Effective Delivery of Apomorphine in the Management of Parkinson Disease: Practical Considerations for Clinicians and Parkinson Nurses

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Abstract: The clinical utility of long-term oral levodopa therapy in Parkinson disease (PD) is often limited by the emergence of motor complications. Over time, many patients with PD experience regular and/or unpredictable "off" periods, despite taking optimized oral medication regimens, with a major negative impact on their ability to undertake routine activities of daily living and consequently on their overall quality of life. One established approach for treating patients experiencing off periods and controlling motor fluctuations refractory to conventional oral drug therapy is the subcutaneous administration of the dopaminergic agonist apomorphine. This article outlines how the pharmacokinetic properties of apomorphine underpin its efficacy for the treatment of PD and provides practical guidance for the 3 main approaches in which it is used: subcutaneous intermittent apomorphine injection as a "rescue" therapy for off states, subcutaneous continuous apomorphine infusion for PD patients with intractable motor fluctuations as an alternative to other dopaminergic treatment, and in the apomorphine response (or challenge) test for assessment of dopamine-induced motor response in patients thought to have PD, or in establishing the optimal tolerated dose of apomorphine in patients already known to have PD. Also discussed is the management of potential adverse events with subcutaneous administration of apomorphine, the majority of which are mild and easily managed in practice. The importance of a multidisciplinary PD team in the optimal management of PD patients is now recognized, in particular the role of the specialist PD nurse.

Key Words: Parkinson disease, treatment, clinical practice, apomorphine injection, apomorphine infusion, pharmacokinetics

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Parkinson disease (PD) is a relatively common neurodegenerative disorder characterized by progressive loss of several monoaminergic systems, including dopaminergic neurons originating in the substantia nigra pars compacta. Although its signs and symptoms can vary greatly from patient to patient, most patients have decreased dexterity and slowness of movement; resting tremor, muscle rigidity, imbalance, and posture disturbance can be prominent features as well. In addition to its typical motor impairments, PD can be associated with nonmotor features such as anxiety, autonomic disturbances, fatigue, mood changes, bladder problems, and pain or sensory symptoms.[1] These nonmotor symptoms are now recognized as having an equal or even greater contribution than motor symptoms to impaired functional capacity and quality of life in PD.[2–5]

The most effective treatment for PD is replacement of striatal dopamine by means of levodopa. However, dopaminergic agonists can also provide substantial benefit. Monoamine oxidase B inhibitors, sometimes used as initial therapy for PD, offer minimal symptomatic benefit in ameliorating parkinsonian symptoms. For most patients, an oral regimen of 1 or more of these drugs can provide adequate control of symptoms in the early stages of the disease, which for most patients would be the first 2 to 3 years after onset of signs and symptoms. However, the clinical utility of long-term oral levodopa therapy is often limited by the emergence of motor complications. Over time, many patients with PD experience regular or unpredictable (or both) "off" periods, despite taking maximal oral medication regimens. These off periods have a major negative impact on the PD patient's ability to undertake routine activities of daily living and consequently reduce overall quality of life, despite continued benefit of medications at other times.[6] Motor fluctuations are experienced by up to half of levodopa-treated PD patients by 2 years after the start of therapy.[7–9]

In view of this experience with levodopa, adjunctive therapies are greatly in need to improve management of a PD patient's symptoms and disabilities. One established and practical approach for treating patients experiencing off periods and controlling motor fluctuations refractory to conventional oral drug therapy is the subcutaneous administration of apomorphine, which is a potent dopamine agonist at D_1 (adenylate cyclase linked) and D_2 receptor subclasses.

This article will outline how the pharmacokinetic properties of apomorphine underpin its efficacy for the treatment of PD and will discuss the 3 main approaches in which it is used:

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subcutaneous intermittent apomorphine injection as a "rescue" therapy for "off" states, subcutaneous continuous apomorphine infusion for PD patients with otherwise intractable motor fluctuations as an alternative to other dopaminergic treatment, and in the apomorphine response (or challenge) test for assessment of dopamine-induced motor response in patients suspected to have PD.

The History of Apomorphine Use in Clinical Practice

Though apomorphine is a highly potent dopamine agonist, it differs substantially in its pharmacological profile from the other dopaminergic agonists that have been used experimentally or in clinical practice to treat PD.[10]

Apomorphine is a derivative of morphine first created in 1869 by Matthiessen and Wright[11] and used in medical practice for much of the next 100 years as an emetic. The first medical use of apomorphine in neurological medicine was by Weill,[12] who attempted to use this drug to treat Sydenham chorea. Because of the structural transformations resulting from its synthesis (by reacting morphine with zinc chloride or hydrochloric acid), its narcotic properties and other opiate effects of the parent compound are eliminated.[13] The primary pharmacological actions of apomorphine are derived from its polycyclic and tertiary amine structures. These allow rapid transport across the blood-brain barrier and which contain a moiety with homology to the dopamine molecule (Fig. 1).[13]

Clinical experience in treating PD with apomorphine goes back to 1951 when limited clinical experimentation showed its potential for achieving relief of parkinsonian symptoms of tremor and rigidity.[14] Although used for many years as an emetic and for several neuropsychiatric indications including insomnia, neurosis, mania, or schizophrenia, apomorphine did not have a rationale for therapeutics until discovery of its dopaminergic properties.[15] It was not until the 1970s that the antiparkinsonian effect of apomorphine was confirmed in clinical trials.[16] However, the discovery (and success) of orally administered levodopa as a treatment of PD and the limitations of adverse effects associated with apomorphine treatment (including nausea, vomiting, postural hypotension, and sedation) resulted in no further development of the drug for many years.[7,17] Furthermore, apomorphine required subcutaneous administration, another limitation for its clinical acceptance. In 1979, studies with the peripherally acting dopamine receptor blocker domperidone demonstrated that major apomorphine adverse effects could be lessened.[18]

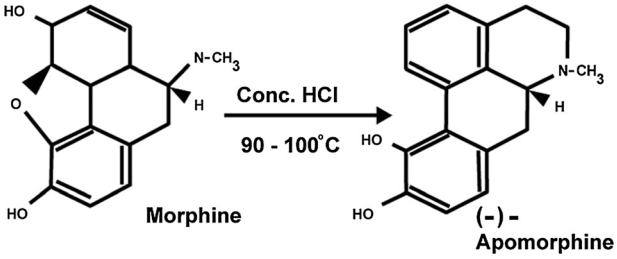

FIGURE 1. Derived from morphine, apomorphine is a potent, nonergot dopamine agonist with a tertiary amine structure that allows rapid transport across the blood-brain barrier. It has no opiate or direct pain-killing properties.

The potential for apomorphine to fulfill roles unmet by levodopa began in the late 1980s. In 1988, studies in London, United Kingdom,[19] reported the results of treating PD patients with either continuous or intermittent subcutaneous apomorphine for treating sudden off episodes. Using apomorphine as a rescue medication, Stibe et al reported that apomorphine was highly effective at reducing daily off time by more than 60%.[19] Also in 1988, Chaudhuri et al[20] showed major benefits against "off" time with infusion of apomorphine by as much as 85%.

