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Review

Subcutaneous apomorphine and non-motor symptoms in Parkinson's disease

Antoniya Todorova*, K. Ray Chaudhuri

National Parkinson Foundation Centre of Excellence, Department of Neurology, King's College Hospital, and King's Health Partners, London, UK

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ABSTRACT

Non-motor symptoms (NMS) are now recognized to occur across all stages of Parkinson's disease (PD) and as a result there has been an increasing focus on their diagnosis, quantification and effective management. While in some subjects, NMS may be present before diagnosis, in advanced PD, NMS can contribute to hospitalization, severe disability and a shortened life expectancy. Strategies for continuous drug delivery have been reported to have a beneficial effect on NMS in PD and while the efficacy of apomorphine on motor function in PD has been confirmed in a number of studies, in addition to its possible anti-dyskinetic effect, a number of reports have also outlined the possible beneficial effect of apomorphine on NMS. This review sets out to examine the efficacy of apomorphine in non-motor aspects of PD, including its effect on neuropsychiatric and gastrointestinal symptoms, sleep (including restless legs syndrome), urinary dysfunction, pain and impulse control disorders. The analysis takes into consideration case reports, and open-label and comparative case–control studies published to date. Results of this review suggest that although data on the effect of apomorphine on NMS in PD patients are limited there is a strong suggestion of a beneficial effect that warrants further investigation in double-blind studies.

Almost 60 years have passed since Schwab and colleagues reported the beneficial effect of apomorphine hydrochloride on tremor and rigidity in patients with Parkinson's disease (PD) [1]. Later, in 1979, Corsini et al. reported the successful use of subcutaneous apomorphine in combination with domperidone [2], and this was confirmed by a series of studies by Hardie et al. [3]. More recently, in 1988, Stibe et al. and Chaudhuri et al. described the successful use of continuous subcutaneous infusion of apomorphine in overcoming refractory on–off oscillations in PD [4,5].

While there is a reasonable body of evidence which confirms the efficacy of apomorphine on motor function in PD, as well as a possible anti-dyskinetic effect [6], there have also been sporadic reports of the possible beneficial effect of apomorphine on non-motor symptoms (NMS) in PD (Fig. 1). Given that NMS are now recognized to be almost universal across all stages of PD and also the key determinant of quality of life (QoL) of people with PD [7], a closer examination of the non-motor effects of apomorphine is justified. A range of different NMS occur in PD and while most are related to the disease itself, some may be drug related, such as impulse control disorders (ICD), hallucinations, somnolence and dopamine agonist withdrawal syndrome (DAWS) [8]. This review sets out to examine the non-motor effects of apomorphine, taking into consideration case reports, and open-label and comparative case–control studies published in the literature (including relevant abstract information) to date and this is summarized in Table 1.

1. Overall effect of apomorphine infusion on NMS as a whole

The various NMS can be studied as a group using the Non-Motor Symptoms Scale (NMSS), validated for PD [9] which provides a comprehensive gradation (severity and frequency) of 30 different NMS allocated to nine specific domains. To date, this is the only dedicated, holistic, validated tool for the overall assessment of NMS as a whole in PD.

Using the NMSS as one primary outcome variable, Martinez-Martin et al. reported a non randomized open label comparative study of 17 patients receiving subcutaneous apomorphine infusion compared to a patient group on conservative therapy with the NMSS, with motor and QoL measures being assessed at initiation of therapy and at 6 months' follow-up as part of routine clinical practice in a real-life study [10]. Apomorphine infusion was found to improve NMSS total score (NMSS-T) significantly ($p = 0.0003$), QoL as measured by PD questionnaire (PDQ-8), and motor state as

* Corresponding author. Department of Neurology, 9th Floor Ruskin Wing, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
E-mail addresses: a.todorova@nhs.net, an.todorova@gmail.com (A. Todorova).

