



Apomorphine for Parkinson's Disease: Efficacy and Safety of Current and New Formulations

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Abstract

Satisfactory management of Parkinson's disease is a challenge that requires a tailored approach for each individual. In the advanced phase of the disease, patients may experience motor complications despite optimized pharmacological therapy. Apomorphine, a short-acting D₁- and D₂-like receptor agonist, is the only drug proven to have an efficacy equal to that of levodopa, albeit with a shorter time to onset and effect duration. Clinical trials have shown that intermittent apomorphine injections provide rapid and effective relief from unpredictable “off” periods. Continuous apomorphine infusion reduced around 50% of the daily “off” time in several studies. Dopaminergic side effects such as nausea, somnolence and hypotonia, as well as administration site reactions, are often mild or treatable, but somnolence and skin reactions in particular can sometimes be reasons for premature discontinuation. We provide an overview of the pharmacological mechanism of action of the drug in light of its effects on Parkinson's disease symptoms. We then summarize the evidence regarding the efficacy and tolerability of apomorphine, both in its established formulations (subcutaneous intermittent injection and continuous infusion) and in the new preparations currently under investigation.

Key Points

Apomorphine is the oldest dopaminergic drug available for Parkinson's disease, and—to date—it remains the only drug with efficacy comparable to that of levodopa.

Subcutaneous apomorphine, delivered as a continuous infusion or as intermittent injections, has proven well-tolerated and effective.

Several alternative routes to simplify delivery of the drug have been tested, and some are in active clinical development.

1 Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease, affecting 1% of the population aged > 60 years and reaching 3% in the highest age groups [1, 2]. Neuropathological hallmarks are progressive loss of dopaminergic neurons in the pars compacta of the substantia nigra, causing striatal dopamine deficiency, and intracellular inclusions containing aggregates of alpha-synuclein. PD is clinically defined by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity or rest tremor). In addition, most patients with PD also experience non-motor symptoms (NMS), adding to the overall burden of parkinsonian morbidity [2].

PD was the first neurodegenerative disease for which highly efficacious treatments became available. Dopamine replacement with oral levodopa is still the gold standard of symptomatic therapy, matched only by apomorphine in its effect size on motor symptoms [3]. The response to levodopa is maintained in the long term, but many patients develop challenging motor complications such as motor fluctuations and dyskinesia as the disease progresses [4, 5]. The current role of apomorphine in the treatment of PD is in the management of levodopa-related motor complications—as either intermittent subcutaneous pen injections or continuous

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subcutaneous mini-pump delivery. We review the pharmacology and clinical studies of the efficacy and safety of subcutaneous apomorphine administration in treating motor fluctuations in PD and give a brief overview of alternative apomorphine formulations currently in clinical development.

2 History of the Molecule Across the Centuries

Today, apomorphine is known as a dopamine agonist for the treatment of advanced PD, but its first use very likely dates to ancient civilizations, with fascinating analogies between cultures as far apart as those of the Mayas and the ancient Egyptians. Abundant clues rest in the iconography of these two civilizations testifying to the central role of *Nymphaea* plants (water lilies) in magical-religious rites. We know today that several aporphines, including apomorphine, can be isolated in the roots and bulbs of water lilies. The plants were most likely used as an emetic in purifying rituals and as an aphrodisiac and hallucinogenic for the higher castes [6–8]. Interestingly, the effects sought and experienced by these ancient civilizations are the very same that were clinically assessed thousands of years later, after the discovery of synthetic apomorphine.

The credit for discovering apomorphine is given to the studies of Matthiessen and Wright [9], who in 1868 synthesized apomorphine hydrochloride by heating morphine with concentrated hydrochloric acid. The compound was named *apomorphia* to highlight its origin and its difference from the mother compound, morphine. While it was only after the experiments by Matthiessen and Wright that apomorphine started to attract interest in both human and veterinary medicine, it is fair to note that Arppe [10] was probably the first to synthesize the molecule in 1845 by heating morphine with an excess of sulphuric acid, therefore naming it *sulphomorphide*.

In the years following its discovery, apomorphine was used in different experiments in animals and humans, showing a range of effects leading to its use in several fields of medicine. By virtue of the studies conducted by Gee, Hare, Pierce, Siebert and Harnack [11–15] in humans and animals, the effects of apomorphine were linked to action on the central nervous system. Most notably, an emetic response was almost invariably observed in humans and dogs with oral and parenteral administrations. An unwanted effect of today's use of apomorphine, emesis became the main indication for the drug for several decades and led to its use in removing foreign objects from the esophagus or in treating poisoning. This emetic response was also used to induce adverse conditioning by administering the drug with the undesired stimulus in cases of drug, alcohol and smoking dependence [16].

Oral apomorphine is subject to extensive first-pass metabolism resulting in low bioavailability, and parenteral delivery of the drug was the preferred administration route in most studies and experiments [17, 18]. The clinical use of apomorphine between the end of the nineteenth century and beginning of the twentieth century covered almost every field of medicine. The sedative effects of the drug were employed in a variety of psychiatric conditions, such as mania, hysteria, schizophrenic excitement, anxiety, dementia and, most importantly, alcohol-related disorders [19]. In these studies, spontaneous erection was noted as an unexpected effect, which would much later lead to the commercialization of apomorphine as an agent to treat erectile dysfunction [20].