Another dopaminergic agonist given by continuous subcutaneous infusion lisuride was also investigated during the early days of studies with apomorphine.[21] In contrast to apomorphine, lisuride infusion was often associated with severe adverse effects. Among these was a particularly high incidence of psychiatric adverse events that were a limiting factor in its use.[22] By contrast, the adverse events associated with subcutaneous apomorphine tended to be more easily managed without need for discontinuation of therapy. Building on this early experience, a number of studies were initiated through to the late 1990s to examine the efficacy and safety of subcutaneous apomorphine through both intermittent injection and continuous infusion.[7]

In addition to subcutaneous administration, alternative routes of delivery have been investigated in an attempt to improve administration of apomorphine.[13] These include sublingual, rectal, intranasal, and iontophoretic transdermal routes. Each of these routes has shown some potential for clinical effectiveness.[13] Iontophoretic transdermal transfer uses the application of a current to an apomorphine patch to drive the charged apomorphine through the stratum corneum and into the deeper layers of the skin, after having started the iontophoresis, apomorphine can be measured in the serum. The clinical response may be improved by the use of surfactants.[23,24] Although the transdermal delivery concept has been demonstrated to be effective, this route is not practical because it would require a patch to deliver at least 50 to 100 mg of apomorphine per day.

Pharmacokinetics and Pharmacodynamics of Apomorphine

The pharmacokinetics of apomorphine imply several key advantages in the clinical management of PD.[13] Its rapidity of onset after intermittent injection (4–10 minutes) makes it a desirable option for the patient who has a predictable but delayed response to levodopa (lasting 15 to 30 minutes or longer) and who wants to achieve an "on" state quickly and reliably. Apomorphine's short elimination half-life, which parallels its clinical response, lasting 45 to 60 minutes, usually does not interfere with the basal drug regimen, but rather fills the gaps in motor functioning. The short elimination half-life is also an advantage if the effect has to stop quickly, which is not the case with levodopa carbidopa intestinal gel.[25–27]

The nonoral route used by apomorphine avoids the major factor interfering with uptake of levodopa, being the gastric delivery of levodopa to the upper regions of the small intestine. Gastrointestinal problems including a delayed gastric emptying are common (and underestimated) in PD patients.[28,29] A dysfunctional gut in PD is recognized to pose the problem of delayed gastric emptying (gastroparesis), resulting in gaps of levodopa benefit despite regular oral dosing. A recent study showed that early morning "off" periods can be frequent and associated with a range of nonmotor symptoms in PD.[30] Often, these are not adequately reversed by oral levodopa (possibly because of gastroparesis or delays in gastric "housekeeping"), although apomorphine injection can reliably overcome this problem.[29]

The structure of apomorphine is shown in Figure 1.[17] As mentioned previously, its dopaminergic actions differ from other dopaminergic compounds used to treat PD, primarily on the basis of its potent D_1 properties, along with agonism at D_2 receptors.[31] Because the D_1 receptor agonist apomorphine provides additional clinical efficacy and may confer greater clinical benefits than pramipexole or ropinirole, both of which act only on D_2 and D_3 receptors.[32] Poor bioavailability after oral intake due to extensive hepatic first-pass metabolism means that apomorphine must be administered parenterally.

When administered subcutaneously, apomorphine is rapidly absorbed and, because of it is highly lipophilic, it readily crosses the blood-brain barrier.[33] The peak plasma concentration is achieved after 10 to 20 minutes, and the maximal concentration is achieved in the cerebrospinal fluid after 30 minutes.[34] Subcutaneous apomorphine follows a 2-compartment pharmacokinetic model with an absorption, distribution, and elimination half-life of 5.8, 4.8, and approximately 30 minutes, respectively.[32,35–37] However, there is high interindividual variability in T_{max}, C_{max}, and plasma concentrations, leading to different areas-under-the-curves.[36,38] Peripheral pharmacokinetics vary in a linear manner with doses across a range of 2 to 8 mg.[36,39,40] The mean duration of antiparkinsonian action is 45 to 60 minutes.[13] Table 1 shows a comparison of the dopamine receptor selectivity and pharmacokinetics of apomorphine with other orally and subcutaneously administered dopamine receptor agonists.[42]

Options for Administering Apomorphine

Apomorphine is available in 2 formulations, apomorphine intermittent injection and apomorphine continuous infusion. The 2 formulations are intended for different types of problems with PD. Patients who have not used apomorphine injection previously can be suitable candidates for apomorphine infusion.

Subcutaneous intermittent injections are administered via a multidose pen, the APO-go Pen (Britannia Pharmaceuticals Ltd), or a similar device marketed in the United States. The European product is a portable subcutaneous injection device containing 30 mg apomorphine hydrochloride in 3 mL solution (Fig. 2). In the United States, the concentration and formulation of apomorphine is the same, although the cartridge contains 20 mL.

Continuous subcutaneous apomorphine infusion is administered via a pump device. A subcutaneous catheter is connected to a small portable APO-go pump (Britannia Pharmaceuticals Ltd), usually worn on a belt or around the neck (Fig. 3). The apomorphine dose can be adjusted for continuous delivery over a period ranging from 12 to 24 (usually 16) hours a day. The most recent APO-go pump even offers the opportunity to program different infusion speeds during the day. If administered over 24 hours, the possible risk of tolerance needs to be borne in mind. Tolerance is present if patients require higher doses to achieve the same clinical benefit. Fortunately, this phenomenon tends to be rapidly

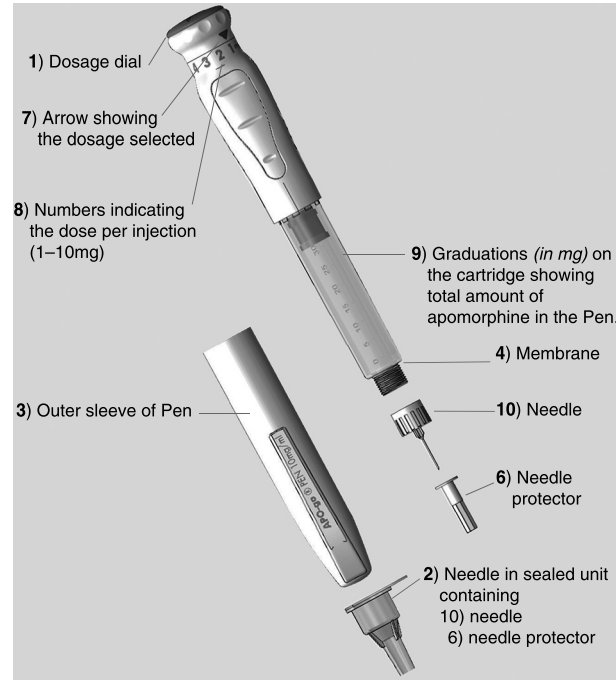

FIGURE 2. The APO-go Pen is a portable subcutaneous injection device containing 30 mg apomorphine hydrochloride in 3 mL solution.

TABLE 1. Comparison of Dopamine Receptor Selectivity and Pharmacokinetics of Orally and Subcutaneously Administered Dopamine Receptor Agonists[41]

Drug	Main Route of Administration	Main Receptor Affinity	Daily Dose, mg	t_{max}	$t_{1/2}$, h	Bioavailability, %
Apomorphine	Subcutaneous	D_1, D_2, D_3, D_4, D_5	10–100	10 min	0.5–1	100
Bromocriptine*	Oral	D_2, D_3, D_4, D_5	15–60	1–2 h	3–8	3–6
Cabergoline*	Oral	D_2, D_3, D_4	0.5–6	1–3 h	64–105†	50–80
Dihydroergocryptine*	Oral	D_1, D_2	30–120	1–2 h	15	5
Lisuride*	Subcutaneous	D_2, D_3, D_4	0.01–2	<1 h	1–2	100
Pergolide*	Oral	D_2, D_3	1–6	2–3 h	6–64	20–60
Piribedil	Oral	D_1, D_2, D_3	150–250	1 h	21	<10
Pramipexole	Oral	D_2, D_3, D_4	2–5	1–3 h	7–12	90
Ropinirole	Oral	D_2, D_3	3–24	1–2 h	6	50

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*Ergot derivative.