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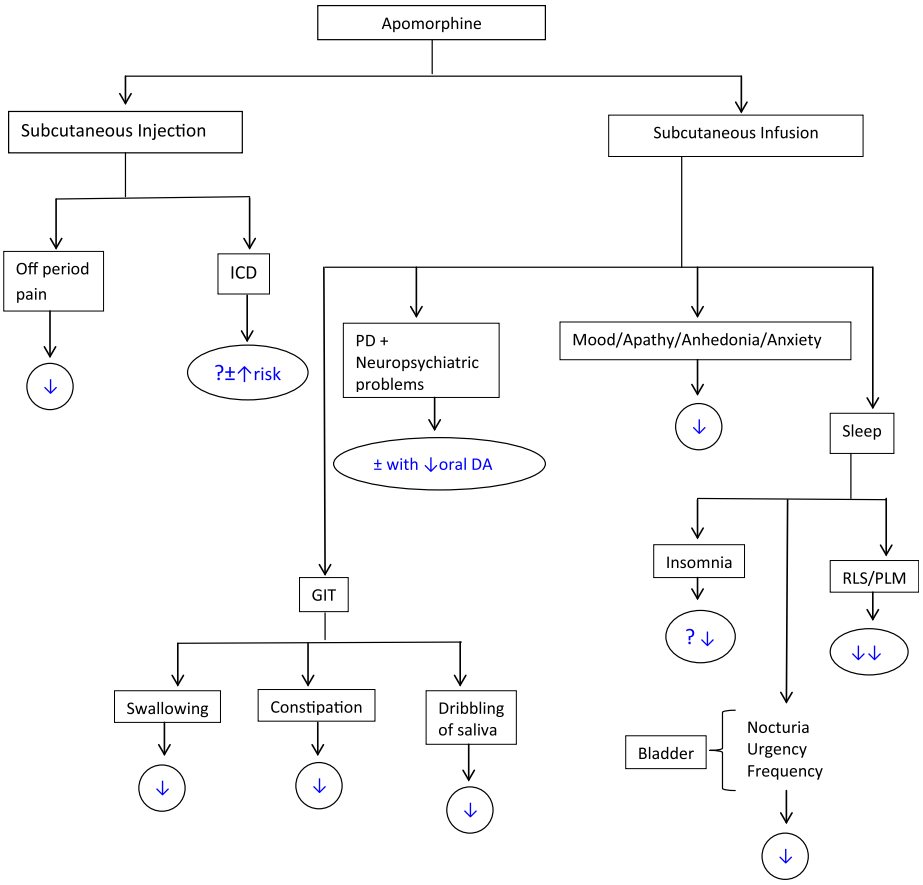

Fig. 1. Effect of apomorphine on non-motor symptoms. ? = possible effect; ± = possible beneficial effect has been demonstrated in some open-label studies/anecdotal case reports; ↑ = increase; ↓ = decrease; DA, dopamine agonist; GIT, gastro-intestinal; ICD, impulse control disorder; RLS, restless legs syndrome; PLM, periodic leg movements.

measured by the Unified Parkinson's Disease Rating Scale (UPDRS) III and IV scores. When the NMSS domains were sub-analyzed, moderate-to-large improvements in effect size of apomorphine were observed in sleep (mainly related to nocturnal restless legs-type symptoms and insomnia), attention, mood, apathy, fatigue, urinary (urgency, nocturia) and gastrointestinal (dribbling, constipation) domains of the NMSS (Table 2) [10]. A further study by Reddy et al. expanded this work across several European centers (the EuroInf survey) in 43 PD patients receiving continuous apomorphine infusion and followed up for 12 months [11]. Reported only in abstract form so far, a significant improvement was found in motor and non-motor scores with a large effect size matching published effects of DBS in PD.

2. Effect of apomorphine on specific NMS

2.1. Apomorphine and neuropsychiatric symptoms

Historically, apomorphine has been used in PD patients with drug-related neuropsychiatric complications [12] and some have argued that the piperidine moiety contained in the structure of apomorphine may have some anti-psychotic properties [13,14]. In specific papers addressing this issue, Chaudhuri et al. and Ellis et al. published a total of 15 case reports on PD patients with previous drug-related neuropsychiatric problems, confirming the possible role of the use of apomorphine in PD patients with neuropsychiatric problems [12,15].

Contrary to common perception, apomorphine therapy can be tolerated in patients experiencing visual hallucinations and delusions, as well as in patients with paranoid ideations [10] however this is controversial. Apomorphine infusion was well tolerated in 12 PD patients experiencing hallucinations in one open-label study [12] and subsequently these findings have been replicated by van Laar and colleagues [16]. Another study comparing apomorphine with deep brain stimulation (DBS) undertaken by Antonini and colleagues reported worsening of Neuropsychiatric Inventory (NPI) scores with DBS but not in the apomorphine arm [17]. Some authors have suggested that apomorphine has antipsychotic properties and may in fact improve visual processing in PD patients with visual hallucinations, in particular increasing contrast sensitivity and decreasing reaction time [16,18].

A recent study by Drapier et al. demonstrated a high level of neuropsychological safety for patients treated with apomorphine infusion at 12-month follow-up [19]. The authors did not find any change in the neuropsychological status of the patients after 12 months on apomorphine treatment, confirming that apomorphine infusion is a safe therapy in PD in terms of patients' cognitive status. These results are in agreement with other studies which compared DBS of the sub-thalamic nucleus with apomorphine in two groups of fluctuating PD patients and failed to find any cognitive change in the apomorphine group [20,21].

However, these data has to be considered with caution as patients with advanced PD are also liable to develop confusional states while on apomorphine possibly linked to other co-morbid complications such as infection. Furthermore, if patients with DLB are accidentally included, neuropsychiatric complications may actually worsen on apomorphine.

Finally, we do not have robust evidence base to support the notion that apomorphine does not worsen hallucinations in PD. Therefore, we would urge readers to exercise caution in translating