It was Weil, in 1884, who first hypothesized that apomorphine could be useful in patients with PD, but without any specific rationale [21]. This was still lacking when sub-emetic doses (0.6–0.9 mg subcutaneously) of apomorphine were finally tried in patients with PD by the American neurologist Schwab and colleagues [22] almost 70 years later. These authors noted marked improvement in rigidity and tremor lasting from 1 to 6 h with enhanced feeling of subjective wellbeing once the initial side effects of nausea and hypotension had resolved. The marked anti-tremor effects of subcutaneous or intramuscular single-dose injections of apomorphine were confirmed shortly after by the German neurologists Struppeler and Von Uexkull [23]. However, the peripheral adverse effects and the need for parenteral administration of apomorphine led to its limited use in clinical practice after these early observations on its antiparkinsonian efficacy. About a decade later, the miraculous efficacy of oral levodopa in PD was discovered, and this superseded all interest in apomorphine [24, 25]. Nevertheless, Cotzias—one of the fathers of levodopa therapy for PD—continued to pursue the drug as an agent to treat PD and described the potent antiparkinsonian effects of subcutaneous apomorphine in 15 patients, albeit with marked emetic side effects in a proportion of subjects [26]. In 1979, Corsini et al. [27] showed that nausea deriving from apomorphine injections could be controlled via the administration of domperidone, a peripheral dopamine antagonist that does not cross the blood–brain barrier. This opened the door for successful introduction into clinical practice pioneered by Stibe et al. [28] in London in the mid-1980s. These researchers were able to show the remarkable efficacy of intermittent subcutaneous injections and continuous infusion of apomorphine in reducing the “off” periods in patients with advanced PD [28]. Over the following years, multiple studies confirmed their findings, leading to the approval of apomorphine as an adjunct therapy to reduce “off” time in advanced PD.

3 Pharmacological Properties

Apomorphine is an aporphine alkaloid derived from acidification of morphine. Its molecular formula is $C_{17}H_{17}NO_2$. Its structure, consisting of a tetracycline aporphine ring, is responsible for the lipophilicity and the affinity to dopaminergic receptors. Specifically, the structural similarity to dopamine is conferred by the ortho-catechol group [29]. Like many antipsychotic drugs, apomorphine also possesses a piperidine moiety. Apomorphine is often described as a dopamine agonist, but it has some differences from other oral dopamine agonists used in PD. Thanks to its catechol moiety, apomorphine acts as a potent dopamine receptor agonist with a broad spectrum on all D_1 - and D_2 -like receptors (D_1 , D_{2S} , D_{2L} , D_3 , D_4 , D_5) [30]. In comparison, the oral dopamine agonists ropinirole and pramipexole mainly bind to D_2 and D_3 receptors without significant affinity to D_1 receptors [31]. Apomorphine's mode of action is therefore more like that of dopamine or its precursor levodopa. In addition, apomorphine has antagonist properties on serotonergic 5HT_{2A}, 5HT_{2B} and 5HT_{2C} and adrenergic α_2A , α_2B and α_2C receptors and agonist properties at serotonergic 5HT_{1A} receptors [32]. Unlike its mother compound, morphine, apomorphine has no affinity for opioid receptors [33].

Apomorphine has very limited oral bioavailability (<4%) [34] because of almost complete first-pass hepatic metabolism where the molecule is metabolized following different pathways, including sulfation, glucuronidation and catechol-O-methylation. Therefore, different parenteral administration routes have been applied in clinical experiments. As a licensed treatment for PD, apomorphine is currently administered via subcutaneous injections or infusions. The drug absorption (bioavailability 100%), volume of distribution, plasma clearance and half-lives ($t_{1/2}$) of subcutaneous injections or infusions are comparable to those of intravenous infusion [35]. However, the latter is not suitable for chronic use because of the possible crystallization of apomorphine in the catheter, leading to the formation of thrombi [36]. Several factors can influence the subcutaneous absorption of the drug: injection site (abdominal injection seems to have the best results), state of the skin (vascularization, skin temperature, body fat), volume and depth of injection [a greater volume leads to a greater area of subcutaneous absorption and influences the time to peak concentration (t_{max})] and the presence of subcutaneous nodules that may hinder absorption, both mechanically and via inflammation-related alteration of the blood flow [35, 37, 38]. After subcutaneous injection, peak concentration in the blood (C_{max}) is reached in around 10 min, with a maximum concentration in the cerebrospinal fluid achieved after 30 min [35].

Apomorphine is extremely lipophilic so it has a considerable volume of distribution and, unlike levodopa, can

cross the blood–brain barrier freely. Additionally, it seems to concentrate in the brain, reaching a brain-to-blood concentration ratio of 8:1 [39]. Its rather rapid metabolism and clearance means that apomorphine has a $t_{1/2}$ of around 33 min [35, 38]. Overall, inter-individual variability in t_{max} , C_{max} , and area under the plasma concentration–time curve (AUC) is high [35, 38, 40] because of a variety of factors, including regional fat, blood flow and differences in metabolic enzymatic profiles. On the other hand, intra-individual variability is low. In clinical practice, this translates into a need for individual titration when starting apomorphine therapy. After a single dose in patients with PD, the onset of a clinical response usually occurs within 7–10 min after the subcutaneous injection and lasts for about 45–60 min [40], making intermittent subcutaneous injections of apomorphine a highly suitable rescue therapy for patients experiencing “on/off” fluctuations during chronic levodopa therapy.