†Uncertain results.

$t_{1/2}$, elimination half-life; t_{max}, time to reach peak plasma concentration.

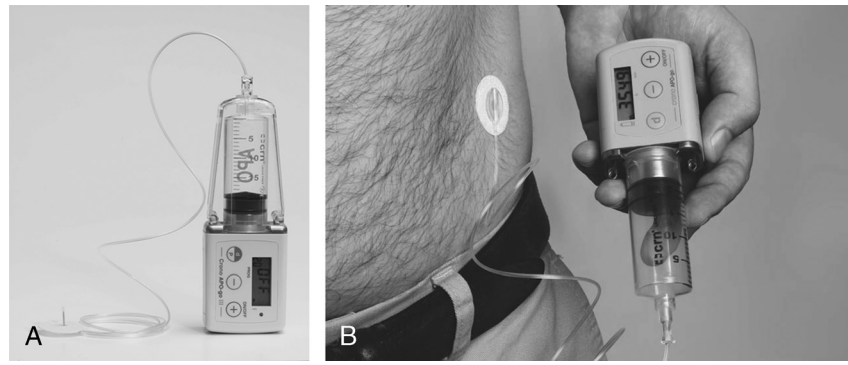

FIGURE 3. Continuous subcutaneous apomorphine infusion is administered via the APO-go pump; a subcutaneous catheter is connected to a small portable pump (A), usually worn on a belt or around the neck (B).

reversible,[42–44] and in such instances, it is recommended that the infusion period is reduced by at least 2 to 4 h/d.

INTERMITTENT APOMORPHINE INJECTION (PEN)

A number of small-scale clinical trials have shown the value of intermittent subcutaneous apomorphine injections. The antiparkinsonian benefits from this treatment are close to those who encountered with levodopa, however, with a much shorter onset of effect. Apomorphine rescue injections can reliably revert off periods even in patients experiencing complex "on-off" motor fluctuations (Table 2).[32]

Suitable Candidates for Intermittent Apomorphine Injection

When assessing the suitability of PD patients for intermittent apomorphine injection (as for continuous subcutaneous infusion, see below), a number of factors should be considered, as outlined in Table 3.

Patients should already be optimized on oral medication, able to recognize the onset of their off symptoms, and above all capable of injecting themselves. If they cannot do this, then they must have a responsible carer who is able to inject apomorphine for them when required. Suitable candidates for intermittent apomorphine injection include the following (there is some overlap in indications):

- Those experiencing gaps in drug effects (switching off) and who require rapid and reliable relief of both unpredictable and predictable off periods; inadequately controlled by oral treatments; off symptoms that may improve off-related (early morning) dystonia, freezing, and nonmotor symptoms, including pain.
- Those who require rescue medication during an "off" state, for example, those patients needing to be mobile as soon as possible after awakening or in certain social situations outside the home, otherwise leading to social isolation.
- Patients with delayed levodopa absorption or gastric emptying problems, such as gastroparesis, that result in delayed or failed "on" and in other situations where absorption of oral levodopa is impaired, for example, shortly after ingestion of a meal.[45] Gastroparesis is recognized as a contributing factor in delay in levodopa time to on (TTO).[46] Apomorphine injection can be beneficial in such patients because its route of administration is not affected by delayed or impaired gastric emptying.[29]

Morning akinesia due to delayed onset of the first daily levodopa dose may occur in up to 50% of patients receiving levodopa after several years.[29] It can significantly affect quality of life in PD patients, consequently impairing the ability to perform daily activities.[6] However, morning akinesia is underrecognized and suboptimally treated, despite the availability of intermittent apomorphine injections.[29] Interim results from the ongoing apokyn for motor improvement of morning akinesia trial study have shown that subcutaneous apomorphine injection produces a rapid and reliable TTO, with 95% of patients with morning akinesia achieving at least a 20-minute reduction in TTO and an average reduction of 40 minutes.[47,48]

Starting Patients on Intermittent Apomorphine Injection

Apomorphine injection is commonly initiated in the controlled environment of a specialist clinic where the patient can be monitored, particularly for the effect on blood pressure (BP). However, there is considerable variation between regions, whereas it is important to stress that at least during the first injections with apomorphine, monitoring of BP should take place, either in the inpatient or outpatient setting. Initiation may be undertaken by a physician experienced in the treatment of PD (eg, a neurologist) or by the Parkinson specialty nurse, under the supervision of the physician. The patient's treatment with levodopa, with or without dopamine agonists, should be optimized before starting apomorphine injections. If possible, the patient should also be established on domperidone or another antiemetic. Because each individual responds to apomorphine differently, the appropriate dose for each patient is established by incremental dose increases on the basis of the magnitude and duration of effect, using the apomorphine response test (see below and the section The Apomorphine Response/Challenge Test).[49] The optimal dose of apomorphine varies between individuals, but once established, it remains relatively constant for each patient.

When starting a patient on intermittent apomorphine injection, depending on the stage of the patient's PD symptomatology, the patient may be able to attend the clinic without taking his or her usual dopaminergic medication that day. Patients who are not well enough to do this should take their usual medication before attending. When the patient experiences the first off period in the clinic, 2 mg apomorphine should be injected subcutaneously, with clinical follow-up during at least 1 hour. Especially time to onset of effect, duration of effect and adverse effects are important to register in order to decide if the given dose was appropriate. Doses may be increased each time with 1 to 1.5 mg per injection. The patient's motor response should be monitored where different schedules are used with different end points, such as the Unified Parkinson's Disease Rating Scale (UPDRS) parts 3 and 4[50,51] or

TABLE 2. Summary of the Main Findings of Double-Blind, Placebo-Controlled Studies Using Intermittent Apomorphine Injection for the Treatment of PD

	Patient Characteristics				Apomorphine Treatment		Results After Apomorphine Treatment
Reference/Study	n	Age, y	Mean Duration of Disease, y	Hoehn and Yahr Stage	Duration of Study	Mean Injection dose, mg	
Van Laar et al 1993[94]	5	54.2	12.4	3–4	10 off periods	2.7	Significant positive effect of apomorphine vs placebo, $P = 0.001$; latency of onset, 7.3 min; duration of response, 96 min.
Ostergaard et al 1995[95]	22	59.3	9.8	2–4	8 wk	3.4	Mean daily duration of off periods reduced by 58% vs placebo; severity also significantly reduced.
Dewey et al 2001[96] (APO202)	29	66	9.2	—	4 wk	5.4	Mean UPDRS motor scores reduced by 62% with apomorphine vs 1% with placebo. Apomorphine successfully aborted 95% of off state events (vs 23% on placebo).
Pfeiffer et al 2007[97] (APO302)	62	65.5	—	—	Single off episode	TED or TED plus 2.0 mg	Greater improvement in mean UPDRS motor scores with apomorphine vs placebo 20 min after administration (−24.2 vs −7.4; $P < 0.0001$); difference also significant after 10 min ($P < 0.0001$)
Pahwa et al 2007[98] (APO303)	56	66	—	—	6 mo (open label)	4.0–10.0	Significant improvement in UPDRS motor scores with 4.0 mg apomorphine vs placebo at 20 min ($P = 0.0002$), 40 min ($P < 0.0001$), and 90 min ($P = 0.0229$)
Stacy and Silver 2008[99] (APO301)	17		—	—	Single off episode	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 ($P < 0.0001$)

TED, typically effective dose.

