

## Apomorphine in the Treatment of Parkinson's Disease

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DOI:10.17925/ENR.2009.04.01.28

### Abstract

The majority of patients with Parkinson's disease (PD) develop motor fluctuations and dyskinesias as their condition progresses. In patients where adjustments of oral (or transdermal) treatment options can no longer adequately control these motor complications, further options include deep-brain stimulation for a minority of selected patients, intrajejunal levodopa (L-dopa) application via a pump or apomorphine infusion therapy. The dopamine agonist apomorphine provides relief from off periods when administered as a subcutaneous injection. When applied continuously via a portable pump system, oral medication can often be reduced considerably and dyskinesias improve in many patients.

### Keywords

Parkinson's disease, apomorphine, motor complications, dyskinesias, motor fluctuations, continuous dopaminergic stimulation

**Disclosure:** Regina Katzenschlager has received fees for speaking and consulting from Britannia and Cephalon Germany.

**Received:** 28 March 2009 **Accepted:** 29 June 2009

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The initiation of antiparkinsonian treatment in early Parkinson's disease (PD) is followed by a phase of good to excellent symptomatic response in nearly all patients; this has been referred to as the 'honeymoon phase'. A stable response may be sustained in some patients throughout the course of their illness, but the majority will go on to develop motor complications, which include fluctuations and dyskinesias or involuntary movements.

In early PD, the clinical effect following an individual levodopa (L-dopa) dose wanes slowly and may still be detectable after days to weeks. As the disease progresses, the duration of effect gradually becomes shorter and patients become aware of a missed or delayed dose as their parkinsonian symptoms and signs re-emerge ('wearing-off'). Eventually, the clinical response closely reflects peripheral L-dopa pharmacokinetics, characterised by a plasma half-life of 1–1.5 hours. More complex forms of on/off fluctuations may emerge, such as unpredictable fluctuations, delayed on or dose failures. All of these changes in motor functioning may cause considerable distress. However, off periods may be associated with non-motor symptoms, such as acute depression, dysphoria or pain, which may be even more disabling than the worsening of motor function.

Dyskinesias may be present at peak doses or during the entire course of the drug. At earlier stages, they may go unnoticed by the patients while carers are aware of their presence and may be socially embarrassed. Patients themselves may prefer mild or moderate forms of dyskinesia to the immobility and non-motor symptoms of off periods, but severe chorea and more complicated patterns, such as ballistic, stereotypic and dystonic dyskinesias, pose a considerable burden on patients. Dyskinesias may be predominant at the onset and end of a dose effect (diphasic dyskinesia). Off-period dyskinesias are

usually dystonic, often affect the feet and toes and may be painful. They typically occur in the early morning hours when dopaminergic plasma concentrations are lowest. Incidence figures for motor complications vary in the literature. In a meta-analysis of prospective studies, the risk after five years was found to be around 40%,<sup>1</sup> while a recent study showed that response fluctuations may be a fairly early phenomenon when subtle signs are considered.<sup>2</sup> In young-onset PD, dyskinesias have been reported in up to 94% of patients.<sup>3</sup>

The exact mechanisms underlying motor fluctuations and dyskinesias are not yet completely understood. While the peripheral pharmacokinetics of L-dopa remain unchanged throughout the course of the illness, pre-synaptic nigrostriatal nerve terminals gradually lose their ability to store dopamine. However, evidence exists for a far more complex basis of the development of motor complications that are likely to be related to long-term unphysiological, pulsatile stimulation of the dopamine receptors and involve changes in striatal gene expression and subsequently in altered firing patterns of the basal ganglia.<sup>4</sup>

The management of motor fluctuations aims to prolong the effect of individual L-dopa doses by adding catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO-B) inhibitors, changing the intervals between intakes and advising patients to avoid taking L-dopa with meals. Oral or transdermal dopamine agonists are added to the drug regime or their dose is increased. While the data for amantadine in motor fluctuations are less robust, they may be a useful addition in some patients. All of these measures are limited in patients in whom dyskinesias have developed and the increase in the overall dopaminergic load used to counteract fluctuations may induce dyskinesias. Therefore, an individual dosing and timing regime must be

identified to prolong the effect of L-dopa without excessive worsening of dyskinesias, but this often means that a compromise must be accepted. Amantadine is the only oral drug with a demonstrated but limited effect on dyskinesias. In some patients, attempts to adjust oral and transdermal medication in the presence of disabling fluctuations and dyskinesias fail after months or years. It is then important to advise patients on further options, which include deep-brain stimulation for selected patients, a pump system that delivers L-dopa to the jejunum via a gastric tube<sup>5</sup> and the dopamine agonist apomorphine, which is delivered subcutaneously either intermittently or continuously.

Apomorphine is the oldest dopamine agonist used in clinical practice. It was first applied in PD patients in 1951, but interest waned when oral L-dopa was introduced. As the long-term complications associated with L-dopa therapy became recognised, apomorphine was investigated further. It has a long tradition of clinical use in the UK and is now also licensed in the rest of Europe. Apomorphine is the only drug that has an effect on parkinsonian motor signs equal to that of L-dopa. Due to its low bioavailability it cannot be administered orally. However, when injected subcutaneously, its bioavailability reaches nearly 100% and injections can be effective in rapidly resolving off states in patients with motor fluctuations. When given as a single dose, symptom relief is equivalent to oral L-dopa, with a considerably faster onset (five to 15 minutes) and shorter duration (mean 40 minutes) of effect.