4 Efficacy

Since the pioneering studies in the 1980s [28], multiple open-label series have confirmed the efficacy of apomorphine in reversing severe, sudden “off” states in advanced PD despite optimized oral therapy [28, 33, 41–45]. In most cases, the primary outcome was the reduction of time spent in “off” obtained with continuous subcutaneous apomorphine infusion (CSAI) or intermittent subcutaneous pen injections. Reduction of dyskinesia severity with chronic subcutaneous infusions was also reported but was inconsistent between studies [18, 46–48]. Studies comparing the efficacy of apomorphine and levodopa have repeatedly shown the two drugs to have equivalent effect sizes [3, 49]. Only a few studies assessing intermittent subcutaneous injection or continuous infusions of apomorphine were placebo controlled, but these have confirmed results from a large body of evidence from open-label use [45, 50].

4.1 Efficacy of Apomorphine Compared with Levodopa

Apomorphine and levodopa show an almost overlapping efficacy when treating PD motor symptoms.

In one crossover open-label study, no difference was observed between apomorphine and levodopa in all outcome variables, including hand tapping scores, walking time, severity of tremor, dyskinesia score and a modified Webster disability scale to evaluate disability due to PD. The mean duration of the motor effect was 56 min (range 30–80) for apomorphine and 211 min (range 145–315) for oral levodopa. Time to onset was 3–14 min for apomorphine (mean 7.9) and 19–75 min for levodopa (mean 35.4) [3]. This

comparative study proved for the first time that apomorphine has virtually indistinguishable efficacy on motor symptoms compared with levodopa but a considerably shorter duration of effect. These results were later confirmed in a double-blind single-dose study using apomorphine or levodopa [49].

4.2 Efficacy of Intermittent Apomorphine Injections

Chronic treatment of PD with levodopa is compromised by the development of motor fluctuations despite optimized oral dopaminergic therapy [51]. This lack of a stable response to therapy has a significant negative impact on quality of life because of the many motor and non-motor disabilities associated with the “off” state and reduced autonomy in planning activities because of the unpredictability of “off” phases. A large observational study in 1000 patients with PD experiencing “off” episodes despite best medical management showed that they had to live with an average of 2–3 h of “off” time per day [52].

Numerous studies have assessed the efficacy of apomorphine injections in patients with PD with fluctuations [18, 28, 42, 46, 50, 53] (Tables 1 and 2). These studies consistently reported a marked reduction in the number of daily “off” periods and other “off”-related phenomena such as early morning dystonia, urinary dysfunction and pain.

Three pivotal randomized, placebo-controlled trials were conducted in the USA between 2001 and 2007, leading to the approval of the drug in an injection pen for the acute

intermittent treatment of “off” episodes in advanced PD [33, 54–56].

The first of these US registration studies (APO202) was a randomized, double-blind, placebo-controlled, parallel-group trial assessing the safety and efficacy of subcutaneous injections of apomorphine hydrochloride for “off” state periods in apomorphine-naïve patients with PD with motor fluctuations despite aggressive oral therapy. The study was divided into two phases. Phase one consisted of an inpatient uptitration of the apomorphine dose to reverse a practically defined “off” period. Phase two involved a 1-month period of outpatient observation of drug effectiveness for reversal of “off”-state events. A 2-week observation period before the inpatient phase allowed the average “off” hours for each patient to be established at baseline. On the first day of the inpatient phase, all subjects underwent an unblinded levodopa challenge with their normal morning levodopa dose to establish their clinical response to dopaminergic therapy. On the second day, patients started in an “off” state and the Unified Parkinson’s Disease Rating Scale (UPDRS) motor response was evaluated with increasing doses of apomorphine or placebo. Apomorphine was started at 2 mg and increased in 2-mg steps to a 10-mg maximum; the dose was uptitrated until patients reached a reduction of the UPDRS motor score of at least 90% of that recorded with the levodopa challenge. The primary efficacy indicator was the change UPDRS part III from predose to postdose. Apomorphine showed a reduction of 23.9 points (62% improvement)

Table 1 Summary of open-label studies assessing the efficacy of intermittent subcutaneous injections of apomorphine in patients with Parkinson’s disease

Study	Pts (N)	Study duration, months	Mean injection dose/mean total daily dose, mg	Minutes to clinical onset	Duration of effect, minutes	Average daily “off” reduction, hours	Average daily “off” reduction, %	Levodopa reduction, mg	Levodopa reduction, %
Poewe et al. [102]	12	6.5	4.0/9.6	5–15	60–150	2.7	56	NR	NR
Poewe et al. [103]	17	7.2	3.8/12.2	NR	NR	3.0	64	– 77	– 8
Frankel et al. [46]	30	13.5	2.2/10.2	7.5	60 (20–120)	4	58	– 39	– 5
Kempster et al. [3]	14	Single dose	2/2	7.9	56 (30–80)	NR	NR	NR	NR
Hughes et al. [17]	15	6 doses	3.4/NR	5–25	10–107	NR	NR	NR	NR
Hughes et al. [104]	49	27	2–5/11.7	NR	NR	3.6	50	– 61	– 7
Esteban Muñoz et al. [105]	11	23	3/9	9.5	60.9	2.8	45	+ 109	+ 15
Pietz et al. [47]	24	22	1.9/9.7	10	47.5 (25–90)	NR	20.5	+ 225	+ 27

NR not reported, PD Parkinson’s disease, pts patients

Table 2 Summary of double-blind studies assessing the efficacy of intermittent subcutaneous injections of apomorphine in patients with Parkinson's disease