TABLE 3. Characteristics of Patients Suitable for Intermittent Apomorphine Injection (Pen) or Continuous Apomorphine Infusion (Pump)

Injection (pen)	•Anticipated rescue when required during motor and nonmotor off periods
	•When absorption of oral levodopa is impaired or the patient has gastric emptying problems (gastroparesis)
	•To treat delayed on
	•To treat early morning motor problems (akinesia and dystonia)
Infusion (pump)	•Patient considers that rescue doses required too frequently
	•Dyskinesias limit further therapy optimization
	•Nonmotor symptoms associated with off periods
	•Simplify complex PD dosing regimens to improve convenience and compliance with therapy
	•As an alternative to surgical therapy or levodopa-carbidopa intestinal gel if these are contraindicated or because of patient preference
	•Absorption or gastric emptying of oral levodopa are impaired

walking tests and computerized tapping tests (such as the bradykinesia akinesia incoordination test).[52,53] The BP (both supine and standing) should be recorded at regular intervals, for example, every 15 minutes up to 1 hour after injection. Alternative end points may consist of a selection of clinical symptoms, based on individual preference. If only tremor should be improved, it may be sufficient to monitor just the tremor severity.

The dose titration can be performed in at least 2 different ways:

1. Wait for another off period to occur and increase the next apomorphine dose by 1 to 1.5 mg until a satisfactory motor response is obtained.
2. Administer another apomorphine dose after 1 hour and every hour thereafter, increased by 1 mg on each occasion, recording motor response and BP during each hour.

The first option is more time-consuming and may not allow the response test to be completed within 1 day; however, it provides an adequate dose for daily practice. The second option is more practical, but it does not predict the optimal dose of apomorphine quite as precisely because the serum levels of apomorphine will accumulate over time. However, it does provide good information about the adverse effects related to different doses of apomorphine, generally regarded as the most important aspect of the test.

Once the appropriate apomorphine dose is determined, the patient can use single subcutaneous injections into the lower abdomen or outer thigh at the first signs of an off episode.[54] Absorption may slightly differ with different injection sites within a single individual, whereas the abdominal wall is the preferred place for injection with apomorphine. The total daily dose of apomorphine administered via injection varies widely between patients, but it is typically within the range of 3 to 30 mg, given as 1 to 10 injections but sometimes by as many as 12 separate injections per day. It is recommended that the total daily dose of apomorphine should not exceed 100 mg and that individual bolus injections should not exceed 10 mg.[54] Commonly, if a patient needs to administer more than 5 to 6 apomorphine injections per day, it will be recommended that he or she changes to using apomorphine continuous infusion.

The practical use of the APO-go PEN is set out in Figure 4. Patients and caregivers should also be advised to rotate the injection site (see section Managing Adverse Events).

CONTINUOUS APOMORPHINE INFUSION (PUMP)

Since its first use for treating motor complications of PD more than 25 years ago,[19,55] continuous subcutaneous apomorphine infusion has been widely utilized in the treatment of more advanced stages of PD. There have been a number of open, uncontrolled studies of the efficacy of apomorphine infusion,[20,56–58] 1 prospective study comparing the effect of continuous subcutaneous apomorphine infusion to conventional therapy,[59] and 3 prospective comparative studies between continuous apomorphine infusion and deep brain stimulation (DBS).[60–62] However, no randomized, double-blind, placebo-controlled studies have been performed until recently, when the clinical trial of apomorphine subcutaneous infusion in patients with advanced Parkinson's disease trial was initiated in 7 European countries. The study investigated treatment with apomorphine versus placebo for 3 months in 102 patients, followed by a 12-month open-label follow-up phase. The uncontrolled studies showed that continuous apomorphine infusion can reduce daily off-time by 50% to 70% in fluctuating PD patients (Table 4). Pooled data from 390 patients included in these studies show that patients experienced an average reduction in off time during the day of 58.2% (range, 38%–80%).[17] Clinical improvement was consistent across studies, being observed in long-term prospective evaluation at a single center as well as in multicenter retrospective assessments by a large number of physicians.[58] Average total daily apomorphine dose was 90.3 mg (range, 38–162 mg). On average, doses of concomitant antiparkinsonian drugs (expressed as levodopa-equivalent doses) were reduced by 45.9%. Average daily treatment duration was 17.1 hours (although a number of different infusion regimens were used, and a few patients used apomorphine infusion through the night.[17]

Peak dose and interdose dyskinesias may improve with apomorphine infusion as well, particularly if accompanied by a significant reduction of oral levodopa doses.[17,63] Extended follow-up studies of up to 8 years have demonstrated long-term maintenance of apomorphine efficacy.

In addition, also monotherapy with apomorphine infusion is associated with marked reductions in dyskinesias.[64] Continuous infusion (usually just during the waking day rather than throughout 24 hours) can maintain an on state, and this may lead to alterations in the motor response of the basal ganglia in such a way that peak dose and interdose dyskinesias may improve.[17] Although this phenomenology is often observed in clinical practice and has been repeatedly reported in open, uncontrolled studies,[20,56–58] no randomized, controlled studies have been performed that confirm the effect of apomorphine infusion at lessening dyskinesias.

As well as treating motor fluctuations, there is accumulating evidence that treatment of PD patients with apomorphine infusion is of benefit for the management of specific nonmotor symptoms of PD associated with "off" periods, including pain, anxiety, panic attacks, fatigue, dysphoria, hyperhidrosis, mood disturbances, and slowness of thinking.[65,66] Other studies showed evidence for the efficacy of apomorphine infusion in respect of nonmotor PD

