delivery of a drug to the basal ganglia [54,55]. Perhaps not surprisingly, the continuous subcutaneous delivery of apomorphine (using implanted polymer rods) to MPTP treated primates avoids the induction of dyskinesia seen with intermittent injections of the drug [56]. Clinically, this is borne out by the reduction in dyskinesia intensity/duration seen in patients initially receiving oral dopaminergic therapy who are subsequently treated with a continuous subcutaneous apomorphine infusion [57–59].

### 1.3. Apomorphine efficacy from clinical trials

The efficacy of apomorphine in reducing OFF time is well established through clinical use over several decades. Like levodopa, apomorphine was first brought into clinical use when the requirements for drug registration and clinical trial design were less rigorous than what is expected today. Apomorphine was already in clinical use (in Europe) long before the results of any randomized, controlled trials (RCTs) of intermittent apomorphine

use in PD were published. Even today, there is a lack of RCT data for apomorphine infusion, and despite the good evidence from open-label studies, this puts apomorphine infusion at a perceived evidence disadvantage versus DBS and continuous levodopa infusion when it is reviewed under the auspices of 'evidence-based medicine', which is mainly based on data from RCTs.

Other routes of administration of apomorphine are currently in development, but so far none have come into clinical use. Table 2 summarizes the main data from double-blind studies evaluating intermittent apomorphine injection for the treatment of PD. The main bulk of RCT data for intermittent injections were collected when required for US registration. Taken together, the studies provide a very strong evidence-base for the efficacy of intermittent injections providing a rapid relief from sudden OFF episodes.

### 1.4. US pivotal trials for intermittent apomorphine injections

The first US registration trial (AP0202) was a prospective, randomized, double-blind, placebo-controlled, parallel-group trial that involved two phases and enrolled apomorphine-naïve patients with advanced PD who experienced a minimum of 2 h of daily OFF time despite optimized oral drug therapy [42]. Phase 1 of this study was conducted on an inpatient basis to determine the therapeutic dose of apomorphine and to demonstrate that apomorphine produces a 'levodopa-like' effect. On the first day of Phase 1, the patients' motor response to their usual morning dose of levodopa/carbidopa was evaluated under open (unblinded) conditions using the Unified Parkinson Disease Rating Scale (UPDRS) Part III. On Day 2, patients started in the practically defined OFF state (PD therapy was withheld overnight), and the UPDRS motor response to increasing doses of apomorphine or placebo was assessed. Apomorphine was initiated at 2 mg and titrated upwards in 2 mg increments to an optimal dose that produced a reduction in UPDRS motor score of at least 90% of that previously recorded with levodopa; the maximum dose allowed was 10 mg. Assessments were performed before dosing and when a clinical ON state occurred (or within 60 min of levodopa or 15–20 min of study drug administration).

This study was one of the first to demonstrate the need for individual titration to so-called 'optimal' doses. While the mean 'optimal' dose of apomorphine was 5.4 mg, 3 of the 20 apomorphine treated subjects had a levodopa-like response at just 2 mg and 7 of 20 subjects had an optimal dose of 4 mg. At optimal dosing levels there was a mean 62% reduction in UPDRS Part III scores with apomorphine at 20 min' post-dose, which was similar to the mean 65% improvement observed 60 min after administration of levodopa/carbidopa (thus demonstrating the symptomatic efficacy of the agonist). The placebo effect was negligible, as indicated by the titration to the maximum dose allowed (in 8 of the 9 placebo subjects; one discontinued due to lack of effect) and the mean 1% reduction in UPDRS Part III scores [42].

Phase 2 was a 4-week outpatient phase, where the aim was to evaluate the efficacy of apomorphine in reducing OFF time versus placebo. Based on patient home diaries, treatment with apomorphine was reported to abort almost all (95%) of OFF episodes versus just 23% with placebo ($p < 0.001$). On average, subjects used study drug to treat 2.5 OFF episodes per day. At baseline, mean daily OFF time was 5.9 h. In the apomorphine group, the reduction in median OFF duration was 2.0 h. Again, the placebo effect was negligible (median change of 0 h per day) [42].

The next two US registration studies were designed to evaluate the continued efficacy of intermittent rescue therapy in patients already treated with this drug. APO301 used a crossover design where patients received either their usual dose of apomorphine or the equivalent volume of placebo on one day and the other treatment the next day. The primary outcome measure was the change in UPDRS Part III scores from pre-dose to 20 min after treatment and the study showed superiority of apomorphine versus placebo

**Table 2**
Data from double-blind studies evaluating intermittent apomorphine injection for the treatment of PD.

| | Study design | Injection dose | Efficacy findings |
|---|---|---|---|
| Cotzias et al., 1970 | • Double-blind, placebo controlled, crossover study<br>• 6 of 15 patients had PD | 0.25–2 mg | • 5 of 6 PD patients showed a rapid improvement (≥20% improvement) in neurologic examination |
| Van Laar et al., 1993 | • Randomized, double-blind, placebo-controlled, cross-over study<br>• N = 5 | Mean 2.7 mg | • Significant positive effect of apomorphine vs. placebo assessed using the CPDS ($p = 0.001$).<br>• Latency of onset: 7.3 min<br>•Duration of response: 96 min |
| Ostergaard et al., 1995 | • Double blind, placebo controlled study<br>• N = 22 | Mean 3.4 mg | • Mean daily duration of OFF periods reduced by 58% vs. placebo ($p < 0.001$)<br>• Severity of OFF was also significantly reduced |
| Merello et al., 1997 | • Double-blind, active comparator (dispersible levodopa/benserazide) crossover study<br>• N = 12 | 3 mg | • Mean ± SE latency to effect (assessed using a modified WRS) was 8.08 ± 3.0 with apomorphine vs 26.8 ± 12.7 with dispersible levodopa<br>• Mean ± SE duration of effect was 56.6 ± 13.6 with apomorphine vs 97.0 ± 35.8 with dispersible levodopa |
| Dewey et al., 2001 | • Randomized, double-blind, placebo-controlled, 2-phase study<br>• N = 29 | Mean 5.4 mg | • Phase 1: Mean UPDRS motor scores reduced by 62% with apomorphine vs. 1% with placebo.<br>• Phase 2: Apomorphine aborted 95% of 'off' state events vs. 23% with placebo |
| Pfeiffer et al., 2007 | • Randomized, double-blind, placebo-controlled, 4-arm study<br>• N = 62 | Typically effective dose (TED) or TED +2 mg | • Significantly greater improvement in mean UPDRS motor scores was seen with pooled apomorphine groups versus pooled placebo groups 20 min after administration (−24.2 vs. −7.4; $p < 0.0001$)<br>• The difference was also significant at 10 min ($p < 0.0001$)<br>•Significant difference vs placebo in WSST at 7.5 min ($p = 0.02$) |
| Pahwa et al., 2007 | • Dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose<br>• N = 56 | 4-10 mg | • Significant improvement in UPDRS motor scores with 4 mg apomorphine vs placebo at 20 min ($p = 0.0002$), 40 min ($p < 0.0001$) and 90 min ($p = 0.0229$).<br>• Significant dose-response was seen at 20 min ($p < 0.0001$), 40 min ($p < 0.0001$) and 90 min ($p = 0.0049$) post-dose. |
| Stacy and Silver 2008 | • Double-blind, placebo-controlled, crossover study<br>• N = 17 | Mean 3.91 mg | • Significant reduction in UPDRS motor scores at 20 min by a mean of 20.0 points with apomorphine vs 3.0 with placebo ($P < 0.0001$) |

CPDS: Columbia Parkinson's Disease Score; TED: typically effective dose; UPDRS Unified Parkinson's Disease Rating Scale; WRS: Webster Rating Score; WSST Webster Step Seconds Test.

at 10, 20 and 60 min post-dosing [60].

APO302 was a placebo-controlled single-visit study designed to determine whether patients receiving long-term apomorphine experienced attenuation of effectiveness requiring higher dosing to reverse OFF episodes [43]. All 62 patients were required to be taking at least 2 doses of apomorphine rescue therapy per day for the management of OFF periods despite optimized oral treatment with levodopa and at least one dopamine agonist. Patients had been taking apomorphine for an average of 14.5 months prior to study entry at apomorphine doses of 1.5–10 mg and were randomized (1:1:1:1) to: apomorphine at the patient's typically effective dose (TED), apomorphine at the TED plus 2 mg, placebo at an equivalent volume to the apomorphine TED, or placebo at an equivalent volume to the apomorphine TED plus 2 mg. The study found no significant advantage in terms of change in UPDRS motor scores with the addition of 2 mg to the usual apomorphine dose, suggesting that the patients' usual dose of apomorphine was optimal and that no tachyphylaxis had occurred. Such data is in line with the long-term clinical experience that once a patient is on a dose that relieves OFF episodes, the dose does not normally change [61–64]. This study assessed a practically highly relevant aspect, the latency to the onset of the clinical effect of apomorphine. The Webster step-seconds test (a test designed to assess gait in PD by measuring the number of steps and time taken on a standardized test) was used as outcome measure and was modified to allow completion of each assessment within 60 s. Apomorphine was shown to significantly improve patient mobility versus placebo as early as 7.5 min after injection and that this benefit persisted for at least 40 min [43].

### 1.5. Open-label studies of intermittent apomorphine injections

Several open-label, naturalistic studies, usually conducted in single expert centers, provided early evidence for the efficacy of intermittent apomorphine injections (doses ranged between 2 and 5 mg) in providing rapid 'rescue' from OFF episodes. When apomorphine was given 'as needed', the mean reduction in daily OFF time was in the range of 2.6–4.0 h. Symptom relief was consistently rapid (typically 10 min) and the effects were reported to last at least an hour [7,62–67]. Of note, several of these studies reported that patients felt they had better control of their symptoms and felt reassured about their ability to come out of OFF episodes [68].

AP0303 was an open-label dose-escalation study with placebo-controlled crossover evaluation of the 4 mg dose in 56 fluctuating PD patients [41]. Patients were evaluated on separate days for response to single increasing doses of apomorphine. The acute response to oral anti-PD medication and APO dose escalation (2–10 mg) was evaluated under unblinded conditions. As in the other studies, apomorphine significantly improved motor function as assessed by changes in UPDRS motor scores; the mean reduction in UPDRS Part III scores from pre-dose to 20 min was significantly greater after 4 mg versus placebo (−11.2 vs. −2.8; $p = 0.0002$; primary endpoint) and significant differences were maintained at 40 min (−13.5 vs.−3.0; $p < 0.0001$) and 90 min (−5.1 vs. −1.6; $p = 0.0229$). All doses of apomorphine showed a numerically greater effect on UPDRS motor scores at 20 and 40 min post-dosing (comparisons versus levodopa were not statistically tested), in keeping with levodopa-like efficacy at even the 2 mg dose. Of importance, this study also demonstrated dose-related improvements in motor function although *post-hoc* analysis of patients who reached the 8 and 10 mg dose levels did not show significant incremental improvement over the 6 mg dose. In those patients who could tolerate the 6 mg dose, the magnitude of motor benefit and duration of response was longer than with the lower doses. In practice, this suggests that once a patient achieves his or her optimal therapeutic dose, there is no additional benefit to increasing the dose further.

More recently, the results of the AM-IMPAKT open-label trial have been reported [69]. The AM-IMPAKT trial was a phase IV multicenter study designed to assess the effect of apomorphine injections in patients with prolonged morning akinesia due to delayed or unreliable onset of benefit after their first morning dose of levodopa. Morning akinesia was defined as a minimum subject-reported time-to-ON of 45 min or more following their usual first daily levodopa dose for a minimum of 3 days during a one-week baseline diary period. Of note, patients in this open-label study experienced a very prolonged time-to-ON with their morning levodopa dose – averaging an hour – and the frequency of levodopa 'dose failures' was high. The reduction in time-to-ON (mean reduction of 37.14 min) and improvements in response reliability (46% dose failure rate with the morning dose of levodopa vs. 7% with apomorphine) was clinically relevant, as evidenced by the significant improvements in patient-driven scales of quality of life and global impression.

### 1.6. Evidence for efficacy of continuous apomorphine infusion

There have been a large number of open, uncontrolled studies evaluating the efficacy of apomorphine infusion as monotherapy or as adjunct to levodopa in patients with advanced fluctuating PD [7,12,37,57,61–64,70–84]. The methodologies of these studies have varied considerably, both in size, duration of follow-up and the outcomes collected. Most of the studies have assessed infusion during waking hours only; some have included patients on 24 h 'round the clock' administration. Collectively, these studies have shown that subcutaneous infusion is consistently successful in reducing OFF time and improving motor function (Table 3). The majority of studies reported very substantial reductions in daily OFF time, and a recent pooled analysis of 552 patients in these studies reported a mean OFF time reduction of 59% [85].

Although there is remarkable consistency of the effect of apomorphine infusion on motor fluctuations, the different studies have reported variable results on dyskinesia. As shown in Table 3, several studies reported a marked attenuation of dyskinesia intensity of up to 65% [74]. However, a number of other studies reported no significant change in dyskinesia severity [81,83]. Most studies that reported effects on dyskinesia found a reduction in the duration/frequency of dyskinesia with apomorphine infusion [63,73,76,79], whereas others did not observe this benefit [83,84]. The discrepancy may, in part, be explained by reported observations that dyskinesia reduction is more marked in those patients who are able to substantially reduce or discontinue their oral dopaminergic therapy. This is in line with the current concept of dyskinesia formation, where both the dose and mode of dopaminergic delivery (continuous versus pulsatile) is important [86].

Antidyskinetic effects have been reported with apomorphine infusion after only a short time period [74]. Other studies report maximum dyskinesia improvement after several months [57,80]. This has led to the suggestion that the reduction may be due to the gradual reversal of plastic changes in the basal ganglia circuitry involved in dyskinesia formation, with a resulting resetting of dyskinesia thresholds [57,80]. In patients with existing dyskinesia, several expert sites now aim to achieve 'apomorphine monotherapy', if well tolerated. This has been defined as waking day infusion with complete discontinuation of oral drugs during the day (oral therapies are used only early in the morning and at night). This is supported by a greater reduction of dyskinesia severity when patients are treated with apomorphine monotherapy compared to those given infusion as add-on therapy observed in

**Table 3**
Data from open-label studies evaluating continuous apomorphine infusion for the treatment of PD.

| Study/year | N | Follow up period (months) | Daily time in OFF (%) | Dyskinesia intensity (%) |
|---|---|---|---|---|
| Stibe et al., 1988 | 11 | 8 | - 62 | |
| Chaudhuri et al., 1988 | 7 | 11 | - 85 | - 45 |
| Frankel et al., 1990 | 25 | 22 | - 55 | |
| Pollak et al., 1990 | 9 | 10 | - 67 | - 20 |
| Hughes et al., 1993 | 22 | 36 | - 59 | |
| Stocchi et al., 1993 | 10 | 12 | - 58 | - 40 |
| Poewe et al., 1993 | 18 | 20 | - 58 | |
| Kreczy-Kleedorfer et al., 1993 | 14 | 26 | - 77 | |
| Gancher et al., 1995 | 6 | 3 | - 58 | |
| Colzi et al., 1998 | 19 | 35 | - 72 | - 65 |
| Pietz et al., 1998 | 25 | 44 | - 50 | - 14 |
| Wenning et al., 1999 | 16 | 57 | - 55 | |
| Stocchi et al., 2001 | 30 | 60 | | |
| Kanovsky et al., 2002 | 12 | 24 | - 80 | |
| Manson et al., 2002 | 64 | 34 | - 49 | - 64 |
| Di Rosa et al., 2003 | 12 | 12 | - 40 | - 37 |
| Morgante et al., 2004 | 12 | 24 | - 60 | - 48 |
| Tyne et al., 2004 | 80 | 25 | | |
| Katzenschlager et al., 2005 | 12 | 6 | - 38 | - 44 |
| De Gaspari et al., 2006 | 13 | 12 | - 51 | No change |
| Garcia-Ruiz et al., 2008 | 82 | 20 | - 80 | - 32 |
| Martinez-Martin et al., 2011 | 17 | 6 | - 65 | |
| Antonini et al., 2011 | 12 | 60 | - 49 | No change |
| Drapier et al., 2012 | 23 | 12 | - 36 | |

Table reproduced with permission from Ref. [85].

uncontrolled studies [57,80]. However, from a clinical point of view, it is important to note that monotherapy is not an absolute target and often is not tolerated by the patients. In many cases, "near-monotherapy", or any meaningful reduction in oral medication, may be sufficient to improve dyskinesia.

Discrepancies in the effect on dyskinesia may also be due to the different clinical patterns of dyskinesia. It has been suggested peak-dose dyskinesia may improve with infusion but patients with biphasic dyskinesia are more prone to develop severe continuous dyskinesia during ON time [62]. In this respect, it is pertinent to note that the study with the largest reported effect on dyskinesia reduction specifically excluded patients with biphasic dyskinesia [74].

### *1.7. How does apomorphine compare with oral levodopa?*

As discussed earlier, apomorphine is the only commercially available dopamine agonist that, like levodopa, stimulates both D1-like and D2-like receptors. This receptor profile is often cited as the reason why apomorphine, but not the other dopamine agonists, is able to induce a similar magnitude of response to that achieved with levodopa. In an early study, Kempster et al. compared the magnitude and pattern of motor responses to single doses of subcutaneous apomorphine and oral levodopa in 14 PD patients – with the conclusion that, although apomorphine produced much shorter motor responses than levodopa, the quality of response to the two drugs was virtually indistinguishable [87]. In many of the clinical studies described above, the optimal dose of apomorphine was defined as that providing at least 90% of the UPDRS response seen with levodopa (i.e. equivalent efficacy). In the US AP0202 study, a 'levodopa-like' effect was further supported by the similar increases in hand tapping speed (increase from 236 taps in the OFF state to 374 taps in the ON state with apomorphine and 356 taps in the ON state with levodopa) and reductions in the Webster steps seconds test (reduction from 431 s in the OFF state to 128 s in the ON state with apomorphine and 124 s in the ON state with levodopa) [42].

It is also important to note that apomorphine acts more rapidly than levodopa, even when levodopa is administered in its dispersible formulation. Among all antiparkinsonian drugs available, apomorphine induces the most rapid relief from OFF symptoms in PD patients with motor fluctuations. In one of the few head-to-head studies, Merello et al. [44] compared the latency and effect duration of apomorphine injections with that of dispersible levodopa/benserazide. In this small but randomized and blinded study, 12 patients with severely fluctuating symptoms were given a single dose of apomorphine or dispersible levodopa on 2 consecutive days. The study showed that the response amplitude was similar with both drugs (using modified Webster scores), but that apomorphine was faster in reversing OFF periods (effect latency of 8.08 min with apomorphine vs. 26.8 min with dispersible levodopa) [44].

How does apomorphine infusion compare with other therapies for advanced PD?

The three main options for advanced PD currently are apomorphine infusion, levodopa infusion and DBS. There are no randomized studies directly comparing these. There is high level evidence of efficacy available from randomized studies for DBS and for intrajejunal levodopa infusion. In contrast, apomorphine infusion has been investigated in numerous uncontrolled studies but robust data from a randomized study are not yet available. To address this, a multicenter, randomized, placebo-controlled 12-week trial has been undertaken in Europe and the results are expected soon (TOLEDO study NCT02006121).

In terms of head-to-head trials, in a small, non-randomized study, patients on a waiting list for DBS of the subthalamic nucleus (STN-DBS) used apomorphine (n = 7) and were compared to those who underwent DBS (n = 9) [88]. The study showed a comparable and significant improvement versus baseline in motor scores for both groups. The study was designed to compare effects of treatment on neuropsychological tests performance, and showed that treatment with STN-DBS, but not apomorphine, was associated with a moderate decline in phonetic verbal fluency and speed of naming at 6 months and a significant worsening in the Stroop test at 1 year. Overall, the study showed no significant effect of apomorphine infusion on dyskinesia severity. We do not have precise information about dose reductions or types of dyskinesia in these patients [88].

These results were replicated in another small (n = 12) and non-randomized 1-year study [80], which also reported significant reductions in OFF time with both apomorphine infusion (−51%) and STN-DBS (−76%), but found that only STN-DBS had a significant effect on dyskinesia. Again, STN-DBS, but not apomorphine infusion was associated with significant worsening in neuropsychological functioning (Neuropsychiatric Inventory). In this study, STN-DBS resulted in greater reductions in dopaminergic medications (from 980 to 374 mg/day vs 666 mg/day to 470 mg/day with apomorphine infusion) and it may be that the dose reduction was not sufficient to see a dyskinesia reduction.

More recently, the multicenter EuroInf study compared apomorphine infusion with intrajejunal levodopa infusion in larger groups of patients [27] but it is important to note that this is was also a non-randomized study. The study concluded that both treatments for advanced PD provide a robust improvement in motor symptoms (UPDRS motor score reductions of 43% and 45%, respectively) motor complications (UPDRS Part IV score reductions of 41% and 56%, respectively), and HRQoL (PDQ-8 summary index improvements of 34% and 30%, respectively).

Does apomorphine have any effect on non-motor symptoms?

The key focus of the Euroinf study was on non-motor symptoms [27]. Whereas the benefits on sleep dysfunction, gastrointestinal and genitourinary function were observed to be significantly better with levodopa infusion, apomorphine infusion showed a significantly greater benefit on mood and apathy symptoms, compared with levodopa infusion. Another prospective multicenter, uncontrolled study showed significant improvement in many non-motor symptoms including fatigue, motivation, anxiety, mood, anhedonia, attention deficit, sialorrhea, urinary dysfunction and hyperhidrosis [12]. Such benefits also have been confirmed by a recent systematic review of the efficacy of apomorphine in non-motor aspects of PD. This broad review included data from 24 studies (including case reports and open-label and comparative case-control studies). The authors concluded that *"although data on the effect of apomorphine on NMS in PD patients are limited there is a strong suggestion of a beneficial effect"* and called for the development of double-blind studies using non motor endpoints as primary outcome measures [89].