Study	Pts (N)	Study duration	Study design	Primary efficacy endpoint	Mean injection dose/ mean total daily dose, mg	Minutes to clinical onset	Duration of effect, minutes	Efficacy findings
Van Laar et al. [106]	5	10 doses	Randomized, double-blind, placebo-controlled, crossover study	Columbia Parkinson's Disease score	2.7/NR	7.3	96	Significant efficacy of apomorphine in improving all scores of the Columbia scale
Ostergaard et al. [107]	22	2 months	Double-blind, placebo-controlled study	"Off" time reduction	3.4/NR	NR	NR	Mean daily "off" duration reduced by 58%; "off" severity also significantly reduced
Merello et al. [49]	12	Single dose	Double-blind, active comparator (dispersible levodopa)	Change in modified Webster disability scale score	3/3	8.1	56.6	Mean effect latency and duration for apomorphine vs. levodopa: 8.08
Dewey et al. (APO202) [50]	Phase 1: 29	Single dose	Placebo-controlled, parallel-group inpatient evaluation	Change in UPDRS motor score	5.4/NR	NR	NR	Significant motor improvement (respectively -23.9 vs. -0.1 change in UPDRS motor score)
	Phase 2: 26	1 month	Placebo-controlled, parallel-group outpatient evaluation	"Off" time reduction	5.8/14.5	22	NR	Significant reduction of reported "off" time (respectively 2.0 vs. 0.0 h)
Pfeiffer et al. (APO302) [108]	62	Single dose	Prospective, placebo-controlled, parallel-group study	Change in UPDRS motor score after 20 min	TED or TED plus 2.0 mg	7.3	NR	Significant improvement for pooled apomorphine vs. placebo (-24.2 vs. -7.4 mean reduction in UPDRS)
Pahwa et al. (APO301) [56]	56	Single dose	Dose-escalation study, randomized, placebo-controlled, crossover evaluation	Change in UPDRS motor score after 20 min	4.0-10.0	NR	NR	Significant improvement in UPDRS motor scores in apomorphine group vs. placebo at 20, 40, 90 min
Hattori et al. [109]	31	3 months (open label) Single dose (blinded evaluation)	Placebo-controlled blinded efficacy assessment following a 12-week unblinded outpatient phase	Change in UPDRS motor score after 20 and 40 min	1.55/4.49	14.2	62.6	Significant improvement in UPDRS motors scores with apomorphine vs. placebo at 20 and 40 min

NR not reported, pts patients, TED typically effective dose, UPDRS Unified Parkinson's Disease Rating Scale

compared with placebo. Apomorphine's inter-individual variability in both pharmacokinetic parameters and efficacy was addressed in this study, with an individual titration reaching an optimal dose. The average inpatient apomorphine dose needed to reach a satisfying "on" (5.4 mg) closely matched the average dose used in the outpatient phase (5.8 mg). No placebo effect was described, and almost all subjects reached the maximum placebo dose in uptitration. During the outpatient phase of the study, apomorphine was decidedly more effective in aborting "off" episodes (95%) than was placebo (23%), measured via patient home diaries. Apomorphine showed an average reduction in "off" time of 2.0 h per day compared with baseline. This was the first study to assess the efficacy of intermittent treatment with apomorphine in reducing "off" time, in both inpatients and outpatients and compared with placebo. Moreover, the predictive nature of inpatient test responses on outpatient therapeutic response was established.

APO301 was a crossover trial enrolling apomorphine-experienced patients: participants received their usual apomorphine dose or a placebo, followed by the other treatment on the next day. Using the motor score of the UPDRS as a primary outcome measure, the study showed the superiority of apomorphine versus placebo at 10, 20 and 60 min post-administration. APO302 was a placebo-controlled, single-visit study to assess the efficacy of apomorphine in patients already receiving apomorphine and who were experiencing "off" periods during the day despite their oral dopaminergic therapy. A subgroup of patients received their usually effective apomorphine dose and an additional 2 mg to evaluate the tolerability of excess drug during administration and to determine whether patients with motor fluctuations receiving chronic apomorphine therapy would benefit from a higher apomorphine dose. The study showed that apomorphine brings fast relief from "off" periods even after long-term treatment. Moreover, once the optimal dose is defined for a patient, no significant advantage (measured as improvement in UPDRS part III) is gained by increasing that dose. Indeed, the only consequence of raising the apomorphine dose in the study was an increased rate of adverse events. These results mirror the common clinical experience that the optimal dose of apomorphine to relieve "off" time in individuals rarely needs to be changed.

APO303 [57] was an open-label dose-escalation study with a placebo-controlled crossover evaluation to further explore the safety and efficacy of apomorphine in patients with advanced PD naïve to apomorphine treatment. The study results again confirmed apomorphine's efficacy in "off" periods assessed as UPDRS motor improvement at 20, 40 and 90 min post-injection compared with placebo. Both efficacy and adverse events were dose related. At doses > 6 mg, motor improvements were not significant, but the incidence of adverse events kept increasing. This finding

suggests no further benefit from increasing the dose of apomorphine in patients who are already receiving their optimal therapeutic dosage. Intermittent apomorphine maintained its effectiveness in improving mobility after 6 months of open-label treatment. APO303 was conducted as a substudy of the larger open-label trial assessing the safety profile of continued use of intermittent subcutaneous apomorphine to treat "off" episodes in patients with advanced PD [57].