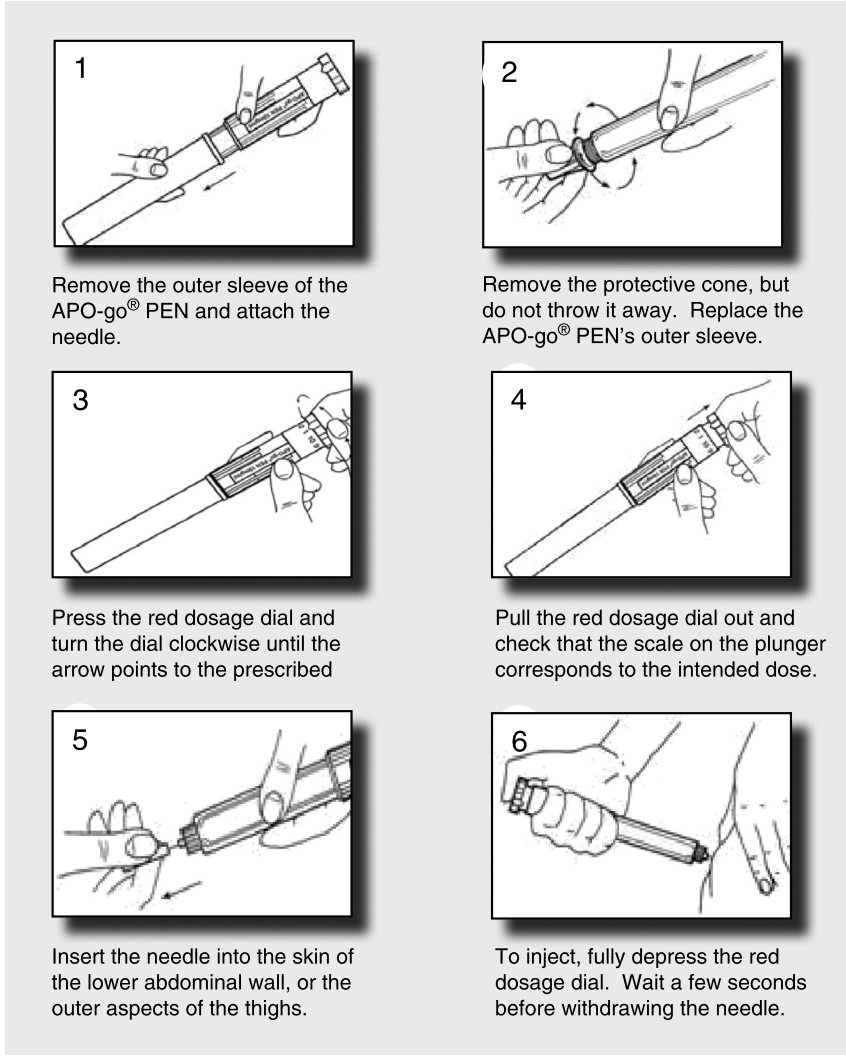

FIGURE 4. Administration procedure for intermittent apomorphine injection. Patients and caregivers should receive detailed instructions in the use of the apomorphine pen injection from the physician or other suitably qualified health care professional.

symptoms, including cognition,[60–62,67] visual hallucinations,[59,68] and sleep.[17,69]

A prospective multicenter study showed that apomorphine infusion had a large beneficial effect on the Nonmotor Symptom Scale (NMSS) in PD patients treated for a mean duration of 12 months.[59] A significant improvement was shown in fatigue, motivation, anxiety, flat mood, anhedonia, attention deficit, dribbling of saliva, urinary dysfunction (particularly urgency and nocturia), and hyperhidrosis.

Impulse control disorders (ICDs) as a consequence of dopaminergic agonist therapy are known to occur in patients with PD. Although they can vary in their severity and particular behavioral manifestations, they are not as rare as initially thought and can have an incidence of 13.6% to 17% in some studies.[70,71] Notably, studies with apomorphine infusion have observed a relatively low risk for the development of ICDs, estimated at 8%. Because this incidence is lower than has been reported for oral and transdermal dopaminergic agonists ropinirole, pramipexole, and rotigotine, this suggests that patients who have experienced ICDs with other drugs can nonetheless be suitable candidates for apomorphine treatment.[58,72–74] Careful monitoring for ICDs is necessary in all patients treated with dopaminergic agonists (even patients without PD, such as those with restless leg syndrome).

Because of the improvement in disabling motor and nonmotor aspects of the advanced stages of the disease, apomorphine infusion has been shown to exert a positive effect on rated quality of life in PD patients.[5]

There are very few direct comparative studies between apomorphine (whether as injection or infusion), levodopa carbidopa intestinal gel, and DBS.[17] The magnitude and pattern of motor responses to a single subcutaneous injection of apomorphine and oral levodopa were compared in 14 patients with PD.[75] Although apomorphine injection produced a shorter motor response than an oral dose of levodopa, the magnitude of response to the 2 drugs was indistinguishable. Alegret et al[60] found reduction in "off" time to be similar with both apomorphine infusion and DBS. In this study, oral antiparkinsonian medication was reduced by 43% in DBS patients and by 70% in patients on apomorphine infusion. In a small series of patients, De Gaspari et al[61] showed a significant reduction in "off" time with both apomorphine infusion (−50%) and DBS (−76%). However, the neuropsychiatric

TABLE 4. Summary of the Main Findings of Open-Label Studies Using Continuous Subcutaneous Apomorphine Infusion for the Treatment of Parkinson Disease (Adapted From Todorova and Ray Chaudhuri[66])

	Patient Characteristics				Apomorphine Treatment			Change After Apomorphine Treatment		
	n	Age (Mean), y	Duration of Disease, y	Hoehn and Yahr Stage (Mean/Median)	Duration of Follow-up, mo	Duration of Infusion, h/d	Total Dosage Per Day, mg	Daily Time in off, %	Dyskinesia Intensity, %	Daily Levodopa Dose, %
Chaudhuri et al,[20] 1988	7	59	17	5	11	8–12	29.7	−85	−45	−39
Pietz et al,[100] 1998	25	64.7	16	4.5	44	24	112.5	−50	−14	−50
Stibe et al,[19] 1988	11	56	14.4	—	8	14	77	−62	—	−73
Frankel et al,[101] 1990	25	58.8	17.8	4.1	22	20.1	89	−55	—	−22
Pollak et al,[102] 1990	9	52	15	5	10	12–24	93	−67	−20	−35
Hughes et al,[103] 1993	22	60.6	19.2		36.5	12.7	70	−59	—	16
Kreczy-Kleedorfer et al,[104] 1993	14	60.2	12.4	3.8	26	24	151.7	−77	—	−81
Poewe et al,[105] 1993	18	60.2	12.4	3.8	20.6	24	160	−58	—	−78
Stocchi et al,[106] 1993	10	60	11.5	3.7	12	12	38	−58	−40	−48
Gancher et al,[43] 1995	7	61.1	17.6	4	3		50.4	−58		−50
Colzi et al,[63] 1998	19				34.8	12	77.6	−72	−65	−80
Wenning et al,[107] 1999	16	60	11	3–5	57	24	162	−55	—	−55
Stocchi et al,[56] 2001	30	62	14	4.2	60	12	52	−55	—	—
Kanovsky et al,[108] 2002	12	64.3	14.4	4.5	24	—	31	−80	—	−23
Manson et al,[109] 2002	64	60.3	15.7	—	33.8	12–24	98	−49	−57	−64
Morgante et al,[67] 2004	12	54	10	3.7	24	—	100	−60	−48	−52
Tyne et al,[110] 2004	80	50.9	10	—	25.1	13.5	69.8	—	—	−24
Katzenschlager et al,[57] 2005	12	61.3	14.5	5	6	13.4	75.2	−38	−31	−55
De Gaspari et al,[61] 2006	13	59	10	3–5	12		74.78	−51	0	−29
García Ruiz et al,[58] 2008	82	67	14.39	—	19.93	14.05	72	−79.51	−34.14	−32.9
Martinez-Martin et al,[59] 2011	17	59.5	12.1	4	12 (variable)	12–16	—	Significant improvements in UPDRS 3 ($P = 0.0003$), UPDRS 4 ($P = 0.0003$), PDQ-8 ($P = 0.001$), and NMSS total ($P = 0.0003$)		−57
Drapier et al,[111] 2012	23	62.3	13.9	—	12	—	—	−36	—	−26

inventory scores and verbal fluency were significantly worse with DBS therapy as compared with apomorphine infusion.

As part of the multicenter Movement Disorder Society Non-Motor Study Group, the EuroInf study compared apomorphine infusion with intrajejunal levodopa infusion.[76] There were no significant differences at baseline between the 2 groups in terms of age, sex, duration of PD, Hoehn and Yahr–based severity level, UPDRS sections 3 and 4, NMSS domains and total score, the PD questionnaire (PDQ-8) summary index, and levodopa equivalent dose. Both treatments also had robust effects on the NMSS total score and on quality of life measures (PDQ-8). When individual nonmotor symptoms were analyzed, sleep and fatigue seemed to show greater improvements with levodopa infusion, whereas mood and apathy showed greater improvements with apomorphine infusion.