### *1.8. Apomorphine derivatives and other routes of apomorphine administration*

Many of the important barriers to apomorphine use (e.g. poor oral bioavailability and rapid metabolism) are related to its chemical structure. For this reason, many derivatives of apomorphine have been synthesized and examined for potential use as oral treatment in PD. Apomorphine derivatives may be esters, ethers, amides, mixed anhydrides, hemiacetals, glucuronates, sulfates or phosphonates, and there are currently existing patents on all of these derivatives. Molecular modifications at certain positions of R (-)-apomorphine have resulted in compounds with increased selectivity for the D2 receptor (higher potency at D2, lower at D1), or in being able to discriminate the high affinity and low affinity states of the D2 receptor, with correspondingly greater behavioral potency and duration of action with oral as well as systemic administration in animal models.

One of the best studied derivatives is N,n-propylnorapomorphine (NPA), which was shown to be 10–20 times more potent than apomorphine [89–92]. However, problems with tolerance [93] halted further development of this analog. Another novel derivative, R-(-)-11-*O*-valeryl-N,n-propylnoraporphine (11-OH-NPa valerate) has recently been tested in the MPTP marmoset model of PD [94]. In this model, oral administration of 11-OH-NPa valerate produced a rapid reversal of motor disability and, at effective dose levels, had a limited propensity to induce dyskinesia [94].

In terms of new routes of administration, a dry powder apomorphine formulation (VR040) has been developed for pulmonary inhalation and has been evaluated in three double-blind studies [94–97]. Despite significant clinical efficacy and very rapid absorption, development is currently not on-going. Other routes of administration have been proposed and have entered into early development, including intranasal [98] and transdermal delivery [99,100] – but these have not yet come to fruition.

The sublingual route of administration has, however, reached clinical development. APL-130277 is presented as a bilayer – with one layer containing apomorphine and the other layer containing a buffer to counteract the acidic nature of apomorphine. Results from a Phase 2a proof of concept study have been reported in abstract form, and sublingual treatment was reported to produce clinically meaningful motor improvement in MDS-UPDRS Part III scores. In this study, 15 of 19 patients were classified as responders, and all these patients were reported to have turned fully ON within 30 min of dosing (6 of 19 patients were fully ON within 15 min) [101].

## 2. Conclusions

PD is characterized by deficits in multiple neurotransmitters, so it makes sense that agents such as apomorphine, which have a rich pharmacology that underlies a multimodal action on several of these systems, will have beneficial effects beyond that of other agents with actions restricted to certain dopamine receptor subtypes. The pharmacology of apomorphine is distinct, and it should not be considered as 'just' a dopamine agonist. Apomorphine is the only drug currently available that provides an antiparkinsonian effect equal to that of levodopa. It is also has the fastest onset of action of all currently used antiparkinsonian drugs.

The mode of apomorphine delivery has important impact in providing two very different therapy approaches to PD. When administered as a subcutaneous injection, it induces reliable and quick relief from OFF periods and offers patients with severe motor fluctuations better control and more independence. Subcutaneous apomorphine infusion treatment via a pump system has been in use for several decades, and excellent improvements in OFF duration have consistently been reported. There is additional evidence suggesting that in those patients who replace most or all of their oral drugs with continuous apomorphine, dyskinesia often may improve as well. Although robust data from randomized trials are available for the other device-based treatments for advanced PD (DBS, levodopa/carbidopa enteral infusion), the vast majority of apomorphine infusion studies have been conducted in an uncontrolled fashion. The results of the first randomized, placebo-controlled multicenter trial investigating change in OFF time are expected shortly.

## Conflict of interest

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# The need for non-oral therapy in Parkinson's disease; a potential role for apomorphine

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Non-oral therapy

ABSTRACT

In the course of Parkinson's disease (PD), oral medication may lose its effectiveness due to several reasons, like dysphagia, impaired absorption from the gastro-intestinal tract and delayed emptying of the stomach. If these problems occur, a non-oral therapy should be considered. Examples of non-oral therapies are transdermal patches, (e.g. rotigotine) which may overcome motor and nonmotor night-time problems, and may serve as well to treat daytime response-fluctuations, if oral therapies fail to do so. Other options are injections with apomorphine to treat early morning dystonia and random off-periods during daytime, as well as continuously infused subcutaneous apomorphine for random fluctuations in PD patients. Low-dose apomorphine infusions also may be useful in the peri-operative phase, when PD patients may not be able to swallow oral medication. Finally, levodopa-carbidopa intestinal gel (LCIG) infusions or DBS have shown to be effective non-oral options to treat PD patients adequately, if they are not properly controlled by oral options.



## 1. The challenge of optimizing medication as Parkinson's disease progresses

Oral levodopa is recognized as the 'gold standard' medication for the control of motor symptoms in patients with Parkinson's disease (PD) and during initial treatment, it generally provides good control of motor symptoms with sustained clinical effects. However, with chronic treatment and disease progression, the duration of benefit after an oral dose of levodopa becomes progressively shorter [1]. Patients begin to experience fluctuations in motor function alternating between ON responses with a good anti-parkinsonian effect and OFF responses when levodopa does not adequately control symptoms before the next dose is taken. These motor fluctuations can include predictable end-of-dose 'wearing-OFF' phenomena, peripheral problems such as 'delayed ON' or 'no ON' (dose failure), and unpredictable 'ON–OFF' periods. A well-known example of predictable off-phenomena is early morning dystonia. Delayed ON and dose failures are known to be significant contributors to total OFF time in PD patients, to a greater degree than wearing OFF [2].

Early morning OFF (EMO) periods due to delayed onset of oral medication are a common problem in PD and can severely affect a patient's quality of life and interfere with their ability to undertake their usual morning routine [3]. An international, multicenter study, EUROPAR, found that EMO periods were reported by approximately 60% of PD patients, even in those already receiving optimized PD treatment [4], so it appears to be a significant problem.

Although PD generally is considered to be primarily a motor disorder, nonmotor symptoms (NMS) also occur in over 90% of patients across all stages of the disease [5,6]. The most frequent NMS include constipation, nocturia (sleep disorders), cognitive impairment, depression, insomnia and restless legs. As disease progresses, fluctuations also can be observed in NMS alongside the motor problems, for example in symptoms of pain, anxiety, depression and fatigue [1].

Increasing the dose of levodopa to try and control motor symptoms may provide some improvement but can also result in involuntary movements or painful dyskinesia which typically occur in association with high plasma concentrations of levodopa. Dyskinesia can interfere with walking and balance and cause social embarrassment [7].

Motor fluctuations present a major management challenge to clinicians, particularly as complications may appear early in the course of the disease: after 5 years of levodopa treatment, about

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50% of patients experience wearing OFF [8] and this figure rises to about 80% after 10 years [9]. It is, therefore, important that clinicians select appropriate PD medications that can manage symptoms effectively and maintain the patient's quality of life. A contributing factor to the problem of delayed ON of oral PD medication is gastrointestinal (GI) dysfunction, which is common in PD patients and can occur almost a decade or more before PD is clinically diagnosed [10–12].

## 2. Gastrointestinal dysfunction in PD

Accumulating evidence now suggests that PD is a multi-system disease which affects areas of the brain that are not directly involved in motor control [13–15]. Pathological characteristics of PD, including the abnormal α-synuclein expression, extend into the peripheral autonomic nervous system and involve the sympathetic ganglia, cardiac sympathetic efferents and the enteric nervous system (ENS).

The ONSET-PD study demonstrated the extensive range of NMS that can develop in early PD patients [16]. The study surveyed 109 newly-diagnosed, untreated PD patients and 107 controls, and found that 17 of a possible 31 NMS were more common in PD patients than in controls, and often preceded the onset of motor symptoms. In >50% of subjects with PD, NMS, including GI symptoms such as constipation and postprandial fullness, were frequently perceived more than 10 years before motor symptoms occurred. Population-based studies support these finding and have shown that constipation is associated with an increased risk of developing PD [17,18].

GI dysfunction is known to be one of the most common problems in PD patients with clinically-established disease. Symptoms include dysphagia and excessive salivation, delayed gastric emptying (gastroparesis), constipation, and anorectal dysfunction [10]. GI issues in PD patients may be related to α-synuclein pathology in the ENS and it has been hypothesized that the spread of α-synuclein pathology in PD in fact originates in the peripheral autonomic nervous system. As a result, recent studies have investigated the potential value of colonic biopsies as a possible diagnostic marker for early or 'pre-motor' PD [19].

## 3. The impact of GI dysfunction on patient outcomes and oral PD medication

GI problems not only have important clinical consequences, for example weight loss or drooling due to dysphagia, but also have a significant impact on patient wellbeing and quality of life [6]. Dysphagia is a common symptom in PD patients and may result in aspiration and a risk of developing pneumonia, as well as leading to adherence problems.

In addition, recent studies have confirmed a high prevalence of small intestinal bacterial overgrowth in PD patients and have demonstrated an association with poor motor function, longer daily OFF time and more episodes of delayed-ON and no-ON [20,21].

Importantly, GI issues, such as gastroparesis (delayed gastric emptying), which is known to affect 70–100% of PD patients [12], can reduce the effectiveness of oral levodopa by delaying its delivery to and absorption from the small intestine into the bloodstream [22,23]. This can result in the emergence of motor fluctuations due to insufficient plasma levels of levodopa, causing delayed ON or even dose failure [11,24].

A range of strategies has been employed to try and overcome the delay in clinical effect of oral levodopa and improve time to ON, but most show limited efficacy or do not turn the patient fully ON. Such strategies include modifying the oral levodopa dosing by giving higher doses, avoiding administering the dose within 30 min of a meal, reducing protein intake around the time of dosing, or taking the tablets with a carbonated beverage [25]. Some patients try using liquid or dispersible levodopa formulations, but inconsistent results have been reported with this approach [26,27]. Adjunctive medications such as monoamine oxidase B (MAO-B) inhibitors or catechol-*O*-methyl transferase (COMT) inhibitors can alleviate the severity of OFF periodsut do not reliably put the patient in an ON state [28]. Long-acting dopamine agonists given orally once-daily, or administered transdermally by means of a patch, are other options that have been shown to improve motor symptoms but again patients may still not be fully in the ON state [29].

It is clear that oral dosing in PD patients is not always reliable and this highlights the need for clinicians to consider non-oral routes of administration that can provide effective symptom control and are not affected by GI issues [26–29].

## 4. Options for non-oral PD medication

A range of second-line, non-oral therapies are available when motor complications no longer respond adequately to oral therapies and when standard therapies do not provide adequate symptom control. These comprise transdermal, subcutaneous, intrajejunal and surgical options. Selection of the most appropriate treatment option for each individual patient is key to the success of therapy and clinicians need to consider which option will best optimize the patient's quality of life and adequately control their motor symptoms, while taking the patient's own personal preference into account.

## 5. Transdermal therapies

### 5.1. Rotigotine patch

Rotigotine is a dopamine agonist with activity against a range of dopamine receptors, from D1–D5, and has been available in a transdermal patch formulation since 2000 for use as an adjunctive PD medication. The patch can be applied once daily to deliver CDS therapy and has been demonstrated in several clinical trials to provide effective control of motor symptoms, with a good safety profile and good tolerability, in both early and advanced PD patients [30–33].

The RECOVER study – a double-blind, randomized, placebo-controlled trial – confirmed the beneficial effects of the rotigotine patch on control of both motor function and nocturnal sleep disturbances, as measured by the PD sleep scale (PDSS), in PD patients with early-morning motor dysfunction [29].

The most common adverse events reported with the rotigotine patch are application site skin reactions and some neuropsychiatric complications.

### 5.2. Rivastigmine patch

Rivastigmine is a cholinergic agent that is a valuable therapy for the management of PD dementia (PDD) and is available in capsule or patch formulations. In a 24-week double-blind, placebo-controlled study by Burn et al. in over 500 PDD patients with and without visual hallucinations, the rivastigmine patch provided benefits on measures of cognitive function and activities of daily living [34]. However, the patch formulation provided markedly fewer GI adverse effects, compared to capsules, and therefore can be titrated to higher dose levels with improved efficacy [35, 36].

### 5.3. Subcutaneous apomorphine

Apomorphine is a dopamine agonist that selectively acts at

dopamine D1 and D2 receptors. Subcutaneous apomorphine is available in two formulations: apomorphine intermittent injection (pen) and apomorphine continuous infusion (administered by removable infusion pump without the requirement for surgery), which have different uses and are intended for different types of patients [37]. They provide flexibility for the clinician to select the most suitable option based on the patient's symptoms and individual circumstances. Subcutaneous apomorphine can be initiated during inpatient hospitalization or in a day hospital setting.

Adverse events with subcutaneous apomorphine formulations are generally mild and easy to manage in clinical practice and usually do not require discontinuation of therapy. The most commonly reported adverse events are injection site reactions and nausea, but nausea can generally be prevented with the initiation of anti-emetic therapy prior to initiation [38]. Accumulated evidence from clinical trials of long-term (>1 year) use of subcutaneous apomorphine shows it to be well-tolerated in most PD patients [38,39].

### 5.4. Intermittent apomorphine injection

Subcutaneous apomorphine injection has been an established PD medication for over 25 years and has been proven in a series of randomized, controlled clinical trials to provide rapid and reliable resolution of OFF periods in PD patients, as measured by a decrease in UPDRS motor scores [40–43]. It is suitable for PD patients who have started to experience motor complications and OFF periods despite taking standard oral therapy [43]. Apomorphine injection is an easy and practical way to help restore mobility and motor function in patients who experience episodes of delayed ON following a dose of oral medication, early-morning OFF periods, predictable or unpredictable OFF periods, or who have impaired levodopa absorption due to gastric emptying problems. It has a rapid onset of effect with improvements in motor function observed within 4–12 min in 95% of patients [44]. The duration of clinical effect ranges from approximately 40–90 min [44].

The AM IMPAKT study, a Phase IV, multicenter, open-label trial, assessed the effect of apomorphine injection as a non-oral treatment option in PD patients with prolonged morning akinesia due to delayed or unreliable onset of the clinical benefit of their first morning dose of levodopa. Patients recorded their time to ON in a diary following their usual morning oral levodopa dose (7-day baseline period) and then for 7-days using apomorphine injection instead of oral levodopa. AM-IMPAKT was able to show that apomorphine injection could significantly improve time to achieve an ON state in these patients compared with oral levodopa. On average, patients achieved an ON state 37 min faster with apomorphine injection and approximately 96% of patients experienced a rapid and robust clinical improvement in their time to ON [45]. Dose failures – defined as when the patient did not turn ON within 60 min – were common during the oral levodopa baseline period, with almost half of diary days recorded as dose failures. With apomorphine injection however, 93% of doses resulted in patients turning ON. These findings suggest that delayed ON and dose failure related to impaired GI delivery and/or intestinal absorption of oral levodopa can be easily and effectively improved with subcutaneous injection of apomorphine.

### 5.5. Continuous apomorphine infusion

In PD patients, consistent striatal dopamine levels depend on adequate peripheral levodopa levels. The short half-life of levodopa when given intermittently, coupled with GI absorption problems, can result in 'non-physiological' variations in plasma levels that then give rise to motor complications. Although apomorphine intermittent injection is a valuable adjunctive therapy manage motor complications for many patients, other options need to be considered in order to provide effective therapy if the patient considers that the injections are required too frequently to adequately control symptoms. Continuous dopaminergic stimulation (CDS) is a therapeutic option that mimics the physiological situation more closely to help minimize the motor complications that occur with oral or other forms of intermittent therapy [46–49].

Continuous apomorphine infusion is a CDS option that has proven efficacy for PD patients with motor fluctuations that are uncontrolled by conventional oral or transdermal medication and is well tolerated [37]. Patients do not need to have used the injection previously to be suitable candidates for the infusion.

A range of open-label clinical studies have demonstrated that apomorphine infusion significantly reduces OFF time in PD patients by up to 85% compared with baseline [37,43] and it can, on average, increase ON time by approximately 5.5 h per waking day [50]. These clinical benefits are maintained with long-term use and there is no development of tolerance to treatment or any requirement for an increase in dose [50,51]. Apomorphine infusion also has been demonstrated to significantly reduces dyskinesia that occurs during ON time by up to 85% compared with baseline [37,43,50] and to reduce the severity of any dyskinesia by up to 65% [37,43]. Studies have shown that treatment with apomorphine infusion allows reductions of up to 81% in oral levodopa doses compared with baseline [37,43].

Although considerable data on the efficacy and safety of apomorphine infusion have accumulated from open label trials and clinical practice, no double-blind trials have been completed to date. The ongoing TOLEDO study is the first multicenter, parallel-group, double-blind, placebo-controlled Phase III trial to evaluate the efficacy and safety of apomorphine infusion. The study includes 102 patients from 24 centers in 7 countries. Results of the initial 12-week, double-blind phase will be available in early 2017.

Overall, evidence suggests that apomorphine infusion can be considered as a therapeutic option in all PD patients who develop features of complicated disease, irrespective of age or disease duration. In addition, it is reversible should the patient wish to try another form of treatment.

### 5.6. Levodopa/carbidopa intestinal gel (LCIG; duodopa)

Another CDS option which has been available for over 10 years is administration of levodopa/carbidopa by infusion into the duodenum/jejunum (LCIG). This requires a percutaneous gastrojejunostomy procedure for the placement of the infusion tube, which is connected to a portable infusion pump.

In an overview of the efficacy and safety of LCIG, Nyholm et al. [52] reported that the large majority of published studies have demonstrated its effectiveness in relieving the symptoms of advanced PD and improving quality of life in comparison with conventional therapy. Olanow et al. undertook a 12-week, randomized, double-blind, double-dummy, double-titration trial of advanced PD patients with motor complications at 26 centers in Germany, New Zealand, and the USA [53]. From baseline to 12 weeks, mean OFF time decreased by 4.04 h for 35 patients treated with LCIG compared with a decrease of 2.14 h for 31 patients treated with immediate-release oral levodopa/carbidopa. Mean on-time without troublesome dyskinesia increased by 4.11 h in the LCIG group and 2.24 h in the oral levodopa/carbidopa.

In terms of tolerability, LCIG demonstrated good tolerability over 12 months in a phase III, open-label, single-arm, multicenter trial in advanced PD patients [54]. In an analysis of combined safety data from prospective clinical studies of LCIG, adverse events associated with the percutaneous gastrojejunostomy tube or

procedure were frequently reported [55]. These complications such as pain, local site infection, and tube detachment, were occasionally life threatening [54]. In the longer term, weight loss, vitamin B12 deficiency, and polyneuropathy have been reported [55]. Other types of adverse events were typical for levodopa treatment in this PD population and overall were associated with a low discontinuation rate.

### 5.7. Deep-brain stimulation

Deep-brain stimulation (DBS) is another device-aided PD therapy that has been available for around 20 years. It requires stereotactic brain surgery to implant electrodes into the brain, generally into the subthalamic nucleus, guided by magnetic resonance imaging. DBS has been shown to be a successful therapeutic option for PD patients who no longer respond satisfactorily to pharmacological management, but there are recognized risks associated with surgery.

The efficacy, safety and tolerability of DBS have been the subject of several reviews [56–58]. The reported reduction in daily OFF time with DBS ranges between 30 and 100% (median 68%) and increases in ON time without dyskinesia range from 47 to 138% (median 71%) [56]. With regard to the effect of DBS on dyskinesia, reductions of 70–100% have been reported, as well as a reduction in dyskinesia severity of up to 83% [56]. DBS reduces the dose of dopaminergic medication required by 56% [59]. DBS is a very useful non-oral therapy for advanced PD patients. However, many PD patients will not fulfill the strict exclusion criteria, such as the presence of significant cognitive dysfunction, which unfortunately limits the scope of this therapy.

### 5.8. Guidance on the use of device-aided therapies

Currently, limited head-to-head comparative data exist to recommend the use of one device-aided therapy – subcutaneous apomorphine, LCIG or DBS – over another. However, a range of clinical practice recommendations and treatment guidelines have been published to inform clinical decision-making in PD when these approaches are being considered, including an Expert Consensus Group report on the use of apomorphine in the treatment of PD [37], the NAVIGATE-PD study, an international consensus on the management of PD patients refractory to non-oral/transdermal PD medications [60], the EUROINF study, comparing LCIG and apomorphine therapy in 87 patients [61] and an evidence-based review by Volkmann et al. of DBS and infusion therapies [56].

### 5.9. Non-oral medication in the perioperative period

Non-oral therapy is an important consideration for patients undergoing surgery and who are unable to take their usual oral medications during and after certain types of surgery (e.g. bariatric surgery). Interruption of PD medication is associated with an increased risk of developing perioperative and postoperative complications including pulmonary embolism, stroke, pneumonia, urinary tract infection, septicemia and acute renal failure, leading to intensive care unit (ICU) admissions, prolonged hospital stays and higher mortality [62,63]. Risk factors for these complications are advanced age, complex PD medication schemes, PD disease severity, comorbidity such as diabetes mellitus and chronic obstructive pulmonary disease, and whether or not the surgery is performed in a medical center [62,63].

Due to withdrawal of oral dopaminergic medication, a multitude of complications may arise, such as respiratory and GI complications, severe motor worsening ultimately leading to an akinetic crisis with dysphagia and dysphonia, and cognitive and psychotic problems due to drug withdrawal [64]. Secondary to the worsened motor function in combination with longer duration immobility, pressure ulcers, constipation, deep vein thrombosis, pulmonary embolism and stroke may occur [62,63].