Additional evidence on the efficacy of the drug came from a recent phase IV multicenter study (AM IMPAKT) assessing the effect of apomorphine injections in patients with prolonged morning akinesia despite their levodopa morning dose [42]. A dose failure was defined as the inability to reach an "on" phase in 60 min after levodopa intake. Patients completed a 7-day levodopa baseline period by recording their time to "on" after each morning levodopa dose. Patients who experienced dose failures were then titrated to an optimal dose of apomorphine (2–6 mg) and started a 7-day treatment period with morning apomorphine injections instead of their normal morning levodopa dose. To prevent nausea and vomiting, subjects were started on antiemetic therapy with trimethobenzamide. The reduction in time to "on" (mean reduction 37.14 min) and the rate of dose failure (46% with levodopa vs. 7% with apomorphine) provided further evidence in favor of intermittent apomorphine injections. The study showed that subcutaneous apomorphine injections provided a rapid and reliable "on" state for patients experiencing morning akinesia, possibly resulting from bypassing problems associated with gastrointestinal delivery and levodopa absorption.

4.3 Efficacy of Continuous Subcutaneous Apomorphine Infusion (CSAI)

CSAI, together with deep-brain stimulation (DBS) and intestinal gel infusions of levodopa/carbidopa (LCIG) is one of the therapeutic cornerstones for advanced PD [58, 59]. Unlike oral therapies, infusion therapies are based on constant drug delivery, aiming for continuous dopaminergic stimulation. Continuous striatal dopamine receptor stimulation not only reduces response oscillations but also has the potential to prevent or reduce drug-induced dyskinesias.

Unlike intermittent apomorphine injections, until recently there has been a striking lack of randomized placebo-controlled studies assessing the efficacy of CSAI. Several uncontrolled open-label studies consistently reported the efficacy of CSAI as monotherapy or in addition to levodopa [47, 60–63], with an average "off" time reduction of 59.3% and a reduction of dyskinesia severity of 32.4% [64]. In line with these results, a prospective study confirmed a marked reduction in the frequency and severity of dyskinesias in patients with PD treated with CSAI [65]. Table 3 summarizes the results of the different studies.

Table 3 Summary of open-label studies assessing the efficacy of subcutaneous apomorphine infusion in patients with Parkinson's disease

Study	Pts (N)	Study duration, months	Infusion duration, h/day	Apomorphine total DD, mg	Daily time in "off" decrease, %	Daily levodopa decrease, %
Frankel et al. [46]	25	22	NR	89	45	22
Hughes et al. [104]	22	36	16.9 (at 12 months)	80.8	40	14 (at 12 months)
Pietz et al. [47]	25	44	24	112.5	50	50
Stocchi et al. [112]	30	60	12	51.6	NR	47
Manson et al. [67]	64	34	12–24	98	49	63.5
Tyne et al. [113]	80	25	13.5	69.8	NR	24 (after 2 months)
García Ruiz et al. [62]	82	20	14	72	79.5	80
Drapier et al. [114]	23	12	15.1	62.6	36	26
Kimber et al. [115]	36	21.5	NR	NR	NR	22.7 (LEDD decrease)
Rambour et al. [116]	81	28	NR	NR	NR	37.8
Martinez-Martin et al. [70]	43	6	15.9	105.9	NR	30
Drapier et al. [117]	142	6	12.7	58.5	NR	24
Borgemeester et al. [63]	125	32.3	16.6	66	NR	32
Sesar et al. [118]	230	26.3	16.3	78	77.7	20.4

DD daily dose, NR not reported, LEDD levodopa equivalent daily dose, pts patients

High-level evidence for the efficacy and safety of CSAI was recently provided by the TOLEDO trial, the first-ever randomized, placebo-controlled, double-blind, multi-center trial to assess apomorphine subcutaneous infusion in patients with PD [45]. Patients with PD with a disease diagnosis for more than 3 years and with motor fluctuations not controlled by optimal medical therapy received either 3–8 mg/h apomorphine or placebo infusion during waking hours (16 h/day) for 12 weeks. During the first 4 weeks, the flow rate of the study drug and the other oral therapies could be adjusted, and the following 8 weeks were a maintenance period. Apomorphine significantly reduced more “off” time than did placebo (– 2.47 vs. – 0.58 h/day). Additionally, the dose and number of oral antiparkinsonian medications was reduced in patients receiving CSAI. It was suggested that CSAI can reduce “off” time without increasing troublesome parallel dyskinesia. These results confirm that CSAI has efficacy comparable to that of LCIG infusion in treating motor fluctuations in advanced PD [66].

Dyskinesia reduction appears to be most pronounced in patients able to rely on CSAI as a monotherapy, since improvements in dyskinesia usually correlate with the concomitant decrease of oral medication [65, 67].

4.4 Apomorphine and Non-Motor Symptoms

While the efficacy of apomorphine in treating motor symptoms of PD has been the main focus of this review, the drug may also have an effect on non-motor aspects of the disease. NMS are experienced by > 90% of patients with PD during the course of the disease and are also important

factors influencing health-related quality of life. The NMS spectrum is quite broad and includes neuropsychiatric symptoms, sleep impairment, pain, cognitive impairment, dementia and depression. Patients with PD experience an average of 8.3 NMS during the course of the disease, with only < 2.5% patients being completely NMS free [68].

An observational open-label study investigated the effects on NMS of CSAI compared with conventional treatment (oral and patch therapy) and reported positive effects on the Non-Motor Symptom Scale (NMSS) after 1 year of follow-up [69]. Specifically, sleep, mood, gastrointestinal (including constipation) and perceptual problems and urinary domains improved. Similar results came from the Euroinf study, which assessed the effects of CSAI and LCIG on NMS and showed that both infusion-based therapies were effective in improving motor symptoms, NMS and quality of life scores [70].