In PD patients undergoing DBS procedures, perioperative withdrawal of dopaminergic medication can lead to an increased risk for neurologic and respiratory deterioration. However, a retrospective analysis of data from 92 patients who underwent DBS surgery for PD found that perioperative apomorphine infusion was safe and well tolerated in this setting and resulted in a reduction in postoperative neurologic deterioration and in the requirement for hospitalization in intensive care.[77] The same procedure is used in many centers around non-DBS surgery, starting apomorphine infusion with a mean infusion speed of 2 to 3 mg/h, in combination with domperidone suppositories, enabling total parenteral control of parkinsonian symptoms presurgery, perisurgery, and directly postsurgery (van Laar et al[68]).

Suitable Candidates for Apomorphine Infusion

There are a number of factors to consider when selecting suitable candidates for continuous apomorphine infusion[17] as outlined in Table 3. Suitable candidates include the following:

- Those with motor complications (particularly motor fluctuations with frequent and prolonged "off" periods) who do not obtain adequate control despite optimized conventional oral treatment.
- Patients who do not wish to receive DBS or do not fulfill the selection criteria for that procedure.
- Those in whom rescue doses of apomorphine intermittent injection are effective but are either required more than 5 to 6 times per day or are associated with peak effect dyskinesia. This criterion does not mean that all patients should have been initially treated with apomorphine injections; in many centers, the majority of patients who start apomorphine pump have not previously used apomorphine injection.
- Patients who have swallowing difficulties that may interfere with their ability to adhere to an oral medication regimen.[78]
- Patients who experience gastrointestinal problems such as delayed gastric emptying (gastroparesis), which can delay or limit levodopa delivery to the small intestine and, hence, its clinical effect.[29,79]

The short elimination half-life of apomorphine is an advantage when the drug is given as a continuous infusion because each change in infusion rate will quickly result in a change of effect. Similarly, any adverse effects tend to diminish quickly after down-titration of the apomorphine dose.

Patients should not be considered for continuous subcutaneous apomorphine infusion if they experience severe or complex patterns of dyskinesias.[17] Also excluded are patients with severe dementia in association with PD or previous severe psychiatric or behavioral adverse reactions with other dopaminergic agonists. Mild dementia is not a contraindication for apomorphine infusion therapy, and the same holds true for mild hallucinations, especially if these are treated adequately with medications such as quetiapine, clozapine, or cholinesterase inhibitors.[68]

Starting Patients on Continuous Apomorphine Infusion

In the opinion of many practitioners, continuous subcutaneous apomorphine infusion should be initiated in the hospital setting.[17] Good clinical practice should include the prior undertaking of electrocardiogram (to exclude prolonged QTc interval duration, tachyrhythmia, bradyrhythmia, atrial fibrillation, and premature ventricular contractions, each of which could be cardiac reactions to apomorphine) and exclusion of preexisting hemolytic anemia. The patient's motor function should also be assessed using validated rating tools.[17]

Where it is available, domperidone should be administered at a low dosage (10 mg orally 3 times daily) before starting apomorphine infusion in view of the increased risk of prolonged QTc intervals with domperidone dosages greater than 30 mg/d.[80] In regions where domperidone is not available, an alternative antiemetic, such as trimethobenzamide, may be used.

The procedure for administering subcutaneous apomorphine infusion is set out in Figure 5. The contribution of specialist nurses (where available) is key during the initiation phase of apomorphine infusion and in subsequent follow-up visits. The role of the specialist PD nurse within in the multidisciplinary PD care team is discussed in detail below (see section Setting Up a Multidisciplinary PD Team).

The appropriate apomorphine dose for an individual patient is established by incremental dosing. Apomorphine infusion should be started at a dose of 1 mg/h during the waking day.[17] A bolus dose of up to 1 mg apomorphine is recommended to achieve rapid clinical improvement; otherwise, it will generally take around 2 to 3 hours to reach a steady state. The apomorphine infusion dosage should be increased by 1 to 1.5 mg/h per day according to patient's clinical response and other treatments withdrawn (catechol-o-methyltransferase inhibitors, oral or transdermal dopaminergic agonists, monoamine oxidase-B inhibitors, and levodopa). The aim should be to titrate the apomorphine dose up to at least 3 mg/h. Levodopa dosage should be progressively reduced by 50 or 100 mg every 3 to 4 days or weekly if hyperkinesia persists. Patients should of course be closely monitored for clinical effectiveness and possible adverse effects. The time taken to optimize subcutaneous apomorphine infusion therapy varies between patients but is usually achieved in a few weeks, although it can take up to 2 to 3 months.[17]

THE APOMORPHINE RESPONSE/ CHALLENGE TEST

As well as being used to assess the appropriate dose of subcutaneous apomorphine with which to treat a patient, the apomorphine response test is also useful in determining the maximal motor response in patients on dopaminergic therapy, the pattern and distribution of dyskinesias, and in the assessment of a patient's suitability for long-term subcutaneous apomorphine therapy, particularly with regard to adverse effects. A challenge with apomorphine is indicated only if high doses of levodopa, up to 400 mg per dose, do not provoke a clinical response, suggesting gastric motility problems. In these cases, apomorphine may show a good effect, suggesting subcutaneous apomorphine as an alternative therapy.

The apomorphine response test may be used in outpatient clinics or day hospitals in patients on long-term PD therapy. There are a number of ways to administer the test, and the details vary from center to center, but all involve a series of subcutaneous