### Intermittent Apomorphine Injection Therapy

Intermittent subcutaneous injection therapy, using an average of 3–4mg per injection, is usually performed via a pre-filled pen (see *Figure 1*) and can be a useful option for quick relief from off periods in selected patients. Patients suitable for this treatment must have offs despite optimisation of their oral drug combination. They must be able to distinguish their off symptoms from other conditions such as dyskinesias and they must be capable of injecting themselves or have a carer able to do so. Patients who suffer from sudden, unexpected offs often benefit from this rescue medication and it generally allows patients with motor fluctuations to be more independent, providing them with a means to better control their mobility. It can also be used very successfully for offs that are associated with non-motor symptoms such as pain, anxiety or dystonia.

Studies investigating the effect of regular apomorphine injection treatment have found reductions in daily off time of up to 50% (see *Table 1*), and effectiveness has been demonstrated in placebo-controlled studies.<sup>6–8</sup> Patient selection and counselling must be based on the fact that the optimum response that can be expected is equal to the patient's best L-dopa response, and that patients whose on periods are associated with dyskinesias will likely experience dyskinesias following apomorphine injections as well.

Pre-treatment assessments include an apomorphine challenge test to determine responsiveness and to establish effective doses, and to observe for side effects, such as nausea, postural hypotension, confusion or somnolence. Domperidone at a dose of 20mg three times daily should be initiated at least three days before any apomorphine treatment to counteract dopaminergic side effects.

### Continuous Subcutaneous Apomorphine Pump Treatment

Apomorphine given via continuous subcutaneous infusion during the waking hours leads to large reductions in daily off time of up to 80%

**Figure 1: Apomorphine Pen**



**Table 1: Apomorphine Injections – Review of Nine Studies**

Number of patients per study	5–49
Average age (years)	60.6
Disease duration (years)	12.3
Study duration (months)	13.7
Dose/injection (mg)	3.4
Injections/day	3.6
% off duration	-43.9
% on with dyskinesia (one study)	+7.7
Levodopa/day	unchanged

*Adapted from Odin, 2005.<sup>7</sup>*

**Figure 2: Apomorphine Pump**



**Figure 3: Patient Using an Apomorphine Pump**



compared with baseline. This has been shown in several open-label studies of up to 33 months in duration, although a randomised head-to-head comparison with other treatment options has not yet been performed.<sup>9–11</sup> Apomorphine-pump treatment is therefore an option for patients with severe motor fluctuations, including those who have previously used apomorphine injections but require too many injections per day.

Moreover, several open-label studies have shown considerable and sustained antidyskinetic effects in patients on continuous subcutaneous apomorphine therapy (44–83% reduction in dyskinesia severity compared with baseline).<sup>9–12</sup> Dyskinesia reduction is more marked in those patients who gradually manage to substantially reduce their oral dopaminergic therapy, or who achieve 'apomorphine monotherapy'. This is defined as pump treatment only during the waking day with complete discontinuation of oral drugs, using oral drugs only early in the morning and at night.<sup>9,11,12</sup>

The observed improvement in dyskinesias is in keeping with the current concept of dyskinesia formation and is believed to be due to the replacement of pulsatile with continuous dopamine receptor stimulation. Maximum dyskinesia improvement has been observed several months following the initiation of pump treatment on mean daily doses of around 100mg. The mean doses tend to remain stable even when patients use this treatment for years.

In practical terms, pump treatment is usually initiated on an inpatient basis. Domperidone is always used as a pre-medication for at least three days and then continued for as long as required. Oral dopamine agonists and subsequently the other oral antiparkinsonian drugs are gradually withdrawn over weeks to months while apomorphine is administered at increasing hourly flow rates. The small and lightweight pump is usually worn on a belt around the patient's waist and the needle is inserted into the abdominal skin into rotating injection sites (see *Figures 2* and *3*). The needle must be replaced daily. While the usual daily duration of pump treatment is around 14–16 hours, some patients with severe nocturnal off symptoms benefit from 24-hour administration.

## Adverse Effects

Potential side effects of continuous apomorphine treatment include dopaminergic effects including nausea, orthostatic hypotension, leg oedema or somnolence. Skin-nodule formation is very common but usually mild. Rarely, medically relevant skin problems such as abscesses or ulcerations occur, which may require surgical treatment. Occasionally, widespread nodules may impair reliable and stable absorption of apomorphine. Haemolytic anaemia is rare but regular checks for full blood count and Coombs test are recommended. Coombs test has been described to turn positive in 6–12.5%, although this may be reversible. Development of haemolytic anaemia requires discontinuation of apomorphine and

treatment in collaboration with haematology specialists. As with other dopaminergic drugs, a small number of vulnerable patients develop impulse control disorders such as pathological gambling, hypersexuality or other behavioural disturbances on higher doses. Confusion or hallucinations may occur. While there is some evidence that neuropsychiatric problems may actually improve compared with baseline, and a positive effect on mood has also been suggested,<sup>13–15</sup> conclusions are limited because none of the available studies of apomorphine pump treatment were randomised.

## Summary

Apomorphine induces reliable and quick relief from off periods when administered as subcutaneous injections and offers patients with severe motor fluctuations better control and more independence. When administered via a pump system, excellent improvements in off duration can often be achieved and additionally, in those patients who replace most or all of their oral drugs with continuous apomorphine, dyskinesias often improve as well. It is clear that the indications for apomorphine pump treatment are very similar to those for intrajejunal L-dopa administration (Duodopa®) and for subthalamic deep-brain stimulation, namely motor complications refractory to oral treatment adaptations.

While apomorphine has potential adverse effects including skin changes and haemolytic anaemia, it is a less invasive treatment than the other two options and in principle is reversible. Older age, mild to moderate cognitive impairment and many medical co-morbidities do not represent strict contraindications for a treatment trial with apomorphine. However, no randomised controlled studies exist comparing these strategies for late-stage PD and, therefore, the choice of treatment depends on whether any contraindications for surgery are present, on availability and local expertise and on the patient's preference. ■



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