Several authors have focused on the effect of apomorphine on neuropsychiatric symptoms, stating that apomorphine seems to be well-tolerated in patients with paranoid ideas and visual hallucinations [71, 72]. One study reported reductions in hallucinations in 12 non-demented patients receiving CSAI concurrent to a reduction in their oral antiparkinsonian medications, but this observation could not differentiate between effects of reductions in oral medications versus the true “antipsychotic” effects of apomorphine [73]. In a 5-year prospective comparative study between DBS and CSAI, a worsening of the Neuropsychiatric Inventory Questionnaire was observed in the DBS group but not in the apomorphine group.

It has been suggested that the hypothesized antipsychotic effects of apomorphine could be related to its structural piperidine moiety, which is also part of several antipsychotic molecules. Along these lines, apomorphine has been claimed to have a positive effect on visual hallucinations and to not exacerbate symptoms in patients with pre-existing visual hallucinations, possibly related to apomorphine's capacity to act as a 5HT_{2A} receptor antagonist [71].

Additionally, when compared with other dopamine agonists, apomorphine therapy seems to be associated with a lower incidence of emergent impulse control disorders (ICDs) [74, 75]. Since activation of D₃ receptors by oral dopamine agonists has been related to the emergence of ICDs in PD [76], the lower D₃:D₂ ratio of apomorphine compared with pramipexole or ropinirole could be a potential explanation for a lowered risk to induce ICDs, although precise data on the incidence of ICDs in patients treated with apomorphine compared with those receiving other dopamine agonists are lacking.

A recent experimental study showed that apomorphine injections reduced intraneural amyloid β protein and improved short-term memory in a murine Alzheimer's disease model [77]. Based on these findings, a recent retrospective clinicopathological study investigated non-demented subjects with PD who used apomorphine antemortem compared with matched controls. The study showed significantly reduced amyloid β protein among apomorphine-treated subjects using amyloid positron-emission tomography imaging, giving rise to speculations that the drug may represent a potential therapy to reduce cognitive impairment in PD [78].

In summary, data on the efficacy of apomorphine in NMS remains very limited but point to a possible benefit in sleep dysfunction, neuropsychiatric symptoms, urinary dysfunction, mood and gastrointestinal symptoms as a corollary to "off" time reduction in patients with fluctuating PD. More studies using non-motor assessments as outcome variables are warranted to improve our understanding of the different NMS subtypes in which apomorphine could be beneficial.

5 Safety

Apomorphine is usually well-tolerated, and adverse events range from mild to moderate in intensity. Overall, the incidence of adverse events seems to be generally higher in patients receiving CSAI than in those treated with intermittent injections [79].

Cutaneous and subcutaneous adverse reactions—including bruising, subcutaneous nodules and, rarely, necrosis or abscess formation at injection or infusion sites—are the most common, followed by nausea and somnolence. Histologically, subcutaneous nodules present as infiltrates containing eosinophils, lymphocytes and histiocytes as well as

melanin-like pigments and, in chronic conditions, fibrosis [80, 81]. Although these cutaneous reactions are usually mild, they can, in rare cases, lead to drug discontinuation because of abscess and necrosis. This risk can be reduced by ensuring thorough skin hygiene, using new needles for each injection, changing the site of injection and using localized massage and ultrasound therapy [82].

Nausea and vomiting in response to apomorphine can be controlled with preventive temporary administration of antiemetics (such as domperidone or trimethobenzamide) [27]. Nausea, vomiting and hypotension mainly occur at initiation of apomorphine, where they seem to be more common in patients treated with intermittent subcutaneous apomorphine than with CSAI [47].

Sedative effects are also common with apomorphine, whereas other central dopaminergic side effects such as confusion, hallucinations and psychosis are less commonly observed than with oral dopamine agonists. The latter may be related to differences in the dopamine receptor subtype affinity of apomorphine [72]. Data on the relationship between apomorphine and ICDs are limited. Binge eating, compulsive sexual disorder and punding have been reported, but the incidence of ICDs seems to be low, with only rare cases requiring discontinuation of CSAI [72, 83, 84].

Hematologic adverse events are a rare complication of apomorphine therapy, but the risk of developing autoimmune hemolytic anemia in patients undergoing CSAI should be appropriately monitored with regular blood cell counts, checks of hemolytic parameters and Coombs test to detect antibodies targeting red blood cells. How frequently these tests should be performed during chronic treatment with apomorphine is somewhat controversial. The mechanism responsible for this autoimmune response remains unclear [85].

Apomorphine has been reported to induce QT interval prolongation in post-marketing surveillance [110]; however, no evidence yet shows a direct link between drug administration, QT prolongation and cardiac arrest. Conversely, apomorphine may have a broader cardiovascular safety margin than originally thought [111].

Safety results from controlled trials of intermittent subcutaneous apomorphine injections reveal a generally mild-to-moderate adverse event profile. In the APO202 study, adverse event rates were almost identical between the placebo and the apomorphine group (89 vs. 85%), and events were almost all classified as treatment-emergent adverse events (TEAEs). Events only reported in the apomorphine group were yawning (40%) and somnolence (35%) [54]. Dyskinesias as an adverse event were reported in 35% of the apomorphine-treated subjects versus 11% of the placebo group. During the inpatient phase of this trial, nausea was reported in 30% of subjects receiving apomorphine, whereas this was almost never the case in the subsequent outpatient

phase. All study participants received trimethobenzamide as antiemetic prophylaxis.