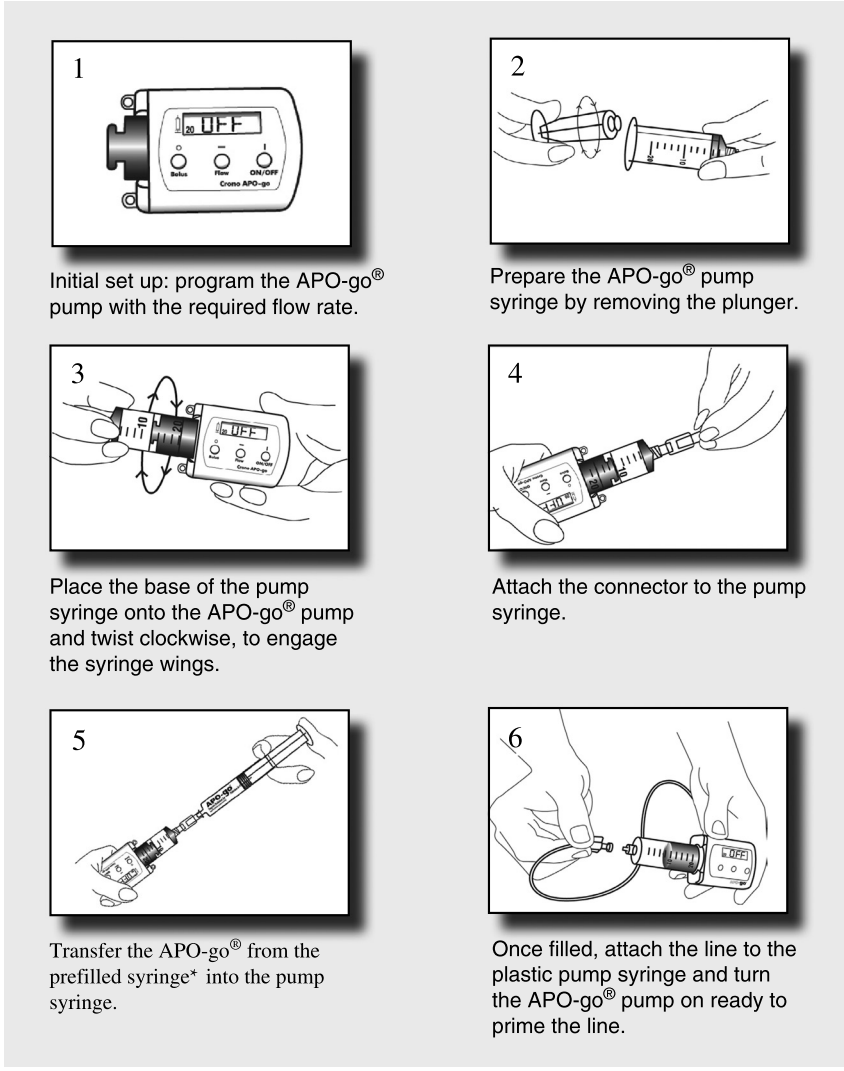

FIGURE 5. Administration procedure for continuous apomorphine infusion. Patients and caregivers should receive detailed instruction in the use of the apomorphine infusion pump from the physician or other suitably qualified health care professional.

injections of apomorphine, followed by movement assessments, determination of TTO, and duration of effect, as well as any adverse effects. Injections are administered at regular intervals, each containing a slightly higher dose than the previous one, as outlined previously.

It is not advisable for the response test to be used to improve differential diagnosis because both the maximum sensitivity and specificity of apomorphine injections in studies has been 70%.[81]

MANAGING ADVERSE EVENTS

Subcutaneous apomorphine is generally well tolerated, and adverse events are generally mild and do not necessitate discontinuation of therapy. Adverse events can occur, however, and effective management of these is key to the success of long-term treatment with apomorphine.

Nausea and the Role of Domperidone

Peripheral blocking of dopamine receptors with domperidone (a peripherally-acting dopamine antagonist)[18] has been regarded the most effective means of reducing the risk for nausea and vomiting when initiating patients on apomorphine, as well as lessening other peripheral adverse effects of apomorphine, such as hypotension. Domperidone does not readily cross the blood-brain barrier (it will only do so when a dosage of 100 mg/d is reached).[82] It acts by blocking dopamine receptors in the area postrema, which is accessible to the drug without it crossing the blood-brain barrier.

In March 2014, because of concerns about possible QTc prolongation, the European Medicines Agency issued updated treatment advice for domperidone.[80,83] Although it may continue to be used for the relief of symptoms of nausea and vomiting, doses should be reduced to no more than 10 mg up to 3 times daily, and it should not normally be continued for longer than 1 week. In practice, most patients do not require an antiemetic drug for long periods because their peripheral dopamine receptors may already be desensitized by receiving conventional antiparkinsonian doses of the oral dopaminergic agonists and levodopa. However, 1 week of domperidone may be insufficient for most patients starting apomorphine, especially because the titration to an optimal dose of

apomorphine often takes longer than 1 week. Domperidone can be stopped after 1 week, but if nausea and vomiting occur afterward, this should not be a reason to withdraw patients from apomorphine, but instead to continue the domperidone for a longer period.

Studies have shown that domperidone produces marked the human ether-a-go-go-related gene channel inhibition and action potential prolongation at clinically relevant concentrations (>30 mg/d) and has proarrhythmic potential.[84] Domperidone has also been shown to be associated with sudden cardiac death, especially at high doses.[85,86] Domperidone should not therefore be used in patients with conditions where cardiac conduction is, or could be, impaired, in those with underlying cardiac diseases (such as congestive heart failure), in those receiving other medications known to prolong QTc interval or potent CYP3A4 inhibitors, or in those with severe hepatic impairment.[80] This means that before starting domperidone, an electrocardiogram and additional laboratory controls should be performed to analyze potential contraindications for its use.

Domperidone is not marketed in the United States, and so an alternative antiemetic, trimethobenzamide, has been used when initiating patients on apomorphine with some effectiveness. Antiemetic drugs with central actions are also effective but have a propensity to exacerbate parkinsonism, so these are not recommended.[7] Ondansetron is not an option and is even contraindicated because in combination with apomorphine, there is an increased risk on hypotension and resulting in loss of consciousness (Food and Drug Administration guideline).

Injection Site Reactions

Local reactions occurring with subcutaneous apomorphine injection or infusion, such as minimal to moderate skin nodule formation at the infusion site, are relatively common but easily managed with conventional methods. These include the following:

- Moving to a different injection site each day to help minimize the chance of infection and skin problems to ensure good drug absorption and to allow the most recently used injection site to heal before another needle is inserted into that area.
- Removing any spillage of apomorphine at the injection site, squeezing away any excess apomorphine under the skin after each injection and washing the area.
- Ensuring the correct angle of insertion depending on the type of needle being used. In the case of butterfly infusion needles, if the angle of injection is greater than 45 degrees to the skin, it may be inserted too deeply or if less than 45 degrees, the drug may be injected into the superficial skin layer. The use of Teflon needles, or Neria or Cleo lines, which are inserted at 90 degrees to the skin, may avoid such problems.
- Maintaining good skin hygiene.
- Choosing a lower concentration, for example, 5 mg/mL or even lower if skin nodules are a problem.
- Massaging the infusion site (using a spiky rubber massage ball or vibrating device) or applying ultrasound treatment.
- Use of silicone gel dressings.
- Managing infections (which occur only rarely) with antibiotics.

Possible Adverse Events

1. Postural hypotension
   - Pharmacological treatment includes screening for possible use of antihypertensives, fludrocortisone, midodrine or droxidopa. Nonpharmacological measures include increased fluid and salt intake, raised bed head at night, slow changes of position, and compression stockings.
2. Neuropsychiatric adverse events (eg, confusion) are usually mild and infrequent. In approximately 10% of the cases, it can be severe. It is recommended to test the cognitive abilities in case of neuropsychiatric events. Clozapine or quetiapine might be a good option in case of psychotic symptoms, eventually combined with cholinesterase inhibitors in case of cognitive deficits.
3. Impulse control disorders. These do not necessarily require discontinuation of apomorphine (the EuroInf study showed a low rate of apomorphine discontinuation) for this problem.[87] In relevant cases, the dose may need to be lowered, and all additional oral dopaminergic agonists should be stopped.
4. Nausea can generally be controlled with domperidone (or as an alternative trimethobenzamide) pre-treatment in the majority of cases.[7]

Rare Adverse Events

1. Hemolytic anemia, although a potentially severe idiosyncratic adverse outcome, is rare, occurring in less than 1% of cases.
2. Eosinophilic syndrome is also rare but can sometimes present severe manifestations, including damage to heart and lung tissue, requiring the drug to be stopped.

Other Effects

Erections have been observed after administration of apomorphine in some PD patients, thought to be mediated by central D_2 dopaminergic receptor stimulation.[88] However, this adverse effect in association with increased libido has also been described with other antiparkinsonian medications, including levodopa, ropinirole, pergolide, and cabergoline.[89–91] In a survey of 15 male PD patients on regular apomorphine, 5 (33%) regularly experienced penile erections associated with intermittent subcutaneous apomorphine.[92] Although some experienced considerable discomfort when erections were induced, others with preexisting sexual dysfunction found the increased erectile function associated with apomorphine desirable. We are not aware of any reports of clitoral tumescence after the administration of apomorphine.