Management of these patients before, during and after surgery challenges the clinician, and many of these complications might be avoided if treatment with non-oral dopaminergic therapy, such as subcutaneous apomorphine infusion or transdermal rotigotine were employed [65]. Although well tolerated, rotigotine is less potent than apomorphine and therefore might be insufficient for patients on higher-dose levodopa. For the more advanced PD patients on higher doses of levodopa (>600 mg/day) and with moderate to severe cognitive impairment, perioperative infusion of apomorphine might be a good solution, to prevent many of the

**Table 1**
Perioperative management of PD patients with apomorphine.

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| **Selection criteria for perioperative apomorphine infusion** |
| Levodopa >600 mg/day |
| Existing response fluctuations |
| Moderate/severe cognitive pathology |
| Presence of visual hallucinations |
| Previous post-surgical complications |
| Use of dopamine agonists |
| **Selection of high-risk surgeries** |
| Duration >4 h |
| General anaesthesia |
| Expected duration of withdrawal of levodopa/DA |
| Need for opiates post-surgery |
| Infection risk |
| **Practical procedures** |
| *Day before surgery* |
| ECG (identification of QTc prolongation) |
| Lab (sodium, potassium, creatinine and urea) |
| Start domperidone orally 10 mg tid |
| Start apomorphine infusion 2 mg/h |
| Stop oral dopaminergic medication at midnight before surgery |
| *Day of surgery* |
| Switch from oral domperidone to domperidone suppositories 30 mg bid |
| Continue apomorphine infusion during surgery |
| Stop apomorphine is patients are awake and able to swallow |

aforementioned complications of surgery. In the University Medical Center Groningen, a protocol was developed for this group of patients, who were selected by the PD nurses, based on a daily analysis of all patients admitted to the hospital using levodopa (Table 1).

Apomorphine infusion was started pre-operatively at 2 mg/h, which was continued during surgery, and stopped in the recovery room when patients were able to swallow oral drugs again. Preliminary data show a drop in the frequency of post-operative complications, like delirium, leading to a shorter overall stay in the hospital. Therefore, proper identification and screening of high-risk PD patients seems to be essential to avoid complications related to withdrawal of dopaminergic medication, along with using apomorphine as an effective temporary replacement therapy in selected cases.

If DBS procedures are performed awake, apomorphine infusion might also be an option in those patients who do not tolerate the pre-operative withdrawal of dopaminergic medication. Apomorphine can be safely combined with DBS surgery, and has a very short elimination half-life, which makes it possible to stop it just 60 min before the clinical testing has to be performed [66]. In a study undertaken in Germany, data from 92 patients who underwent DBS surgery for PD were analyzed retrospectively and it was found that perioperative apomorphine infusion was safe and well tolerated, and also resulted in a reduction in postoperative neurologic deterioration and in the requirement for hospitalization in intensive care.

## 6. Conclusions

Many PD patients suffer from a suboptimal therapeutic response to oral medication at some point in the course of their disease. This might have several causes, like dysphagia, impaired absorption from the gastro-intestinal tract and delayed emptying of the stomach. If these problems occur, non-oral therapies, as discussed above, should be considered earlier and more frequently, in order to improve the quality of life and ADL function of PD patients with suboptimal responses to oral medication.

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# The efficacy of apomorphine – A non-motor perspective

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ABSTRACT

Non-motor features have a great impact on progression and quality of life in individuals with Parkinson's disease. Current treatments for PD are limited and apomorphine is one of the advanced therapies available with advantageous effects on motor complications. Several studies have suggested that apomorphine has potential benefits in PD patients beyond its established role in the treatment of motor fluctuations and levodopa-induced dyskinesia. This review examines the efficacy of apomorphine in the treatment of non-motor symptoms (NMS), describing recent studies that highlight its possible effect on cognition. Despite a limited number of studies, the available evidence shows that apomorphine has an overall beneficial effect on NMS of PD patients, including neuropsychiatric symptoms, sleep disturbances, pain, urinary dysfunction, and impulse control disorders. If the effects of apomorphine on amyloid deposition are confirmed in the future, its place in the armamentarium of PD treatment could see a shift towards younger and non-demented PD patients.



## 1. The role of apomorphine in the management of Parkinson's disease

Subcutaneous apomorphine has played a valuable role in the treatment of the motor symptoms of PD for several decades and continues to be a valuable therapy today.

Schwab and colleagues first reported the beneficial effect of apomorphine hydrochloride on tremor and rigidity in PD patients [1]. The successful use of subcutaneous apomorphine in combination with domperidone was confirmed in later studies by Corsini et al. [2] and Hardie et al. [3]. In 1988, pivotal studies by Stibe et al. and Chaudhuri et al. reported the efficacy of continuous subcutaneous infusion of apomorphine in managing refractory 'on–off' oscillations in PD [4,5] and led to the product receiving marketing authorization in the UK.

Since that time, subcutaneous apomorphine injection has, in a range of open-label and double-blind trials, demonstrated the capability to provide rapid and reliable resolution of 'off' periods in PD patients [6–8] and to be well tolerated [9]. Subcutaneous apomorphine infusion also has proven efficacy for PD patients with complex motor fluctuations that are uncontrolled by conventional oral or transdermal medication, or that require frequent apomorphine injections [10]. Open-label pooled data suggest that apomorphine infusion can achieve a mean 58.2% reduction in 'off' time, a reduction in both duration and severity of dyskinesia [11], and has a levodopa-sparing effect [12–14]. The efficacy of apomorphine for the management of PD has been summarized in several recent review papers [10,13,15,16].

In addition to the reported efficacy of apomorphine on motor function in PD, there have also been reports of beneficial effects on NMS in PD (Fig. 1). The non-motor effects of apomorphine were reviewed by Todorova and Chaudhuri in 2013 [35] who took into consideration the available case reports, and open-label and comparative case-control studies published in the peer-review literature at that time. This paper provides an update on current data evaluating the non-motor effects of apomorphine (Table 1).

## 2. The impact of non-motor symptoms in PD

Although PD is generally considered to be a movement disorder, NMS occur in over 90% of patients across all stages of the disease

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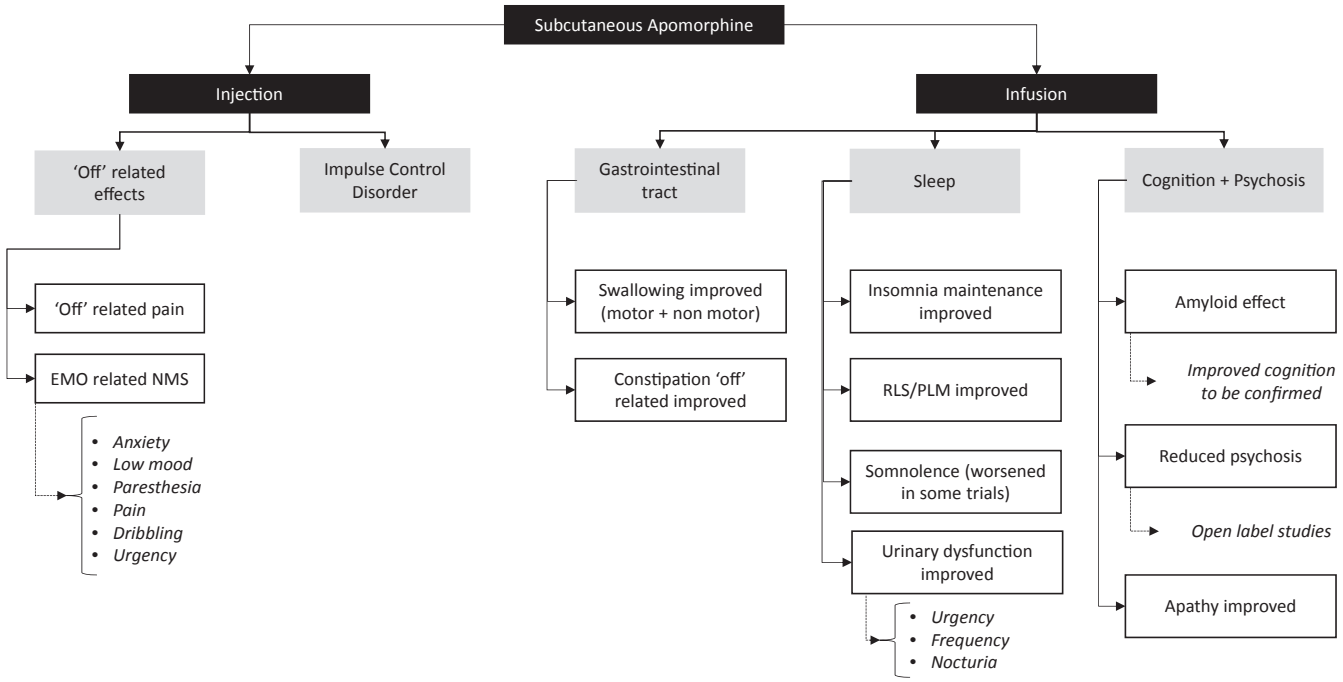


**Fig. 1.** Potential effects of apomorphine on non-motor symptoms.
Legend: EMO: Early morning 'off', RLS: Restless legs syndrome, PLM: Periodic limb movements.

[17,18]. Symptoms are wide ranging and include neuropsychiatric and autonomic dysfunction, sleep disturbances and pain [19–21]. NMS, such as sleep dysfunction, dementia and depression, represent a significant burden in PD with numerous studies highlighting the importance of NMS both in the 'pre-motor' phase of PD and throughout the disease course [17,22]. Surveys report an average of 8–13 NMS per patient, with some patients reporting around 30 NMS and only ≤2.5% patients being free of NMS [23].

These findings partly underlie the proposed re-definition of PD by the International Parkinson and Movement Disorder Society (IPMDS) task force to incorporate NMS and not base a diagnosis solely on motor symptoms [24], as well as recommendations that NMS should be assessed in the clinic alongside motor symptoms [25,26].

Unlike motor subtypes within PD, which have been long-recognized and investigated [27], NMS subtyping in PD is a new concept but has been shown to be both clinically relevant and feasible in clinical practice [28]. Recent clinical and neurobiological research suggests the existence of discrete non-motor subtypes in PD, particularly in untreated (drug naïve) and early PD patients [29–32].

Many NMS occur early in PD and some even predate the occurrence of motor signs [21]. Moreover, impulse control disorders (ICD), hallucinations, somnolence and dopamine agonist withdrawal syndrome might further complicate disease course following dopaminergic PD medication [17]. The overall burden of NMS contributes to significant morbidity and disability; it also impacts health-related quality of life (QoL) of people with PD [17,33], in many cases to a greater degree than the motor aspects of PD [34].

## 3. Evaluating the effect of apomorphine infusion on total NMS burden

The Non-Motor Symptoms Scale (NMSS) currently is the only dedicated, holistic, and validated tool for the assessment of NMS in PD [36]. It provides a comprehensive gradation (of both severity and frequency) of 30 different NMS across nine specific domains.

Martinez-Martin and colleagues undertook a non-randomized, open-label, study in 17 patients of the effect on NMS and health-related QoL of subcutaneous apomorphine infusion compared with conservative therapy. NMSS scores, Unified Parkinson's disease Rating Scale (UPDRS) motor scores and QoL measures were assessed at initiation of therapy and at 6 months' follow-up as part of routine clinical practice in this real-life study [37]. Treatment with apomorphine infusion resulted in highly significant improvements in UPDRS III ($p = 0.0003$), UPDRS IV ($p = 0.0003$), Parkinson's disease questionnaire (PDQ-8, $p = 0.001$) and NMSS total score ($p = 0.0003$). In addition, apomorphine was tolerated in patients with visual hallucinations, illusions and paranoid ideations, while significant improvements were observed in specific NMS such as hyperhidrosis, nocturia, urgency of micturition, and fatigue (Table 2) [37].

Further investigation of the effects of infusion-based PD therapies – subcutaneous apomorphine infusion and intrajejunal levodopa infusion (IJLI) – on NMS was undertaken in the EuroInf study across several European centers [38]. This open-label, prospective, observational, 6-month, multicenter study compared 43 patients on apomorphine infusion (48.8% males, mean age 62.3 years; mean disease duration: 14 years; median H & Y stage 3) and 44 on IJLI (56.8% males, mean age 62.7; mean disease duration: 16.1; median H & Y stage 4). Large effect sizes were observed for both therapies with respect to total motor, non-motor, and QoL scores (Table 2). When compared with baseline, NMS domains for cardiovascular, sleep/fatigue, gastrointestinal, urinary, and miscellaneous showed greater improvement with IJLI, whereas apomorphine infusion produced improvement in the mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary domains (Table 3). The authors concluded that controlled, randomized studies were required to investigate these effects further.

**Table 1**
Clinical details and a summary of key outcomes from studies using apomorphine injection/infusion in PD addressing non-motor effects (NA = no data available).

| Study/year | N | Study setting | Study design | Key findings | Reported adverse events and intolerance |
|---|---|---|---|---|---|
| Martinez-Martin et al., 2011 | 17 | International multicenter | Nonrandomized, open-label, comparative study | Improvement in specific NMS-hyperhidrosis, nocturia, urgency, fatigue | NA |
| Martinez-Martin et al., 2015 | 43 | International multicenter | Nonrandomized, open-label, comparative study | Improvement in mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary domains of NMSS | Severe somnolence occurred in 3 cases, ICD complicated 4 cases, none requiring discontinuation of therapy |
| Ellis et al., 1997 | 12 | Single center | Open-label study | Reduction of neuropsychiatric complications | NA |
| Chaudhuri et al., 1991 | 3 | Single center | Case reports | Reduction of neuropsychiatric problems | NA |
| Van Laar et al., 2010 | 10 | Single center | Open-label study | Reduction in severity of pre-existing visual hallucinations | NA |
| Geerligs et al., 2009 | 4 | Single center | Open-label study | Positive effect on contrast sensitivity; significantly negative effect on attention | NA |
| Drapier et al., 2012 | 23 | Single center | Open-label study | No change in neuropsychological status | NA |
| Alegret et al., 2004 | 7 | Single center | Open-label study | No significant changes in neuropsychological tests | NA |
| De Gaspari et al., 2006 | 13 | Single center | Open-label study | No change in NPI, MMSE and Hamilton depression scores | NA |
| Borgemeester et al., 2015 | 125 | Single center | Retrospective open-label study | Reduction of visual hallucinations in 23 patients<br>The increased dose of clozapine and reduced dose of dopamine agonists were more pronounced in patients that improved much compared to patients with less improvement (non-significant)<br>Improvement of night-time sleeping problems in 19: no improvement in 2<br>No worsening of sleeping problems was seen | Subcutaneous nodules: 50%<br>Visual hallucinations: 20%<br>Peripheral edema: 7%<br>Orthostatic hypotension: 6%<br>Nausea or vomiting: 6%<br>Hyperventilation: 6%<br>Tachycardia: 3%<br>Hemolytic anemia: 2%<br>Reasons for discontinuation:<br>Subcutaneous nodules: 3%<br>Visual hallucinations: 3%<br>Orthostatic hypotension: 3%<br>Peripheral edema: 2%<br>Nausea or vomiting: 2%<br>Hyperventilation: 1% |
| Tison et al., 1996 | 8 | Single center | Open-label study | Improvement of swallowing in a subset of patients | NA |
| Hunter et al., 1997 | 15 | Single center | Open-label study | Improvement of pharyngeal phase of swallowing for semisolids | NA |
| Mathers et al., 1989 | 4 | Single center | Open-label study | Functional improvement of the defecatory mechanism | NA |
| Edwards et al., 1993 | 8 | Single center | Open-label study | Improvement of anorectal dysfunction | NA |
| Reuter et al., 1999 | 6 | Single center | Open-label study | Improved nocturnal discomfort and leg movements | NA |
| Garcia Ruiz et al., 2006 | 1 | Single center | Case report | Improvement of insomnia | NA |
| Priano et al., 2003 | 12 | Single center | Open-label study | 15% improvement in the PLM index | NA |
| Factor et al., 2000 | 1 | Single center | Case report | Improved 'off' period pain | NA |
| Dellapina et al., 2011 | 25 | Single center | Randomized, controlled double-blind study | No effect on pain processing | NA |
| Christmas et al., 1988 | 10 | Single center | Open-label study | Improved voiding efficiency | NA |
| Aranda et al., 1993 | 12 | Single center | Open-label study | Improved detrusor hyperreflexia | NA |
| Winge et al., 2012 | 9 | Single center | Open-label study | Improvement to the same extent as conventional therapy or DBS | NA |
| Magennis et al., 2012 | 31 | Single center | Retrospective open-label study | Reduced ICD | NA |
| Todorova et al., 2013 | 41 | Single center | Open label, observational study | 7 pre-existing cases – attenuated<br>6 new cases developed | NA |
| Garcia-Ruiz et al., 2008 | 82 | Multicenter | Open label study | Good tolerance to apomorphine | Hypersexuality: 8%<br>Confusion: 17%<br>Hallucinations: 18%<br>Skin nodules: 16%<br>Hypotension: 2%<br>Confusion: 3%<br>Hallucinations: 5% |

Legend:
NA – no data available.
ICD – Impulse control disorders.
NMSS – Non-motor symptoms scale.
NPI – Neuropsychiatric inventory.
MMSE – Mini-mental state examination.
PLM – Periodic limb movements.
DBS – Deep brain stimulation.

**Table 2**
Data from the Martinez-Martin et al. 2011 study: Magnitude of the change from baseline to follow-up for each group of treatment.

| | Control | | | Apomorphine | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | *p* | Baseline | Follow-up | *p* |
| Cardiovascular | 1.29 (2.97) | 1.18 (2.90) | 0.45 | 4.65 (5.63) | 2.76 (3.51) | 0.03 |
| Sleep | 12.29 (9.58) | 12.06 (9.32) | 0.90 | 22.06 (11.47) | 10.71 (9.63) | 0.0003 |
| Mood/apathy | 8.35 (10.33) | 8.06 (8.78) | 0.79 | 22.76 (19.85) | 11.29 (13.04) | 0.0005 |
| Perceptual | 2.23 (5.03) | 2.59 (6.26) | 0.90 | 4.59 (6.92) | 1.88 (3.35) | 0.04 |
| Attention | 6.00 (8.40) | 7.18 (7.76) | 0.16 | 12.82 (9.62) | 8.71 (7.75) | 0.006 |
| Gastrointestinal | 5.94 (5.97) | 7.12 (6.49) | 0.24 | 7.35 (7.35) | 4.41 (5.11) | 0.002 |
| Urinary | 4.29 (3.57) | 6.23 (4.26) | 0.06 | 10.70 (8.93) | 5.71 (6.72) | 0.001 |
| Sexual | 3.12 (6.58) | 3.29 (6.12) | 0.97 | 18.47 (14.54) | 9.47 (9.70) | 0.0003 |
| Miscellany | 4.12 (5.67) | 4.29 (5.55) | 0.61 | 18.47 (14.54) | 9.47 (9.70) | 0.003 |

Benjamini-Hochberg correction: $p < 0.027$.

**Table 3**
Data from the EuroInf study: Magnitude of the change from baseline to follow-up for each group of treatment.

| | Control | | | Apomorphine | | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | *p* | Baseline | Follow-up | *p* |
| Cardiovascular | 3.36 (3.36) | 1.86 (2.67) | 0.0076 | 3.19 (4.57) | 2.07 2.49) | 0.23 |
| Sleep/fatigue | 16.68 (10.97) | 8.64 (8.26) | <0.0001 | 16.98 (10.12) | 12.98 (10.13) | 0.024 |
| Mood/apathy | 15.79 (12.85) | 11.89 (13.04) | 0.021 | 18.81 (18.00) | 9.98 (10.17) | 0.0003 |
| Perceptual/hallucinations | 3.54 (5.54) | 1.95 (4.51) | 0.010 | 3.02 (5.18) | 1.40 (3.14) | 0.003 |
| Attention/memory | 10.20 (9.35) | 7.60 (8.68) | 0.011 | 8.77 (8.24) | 5.79 (6.35) | 0.003 |
| Gastrointestinal | 9.48 (7.68) | 4.25 (4.80) | <0.0001 | 6.21 (5.82) | 4.65 (5.49) | 0.003 |
| Urinary | 11.5 (10.42) | 5.48 (5.78) | 0.0001 | 9.07 (7.40) | 7.93 (8.03) | 0.002 |
| Sexual functioning | 5.73 (7.93) | 2.32 (4.12) | 0.014 | 2.56 (5.29) | 1.93 (3.59) | 0.18 |
| Miscellaneous | 14.66 (9.25) | 9.68 (7.78) | 0.0008 | 13.77 (10.94) | 9.49 (8.15) | 0.50 |

Significant if $p < 0.027$.

## 4. Effect of apomorphine on specific NMS

### 4.1. Apomorphine and neuropsychiatric symptoms

Neuropsychiatric symptoms in PD are complex and may occur throughout the entire course of the disease. The phenomenology of psychotic symptoms appears to be unique in PD [39]. Some authors argue that they are a reflection of the disease itself, with dopaminergic treatment being a precipitating factor [39,40]. The clinical phenomenology of neuropsychiatric symptoms in PD is broad - psychosis, cognitive impairment, depression, anxiety and apathy – and, despite the frequent association between some of them, there is increasing evidence that they co-exist in a clinical continuum [39]. The potential presence of other comorbid neuropathologies needs always to be considered [41]. Despite all of this, apomorphine may have a potential beneficial effect in the treatment of some neuropsychiatric symptoms of PD patients, including psychosis [42–46] and, more recently, in cognitive impairment at least in a subset of patients [47].