APO401 was a large open-label study ($n=546$) assessing the long-term safety of intermittent subcutaneous apomorphine [33]. During the 12-month treatment period, 93% of all patients with PD in the study experienced at least one adverse event. Most of these events were regarded as mild or moderate in severity. The most common TEAEs were nausea and vomiting (33%), falls (33%), dyskinesias (24%), dizziness (22%), somnolence (21%), hallucinations (19%), yawning (16%) and injection site bruising (15%). A total of 187 patients discontinued treatment because of adverse events. Serious adverse events were reported in 199 (36.4%) patients, but most were considered only remotely related or definitely unrelated to apomorphine. In total, 19 patients experienced 27 serious adverse events that were possibly or probably related to apomorphine. Among these 27, the most common were syncope ($n=3$), drug-induced psychosis ($n=3$), postural hypotension ($n=2$) and falls ($n=2$). Safety assessment from the only placebo-controlled trial with CSAI (TOLEDO) reported adverse events in line with the evidence presented by previous observational studies [45]. Apomorphine infusion was well-tolerated, and no unexpected safety signals were observed in this trial, with most of the adverse events being of mild or moderate intensity. Overall, 93% (50/54) of patients in the apomorphine group had at least one TEAE compared with 57% (30/53) of patients in the placebo group. The most common TEAEs were skin reactions (44 vs. 0%), nausea (22 vs. 9%) and somnolence (22 vs. 4%). Not surprisingly, neuropsychiatric TEAEs occurred more commonly in the apomorphine group (mild hypersexuality, $n=1$; mild punding, $n=2$; mild to severe confusion episodes, $n=1$; moderate psychosis, $n=1$; and mild to moderate hallucinations, $n=2$) than in the placebo group (episodes of mild confusion, $n=2$; mild hallucinations, $n=2$). With dose reduction, almost all neuropsychiatric TEAEs were resolved. Six patients (11%) in the apomorphine and none of the placebo group withdrew from the study because of treatment-related adverse events. Half of the patients withdrew because of serious adverse events (severe orthostatic hypotension, $n=1$; myocardial infarction, $n=1$; abnormal persistent non-hemolytic hematology test results). The other patients withdrew because they experienced visual hallucinations ($n=1$), moderate gait disturbance ($n=1$) or mild infusion-site erythema ($n=1$). All events leading to study withdrawal, except for myocardial infarction, were thought to be treatment related. Indeed, all were resolved after cessation of apomorphine.

Some possible drug–drug interactions should be considered with apomorphine treatment. These include the concomitant administration of apomorphine with 5HT₃ antagonists such as ondansetron, which may induce severe hypotension and syncope, and combination with drugs

associated with QT/QTc interval prolongation, especially when domperidone is given for antiemetic prophylaxis. Indeed, domperidone may cause QT/QTc prolongation and is associated with increased risk of ventricular tachyarrhythmia and sudden cardiac death in patients with PD with pre-existing cardiac disease [86]. Given the potential for cardiac side effects with domperidone, its use has been restricted by the European Medicines Agency [87].

Apomorphine should be used carefully in patients with orthostatic hypertension because its ability to lower systolic and diastolic blood pressure may aggravate symptoms.

When initiating apomorphine therapy, antiemetic prophylaxis and close medical supervision are recommended to maximize adherence.

6 Apomorphine in Parkinson's Disease: Practical Considerations

Intermittent injections are a viable rescue medication for patients who are already optimized on oral medications and are still experience troubling “off” periods. Apomorphine injections can also be beneficial in patients with impaired gastric emptying that results in delayed levodopa absorption. Suitable candidates for intermittent apomorphine injections should be capable of injecting themselves or have a caregiver able to inject them when needed [88]. Exhaustive injection training (or pump training for patients starting continuous infusion) for patients and caregivers with a physician or a nurse experienced in the treatment of advanced PD plays a fundamental role in therapy compliance and in preventing adverse events. The injections are given via a multidose pen loaded with a solution of apomorphine hydrochloride 10 or 20 mg/mL. When beginning intermittent apomorphine injection therapy, the patient is asked to come to the clinic without taking their usual dopaminergic medications for dose titration; once the patient reaches an “off” episode in clinic, a first dose of apomorphine 2 mg should be administered. Time to onset of effect, duration of effect and adverse effects must be recorded during a monitoring period of 1 h from injection. Until the desired motor response is obtained, the dose can be increased by 1–1.5 mg; the optimal dose for most patients usually ranges from 2 to 6 mg and, once it is achieved, further dose adjustments over time are not usually required. The daily number of injections varies considerably between patients, but subjects who require more than five or six injections per day are usually recommended to switch to CSAI [88].

CSAI is administered via a portable pump system that delivers a continuous dose, with the possibility of releasing a rescue bolus if needed. The duration of infusion is normally 12–16 h (waking time), but a 24-h regimen can also be programmed for patients experiencing nocturnal hypokinesia

[89]. Patients with PD who have “off” periods no longer controlled with optimized oral therapy or who need apomorphine rescue doses too frequently are suitable candidates for CSAI. The pump can also be an alternative to surgical therapy or to enteral levodopa infusion [90]. For patients starting CSAI in the inpatient setting, domperidone 10 mg (or trimethobenzamide in countries where domperidone is not available) three times daily from 1 day before initiation to 3–7 days in total is strongly recommended to prevent nausea [90]. On the first day, apomorphine treatment is started at a dose of 0.5 or 1 mg/h. Uptitration is usually with 0.5 or 1 mg/h daily increments, and the optimal infusion rate ranges from 4 to 7 mg/h for most patients. Concomitantly, oral dopamine agonists and other antiparkinsonian drugs are gradually discontinued. During the titration phase, levodopa is also usually reduced, and discontinued if possible in patients with dyskinesia [90]. The same uptitration protocol should be used for outpatients but with a slower increase in infusion rates.