SETTING UP A MULTIDISCIPLINARY PD TEAM

It is now recognized that optimal care of PD patients should involve a multidisciplinary team (MDT) of health professionals, including neurologist or geriatrician, PD nurse specialist (PDNS), physiotherapist, occupational therapist, speech and language therapist, dietitian, clinical psychologist, and social worker, among others.[93] This section focuses primarily on the pivotal role of the PDNS within this team.

Explaining Apomorphine Therapy to a Patient and Carer—The Role of the PDNS

The decision to start a patient on subcutaneous apomorphine is usually made in the clinic by the consultant after an initial consultation with the patient and after having received their verbal informed consent. When explaining apomorphine therapy to the patient and their carer for the first time, it is helpful to have an information pack available for the chosen formulation, either the intermittent injection (Penject) or the continuous infusion (pump), as an explanatory aid. Such packs are provided by manufacturer or distributor in some countries. A key aspect of the decision-making process is an assessment of whether the patient and carer are able to adequately manage the equipment necessary for administration of subcutaneous apomorphine.

Importantly, there are some common misconceptions about apomorphine therapy that need to be addressed and the correct

information needs to be clearly explained to the patient at the outset. First, apomorphine infusion is classified as an "advanced therapy," a term that can be frightening for some people. The patient should be reassured that this does not necessarily mean that their condition has progressed, only that it has become more complex and therefore requires alternative treatments to the oral or transdermal medications they may have used previously. In addition, despite what its name might suggest, apomorphine is not a controlled drug and does not have the narcotic properties or opiate effects of morphine; the 2 compounds have different chemical structures resulting in different clinical effects. When patients and carers are told about "apomorphine," they sometimes mistakenly hear "morphine" and associate it with palliative care. As a result, they may resist or delay starting the treatment, fearing they have reached the end stage of their condition.

Once the decision to start the patient on subcutaneous apomorphine injections or continuous infusion, it is helpful to explain carefully to both the patient and carer the correct administration procedure, including the use of suitable needles or infusion lines, using a diagram (eg, see Figs. 5, 6) or by using a placebo pen or pump. It is essential that the patient and carer understand the need for good skin care and are advised of measures that can be taken to minimize the development of skin nodules (see section Managing Adverse Events).

At this stage, it is also helpful to check if the patient is constipated and whether there is sufficient fluid intake. These both need to be addressed before undertaking an apomorphine response/challenge test because dehydration can result in postural hypotension.

For some PD patients, "off" motor symptoms may limit the ability to prepare apomorphine solutions and manipulate syringes and infusion pumps without the assistance of a caregiver. In such cases, PDNS nurses can play an important role in educating patients about timing their intake of oral medication to ensure they are in an on state before setting up the pump to administer an apomorphine infusion.

Liaison With the Primary Care Team

If the patient elects to receive apomorphine therapy, a clinic letter should be sent to the patient's general practitioner explaining the decision to start apomorphine treatment and accompanied by information sheets on the chosen formulation and the response test procedure.

The Multidisciplinary Team

The MDT is a group of specially trained professionals who are brought together to improve each of the different aspects of PD that impact the patient, including medication, emotional and psychological symptoms, mobility, drooling, and diet, providing advice on adaptations to their daily lives (Fig. 6). These professionals will vary from country to country, and so there is no standard template regarding who should be included in a MDT. The ultimate aim of the MDT is to minimize the impact that PD has on the patient's everyday activities. Speech and language therapists can assess both speech and the patient's capacity to swallow. Physiotherapists can assess mobility and balance as well as providing strategies for the prevention of falls and good exercise programs. Occupational therapists can provide information for younger PD patients on adaptations to computer equipment, cutlery, and other home equipment. To provide the most optimal care the patient and carer ideally would need access to a MDT as described above right from the initiation of apo therapy coordinated through the PD nurse specialist.

CONCLUSIONS

The clinical utility of long-term oral levodopa therapy in PD is often limited by the emergence of motor complications. If a PD patient experiences motor fluctuations or dyskinesias that cannot be adequately managed by adjustment of oral medication regimens, the intermittent injection of apomorphine can provide rapid and reliable relief of both unpredictable and predictable "off" periods.[7,13]

Patients for whom apomorphine injections provide effective control but who find that these intermittent treatments are required

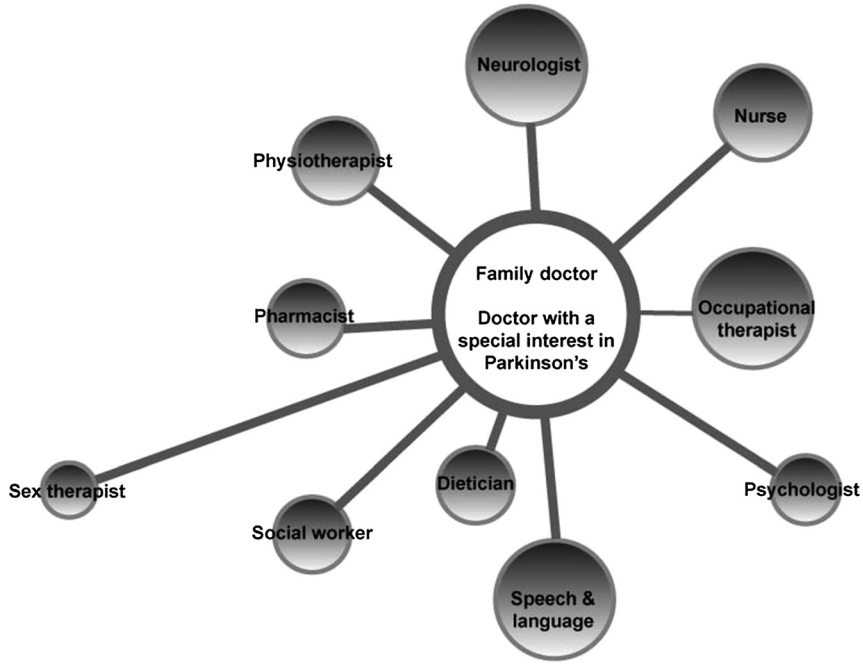

FIGURE 6. Possible collaborators in the MDT involved in PD patient care.

too frequently (ie, >5–6 times a day) or who are experiencing peak effect dyskinesia from apomorphine may be better suited to receive continuous subcutaneous infusion of apomorphine. Patients with medically intractable motor fluctuations are also suitable candidates for apomorphine infusion, without necessarily having been given intermittent apomorphine injections first.

In addition to being used to assess the appropriate dose of subcutaneous apomorphine with which to treat a patient, the apomorphine response (or challenge) test is also useful in determining the maximal motor response in patients on dopaminergic therapy, the pattern and distribution of dyskinesias, and in the assessment of a patient's suitability for long-term subcutaneous apomorphine therapy, particularly with regard to adverse effects.

Subcutaneous apomorphine is generally well tolerated, and adverse events are generally mild and do not necessitate discontinuation of therapy. Adverse events can occur, however, and effective management of these is key to the success of long-term treatment with apomorphine.

Apomorphine treatment is most effectively delivered with the support of a multidisciplinary PD care team, particularly during the initiation phase of apomorphine infusion and in subsequent follow-up visits. The specialist PD nurse plays a vital role, especially with regard to communication with the patient (and carer) and in patient follow-up.

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