Positive results of apomorphine on mood were first observed in schizophrenic patients in whom negative symptoms were attenuated with apomorphine but not placebo [48]. Despite early studies suggesting that apomorphine has deleterious effects on psychosis in PD patients [49–51], most recent studies have reported that apomorphine is safe and even may have the potential to ameliorate psychotic symptoms [42–46]. The underling mechanisms responsible for improvement in psychosis might be related to the reduction of potentially aggravating drugs and/or the relatively low proclivity of apomorphine to induce visual hallucinations. Some authors have argued that the possible serotonin antagonistic effect of the piperidine moiety [40,42] and the potential ability of apomorphine to increase lower-order visual perception are possible explanations for these observations [40].

The close association between psychosis and dementia in PD patients comes from the impression that the presence of one precedes or often complicates the other, but some authors have argued that there is no simple link between cognition and psychotic symptoms [39]. Dementia is a very important issue in PD. Epidemiologic studies have shown that, in the long term, cognitive impairment is present in more than 80% of PD patients, and that the relative risk of PD patients to develop dementia ranges from 2 to 6 compared with non-PD subjects [52]. Furthermore, 10–15% will meet the criteria for mild cognitive impairment (MCI) early in the course of PD, and there is some evidence that most patients with MCI will progress to dementia within five years [53–55].

Cognitive status often plays an important role when patients with PD are being considered for advanced therapies and those with cognitive impairment typically are not considered for deep brain stimulation (DBS). Apomorphine often is regarded as a safer alternative in this subset of patients. Drapier et al. have shown in an open-label study with 23 advanced PD patients that apomorphine infusion did not have a significant deleterious effect on a battery of cognitive tests assessing executive functions, visuospatial construction and memory at 12-month follow-up [56]. These results are in agreement with other studies, which compared DBS with apomorphine infusion [57,58]. The first evidence of its potential role in amyloid deposition in the brain came from a study with an Alzheimer's disease mouse model. Himeno et al. showed that the treatment of 3xTg-AD mice with apomorphine resulted in improvement of memory function and a decrease in intraneural Aβ and p-tau levels [59]. Yarnall et al. observed that in cognitively normal PD cases, significantly reduced brain Aβ deposition was found in those with ante mortem apomorphine exposure compared with apomorphine-naïve patients [47]. If these results are confirmed in future studies, including *in vivo* PD subjects, the use of apomorphine might shift towards younger and cognitively intact PD patients, expanding the current clinical scenario in which it is considered to be a safer treatment, compared with DBS, in older PD patients. Despite the potential effects of apomorphine on neuropsychiatric symptoms of PD patients, the individual characteristics

of patients play an important role and need to be considered.

In summary, apomorphine appears to be effective in the control of some neuropsychiatric problems of PD patients, appears to be relatively safe, and some of its observed effects may be independent of its dopaminergic properties. Furthermore, it has been shown that it triggers metabolic changes in brain areas involved in cognition and emotion, besides mobility [60], indicating that further research is warranted.

### 4.2. Apomorphine and gastrointestinal symptoms

Dysphagia affects more than 80% of PD patients, is challenging to assess, and constitutes a major risk for aspiration pneumonia. PD affects all swallowing phases – oral, pharyngeal and esophageal – most likely through both dopaminergic and non-dopaminergic mechanisms [61]. Several studies have addressed the effects of dopaminergic therapy on dysphagia, but only two have analyzed the role of apomorphine using gold standard instrumental methods [62]. Tison et al. studied the effects of apomorphine on buccolinguofacial motor function and on various phases of swallowing using videofluoroscopy in 8 PD patients with dysphagia [63]. The authors concluded that apomorphine improved swallowing abnormalities and total swallowing time in only a subgroup of PD patients, mainly in the volitional swallowing phase and buccolinguofacial motor scores. Hunter et al. reported less robust beneficial results [64]. Comparing the effects of levodopa/carbidopa and apomorphine in 15 patients using the modified barium swallow study, the authors observed that improvement with apomorphine treatment only reached statistical significance, compared with baseline measures, in its effect on the pharyngeal phase for semi-solids. Drooling of saliva, an important predictor of dysphagia, might improve with continuous apomorphine infusion [37,61].

Very few studies have investigated the effect of apomorphine on defecatory dysfunction. In 6 PD patients with chronic constipation, Mathers et al. studied the striated anal sphincter function using electrophysiological tests and defecating proctography, and found functional improvement following the administration of apomorphine in 4 patients [65]. Edwards et al. reported improvements of defecographic abnormalities and manometric parameters following the administration of apomorphine in a cohort of 8 PD patients. The authors concluded that anorectal dysfunction may be a consequence of dopamine deficiency secondary to the PD process and that apomorphine treatment can correct these abnormalities [66].

### 4.3. Apomorphine and sleep

Sleep disorders in PD are common and include a wide range of clinical presentations spanning from insomnia and hypersomnia to rapid eye movement (REM) sleep behavior disorder. Some sleep disturbances might result from the neurodegenerative process of PD itself, but secondary causes related to motor signs and dopaminergic treatment adverse effects often co-exist and might have an important role as well [67]. Apart from the studies addressing NMS using the NMSS [37], there is very scarce information on the effect of apomorphine on sleep disorders in PD. Reuter et al. first addressed the potential effects of apomorphine in PD patients with nocturnal symptoms or restless legs syndrome, suggesting beneficial properties [68]. In a more recent study of 12 PD patients, Priano et al. reported improvement of the periodic limb movements in sleep index, motor symptoms and sleep architecture using standard polysomnography [69]. Taking advantage of a more practical method with actigraphy to study sleep disturbances, Garcia Ruiz et al. documented the case of a 66-year-old woman, whose severe insomnia and sleep fragmentation improved with nocturnal subcutaneous apomorphine infusion [70]. Studies addressing the role of apomorphine in non-PD patients with restless legs syndrome [71] suggest that it may have a role in selected PD patients as well. In a recent study, Borgemeester et al. reported improvement of night-time sleep problems in 17 out of 20 patients who had their sleep symptoms documented in a retrospective single center study [72].

### 4.4. Apomorphine and sensory symptoms

Sensory symptoms in PD can include pain, olfactory and visual disturbances. A number of different subtypes of pain have been described, including musculoskeletal pain, PD-related chronic pain, fluctuation-related pain, nocturnal pain, oro-facial pain and peripheral limb/abdominal pain. Some, but not all, of these subtypes may be responsive to dopaminergic therapy [34].

Timed injections of apomorphine may help specific symptoms, such as 'off' period pain [73,74]. However, in a randomized, controlled, double-blind study, Dellapina et al. reported that apomorphine has no effect on pain processing (pain threshold and pain-induced cerebral activity) in PD, compared with placebo [75]. Further research is necessary to explore the potential role of apomorphine in sensory symptoms.

### 4.5. Apomorphine and urinary dysfunction

Evidence exploring the effect of apomorphine on urinary dysfunction is sparse; however a positive impact has been described. Christmas et al. demonstrated improvement in voiding efficacy via increased mean and maximum urine flow following administration of subcutaneous apomorphine in PD patients [76]. They also reported that apomorphine could either reduce or increase detrusor muscle activity. In contrast, Aranda et al. found apomorphine to overall improve detrusor activity [77]. In a rat model of PD, bladder overactivity was suppressed by administration of a dopamine D1 receptor agonist (SKF38393) [78]. Since apomorphine is one of the few dopamine agonists currently used with agonist action at D1 receptors, this may in part explain its apparent beneficial effects on bladder function.

In one study, apomorphine pumps were reported to be useful in treating lower urinary tract symptoms; however this was no different than using other forms of PD treatments including DBS [79]. Apomorphine may have a positive impact on urinary dysfunction, but this is an under-researched aspect of PD that needs further exploration.

### 4.6. Apomorphine and impulse control disorders

Available data exploring the relationship between apomorphine and ICD are currently limited to retrospective and open-label studies. A large retrospective multicenter study of 82 patients by Garcia Ruiz et al. reported only one patient with severe hypersexuality over a mean follow-up period of 19.93 ± 16.3 months, however, other forms of ICD were not mentioned [46]. Small open-label studies suggested a low rate of ICD in patients on continuous apomorphine infusion, and a recent three-year prospective study reproduced these initial findings [80–82]. Forty-one patients on apomorphine were prospectively screened for the development of NMS and ICD every 3 months; 7 new ICD cases were diagnosed but apomorphine discontinuation was required in only 1. Previous cases and the remaining 6 de novo cases improved or completely resolved without stopping apomorphine treatment [82]. In the open-label prospective study by Martinez-Martin et al., only 4 new cases of ICD developed on apomorphine infusion, and none required discontinuation of therapy [38].

A recent review of serious adverse drug event reports about ICD received by the US Food and Drug Administration from 2003 to 2012 stated that apomorphine appears to be the dopamine agonist least often associated with ICD, compared with oral dopamine agonists such as pramipexole and ropinirole [83]. Differences in ICD related events during dopaminergic therapy might be related to the method of delivery of the drug and/or the different receptor affinity profiles of the current 6 available dopaminergic therapies [82–84].

## 5. Effects of long-term apomorphine therapy

Hughes et al. reported that patients who had continuous apomorphine infusion or intermittent injection to have a reduction of 50% in 'off' time with no tolerance concerns [85]. Furthermore, Manson et al. suggested that apomorphine is an effective therapy to reset the dyskinesia threshold in patients being treated with levodopa [86] and Tyne et al. reported apomorphine to be generally well tolerated with a few mild adverse side effects (hypotension, confusion) in a cohort of 107 PD patients on long-term therapy [87]. Garcia Ruiz et al. reported a significant reduction in 'off' time, UPDRS and dyskinesia severity scores with continuous subcutaneous apomorphine infusion [88]. Studies exploring long-term apomorphine efficacy and tolerance have not given NMS much attention. Recently, Borgemeester et al. reviewed long-term outcomes of apomorphine infusion on both motor symptoms and NMS in a Dutch cohort of 125 PD patients. They reported a reduction in visual hallucinations in 68% of patients treated with apomorphine infusion as well as improvements in night-time problems in 25% of subjects.

## 6. Conclusion

Since the review by Todorova and Chaudhuri [35] on the effects of apomorphine on NMS of PD patients, few studies have been published. Nevertheless, the limited data available strongly suggest a beneficial effect. Using the NMSS, multicenter studies addressing apomorphine's potential role demonstrate beneficial effects on specific domains, such as mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary domains. This is backed by our own clinical experience. Always keeping in mind the individual characteristics of the patient, available data suggest that apomorphine is a possible and safe alternative to consider in patients with psychosis and cognitive impairment. Additionally, the rate of ICD seems to be lower with apomorphine than with other oral dopamine agonists. Further studies are needed to help delineate possible new roles for apomorphine beyond its established place in the current advanced PD therapies.

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# Quantitative demonstration of the efficacy of night-time apomorphine infusion to treat nocturnal hypokinesia in Parkinson's disease using wearable sensors

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ABSTRACT

*Background:* Nocturnal hypokinesia/akinesia is one of the common night-time symptoms in patients with Parkinson's disease (PD), negatively affecting quality of life of patients and caregivers. The recognition of this problem and treatment options are limited in clinical practice.
*Objectives:* To evaluate the efficacy of nocturnal apomorphine infusion, using a wearable sensor, in patients who are already on daytime continuous subcutaneous apomorphine infusion and still suffer from nocturnal hypokinesia.
*Methods:* Nocturnal parameters in 10 PD patients before and during nocturnal infusion were assessed over two nights at their homes, using a wearable sensor (trunk). Nocturnal parameters included number, velocity, acceleration, degree, and duration of rolling over, and number of times they got out of bed. Correlations with validated clinical rating scales were performed.
*Results:* Following nocturnal apomorphine infusion (34.8 ± 6.5 mg per night), there were significant improvements in the number of turns in bed ($p = 0.027$), turning velocity ($p = 0.046$), and the degree of turning ($p = 0.028$) in PD patients. Significant improvements of Modified Parkinson's Disease Sleep Scale ($p = 0.005$), the axial score of Unified Parkinson's Disease Rating Scale ($p = 0.013$), and Nocturnal Akinesia Dystonia and Cramp Scale ($p = 0.014$) were also observed.
*Conclusion:* Our study was able to demonstrate quantitatively the efficacy of nocturnal apomorphine infusion in PD patients with nocturnal hypokinesia and demonstrated the feasibility of using wearable sensors to yield objective and quantifiable outcomes in a clinical trial setting. More studies are needed to determine the long-term efficacy of this treatment in a large prospective cohort of PD patients.


## 1. Introduction

Noctunal hypokinesia or akinesia is a condition where individuals have difficulty in moving their body during sleep so that rolling over or turning in bed and getting out of bed is restricted [1]. Its manifestations primarily involve poor axial rotation, whole body bradykinesia, postural instability, and axial rigidity [2]. It is a common night-time manifestation affecting at least 50% of patients with Parkinson's disease (PD), that impairs both sleep quality and quality of life (QOL) of patients and poses a significant burden for caregivers [3–5]. Unfortunately this problem is often neglected in clinical practice and lack of treatment can result in serious consequences for patients, including the development of pressure ulcers, predisposition to aspiration pneumonia, and asphyxia, which can be fatal in PD patients [6,7]. Although the mechanism underlying nocturnal hypokinesia is likely to be complex, several lines of

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evidence support the presence of a low nocturnal dopamine level (similar to an off-state) as a major contributing factor [3,8]. Nocturnal hypokinesia is viewed as the longest 'off' period of all wearing-off symptoms which emphasizes the need to utilize a 24-hr or a near-24-hr treatment strategy to effectively control both day- and night-time symptoms [3,9].

Although nocturnal hypokinesia may be present throughout the night in PD patients, one might predict it would get worse as the night progresses. This suspicion was recently confirmed by our sensor-based study demonstrating significantly fewer turns in bed during the latter half of the night when compared to the first half of the night in moderate stage PD patients [10]. This finding has significant therapeutic implications as it suggests that continuous dopamine replacement throughout the night is required to achieve a sustained therapeutic benefit, especially in the second half of the night [11]. Simply adding a single dose of dopaminergic medication at bedtime is unlikely to be adequate to abolish the symptoms of nocturnal hypokinesia as shown by a lesser benefit of controlled-release levodopa in the treatment of early morning off than other nocturnal disabilities [12,13]. To test the viability of continuous dopaminergic delivery, a number of clinical trials have been conducted in advanced PD patients by giving continuous infusion of either levodopa carbidopa intestinal gel (LCIG) or apomorphine during the night with outcome measures being assessed via sleep diaries, the Modified Parkinson's Disease Sleep Scale (PDSS-2), sleep questionnaires, and related clinical rating scales [14–16]. Significant improvements in various sleep domains, including nocturnal 'off' periods, pain, dystonia, nocturnal awakening, and sleep quality support the use of nocturnal infusion for the treatment of nocturnal hypokinesia and related disabilities. However, these outcomes are based on clinical interviews in which many nocturnal symptoms can be overlooked, and do not objectively determine the ability to turn in bed, which is the major manifestation of nocturnal hypokinesia [11,17]. With the advances in sensor technology, the NIGHT-Recorder, which is an inertial sensor that is capable of giving continuous data on axial rotation of PD patients while in bed, and has been shown to provide an accurate and reliable assessment of nocturnal hypokinesia in both PD patients and controls [1,18]. Therefore, by using the NIGHT-Recorder, this study has sought to determine if an extension of daytime continuous subcutaneous apomorphine infusion (CSAI) into the night-time will objectively improve nocturnal hypokinesia in advanced PD patients with subjective complaints of impaired bed immobility.

## 2. Patients and methods

### 2.1. Patient inclusion and rating scales

Participants in this study were PD patients at Chulalongkorn Center of Excellence for Parkinson's Disease & Related Disorders (www.chulapd.org) with the diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, and who were already under daytime CSAI (Britannia Pharmaceuticals, Surrey, UK), but still suffering intractable nocturnal hypokinesia. Exclusion criteria were: 1) patients who were bedridden; 2) history of neurological disorders (except PD) or other muscle and joint diseases; and 3) a history of hypnotic or sedative drug use. The study was approved by the Human Ethics Committee of the Faculty of Medicine, Chulalongkorn University. All subjects gave informed consent before entering the study in accordance with the declaration of Helsinki.

Demographic and clinical characteristics were recorded including disease duration. Disease stage was rated using the Hoehn and Yahr (HY) staging system during the 'on' period. In order to accurately determine the severity of PD during the night, Unified Parkinson's Disease Rating Scale section 3 (UPDRS-3) was rated by JS at 2100 h in all subjects in their homes before and during nocturnal apomorphine infusion. The UPDRS axial score was calculated as the summation of items 18, 22, 27, 28, 29, and 30 of the UPDRS-3 [19]. As verified by sleep diaries, all subjects went to sleep after 2100 h. To quantify the severity of nocturnal symptoms, the Modified Parkinson's Disease Sleep Scale (PDSS-2) and the Nocturnal Akinesia Dystonia and Cramp Scale (NADCS) were recorded in all patients [1,20]. Overall dopaminergic treatment was quantified by calculating the levodopa equivalent dose (LED) in mg per day [21]. In addition, nocturnal dopaminergic treatment was estimated from the dopaminergic dose taken before going to bed and expressed in LED.

### 2.2. Selection of patients for nocturnal apomorphine infusion and experimental protocol

Patients were selected to undertake a semi-structured interview if they reported the symptoms of difficulty turning around or finding a comfortable sleep position consistent with impaired bed mobility during the past week [17]. To confirm the subjective complaints of impaired bed mobility, they must have reported the severity of at least 1 on item 9 of the PDSS-2 ('Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?') and a severity of at least 0.5 on the nocturnal akinesia sub-score of the NADCS [20,22]. The severity of both scales was evaluated by two independent neurologists (RB and JS) who were required to agree on their rating assessment. In case of the disagreement, both physicians assessed the evidence again, and arrived at a consensus. In order to fulfill the selection criteria for nocturnal apomorphine infusion, nocturnal hypokinesia had to be present as identified by both rating scales. In addition, the infusion dosage of daytime CSAI and all other dopaminergic medications must have been kept unchanged for at least one month prior to the addition of nocturnal infusion.

Before entering into the nocturnal infusion study, all subjects were given their daytime CSAI between 0800 h and 2000 h using the Crono Apo-Go III portable infusion pump (Genus Pharmaceuticals Ltd., Berkshire, UK) for ambulatory use connected to a subcutaneously inserted cannula. Due to a concern of possible tolerance, the Food and Drug Administration (FDA) of Thailand stipulates an overnight period without apomorphine treatment of at least four hours [23]. Therefore, in all subjects, the daytime CSAI was continued as a night-time infusion at the same infusion dosage until 0400 h the following day giving a total of a 20-h continuous infusion for a 24-h period (Fig. 1). All subjects had a 4-h period without infusion between 0400 h and 0800 h, before starting the next CSAI at 0800 h. The main reason that an infusion free period was chosen between 0400 h and 0800 h was because all subjects were stabilized with daytime CSAI prior to the enrollment of this study and we did not want to compromise patient's daytime symptoms by omitting infusion during the daytime. Moreover, it was practically difficult for subjects and caregivers to omit CSAI in the early evening and to restart CSAI again in the late hours of the night.

### 2.3. Wearable sensors

The inertial sensor (NIGHT-Recorder) used in this study was developed by our group with technical development and experimental verification described elsewhere [18]. In brief, the NIGHT-Recorder consists of a 16-bit digital-output triaxial integrated microelectromechanical system (iMEMS) accelerometer and gyroscope that are capable of measuring linear and angular accelerations in three translational planes (*x,y,z*). The recordings were

obtained using a 10-Hz sampling rate with a low pass filtering at 12 Hz. This sampling rate was found to be suitable for recording nocturnal movements where the movements tend to be slow.

All subjects wore the NIGHT-Recorder on their trunk for two nights in their normal bedroom environment. The orientation of axis *x,y,z* on the patient is shown in Supplementary Fig. 1. The NIGHT-Recorder was fastened with a Velcro band and worn above the nightclothes at the sternum about 5 cm below the jugulum, chosen because it is a rigid body structure close to the center of mass and to reduce artifacts caused by arm movements [18]. Signal processing was performed using a forward derivative method on the angular data to obtain its derivatives on the Sleep Motion Analyzer software (version 1.0) running on MATLAB (version 7.8.0.347, R2009a). The detailed technical analysis of the data has been described previously [18]. All subjects were instructed to complete a sleep diary to record sleep times and episodes of getting out of bed if awakened during the night. Sleep times were defined as the period that the subjects were in bed excluding the first and last 5 min. In this study, all subjects woke up after their night-time infusion was completed at 0400 h. If any discrepancies occurred between sleep times provided by subjects' records and sleep times registered by the sensor, the registration by the sensor was synchronized with the data reported by the subjects for clarification. All subjects were allowed to continue on their usual medications.

### 2.4. Nocturnal parameters

Nocturnal parameters that were included in this study were the number of times the subjects turned in bed, and the number of times they got out of bed. Detailed descriptions of outcome parameters in categories, descriptions, and units is described elsewhere [18]. The recorded characteristics of turning in bed include degree, duration, velocity, and acceleration. Turning in bed is defined as a series of unconscious motions during sleep involving rotational body movements [24]. In this study, we adopted the same operational definition of turning in bed as stated in a previously published study as a series of rotational movements of the trunk from one static position to another static position that is sustained for at least 5 min in a *y*-axis plane [1]. We identified episodes of getting out of bed from the recordings by detecting rapid rises of acceleration in the x-axis of more than 45° from either static or rotational movements [1].