7 Alternative Apomorphine Delivery Strategies

To date, the main administration route for apomorphine in PD has been subcutaneous, either as a continuous infusion or as an intermittent pen injection. This route has proven effective, but skin reactions are among the most common adverse events and can complicate treatment or lead to withdrawal. For some patients, this delivery may also be problematic because of needle phobia; for others, the pen injection may prove challenging for resolving an acute “off” phase because of bradykinesia and tremor. Despite its remarkable efficacy, apomorphine suffers from the lack of an “easier” and less invasive delivery system. Several alternative delivery routes have therefore been tested, and some are in active clinical development.

Pulmonary delivery of drugs has the potential of very rapid entry into the systemic circulation through the lung’s extensive alveolar surface with no hepatic first-pass effect, making it an attractive strategy to achieve rapid onset of effect to “rescue” patients from “off” periods. An apomorphine powder formulation for delivery via an inhaler device (VR040) has been developed and used in a single-center, placebo-controlled, randomized study in patients with motor fluctuations. Inhaled apomorphine proved to be well-tolerated, but efficacy was limited [91]. Two larger studies followed, in which the drug proved to have rapid absorption (2–7 min) mirrored by a rapid clinical reversal from the “off” state (10 min) [92, 93]. These short-term studies reported no pulmonary safety concerns, but no reports of further clinical development of this agent have been released.

Oral apomorphine is considered infeasible because of the almost complete first-pass hepatic metabolism of the molecule [35]. However, the administration of apomorphine and its prodrug (dipalmitoyl apomorphine) via oral lipid-based formulations has recently been reported in animal models of PD. This formulation is still in the preclinical phase but may have the potential to achieve steady dopaminergic stimulation because of its sustained drug release [94].

Sublingual formulations of apomorphine have been recognized as a viable alternative to the subcutaneous route for decades [95–97]. A sublingual formulation needs no needles, causes no pain and is easily administered, even during a severe “off” phase. A novel sublingual apomorphine formulation consisting of a two-film strip that contains apomorphine in a bilayer (APL-130277) has been shown to reliably revert “off” periods in several clinical trials. A proof-of-concept study for this new formulation was conducted with patients with PD coming to the clinic in an “off” state and receiving APL-130722 (10–30 mg). Of the 19 patients, 15 achieved a full “on” response in < 30 min, with the response lasting 50 min on average [98]. A phase III double-blind placebo-controlled trial enrolling 109 patients showed significantly greater improvements in UPDRS motor scores 30 min post-dosing with APL-130722 (primary endpoint) and a significantly greater proportion of patients achieving a full “on” state after 30 min (key secondary endpoint). Nausea, daytime somnolence and oral cavity-related adverse events (mucosal erythema, glossodynia, dry mouth, lip edema, throat irritation) were more common with active drug than with placebo [99]. A phase III open-label, randomized, crossover trial with blinded rating to evaluate APL-130277 compared with subcutaneous apomorphine in patients with PD with motor fluctuation is currently underway (ClinicalTrials.gov identifier: NCT03391882).

Finally, despite the already discussed drawbacks of subcutaneous delivery, room to improve pump technology for more user-friendly modes of the traditional apomorphine delivery route exist. Patch pumps of small size and weight are in routine clinical use in different fields, including insulin delivery in diabetes. They have in-built technology to program delivery rates and external control of needle insertion and delivery, with minimal inconvenience to patients. Their use for CSAI requires novel apomorphine formulations with enhanced solubility, enabling smaller volumes to meet daily dose requirements. Experiments conducted in minipigs with a novel apomorphine formulation (ND0701) have shown better local safety profiles and tolerability than regular apomorphine hydrochloride [100]. Potentially, this would allow for safer, more comfortable and easier delivery in advanced PD. First results coming from a phase I clinical study suggest that ND0701 may have better tolerability and safety than and similar bioavailability to the injectable formulations available on the market [101].

8 Conclusions

Apomorphine has a long and interesting history as the oldest dopamine agonist used in PD. Despite being initially received with skepticism, it has proved to have efficacy comparable to that of levodopa, the gold standard therapy for all stages of PD. Thanks to the cumulative evidence provided by several studies, apomorphine should be considered as a monotherapy or an effective adjunctive treatment for patients with advanced PD and levodopa-related motor complications. Its lipophilic molecule allows for rapid and effective treatment of “off” episodes. Its low bioavailability has limited its administration to subcutaneous intermittent injections or continuous subcutaneous infusion. Intermittent injections of subcutaneous apomorphine in addition to the oral therapy provide great relief in patients with unpredictable “off” phases, and temporary coadministration with an antiemetic drug has significantly increased tolerability. Delivered as a continuous infusion, apomorphine leads to a remarkable decrease of time spent in “off” with no concurrent increase in dyskinesia. While this delivery method is effective, research is moving toward new strategies and new formulations of the drug to decrease complications and increase the handiness and safety and efficacy profiles. New studies are also warranted to explore the possible efficacy of apomorphine earlier in the course of the disease [58].

Compliance with Ethical Standards

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