### 2.5. Statistical analysis

Baseline characteristics of both PD patients and their spouses were summarized using either means, standard deviation, or frequencies and percentages as appropriate. Wilcoxon's signed-ranks test was used to compare outcome parameters before and during nocturnal infusion. Correlations between nocturnal parameters and the clinical severity as determined by rating scales were tested with Spearman's correlation. The correlation coefficient (r) was used to determine the strength of correlations as weak, moderate, or high correlation. A $p$ value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 17.0 software (SPSS Inc., Chicago IL).

## 3. Results

10 PD patients (4 M, 6F, mean age 65.4 ± 12.35 years) participated in the study. Demographic data and disease characteristics of all subjects are shown in Table 1. The mean disease duration was 9.6 ± 3.31 years with the mean HY staging of 3.25 ± 0.72. The mean daily apomorphine dosage was 80.41 ± 20.77 with a mean rate of 5.87 ± 1.58 mg/h, infused over 20 h/day. All participants were able to complete a two-night assessment with the NIGHT-Recorder. There was no significant difference between the mean sleep time before and during nocturnal apomorphine infusion

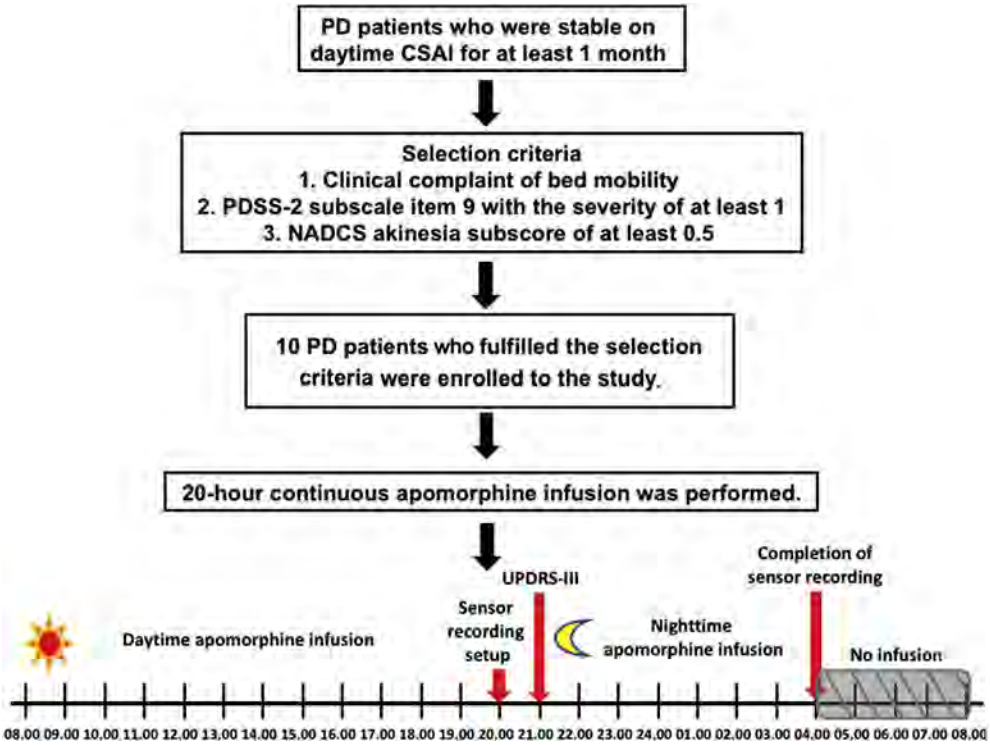


**Fig. 1.** Diagram illustrating the study design. PD: Parkinson's disease; CSAI: Continuous Subcutaneous Apomorphine infusion; PDSS-2: Modified Parkinson's Disease Sleep Scale; NADCS: Nocturnal Akinesia Dystonia and Cramp Scale; UPDRS-III: Unified Parkinson's Disease Rating Scale-Motor section.

(392.0 ± 93.34 min vs. 367.4 ± 75.15 min, $p = 0.484$). None of the patients were able to achieve CSAI monotherapy and the mean total daily LED during trial participation was 488.25 ± 349.93 mg, a 54.84% reduction of the mean total LED from before starting CSAI. Nine out of ten patients were taking single dose dopaminergic medications at bedtime (2000 h) with the mean night-time LED of 125.2 (SD = 116.43). Details of their bedtime medications were provided in Table 1. Similar to what was reported when subjects received only daytime CSAI, 50% of the patients reported subcutaneous nodules, which are successfully managed locally with massage ball, and rotations of needle sites. One subject (10%) reported a mild form of compulsive shopping, which developed one week after starting nocturnal infusion. There were no reports of serious adverse events.

Following nocturnal apomorphine infusion (on average 34.8 ± 6.5 mg per night), there was a significant improvement in the number of turns in bed ($p = 0.027$), turning velocity ($p = 0.046$), and the degree of turning ($p = 0.028$) in PD patients (Table 2). However, there was no significant difference in the numbers of getting out of bed, identified from the sleep diary as nocturia ($p = 0.783$), or in acceleration of turning in bed ($p = 0.116$). While the total night-time UPDRS-3 before and during nocturnal apomorphine infusion was not statistically different, we observed a significant improvement in the nighttime UPDRS axial score following the infusion ($p = 0.013$), in particular on posture (item 28, $p = 0.011$), and postural instability (item 30, $p = 0.034$) (Table 2). The effect of nocturnal infusion was also demonstrated on the significant improvement of PDSS-2 ($p = 0.005$), and NADCS ($p = 0.014$), especially on the akinesia ($p = 0.026$) and cramp ($p = 0.03$) sub-scores. Correlations were performed between the nocturnal parameters, and infusion doses, total LED, bedtime LED, HY staging, UPDRS-3, UPDRS axial, PDSS-2, and NADCS scores. A high and significant correlation was observed between the number of turns in bed and mean daily dosage of apomorphine infusion ($r = 0.783$, $p = 0.022$).

## 4. Discussion

Our study has established that nocturnal dopaminergic delivery significantly improves nocturnal hypokinesia in PD patients as demonstrated by the improvement the ability of patients to turn in bed, including increases in the number, velocity, and size of turns. These findings support a treatment strategy which consists of continuous dopaminergic delivery over both day- and night-time to improve symptom control. Although previous studies documented the improvement of nocturnal symptoms by means of rating scales and questionnaires [14,16], our study provides a set of new outcomes used in an objective and quantitative manner in a clinical trial setting.

Although the mechanism underlying nocturnal hypokinesia is likely to be complex, significant improvement in symptoms seen with continuous dopaminergic delivery, as shown in our and others studies, further supports the existence of low nocturnal dopamine in PD patients [11]. As normal physiological dopamine is low during sleep, associated with a paucity of dopamine secretory peak, it is plausible that nocturnal dopamine in PD patients could be even lower contributing to the manifestation of nocturnal hypokinesia [11,25]. Therefore, in order to replace dopamine nocturnally, the administration should be continuous or involve the use of long-acting dopaminergic agents. This suggestion is supported by a number of recent studies indicating the beneficial effects of apomorphine, LCIG, rotigotine transdermal patch, cabergoline, and ropinirole prolonged delivery in the treatment of nocturnal hypokinesia [11,14–16,22,26–28]. However, none of them utilized sensors to quantify the presence and severity of nocturnal hypokinesia as demonstrated in this study. In healthy individuals, low physiological night-time dopamine is required to facilitate restful sleep, therefore, in PD patients, use of high dose dopaminergic agents may have a negative effect on sleep efficiency and enhance wakefulness, and it is reasonable to consider lowering the dosage of dopaminergic agent at night when attempting to replace nocturnal dopamine in PD patients [29,30]. However, there is no clear evidence on the optimal dosage of dopaminergic agents for the treatment of nocturnal hypokinesia and practices may vary [16,26]. As described in the prior literature, we determined the dosage of apomorphine that switched patients from 'off' to 'on' state and applied the same infusion rate in both day and night [16]. There were no reports of increased insomnia among subjects during nocturnal infusion and sleep times before and during infusion were not significantly different. However, the development of compulsive shopping in one of our subjects following nocturnal infusion may be related to the total daily dosage of apomorphine.

As required by the Thai FDA due to concerns of possible tolerance with apomorphine, patients were not allowed to have CSAI for a full 24-h period, and an infusion-free gap of at least four hours is required for each 24-h infusion period [23]. Tolerance has been shown to develop in PD patients after apomorphine exposure and the loss of response was found to be greater after longer periods of apomorphine administration, but not influenced by the infusion dosage [31,32]. The reports of tolerance with CSAI in the literature have been scarce and contradictory. One study observed the tolerance phenomenon following a very brief 30-min of CSAI; another did not identify any cases of tolerance out of 15 patients with 24-h CSAI with a mean treatment duration of 32 months [33,34]. Although the criteria for long periods of apomorphine infusion have not been established, the duration of response to apomorphine bolus doses becomes shorter with administration at 2-h intervals, but remains equal if the doses are separated by four hours, suggesting that tolerance to apomorphine seems to reset itself very quickly [35,36]. In our study, we only included subjects who had been stable on daytime CSAI for at least one month before extending their infusion nocturnally, and we did not observe any changes in motor response or an alteration of infusion dosage in our subjects. No reports of tolerance were documented in a prior study of nocturnal apomorphine infusion, but two out of six PD patients reported rebound morning stiffness after discontinuing apomorphine and 50% of patients received 24-hr apomorphine infusion [16].

In addition to the improvement of nocturnal hypokinesia, the

**Table 1**
Demographic data and disease characteristics of 10 Parkinson's disease patients.

| | Parkinson's disease patients |
|---|---|
| | Mean (SD) |
| Age (years) | 65.40 (12.35) |
| Age of onset (years) | 55.8 (14.67) |
| Duration of disease (years) | 9.6 (3.31) |
| HY staging | 3.25 (0.72) |
| Total LED (mg/day) | 488.25 (349.93) |
| Night-time LED | 125.2 (116.43) |
| - Controlled-release levodopa LED | 52.5 (36.23) |
| - Rotigotine LED | 36.0 (64.5) |
| - Ropinirole prolonged delivery LED | 12.0 (27.0) |
| Apomorphine infusion | |
| - Duration of apomorphine use (months) | 10.6 (7.6) |
| - Total apomorphine dosage (mg) | 80.6 (22.5) |
| - Night-time apomorphine dosage (mg) | 34.8 (6.5) |
| - Infusion dosage (mg/hour) | 5.87 (1.58) |
| - Duration of daytime infusion (hours) | 14.3 (1.9) |
| - Duration of night-time infusion (hours) | 6.3 (1.2) |

HY: Hoehn & Yahr; LED: Levodopa equivalent dose.

**Table 2**
Comparison of nocturnal parameters and clinical rating scales before and during nocturnal apomorphine infusion.

| Parameters | Before nocturnal infusion | During nocturnal infusion | *p* value |
|---|---|---|---|
| Duration of sleep (min) | 402.3 (85.13) | 372.99 (69.85) | 0.241 |
| Number of turns in bed | 0.5 (0.93) | 2.5 (2.56) | 0.027* |
| Turning velocity (radiance/sec) | 0.623 (1.196) | 2.325 (1.84) | 0.046* |
| Degree of turning (degree) | 7.27 (13.76) | 34.15 (27.75) | 0.028* |
| Acceleration of turning (radiance/sec$^2$) | 0.07 (0.155) | 0.225 (0.199) | 0.116 |
| Number of getting out of bed (Nocturia) | 0.5 (0.76) | 0.63 (0.92) | 0.783 |
| UPDRS-3 | 22.2 (12.6) | 18.1 (10.35) | 0.182 |
| UPDRS axial sub-score | 8.3 (4.81) | 5.5 (4.65) | 0.013* |
| UPDRS item 18 | 0.9 (0.74) | 0.7 (0.68) | 0.317 |
| UPDRS item 22 | 1.3 (0.82) | 0.8 (0.79) | 0.096 |
| UPDRS item 27 | 0.8 (1.22) | 0.9 (1.0) | 0.564 |
| UPDRS item 28 | 1.9 (1.29) | 0.9 (1.0) | 0.011* |
| UPDRS item 29 | 1.4 (1.27) | 0.9 (1.0) | 0.129 |
| UPDRS item 30 | 2 (1.25) | 1.3 (1.25) | 0.034* |
| PDSS-2 | 27.6 (10.31) | 20.1 (10.51) | 0.005 |
| NADCS | 5.35 (3.25) | 3.75 (2.92) | 0.014* |
| Akinesia sub-score | 2.6 (1.33) | 1.95 (1.46) | 0.026* |
| Dystonia sub-score | 0.95 (1.5) | 0.9 (1.29) | 0.785 |
| Cramp sub-score | 1.8 (1.48) | 0.9 (1.29) | 0.014* |

*Denoted statistical significant results with $p \leq 0.05$.
UPDRS-3: Unified Parkinson's Disease Rating Scale part 3; NADCS: PDSS-2: Modified Parkinson's Disease Sleep Scale; Nocturnal Akinesia Dystonia and Cramp Score.

benefits of apomorphine have been observed on other night-time symptoms in PD patients. These include a significant reduction in nocturnal pain, dystonia, periodic limb movements, and awakenings [16]. A single case report demonstrated the beneficial effect of a low dose night-time infusion in a PD patient with severe insomnia, suggesting that apomorphine may help to restore circadian rhythm [26]. A significant improvement in sleep architecture (increased sleep efficiency and stage 3 and 4 non-REM sleep, and reduction of arousal index) was confirmed in a separate study involving 12 PD patients with polysomnography following the use of transdermal apomorphine [37]. Another multi-center observational study reported a significant improvement in the severity and frequency of insomnia in PD patients with daytime infusion [38]. Similar observations were documented in a large cohort study of 125 PD patients in whom 72% of those with sleep problems reported an improvement in sleep with CSAI, and 35% of patients (12 out of 34 patients) continued with nocturnal infusion [34]. Importantly, there were no reports of cases with worsening sleep following CSAI in this study. Several aspects of nocturia also were ameliorated during CSAI, suggesting a role for central dopaminergic transmission on bladder function [39]. Recently, the benefits have extended to the improvement of morning akinesia as demonstrated by a better time-to-on following the use of apomorphine injections [40].

Although the strength of our study involves the use of nocturnal sensors in the patient's sleeping environment, which provided objective and quantifiable parameters that demonstrated significant changes in this clinical trial, there are certain limitations associated with this study. The first is the absence of a control group, although objective improvements were evident from both sensor parameters and clinical rating scales. The second is the small number of subjects in this study, which could limit the spectrum of findings associated with nocturnal infusion and statistical power of the analysis. In addition, the lack of simultaneous polysomnographic recordings limits a correlation between sleep architecture and axial movements. As imposed by the FDA of Thailand, an infusion-free period between 0400 h and 0800 h limited the analysis of early morning symptoms as well as the full interpretation of nocturnal disabilities. It is plausible that more significant improvement of nocturnal parameters would have been evident if subjects had received a 24-hr CSAI. The results from our study may not be generalized to all PD patients since subjects were preselected for patients who were already on daytime CSAI, but still suffering nocturnal hypokinesia.

In conclusion, our study was able to demonstrate quantitatively the efficacy of nocturnal apomorphine infusion as a treatment of nocturnal hypokinesia in PD patients with clinical complaints of bed immobility by demonstrating a significant improvement in turning in bed parameters. No serious adverse events were reported with this procedure. Our findings provide further therapeutic evidence supporting the use of continuous dopaminergic delivery as a treatment of nocturnal hypokinesia in PD patients and the feasibility of wearable sensors to yield objective and quantifiable outcomes in a clinical trial setting. However, more studies are needed to determine the long-term efficacy of this treatment in a large prospective cohort of PD patients. Since night-time problems are often neglected and under reported by PD patients, ambulatory nocturnal monitoring may provide not only a practical method of night-time assessment, but direct information to determine therapeutic responses in a clinical setting when clinical information from patients and caregivers is likely to be limited.

## Conflict of interest

The authors have no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.11.016.

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# Practical management of adverse events related to apomorphine therapy

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ABSTRACT

The potential for adverse events is often cited as a barrier to the use of subcutaneous apomorphine therapy (intermittent injections and continuous infusion) in the management of Parkinson's disease. However, with proactive management most adverse effects are manageable if reported and tackled early enough. As such, proper clinician and patient awareness of the potential adverse effects is important to minimize their impact on the overall clinical utility of this efficacious antiparkinsonian agent. In this paper, we review the key local and systemic adverse effects reported during apomorphine titration, initiation and long-term treatment, and discuss practical management strategies.



## 1. Introduction

It is well accepted that apomorphine is a suitable therapeutic option for patients with Parkinson's disease (PD) who experience troublesome OFF periods despite optimized treatment with oral PD medications. Even though apomorphine has an excellent efficacy profile, it continues to be underutilized in routine clinical practice [1]. One important reason for this is probably a perception of difficulty in using the agent – including management of its adverse events (AEs). However, discontinuation due to AEs is not as common as often believed. In one of the largest retrospective studies of apomorphine infusion (involving 166 patients treated in 35 Spanish tertiary hospitals) around one in ten patients discontinued because of secondary side effects [2]. It is therefore important for clinicians and patients to understand that, although AEs may develop, they are mostly manageable if patients, caregivers, physicians, and nurses work as a team to actively manage them as early as possible. In this paper, we review the key AEs reported with apomorphine use and discuss practical management strategies.

Currently, there are two main ways of delivering apomorphine to achieve a therapeutic effect: intermittent subcutaneous injection and subcutaneous continuous infusion. Adverse event rates have been reported for other routes of administration (e.g. inhaled, intranasal, rectal), but these methods of delivery have so far been largely abandoned [3] and, thus, are outside the scope of this practical review. We provide an overview of the AEs in the published literature; including prevalence rates, mechanism (if known) and potential risk factors. Table 1 shows the relative frequency of each AE. For each AE, we suggest practical management strategies, based both on the available evidence and our own clinical experience. In clinical practice, AEs often can be categorized as those which occur during initiation and titration of apomorphine and those which occur during maintenance. Within each of these time frames, patients can experience both local and systemic AEs and these are discussed in turn.

## 2. Management of adverse events during apomorphine titration and initiation

A patient's first experience with a new medication (and route of administration) often is crucial to patient retention. Hence, it is very important that patients fully understand the process of treatment initiation and have reasonable expectations of the usually transient

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**Table 1**
Reported incidence of AEs with subcutaneous apomorphine as reported in the current prescribing information.

| Adverse events related to apomorphine therapy | Risk |
|---|---|
| Administration site reactions (subcutaneous nodules, induration, erythema, tenderness and panniculitis) | +++ |
| Yawning | ++ |
| Nausea | ++ |
| Vomiting | ++ |
| Transient sedation | ++ |
| Somnolence | ++ |
| Dizziness | ++ |
| Neuropsychiatric disturbances (confusion and hallucinations) | ++ |
| Coombs positive hemolytic anemia | + |
| Injection site necrosis and ulceration | + |
| Dyskinesia | + |
| Sudden onset sleep | + |
| Postural hypotension | + |
| Breathing difficulties | + |
| Allergic reaction* | − |
| Eosinophilia | − |
| Impulse control disorders | ? |
| Peripheral edema | ? |

+++ Very common, (≥1/10), ++ Common (≥1/100 to <1/10), + Uncommon (≥1/1000 to <1/100), − Rare (≥1/10,000 to <1/1000), ? incidence not known (cannot be estimated from current data). *Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur.

AEs that are commonly experienced during the titration and initiation phases. It is important to give the patient and caregiver a realistic idea of how much time it may take before the optimal balance between apomorphine and per oral medication is reached. Compliance is of paramount importance in the treatment of advanced PD. To increase adherence in apomorphine treatment, we advise performing an apomorphine test. This not only will guide the clinician as to both beneficial and adverse effects in a particular patient, but also will give the patient a good idea of what to expect from treatment, which also helps to increase adherence. The test can be performed in a number of ways – usually as an outpatient [4].

### 2.1. Nausea and vomiting

As with other dopamine agonists, some of the most common AEs associated with apomorphine are initial nausea and vomiting [5], which can be a cause of discontinuation. In the placebo-controlled trials used for US registration, nausea occurred in almost a third (31%) of patients and led to treatment discontinuation in 3% of patients. Vomiting was reported for 11% of patients and led to discontinuation in 2% of patients [5–8].

Nausea and vomiting are more commonly reported with intermittent injections than with continuous infusion therapy [9], which is likely due to a down-regulation of medullary dopamine receptor sensitivity with the continuous dopaminergic stimulation [10]. These peripheral dopaminergic effects are usually well controlled by the co-administration of an appropriate antiemetic until tolerance emerges (typically 3–6 weeks after initiation of apomorphine therapy). As such, the need for an anti-emetic should be regularly reviewed, and most patients can down titrate and stop treatment within the first 2 months of starting apomorphine treatment. Patients who inject apomorphine less than 4 times per day are potential exceptions to this rule, since they have been shown to be more prone to nausea and might require antiemetic prophylaxis for a longer period of time [9].

The peripheral dopamine D2-receptor antagonist domperidone is the recommended antiemetic in Europe and many other regions of the world, while trimethobenzamide is the only recommended antiemetic in the USA because it does not exert significant central dopamine antagonistic effects. Antiemetic drugs with central actions (e.g. the phenothiazines and metoclopramide) also are effective against nausea, but can exacerbate parkinsonism and are therefore not recommended [11]. In particular, ondansetron is not an option and is even contraindicated because the combination of ondansetron and apomorphine increases the risk for hypotension and resultant in loss of consciousness [12].

Over 30 years ago, concerns with QT-prolongation and cardiac adverse events led to the withdrawal of intravenous domperidone. Such concerns have recently resurfaced with oral formulations [13]. In January 2016, the European Medicine Agency (EMA) issued a recommendation to use the lowest effective dose and discontinue as soon as possible. Risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk before the decision to initiate domperidone and apomorphine treatment is made. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbances. The presence of medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval also should be assessed. The EMA also advises that an ECG should be performed prior to treatment with domperidone, during the treatment initiation phase and as clinically indicated thereafter [14]. The UK is one of the countries with the most experience of apomorphine use, and the Association of British Neurologists (ABN) has recommended that the initiation of apomorphine therapy be covered by domperidone at a dose of 20 mg three times daily commencing 2 days before the first dose [15]. The dose should be reduced to 10 mg three times daily after 2 weeks if the patient is not experiencing nausea. If nausea persists or returns on reducing the dose, domperidone can be continued in the same dose.

The use of trimethobenzamide as prophylactic treatment for nausea and vomiting associated with apomorphine has recently been prospectively evaluated in a USA trial using a phased withdrawal design (from trimethobenzamide to placebo) [16] [17]. In this study, a significantly lower incidence of nausea, vomiting and retching was found for trimethobenzamide between Period 1 (days 1–28) and Period 2 (days 29–56), but this significant difference was lost after this time point (Period 3; days 57–84). These data suggest that trimethobenzamide helps reduce nausea/vomiting during the first 8 weeks of apomorphine therapy, but generally is not needed thereafter. *Post-hoc* analysis of in this study indicated that patients who were receiving dopamine agonist therapy at baseline experienced significantly less nausea and/or vomiting

than subjects not on a dopamine agonist. This is in line with the anecdotal experience that patients already on a dopamine agonist experience less nausea and vomiting than those not already on a dopamine agonist when subcutaneous apomorphine is introduced.

In a recent Japanese study of apomorphine in PD, prophylactic antiemetic use was prohibited except in patients who had been receiving antiemetic treatment before the entering the study [17]. Around 1 in 5 patients reported gastrointestinal AEs, including nausea and vomiting, of which only some required an antiemetic or reduction of apomorphine dose. The nausea disappeared soon after these actions were taken. No patients discontinued the study due to gastrointestinal AEs, suggesting that it is feasible to start apomorphine treatment without antiemetic pretreatment. This is in keeping with our own clinical experience.

In summary, when initiating patients on apomorphine treatment, use of prophylactic anti-emetic treatment can help reduce the peripheral effects of nausea and vomiting. Following successful initiation of apomorphine therapy, the need for an anti-emetic should be regularly reviewed, as most patients develop tolerance within the first 3–6 weeks of apomorphine treatment. Due to potential cardiac concerns, in all patients in whom domperidone is being considered, an electrocardiogram should be performed before initiating domperidone treatment. If there is a wish to avoid antiemetic prophylaxis, this is usually possible by a slow up titration schedule.

### 2.2. Orthostatic hypotension

Another AE that occur during titration and initiation is orthostatic hypotension, which is reported to occur in $\leq$1% of patients [10]. In the clinical studies submitted to the FDA, dose-dependent mean decrements in systolic blood pressure ranged from 5 mmHg after 2 mg to 16 mmHg after 10 mg apomorphine and dose-dependent mean decrements in diastolic blood pressure ranged from 3 mmHg after 2 mg to 8 mmHg after 10 mg. These changes were observed at 10 min, appeared to peak at about 20 min after dosing, and persisted up to at least 90 min post-dosing [18].

As with nausea and vomiting, this peripheral complication appears to be less common in patients with a long history of dopaminergic treatment and is usually mild and transient [19]. Nevertheless, particular care in monitoring blood pressure should be exercised in patients with cardiac disease and in patients taking antihypertensives and/or vasodilators, especially in those with pre-existing postural hypotension. Patients should be advised that alcohol should be used with care when using apomorphine as the effects of apomorphine on blood pressure may be increased by the concomitant use of alcohol [18]. When orthostatic hypotension occurs, it typically can be managed well with general anti-orthostatic therapy. In mild cases, this may entail ensuring sufficient fluid intake (2–2.5 L/day), salt intake, raising the patient's head at night, advising slow changes of position and using compression stockings. Starting apomorphine infusion therapy in a recumbent position has been advocated by some experts to reduce the risk of symptomatic orthostatic hypotension, particularly during the first few days of infusion. In symptomatic cases, pharmacological therapy such as fludrocortisone (0.1 mg once daily, usually in the morning), midodrine (2.5–10 mg per dose as needed, but not at bedtime) or droxidopa (100 mg three times daily) is usually helpful [20]. The effect of fludrocortisone can be optimized with the co-administration of salt intake in a range of 6–12 g/day. In addition, ibuprofen can also be helpful. If orthostatic hypotension is troublesome, a critical review of the patient's medication in general is always advisable.

### 2.3. Arrhythmias

Since apomorphine, especially at high doses, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia (e.g. those with hypokalemia, hypomagnesemia, bradycardia) and when using other agents that are known to increase the QT interval [18]. Indeed, there have been occasional cases of atrial fibrillation [21,22], ventricular bigeminy [23] and transient cardiac arrest [24] reported. However, given that the reported incidence of cardiac events is uncommon (between 1/100 and 1/1000 patients), physicians should exercise their clinical judgment in deciding which patients of theirs might require closer cardiac monitoring during titration and treatment with apomorphine.

### 2.4. Dyskinesia

The potential benefits of apomorphine therapy for patients with dyskinesia are discussed elsewhere in this supplement (e.g. long-term apomorphine infusion is associated with less dyskinesia). However, it is pertinent to note here that patients with preexisting levodopa-induced dyskinesia will often exhibit some increase in the duration and intensity of their dyskinesia during the first few weeks of apomorphine therapy with intermittent apomorphine injections. In the USA registration trials for apomorphine injections, 24% of patients reported dyskinesia as an AE, and this led to discontinuation in 2% of patients [6–8]. When it occurs, dyskinesia can usually be improved by adjustment of oral therapy, either by reducing the dose or altering the timing of levodopa. Patients should be informed that injecting a dose of apomorphine too close to oral therapy increases the risk for dyskinesia, and it is often beneficial to ask the patient to complete a diary to determine the timing of dyskinesia in relation to apomorphine injections. In the case of apomorphine infusion, initial hyperkinesia can be observed, but will usually be reduced, when the oral medication is gradually lowered.

### 2.5. Sedation

Transient sedation or somnolence is another common AE experienced during the initiation of apomorphine therapy [10]. In clinical trials in the USA, somnolence was reported in 18% of patients and led to discontinuation in 2% [5]. Increased daytime somnolence and sleep attacks have now been recognized as an AE of all dopaminergic drugs [25,26], and there have been case studies of apomorphine-treated patients suddenly falling asleep [27,28].

When initiating apomorphine therapy it is necessary to inform patients about the potential dangers of driving, operating machinery or engaging in activities where impaired alertness may put themselves or others at risk. Indeed, European agencies recommend that PD patients taking dopamine agonists should be warned to not drive if they experience symptoms of excessive daytime sleepiness [29]. It can be helpful to ask the caregiver about the patient's sleep habits, since patients may not recognize that they are sleepy, having become tolerant to always being tired. To identify excess sleepiness, the Epworth Sleepiness Scale (ESS), which assesses the propensity of the patient to fall asleep may be of help [30]. Introducing good sleep hygiene is the cornerstone of effective management of any sleep disorder. It may also be helpful to reduce the total dopaminergic load, for example by reducing night-time dosing. The efficacy of wakefulness-promoting drugs, such as modafinil, remains controversial.

## 3. Local injection site adverse events

Local skin reactions, in the form of subcutaneous nodule development, occur in virtually all patients receiving continuous apomorphine infusion, and in about half of patients receiving intermittent apomorphine injection (Fig. 1a). If ultrasound treatment of the nodules is started from the beginning, bothersome nodule formation often is avoided [31]. Some patients will need this treatment once a week, some twice and a subset of the patients not at all. It should be performed by a trained physiotherapist. These nodules can be tender and they may in rare cases become infected, forming abscesses that necessitate antibiotic treatment or surgical debridement [10]. When very severe, nodule formation may interfere with the absorption of apomorphine leading to suboptimal efficacy [32]. The histopathology of apomorphine nodule formation remains poorly understood, but a local inflammatory reaction (panniculitis) in the subcutaneous tissue has been suggested [32]. Severe skin nodules can have psychological consequences leading to discontinuation in some cases. In the large Spanish study, skin nodules were one of the more common AEs leading to discontinuation (4 of 166 patients treated with subcutaneous infusion discontinued due to skin nodules) [2].

From a practical perspective, the long-term experience is that skin nodule formation seldom is the reason for discontinuation of therapy [33]. However, a new nodule may form every time the infusion needle is re-sited and if the tissue hardens over extensive areas, this can reduce the potential sites available for placing infusion needles. To minimize nodule formation, it is vital that good injection practice is maintained. In a case series of 24 patients, observation during home visits found that self-administration was not always satisfactory [34]. Examples of poor injection practice included poor hygiene, frequent casual re-siting of needles felt to be uncomfortable, removal of the needle by tugging the line sharply, and siting the needle in areas that were visibly inflamed [34]. Simple recommendations for good injection practice are provided in Table 2. It is vital that patients, caregivers and in some cases the community nurse are given sufficient training in administration. In addition, there is anecdotal information that infusion into the upper part of the back may be associated with a lower risk of nodule formation [11].

Once nodules have formed, many patients find that massaging the infusion site (using a spiky rubber massage ball, Fig. 1b) and/or silicone gel dressings are useful for tissue softening. Local massage should be continued for at least a few days after the needle is withdrawn. Change from a steel needle to a silicon needle is often helpful. It also has been reported that massaging tea tree oil around the needle site helps to reduce and relieve nodule formation [35]. Pilot studies have also reported the effectiveness of low-frequency ultrasound therapy as a treatment of nodules [35].

Other local AEs include pain, displacement of needles and skin bruises. If apomorphine is exposed to air, an oxidation reaction changes the color from colorless to green. This can cause discoloration of clothing and immediate application of lemon juice or similar acid solution can minimize this.

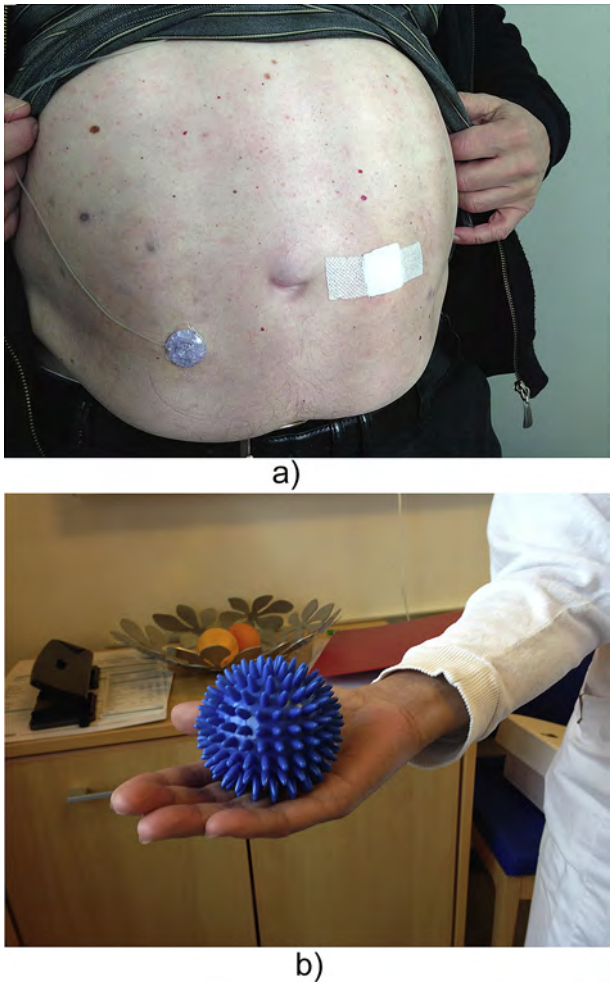


**Fig. 1.** (a) Skin nodules with subcutaneous apomorphine (b) an example massage ball, which are widely available, may be helpful in the management of skin nodules.

## 4. Systemic adverse events

### 4.1. Neuropsychiatric AEs

Neuropsychiatric AEs such as confusion, hallucinations, agitation and psychosis are well-known complications of dopaminergic treatment in PD, and can represent a significant barrier to treatment. Such AEs also are encountered with apomorphine, and have been a cause for discontinuation from clinical trials of apomorphine treatment (up to 14% of patients in the US clinical trials experienced neuropsychiatric AEs [hallucinations] and 1% discontinued) [6–8,10]. In the Spanish study, psychosis was the leading cause for discontinuation (5% patients) [2]. Neuropsychiatric AEs are reported to be more likely to develop during apomorphine use in patients who have experienced similar complications with other therapies [9,36] and a systematic review of therapies for advanced disease found there was a frequent induction or aggravation of visual hallucinations and paranoid psychosis with apomorphine [37].

Probably the risk of neuropsychiatric AEs is higher in patients treated with infusion therapy 24 h compared to day time use only [11]. Several studies report a relative lack of neuropsychiatric side effects in PD patients treated with apomorphine. In one case series of fluctuating, non-demented patients with drug-related neuropsychiatric AEs (visual hallucinations and/or psychosis), switching from oral therapy to apomorphine led to the abolition or reduction of neuropsychiatric complications in all patients [38]. Other studies with continuous apomorphine infusion report a relatively good neuropsychiatric tolerability profile for apomorphine [39,40], with one study showing worsening of neuropsychiatric symptoms (as assessed by the Neuropsychiatric Inventory) with deep brain stimulation – but not with apomorphine [41]. Hence it is speculated, that the pulsatile administration of apomorphine is more prone to give neuropsychiatric complications than the continuous i.e., when using infusion.

**Table 2**
Good injection practice.

- Sites should be rotated daily and previously used injection sites should be allowed to fully heal before another needle is inserted into that area.
- New needle/injection line every day
- No reuse of needle if it falls out
- Maintenance of good hygiene and using emollients at the injection site.
- Remove any spillage of apomorphine at the injection site, squeezing away any excess apomorphine under the skin after each injection.
- Ensure that there is no apomorphine in the needle when inserted into the skin.
- Ensure that the angle of insertion is correct for the type of needle used. In the case of butterfly infusion needles, an injection angle >45° to the skin can result in the needle being inserted too deeply, while an angle <45° can mean that the drug is injected into the superficial skin layer.
- Switch to Teflon needles, or Neria or Cleo lines, if troublesome nodules develop [12].
- Avoid long term skin problems by ensuring sufficient protein intake in general
- If troublesome nodules develop, dilute the apomorphine solution from 0.5 to 0.25%
- Adverse events are often cited as a barrier to the use of apomorphine therapy.
- Most adverse effects are manageable if reported and tackled early enough.
- We review the key adverse effects and provide practical management strategies.

From a practical management perspective, it is of note that high apomorphine doses and cognitive impairment and/or previous psychosis increase the likelihood of developing neuropsychiatric AEs [33,42]. It is therefore strongly recommended to implement a cognitive screening before initiation of apomorphine. Particular care should be taken if considering apomorphine in patients who have previously exhibited psychotic symptoms. Patients with concomitant Lewy body or Parkinson's disease dementia should not be treated with apomorphine infusion, as this may worsen neuropsychiatric complications, although some advocate the use of apomorphine infusion in carefully selected cases if the cognitive symptoms are relatively mild and the patients are optimally treated with cholinesterase inhibitors with a plan of frequent follow up visits. In patients at higher risk of developing neuropsychiatric symptoms (e.g. patients prone to psychiatric effects on oral medications), avoidance of round the clock infusion in favor of working day infusion protocols has been advocated [10]. Although marked psychosis and mania rarely develops, such symptoms usually can be well controlled by quetiapine or clozapine, which do not appear to worsen motor symptoms [43].

### 4.2. Impulse control disorders

Impulse control disorders, especially hypersexuality, may occur as with any other dopamine agonist. Punding (the display of stereotyped, repetitive behaviors) may become problematic and dopamine dysregulation syndrome has been observed with apomorphine [44].

While there is little specific data on the relationship between ICDs and apomorphine, the evidence suggests a lower rate of development of ICDs versus the other dopamine agonists. A recent retrospective disproportionality analysis of serious adverse drug event reports received by the US Food and Drug Administration (FDA) between 2003 and 2012 identified a total of 1580 ICD events (710 for dopamine receptor agonist drugs and 870 for other drugs). Of the six dopamine agonists assessed, the association was strongest for the dopamine agonists with preferential affinity for the dopamine D3 receptor (pramipexole and ropinirole) and lowest for apomorphine, which had 12 ICD serious AE reported (versus 410 with pramipexole and 188 with ropinirole) [45]. Evidence is also accumulating that in patients with moderate to advanced PD, the incidence of ICDs is substantially lower with continuous apomorphine infusion. In a multicenter study only one of 82 patients treated with apomorphine infusion developed an ICD over a mean follow-up of almost 20 months, while the overall rate was 8% [2]. Likewise, in another observational study of 41 patients receiving apomorphine infusion, seven had pre-existing ICDs all of which resolved or attenuated after the initiation of continuous therapy [46]. However, the true incidence of ICDs with apomorphine infusion compared with other dopamine agonists cannot be determined from these reports.

As with all other dopamine agonists, it is important to inform the patient and the caregiver of the risk of non-motor symptoms and impulse control behaviors and make regular enquiries into these. Sensible precautions include prompt reporting of new behaviors, and monitoring of medication compliance. The standard management procedure for ICDs is dopamine agonist reduction or discontinuation [47]. In relevant cases, the dose of apomorphine may need to be lowered, and all additional oral dopaminergic agonists should be stopped. In addition, quetiapine or clozapine may also be useful in the management of extreme pathological gambling or hypersexuality [48]. After any change in medication, careful follow up is always important particularly to monitor for the development of new impulse control disorders and dopamine agonist withdrawal syndrome, which may manifest in patients with baseline ICDs. Of note, a red flag for dopamine dysregulation syndrome is frequently ‘running out’ of medication. In these patients, it should be ascertained that the patients are not obtaining alternative supplies of short-acting preparations (e.g. apomorphine injections) from the internet, other patients or physicians [47].

### 4.3. Hemolytic anemia

Peripheral blood eosinophilia may appear transiently in some patients shortly after starting apomorphine therapy but often resolves with continued treatment [10,49,50]. Coombs positive hemolytic anemia is a rare AE of apomorphine that also may occur with levodopa treatment. It has been reported to occur in up to 6% of patients treated with continuous apomorphine infusion [51]. In addition, around 2% of patients may develop autoimmune hemolytic anemia, which usually resolves with discontinuation of apomorphine. Eosinophilic syndrome is rare, but can cause very rarely present severe manifestations, including damage to heart and lung tissue, that necessitate apomorphine discontinuation [19].

Although hemolytic anemia is a very rare complication it can be serious [56]. Once it occurs, progression usually is rapid. Baseline hemoglobin, reticulocyte count, and Coombs' tests should be obtained to initiation of apomorphine. The most common symptom of anemia is fatigue, although other symptoms such as shortness of breath, dizziness, headache, cold hands and feet, pale skin, and chest pain also may occur. Some patients with hemolytic anemia may develop jaundice. Patients who have mild hemolytic anemia often have no signs or symptoms, and a Coombs test should ideally be performed at half-yearly intervals. Hematologic consultation is recommended if Coombs’- positive hemolytic anemia does develop, and although not mandatory, cessation of therapy is advised. Caution should also be exercised in patients with pre-existing connective tissue disorders, since their presence may

suggest a higher risk for immune-mediated AEs.

### 4.4. Erectile dysfunction

There is a wealth of evidence to demonstrate that apomorphine can improve erectile dysfunction in male patients with PD [52,53]. While this can be of benefit to some patients [54], there have been case reports of priapism [18] and patients and their partners should be aware of this AE of treatment so as to promote more open discussion if this becomes problematic. Clitoral tumescence has not been reported in females.

### 4.5. Yawning

Yawning at the onset of clinical response is relatively unique to apomorphine treatment and is thought to occur as a result of acute centrally mediated effects through the activation of D1 receptors [55]; this AE rarely is troublesome to the patient.

## 5. Conclusions and importance of patient education

Proper awareness of AEs ensures that they are kept to a minimum or are quickly identified to reduce discomfort and distress. For example, a good understanding of the transient nature of nausea during the titration period can greatly enhance patient retention. Likewise, if caregivers are aware of potential neuropsychiatric effects and ICDs, they may be more likely to notice and report them earlier, which is important as these AEs usually require prompt specialist attention. All patients and caregivers should receive education and guidance on the proper administration of apomorphine (intermittent injections and continuous infusions) to avoid and minimize site reactions. Involvement of a multidisciplinary team can be pivotal in the early recognition and management of AEs.

Proper counseling, support and monitoring are therefore essential components to the ongoing management of patients receiving apomorphine. However, with proactive management, most AEs are manageable and the benefits of apomorphine can be life-changing in reducing PD symptoms and improving quality of life.

## Conflict of interest

RB, PGR and TH report fees for consultancy from Britannia Pharmaceuticals. PGR also receives consulting fees from Italfarmaco.

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# Understanding the role of the Parkinson's disease nurse specialist in the delivery of apomorphine therapy

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ABSTRACT

Optimal care of Parkinson's disease (PD) patients should involve a multidisciplinary team (MDT) of which a PD nurse specialist (PDNS) is a key member. The role of a PDNS is particularly prominent in the care of advanced PD patients suitable for apomorphine because, in addition to nursing skills, apomorphine treatment requires liaison, training, interaction and coordination with patients, caregivers and other members of the MDT as well as the interface with primary care physicians. The therapeutic success of apomorphine therapy depends not only upon the pharmacologic drug response, but also on how well the patient understands his/her disease and how to handle the therapy. In this respect, a PDNS is a vital member of the MDT who provides education and training, support, and is available for consultation when problems arise. In this article, we review the literature on the contribution of PDNSs in both continuous subcutaneous apomorphine infusion and intermittent subcutaneous apomorphine injection and highlight the various beneficial aspects of PDNS care, supported by scientific evidence when available. Despite a low level of published evidence, there is strong clinical evidence that the impact of PDNSs on the management of apomorphine therapy is vital and indispensable for the success of this treatment.


## 1. Introduction

Recent evidence suggests the efficacy of a multidisciplinary care team in the management of Parkinson's disease (PD) [1,2]. This is particularly true in the care of advanced PD patients, where the PD nurse specialist (PDNS) plays an important role in enabling patients to adjust to the different types of therapy offered, extending from oral medications to infusion therapies (both apomorphine and levodopa carbidopa intestinal gel) and deep brain stimulation. A holistic healthcare model in PD focuses on patient-centered outcomes supported by multidisciplinary professionals, but the PDNS is involved in all aspects of PD care starting right from diagnosis, assisting patients through the various types of treatment, addressing non-motor symptoms (NMS), initiating palliative care, and finally, following death, supporting caregivers and bereaved families. PDNSs not only provide the nursing skills required for the management of PD, but act as the pivotal liaison for the PD patient and the MDT, collaborating, interacting and coordinating with other care providers to ensure the holistic model of care is provided. The inclusion of PDNS support delivers a more comprehensive care by providing professional competence, nursing support, continuity of contact, and emotional support [3]. The networks of PDNS are now well established, providing

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considerable cross-cutting knowledge based initiatives that result in the development of pathways of advanced therapies. However, the nurses' involvement should be tailored to individual patients. In this article, we describe the role of the PDNS in the apomorphine treatment of advanced PD patients by reviewing relevant literature, together with expert inputs from international tertiary PD centers that have extensive experience in apomorphine treatment.

## 2. The concept of Parkinson's disease nurse specialist

The concept of training nurses with a special interest in PD, or PDNSs, has been proposed for more than 20 years to allow the provision of specialized nursing services in all clinical, educational, and professional aspects of PD care [4–7]. Community nursing teams are usually responsible for the day-to-day management of PD in the community, supported by training from a PDNS [8]. However, the setup, organization, prescribing role, and availability of nurses involved in the management of PD varies across countries, subject to different policies and resources. Recently, the trend to include a PDNS as part of the multidisciplinary care team for PD has spread to many countries and regions and has highlighted the diverse roles provided by PD nurses in the various settings in which they practice, depending on the specific local needs and organizations.

## 3. Parkinson's disease nurse specialist as a recognized status

The PDNS status is officially recognized in the UK where training is formally provided with support from the UK Parkinson's Disease Society (www.parkinsons.org.uk) and Parkinson's Disease Nurse Specialist Association (www.pdnsa.org). According to the UK's national clinical guideline for diagnosis and management of PD (NICE guideline), the key roles and responsibilities of a PDNS are: 1) making and receiving referrals to create integrated and responsive service for PD; 2) admitting and discharging patients; 3) managing caseloads; 4) providing information, education, and support to patients in their homes, in clinics and in hospitals; 5) prescribing medicines and treatment and monitoring the effectiveness of changes; 6) using the latest information technology (IT) to triage PD patients; and 7) using IT to identify patients at risk [9]. In addition, PDNSs are also available in Thailand, Denmark and the Netherlands whose experts are represented in this review. Nurses with specialized PD knowledge also work in many other countries, such as the other Nordic countries, Germany, Australia, and the USA. The role of a PDNS also has been extended to support specific advanced therapies. Many centers in the UK, Denmark and Thailand have specific PDNS who specialize in DBS, apomorphine, or levodopa infusion therapy, and effectively run the coordination of such services [6,10]. Clinical experiences suggest that availability of a PDNS leads to greater adherence to advanced therapy as well as maintenance of therapy [11]. In North America, PDNSs are attached to specialty clinics, and are funded by research grants and specific funding from foundations (e.g. the National Parkinson Foundation) through their outreach and Center of Excellence programs [4]. In some cases, nurses are trained on the job and the amount of autonomy given will depend on the philosophy of the director. Some are exclusively associated with clinical trials and others have taken on the role of educator and counsellor for patients attending routine clinics.

## 4. Evidence-based on the role of Parkinson's disease nurse specialist

Despite the diverse and essential roles of the PDNS as described above, the evidence supporting the effectiveness of PDNSs still remains inconclusive, largely due to limitations in study design, interventions and outcome measures used [12–15]. Another reason for a lack of efficacy may be because the studied outcomes are broad and not specific to certain types of intervention (e.g. apomorphine treatment). Nevertheless, patients, caregivers and physicians frequently have the clinical impression that PDNSs make a definition contribution to the care of patients with PD [13]. The clinical experience of the authors is that PD patients from centers with experienced PDNSs have a much better adherence to therapy. A good example is with apomorphine therapy, in which the PDNS plays a role in all therapeutic steps, beginning with the selection process and continuing on through initiation of treatment, maintenance of therapy, troubleshooting problems, and provision of regular education, consultation, and psychological support to both patients and caregivers [16]. Therefore, in this article, we review the literature on the contribution of PDNSs in both continuous subcutaneous apomorphine infusion (CSAI) and intermittent subcutaneous apomorphine injection (ISAI). However, before going into the details of the PDNS's role in apomorphine treatment, it is important to first understand the concept of multidisciplinary team (MDT) as the optimal care model in PD.

## 5. Multidisciplinary team as the optimal care model in PD: an emphasis on nurse's role

Optimal care in PD no longer is viewed as a one-to-one physician-patient relationship. With the current understanding of the complexity and heterogeneity of motor and non-motor symptoms, comorbidities and polypharmacy in PD, it is now clear that one treating physician alone cannot deliver a comprehensive management of this disorder. A number of recent studies also support the concept of integrating all the participating disciplines into a streamlined care team with the PD patients at the center, supported by a single or group of dedicated coordinators [1,17,18]. However, the nature of multidisciplinary treatment may vary across countries and even between centers within a given country [19]. In this respect, the PDNS's role can be viewed as a multidisciplinary one as he/she acts as a professional as well as the person who is close to the PD patient and is able to work in an interdisciplinary environment consisting of experts from different health professions, either in a community or hospital-based setting (Fig. 1) [5,12,20]. Many PDNSs run their own clinics, make home visits, refer to other experts and coordinate care packages according to a patient's needs (Fig. 2). In some centers in Denmark, PDNS even have a restricted

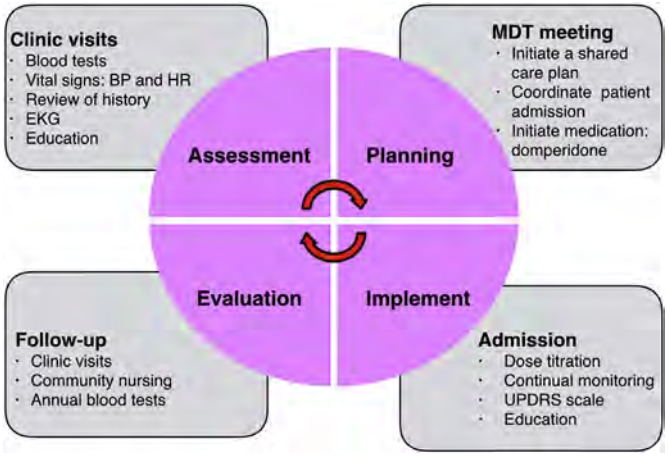


**Fig. 1.** The diagram illustrating the role of Parkinson's disease nurse specialist list. MDT: Multidisciplinary team.

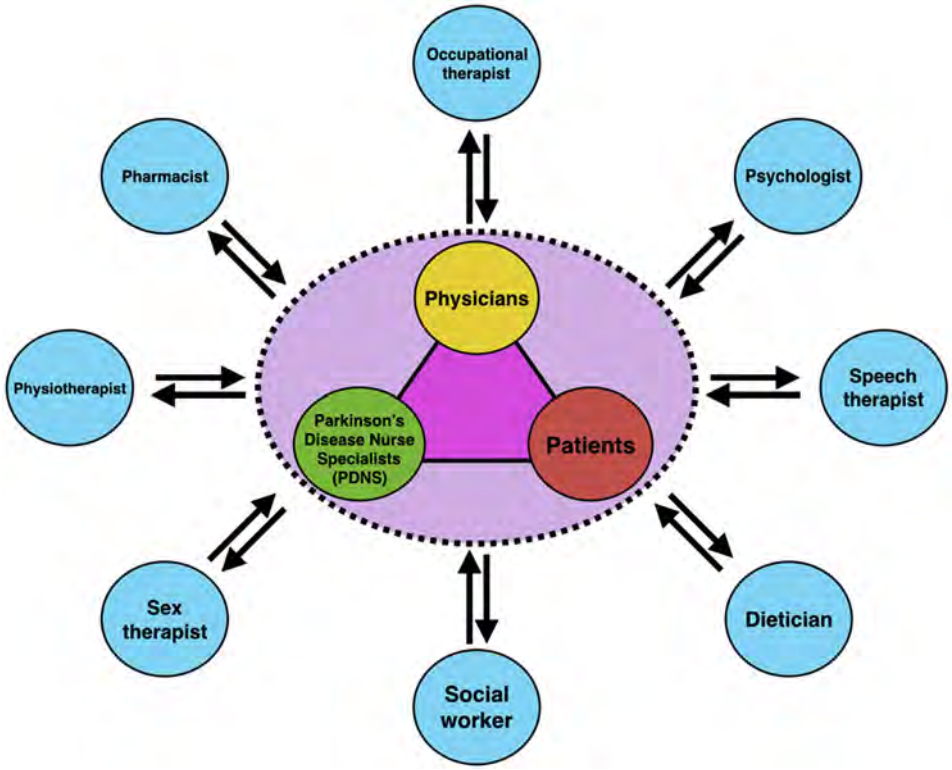


**Fig. 2.** Members of the multidisciplinary care team with patients at the center along with physicians and Parkinson's disease nurse specialists who are involved in the care of each patient on a regular basis.

license to prescribe antiparkinsonian medications, and in some centers in the UK, PDNSs serve as consultants with full prescribing authority, running their own clinics for specialized treatment. Community nurses also have an important role in monitoring and administering on-going drug therapy, such as monitoring skin health and apomorphine therapy at home. In addition, they help reduce the workload of neurologists and geriatricians who are in short supply not only in developing countries like Thailand, but also in many developed countries, such as England [21,22].

Evidence is growing to support the effectiveness of various allied health disciplines in PD. While the case already is strong for specific physiotherapy techniques, and the evidence supporting the important role of the PDNS in disease management is starting to emerge. At a randomized controlled trial level, PD patients attended by a PDNS had significantly better scores on the Global Health Questionnaire at a 2-year follow up, better communication scores on the 39-item Parkinson's Disease Questionnaire, an improved sense of wellbeing with no increase in healthcare costs, and better access to information and referrals to other healthcare agencies [13,14,23,24]. In addition, the results from an independent assessment of patient satisfaction demonstrated the usefulness of nursing intervention and the high preference for home visits [23]. A recent, albeit, weaker, study involving qualitative interviews also reported the beneficial impact of PDNSs in providing individually tailored and competent care that focused on alleviating the impact of the disease on daily life [3]. Compared to neurologists, PDNSs were found to provide longer consultations and pay more attention to patients' concerns [13]. In the evaluation of a nurse-led multidisciplinary inpatient rehabilitation program, significant improvement was observed in health-related quality of life of patients following a short intervention of 5–10 days [25]. A longer study documented high patient and stakeholder satisfaction with nurse-led Parkinson's services, which helped patients understand their care plans and achieve patient self-management, when measured at a 2-year follow-up [26]. However, the high workload of PDNSs has been highlighted as a major constraint on the implementation of outreach services and national guidelines, at least in England and Australia [21,26].

Although the effectiveness of nursing care for PD has not been widely studied, what little evidence is available supports the value of PDNSs. In clinical terms, it is clear that the PDNS is an essential member of the MDT, with a vital role in providing clinical monitoring and medication adjustment and acting as a continuing point of contact for support and education for PD patients and their caregivers at all stages of the disease. The value of PDNS involvement should not be based on the direct cost effectiveness, but also on the indirect savings due to the reduction of costly hospital admission and extended hospital stays [27].

## 6. Continuous subcutaneous apomorphine infusion: a nurse's role

CSAI therapy is indicated in PD patients with unpredictable 'off' periods that can no longer be adequately controlled by oral treatment, or when rescue doses of apomorphine injections are effective but either are needed too frequently or are associated with unacceptable dyskinesia [16,28]. With the support of PDNS, several steps as detailed below are needed to ensure the successful implementation of CSAI.

### *6.1. Selecting candidates for continuous subcutaneous apomorphine infusion*

Although the decision regarding the suitability of suitable candidates for CSAI therapy is the responsibility of treating neurologists who have experience in the management of PD, PDNSs can assist

physicians in the process by screening patients with motor complications for those with frequent and prolonged 'off' periods associated with swallowing difficulties or gastrointestinal problems [16]. This information can be retrieved easily by reviewing patient's diaries and obtaining confirmation from direct communication with district nurses or caregivers (Fig. 3). The PDNS also can assist treating neurologists by ensuring the use of validated screening tools (e.g. the Non-Motor Questionnaire, NMSQuest) in the review of profiles of potential candidates for possible exclusions, such as severe dementia and psychiatric and behavioral disorders [16].

Once potential candidates for CSAI therapy are identified, it is usually the PDNS who leads a group discussion involving the patient, caregiver, and the treating neurologist to ensure that the patient understands the treatment goals, what to expect, possible adverse events and what support that is available to them. Whenever possible, information from a peer in a local Parkinson's Association is often very helpful. Basic education is usually provided at this stage so that a patient can recognize their 'on' and 'off' periods as well as dyskinesias and other dose-related adverse effects. Before starting on CSAI therapy, it is important that patients understand how apomorphine therapy works and the rationale for its use and that they are able to keep reliable 'on/off' diaries [29]. Questionnaires such as Questionnaire 10 (AQ10) and information booklets on apomorphine may be administered or given at this stage [30]. Once patients pass the evaluations that include ECG (to exclude prolonged QT interval, arrhythmias) and blood tests confirming no signs of hemolytic anemia, the consent for CSAI therapy can be obtained, followed by a schedule for apomorphine titration.

### *6.2. Starting patients on continuous subcutaneous apomorphine infusion and setting up educational training*

The setup of the initiation phase of CSAI therapy may differ across PD centers depending on local guidelines, resources, and the philosophy of the MDT. However, all centers share the same goal of establishing a good therapeutic response to apomorphine and teaching the patient and caregiver how to manage the infusion. Although most guidelines recommend hospitalization during the initiation, a recent consensus statement offers the possibility of starting CSAI therapy as an out-patient or day-care patient if the team is equipped and experienced in such settings [28]. The PD centers at King's College in London and Chulalongkorn University in Bangkok have adopted the day-care approach for the titration based on experience from many years of apomorphine therapy [6,16]. Some centers initiate the treatment with an apomorphine challenge test performed by the PDNS who gradually increases the doses of apomorphine given during a period of 5 h. The effects of the injections are registered by the PDNS, along with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III), and video documentation in some cases.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.11.014.

In most places, PDNSs usually take a lead in the arrangements, including activating local pathways (in the UK, known as shared care), pre-appraising the primary care physician regarding the plan to start apomorphine, and ensuring that all home support is in place. Pre-treatment with domperidone for at least 3 days is

| Name: Mr. XXX XXX | | Date. 23/3/16 | | | | | Day 1 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose | | | | | | | | | | | | |
| Test time | 8:45 | | 10:00 | 11:00 | 12:00 | 13:00 | 14:00 | 15:00 | 16:00 | 17:00 | | |
| Injection time | | 9:00 | | | | | | | | | | |
| Bolus dose | | | | | | | | | | | | |
| Continuous dose | | 0.5 mg | 1 mg | 1 mg | 1.2 mg | 1.4 mg | 1.6 mg | 1.8 mg | 1.8 mg | 1.8 mg | | |
| Additional dose | | | | | | | | | | | | |
| Blood Pressure | 132/68 | | 129/68 | 118/62 | 110/53 | 135/62 | 161/70 | 135/66 | 144/66 | 138/72 | | |
| Pulse | 66 | | 58 | 76 | 70 | 63 | 70 | 57 | 67 | 64 | | |
| Tapscore Right (times in second) | 96 | | 88 | 90 | 92 | 100 | 132 | 84 | 88 | 86 | | |
| Tapscore Left (times in second) | 76 | | 76 | 78 | 76 | 80 | 120 | 64 | 80 | 76 | | |
| Walking test (steps in seconds) | 23 | | | | 55 | 16 | 19 | 23 | 12 | 14 | | |
| Walking test (Steps in seconds) | 26 | | | | 37 | 22 | 15 | 20 | 16 | 18 | | |
| UPDRS III | off:52/on:31 | | | | | | | | | | | |
| Side effect | | | dizziness | | | | | dizziness | | | | |
| +3 Very dyskinesia | | | | | | | | | | | | |
| +2 Moderate dyskinesia | | | | | | | | | | | | |
| +1 Mild dyskinesia | | | | | x | x | | x | x | | | |
| 0 Normal | x | x | | | | | x | | | x | | |
| -1 Light rigid | | | x | x | | | | | | | | |
| -2 Moderate rigid | | | | | | | | | | | | |
| -3 Very rigid | | | | | | | | | | | | |
| Medications / Time | 5 | 8 | | 11 | | | 14 | | | 17 | 20 | hs |
| Levodopa/ benserazide (200/50) | 3/4 | 1/2 | | 3/4 | | | 1/2 | | | 1/2 | 1/2 | 0 |
| Levodopa/ benserazide HBS (100/25) | 1 | 0 | | 1 | | | 0 | | | 1 | 0 | 1 |
| Rivastigmine patch | 1 | | | | | | | | | | | |
| Rotigotine patch (4) | | | | | | | | | | | 0 | |
| Quetiapine (25) | | | | | | | | | | | 1/2-1 | |
| Clonazepam (0.5) | | | | | | | | | | | 1/2-1 | |
| Domperidone (10) | | 1 | | 2 | | | | | | 1 | | |

**Fig. 3.** An example of electronic medical record for apomorphine titration.

provided to patients in most, although not all centers. PDNSs also can determine the infusion dosage by evaluating a patient's motor response at hourly intervals under the supervision of the treating neurologist (Fig. 3). One option is to run both patients' and PDNS's diaries in parallel, which are continually reviewed for concordance during this period. Another option is to use an ambulatory objective monitoring device to evaluate motor responsiveness, reported as the severity of bradykinesia and dyskinesia. Apomorphine is usually initiated at a low rate (1–2 mg/h). The dosage is slowly titrated over 5–7 days until the optimum dose is reached or unacceptable side effects develop [16,28]. Experience suggests that a slower increase in the hourly flow rates may be appropriate for the out-of-hospital settings [28]. However, a recent case series of PDNS lead titrations of CSAI in a wide variety of settings including day hospitals and patients' own homes, reported good tolerability to a rapid titration schedule with most patients successfully titrated within 2 h [31]. In the published literature, several protocols are available for commencing CSAI therapy, details of which are beyond the scope of this review [32–36]. During the titration, PDNSs should look for potential adverse events, including nausea, vomiting, and hypotension, which commonly occur at both initiation and dose escalation. Reviewing injection sites for any problem also is important.

In the titration period, the PDNS should set aside time on a daily basis to provide the patient and caregiver with information and education, to encourage discussion, and to answer any questions. Hands-on training for both patient and caregiver can be provided at this stage to review injection and needle-insertion techniques and how to handle and operate the device. Training should be given in a structured manner and not left to chance. An objective worksheet signed by both PDNS and patient/caregiver is one way that the PDNS can ensure that various aspects of training are covered and understood by both patient and caregiver [34]. This worksheet also provides good evidence that training was given and that the nominated person is proficient in performing the needle insertion and administering the pump. In most cases, apomorphine is currently administered via the Crono Apo-Go III portable infusion pump (Genus Pharmaceuticals Ltd., Berkshire, UK) for ambulatory use connected to a subcutaneously inserted cannula. This pump is specifically designed for the purpose of delivering apomorphine. It is portable and can be carried in a pocket, placed under a shirt, attached to a belt, or worn around the neck (Fig. 4). The pump is only licensed for the use with apomorphine, so it is possible that many healthcare professionals will be unfamiliar with it. The PDNS usually is responsible for teaching patients, caregivers, district nurses, or local nurses on how to use the pump. Our center in Thailand provides a useful video and step-by-step guide to give practical information about the Apo-Go pump (Supplementary data 1). The level and the quality of the education given to patients on CSAI can influence the compliance with and the success of this treatment. Patients with inadequate education and support often discontinue apomorphine therapy within weeks [8].

Close interaction between patient and PDNS (preferably with caregiver as well) is crucial to ensure that patients are able to handle the device correctly, that they know how, where, and when to administer apomorphine and how to take the best possible advantage of the treatment (Fig. 4). The length of the initial setup depends on when a reasonably balanced clinical state can be reached and when the patient is able to handle the pump safely. According to most published literature as well as our own experience, this process usually takes at least a week [16,28,29]. The first follow-up visit after discharge usually takes place within a week and can be at the patient's home or in the medical center, depending on local availability.

### 6.3. Maintenance of continuous subcutaneous apomorphine infusion

The focus during the maintenance of CSAI therapy is to ensure that patients are able to manage treatment independently or with the help of their caregiver, or if necessary with outside assistance from a PDNS or community nurse. Independent management of CSAI therapy by the patient is associated with a higher success rate [33]. Although the patient is encouraged to be independent with the administration of infusion, it is vital for patients to have access

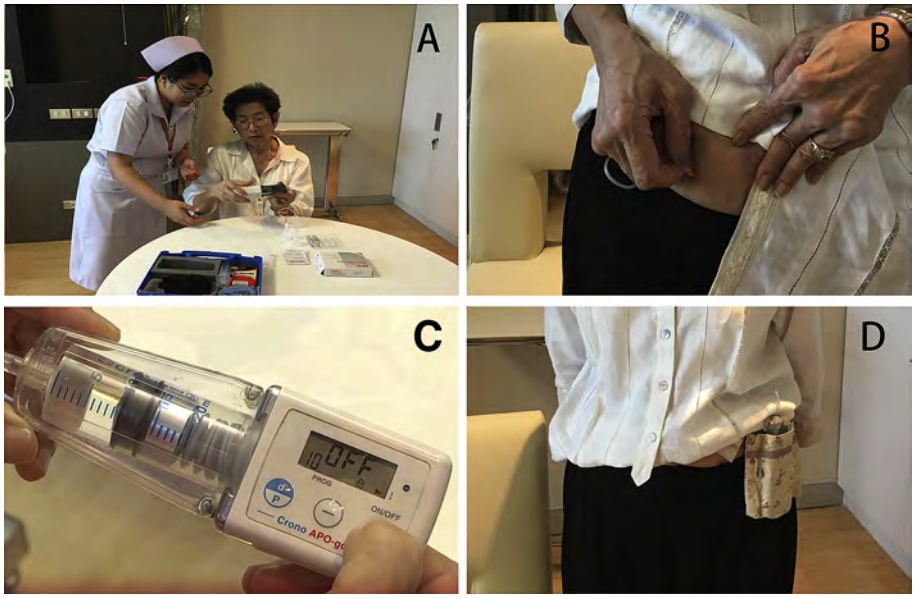


**Fig. 4.** The set of photographs illustrating a role of Parkinson's disease nurse specialist (PDNS) during the titration of a patient for continuous subcutaneous apomorphine infusion. A: A PDNS taught a patient on how to operate the pump; B: A patient performed self-placement of the injection needle; C: A patient operated the pump by herself; D: This patient made her own pouch for carrying apomorphine pump, attached to a belt.


**Fig. 5.** The set of photographs illustrating a role of Parkinson's disease nurse specialist (PDNS) in teaching patient on how to perform a subcutaneous apormorphine injection. A: A PDNS taught a patient on how to operate a penject; B: A PDNS cleaned patient's skin at the injection site; C–D: A patient performed self-injection under a supervision of PDNS.

to, and support from, PDNSs, even after they have completed the initiation period [8]. A step-by-step guide, Shared Care guidelines, and contact details for the patient's PDNS should be made readily available to the patients and caregivers [34]. In our experience, many problems can be solved with a direct telephone consultation with a PDNS. In certain circumstances, a district nurse or PDNS should be available to provide home visits to relieve the stress or burden that may be put on the patient's family [8]. The availability of such support may be different across PD centers depending on local guidelines and resources.

### *6.4. Prevention and troubleshooting of potential side effects*

One of the key success factors of CSAI therapy is to prevent or minimize potential side effects with apomorphine therapy. Secondary adverse effects are one of the main reasons for discontinuation of CSAI [37]. Although most patients (over 80%) in a long-term efficacy study of CSAI therapy reported at least one adverse event, there were usually manageable and no serious adverse effects were documented in this study [37]. The three most common adverse events in this study were skin reactions (87%), followed by confusion and hallucinations (35%), and sedation/drowsiness (29%) [37]. District nurses and general practitioners have a vital role in identifying and reporting these adverse effects to the PDNS or medical team before they become problematic [8].

Local skin reactions can range from temporary flushing or itching of the abdominal wall to formation of skin nodules, infection and development of abscesses, or in the worst cases, necrotic ulcers [38]. Of these, skin nodules are the most common and are frequently associated with discoloration and scarring. The duration of the reaction and the size, severity and appearance of nodules can vary considerably between individuals and is linked to the dose of apomorphine, skin type, body mass index, needle type, and insertion techniques [39]. A minority of patients discontinue CSAI therapy because of skin reactions [33]. Therefore, proper instructions on needle insertion techniques and a record chart, completed by patients, caregivers, or nurses, are crucial to prevent or minimize the severity of nodule formation. Several methods, mostly based on expert opinions, have been described for effective management of skin nodules but details are beyond the scope of this review [16,28,38,39].

## 7. Intermittent subcutaneous apomorphine injection (penject): a nurse's role

Due to its rapid onset of action and its reliable effect, ISAI is suitable as a rescue therapy for PD patients with motor and non-motor fluctuations who experience unpredictable 'off', symptomatic early morning akinesia with dystonia, delayed 'on' due to poor levodopa absorption, or require reliable and fast relief when anticipating an 'off' [16,28]. In the most commonly used form, ISAI comes in a pre-filled penject device so it does not require much preparation by the patient or caregiver. However, the patient needs to learn when to administer the injections; therefore, the patient must be able to recognize the 'off' and 'on' stages of his/her symptomatology. Since ISAI usually is administered on an 'as needed' basis, on most occasions, the injection is performed by the patient. Caregivers also may be trained as a backup for situations in which the patient is unable to perform the injection. Training can be delivered on as an outpatient basis and should focus on teaching the patient how to operate the penject and perform the injection with confidence, particularly during the 'off' state when some patients may find it difficult to handle the device leading to stress and anxiety (Fig. 5) [34]. For best results, injections should be given at the very beginning or, ideally, in anticipation of an 'off' state [40]. Patients should be instructed to recognize and respond promptly to the earliest, and often extremely brief, premonitory signs of impending immobility [40]. It is the responsibility of the PDNS or physician to ensure sufficient training for patients so that they are able to handle the injection device and administer the injection in a safe and correct manner.

## 8. Conclusion

The therapeutic success of apomorphine therapy is related not only to the pharmacologic drug response, but also to how well the patient understands his/her disease and how to handle the delivery of their therapy. In this respect, the PDNS, as a vital member of MDT,

makes an especially important contribution by ensuring adherence to therapy, providing education and training and ongoing support, and being available as a backup for consultation when problems arise. The PDNS can ease caregivers' burden and relieve physicians' workload pressures by providing ongoing management of PD patients on a daily basis. In this respect, the contribution of a PDNS can be appreciated throughout the apomorphine therapy process, from candidate selections to dose titration and maintenance of treatment and reduction of adverse events. Despite a low level of published reports, there is strong clinical evidence that the high level of competence, continuity and availability of PDNSs in the management of apomorphine is vital and indispensable for the success of this treatment.

## Conflict of interest

The authors have no conflict of interest.

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# Apomorphine therapy in Parkinson's disease and future directions

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ABSTRACT

Apomorphine infusion or injection is an important dopamine agonist non-oral therapy usually used in advanced Parkinson's disease (PD) with refractory motor fluctuations. The drug also has appreciable efficacy for nonmotor fluctuations and is the quickest to reverse predictable "off" periods. Current subcutaneous administration, however, is complicated by problems associated with needle-based therapies, such as skin nodule formation, skin irritation, and avoidance of this treatment option by needle-phobic subjects.

In this review we focus on what the future might hold for apomorphine injection/infusion. We discuss interesting and novel delivery strategies of apomorphine or esters via oral, buccal, inhalation and a novel pump-patch route. We also discuss recent research that has highlighted some important properties of apomorphine in animal models, such as a potential anti-amyloid effect and its potential impact in the management of PD dementia or perhaps even Alzheimer's disease. A potential role for apomorphine infusion in cases with impulse control disorders and other nonmotor issues is also discussed.



## 1. Introduction

Apomorphine therapy for Parkinson's disease (PD) has a rich and extensive past, being described as useful for the management of PD by Weil in the 19th century. Fast forwarding, Schwab et al. reported that apomorphine hydrochloride attenuated tremor and rigidity in PD patients, a finding that has been successfully translated to clinical therapy for PD in the 20th century [1–5]. This short review focuses on what the immediate and more distant future may bring in terms of apomorphine therapy for PD, in terms of delivery systems as well as efficacy for management of some symptoms regarded as key unmet needs in PD.

## 2. The immediate future

### 2.1. The TOLEDO study

This will entail the release of the data from the TOLEDO study (ClinicalTrials.gov Identifier: NCT02006121), a multicenter, parallel-group, double-blind, placebo-controlled phase III study that was designed to evaluate the efficacy and safety of subcutaneous apomorphine infusion in PD patients with complicated motor fluctuations refractory to conventional medical treatment. The study was conducted in 7 countries and 23 hospitals. Recruitment and enrolment are completed and outcome data are being analyzed. It is expected that there will be a greater reduction of "off" periods in the apomorphine arm compared with placebo, but the secondary efficacy variables, such as the effect of apomorphine versus placebo on the nonmotor symptoms scale of PD (NMSS), both in relation to the individual domains and total score, also will be of great interest. This is because several open-label and comparative studies point towards the efficacy of apomorphine on some nonmotor symptoms such as sleep, mood and nonmotor fluctuations [6–8].

## 3. Apomorphine delivery strategies: what does the future hold?

The subcutaneous route has been the mainstay for apomorphine therapy, either as a pen delivered injection or continuous infusion. Although effective, skin nodules complicate such therapy and in some cases become problematic. For some patients, the treatment cannot be used because of needlephobia. The development of alternative routes of delivery of apomorphine is, therefore, an

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**Fig. 1.** Device for inhaled administration of apomorphine.

unmet need and strategies are being developed.

### 3.1. Inhaled apomorphine

One such route is the pulmonary route in which apomorphine is administered by an inhaler device (Fig. 1). The pulmonary route bypasses the gastrointestinal tract and provides rapid delivery of the drug to the central nervous system. This is further aided by the fact that the pulmonary system is highly vascular. An inhaled version of apomorphine (VR040) has been developed and has been utilized in a phase 2, placebo-controlled, double-blind clinical trial at a single center in the UK (ClinicalTrials.gov Identifier: NCT01683292). The product is aimed at a quick rescue from "off" periods and, in the clinical trial, 3 doses (0.2, 0.5 and 0.8 mg) were studied. At 0.5 and 0.8 mg "off" was reversed and "on" state was achieved at 40 and 20 min respectively; the product was well-tolerated [9]. A subsequent study, with higher doses up to 4 mg, showed good efficacy with a peak plasma level at 2–7 min after inhalation and "off" period reversal at a mean of 10 min. Long-term efficacy data and multicenter trials are still required, but inhalation may become a feasible delivery route for apomorphine rescue therapy in the future [10]. Pulmonary irritation on long term exposure and the ability of PD patients to handle the inhaler device during severe motor "off" periods remain concerns.

### 3.2. Apomorphine via the patch pump technology

The transdermal patch-pump is a technology where a mini-pump is attached to a skin patch and delivers the drug via the transdermal route (Fig. 2). The method has been utilized for levodopa delivery and an apomorphine product (ND0701) has been developed for use by this route in advanced PD as an alternative option to apomorphine infusion. The safety and tolerability of this delivery system needs to be further established.

### 3.3. Apomorphine via the sublingual route

A buccal formulation of apomorphine (APL-130277) is being developed for use as a rescue medication in overcoming "off" periods (Fig. 3). The product is a thin-film strip containing apomorphine in a bilayer (to avoid oral irritation) and patients are instructed to keep the film under the tongue for the drug to be absorbed through the oral cavity for rapid delivery. In initial studies, 15 of 19 patients studied experienced reversal of their "off" periods within 30 min (average time to full "on" was 22 min) with the "on" lasting for a mean duration of 50 min [11]. No major adverse events have been reported and there is no report as yet of any problematic mucosal irritation in the mouth. Phase 3 trials with APL-130277 are now under way in doses ranging from 10 to 30 mg in what promises to be an important new development for rescue therapy in PD (ClinicalTrials.gov Identifier: NCT02469090).

Another sublingual device, delivering a buffered solution of apomorphine (RN-101, Apotone) is also being developed. Using buffered solutions at a pH of 7.6 in an early trial the product, which is delivered by a dual chambered device, has shown time to T-max and C-max being comparable to a single dose of subcutaneous apomorphine.

### 3.4. Oral delivery of apomorphine and derivatives

Oral therapy with apomorphine could avoid many of the problems associated with a needle based subcutaneous therapy, but intestinal absorption of apomorphine remains a key problem. Borkar et al. [12] used a Caco-2 monolayer that is grown on a filter support and is known to be a good model for assessing intestinal permeability and have shown that of two apomorphine esters, monolauroyl apomorphine (MLA) and dilauroyl apomorphine (DLA), MLA can be transported and DLA needs to be converted to MLA for transport. Another study has described the beneficial motor effects of the orally active compound, R-(-)-11-*O*-valeryl-*N*-*n*-propylnoraporphine, in 1-methyl-4-phenyl-1,2,3,6-

**Fig. 2.** A patch-pump device for delivery of the drug via subcutaneous route.

**Fig. 3.** The buccal strip containing apomorphine in a bilayer format.

tetrahydropyridine (MPTP)-treated, levodopa-primed dyskinetic common marmosets [13]. Reversal of motor disability and improvement of dyskinesia in these preclinical studies is described as paving the way for future clinical trials of apomorphine esters as oral prodrugs for PD patients.

### *3.5. Controlled release drug delivery systems: poly(lactic-co-glycolic acid) (PLGA) copolymers*

The PLGA polymers could help in promoting slow release of apomorphine in humans if implanted. Experimental studies by Regnier-Delplace et al. [14] suggest that novel types of PLGA co-polymers, which either bear free or esterified -COOH groups in the side chains, provide efficient protection against degradation of products during storage, remove toxic solvents, and provide controlled release of apomorphine at a constant rate, thus offering the potential for future therapeutic approaches.

## 4. Apomorphine: brain, behavior and cognition

### *4.1. Apomorphine link with striatal dopamine transporter*

Apomorphine has been linked to improvement in behavior in previous studies and open-label observations suggest its safety and efficacy in PD patients with psychosis and neuropsychiatric symptoms and in managing the negative symptoms of schizophrenia [15–17]. Passamonti et al. [18] reported that individual differences in striatal dopamine transporter (DAT) levels and levels of nigrostriatal degeneration, measured with DaTscan, drove striatal neural activity during working memory exercises in PD, via a D2-receptor-mediated mechanism. The data suggest that apomorphine challenge increased the striatal response but reduced activation of the superior frontal gyrus during working memory in these patients (Fig. 4). It is possible that these findings could be translated to clinical paradigms to address the behavioral effects of apomorphine using a combination of functional magnetic resonance imaging (f MRI) and quantitative DAT imaging studies.

### *4.2. Apomorphine and brain amyloid deposition: is there a role?*

Up to 80% of patients with PD develop functionally significant cognitive impairment [19,20]. Studies in rodent models of Alzheimer's pathology and neuropathological studies based on brain bank studies in PD patients suggest that apomorphine might have a role as a potential modifier of amyloid deposition as well as autophagy and anti-oxidation [21,22]. In 3xTg-AD mice, apomorphine infusion appears to improve memory function with a decrease in intraneuronal amyloid deposition [21]. A retrospective brain bank-based study of non-demented PD cases suggested a potential anti-amyloid effect of apomorphine [23].

Whether these observations may translate into a clinical therapeutic option for apomorphine as therapy for cognitive impairment in Alzheimer's disease or PD remains to be established via large scale controlled clinical trials, perhaps with surrogate amyloid imaging.

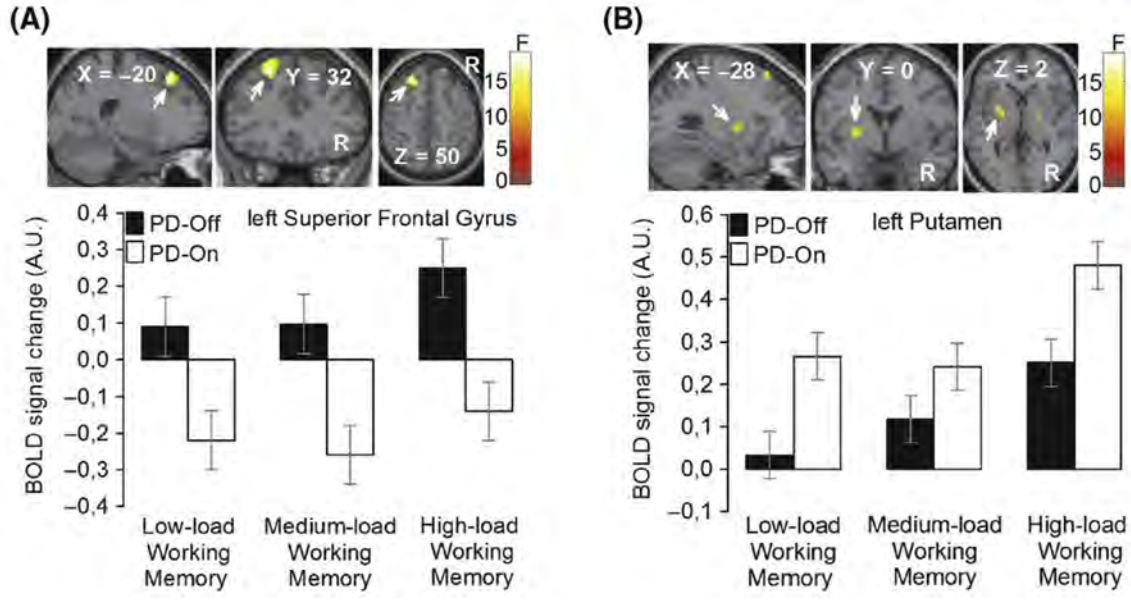


**Fig. 4.** Activation (reduced) of superior frontal gyrus by apomorphine during working memory load (panel A) versus increased striatal activation by apomorphine (panel B). Taken from Passamonti et al. [18].

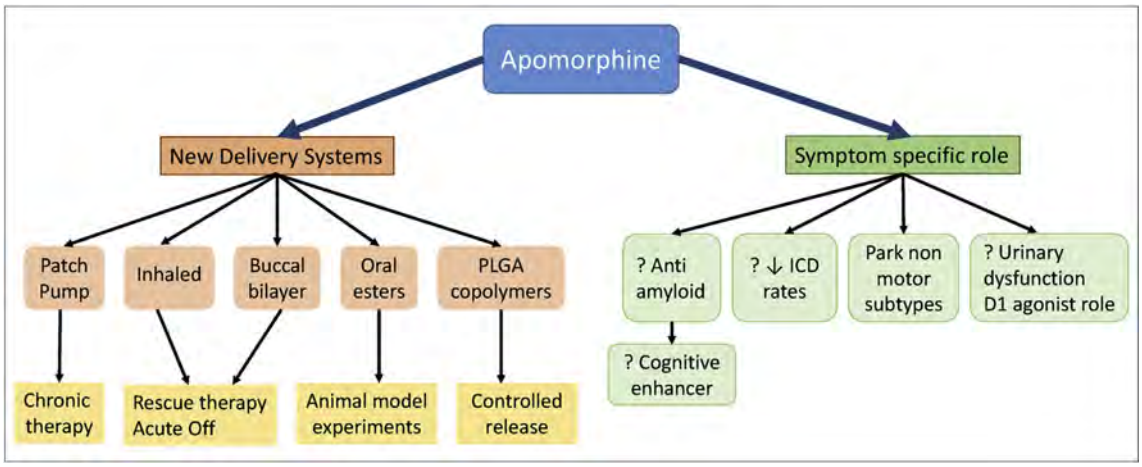


**Fig. 5.** A summary of possible future roles of apomorphine driven by symptoms and variable delivery strategies.

### 4.3. Impulse control disorders and apomorphine infusion

Impulse control disorders (ICD) have emerged as a key challenge to dopaminergic treatment in PD, particularly the use of dopamine agonist therapy, which also is complicated by the potential for dopamine agonist withdrawal syndrome [24]. Recent evidence suggests that ICD rates may be lower when dopamine agonists are administered in a continuous drug delivery strategy rather than as pulsatile therapy. Evidence for this has emerged with low rates of ICD being reported with rotigotine transdermal patch therapy in an open-label, observational, multicenter study compared with oral dopamine agonists [25]. A 3-year clinical observational study that screened a cohort of patients receiving apomorphine infusion and intrajejunal levodopa infusion for specific development of ICD reports a relatively low rate (9.7%) of new cases on apomorphine infusion with clinically relevant ICD. However, apomorphine had to be discontinued in only 1 case because of ICD [26]. It is intriguing to consider whether apomorphine infusion in suitably selected cases of patients with ICD may be a feasible option to consider, as has been suggested in a review of management of ICD in PD [27].

### 4.4. Apomorphine and the future (Fig. 5)

Can apomorphine be used for specific nonmotor indications? Open-label and two open-label comparative studies (one against best medical treatment and one versus intrajejunal levodopa infusion) suggest specific nonmotor efficacy of apomorphine in addition to postulated benefits on neuropsychiatric states [6–8]. Aspects of sleep (refreshment, restless legs, nocturnal akinesia, early morning “off” related symptoms), “off” related pain, urinary dysfunction and mood improve consistently [7,8]. Controlled studies should indicate whether in the future apomorphine therapy might be specifically selected for PD nonmotor subtypes [28]. Specifically, the role of apomorphine in the management of urinary dysfunction (in part mediated by the strong D1 agonist action of apomorphine), sleep (nocturnal motor intrusions), mood and nonmotor fluctuations needs to be addressed.

## Conflict of interest

Authors report no conflict of interest.

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Aims and Scope

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