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

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ABSTRACT

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

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

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

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

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

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

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

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

2. Gastrointestinal dysfunction in PD

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

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

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

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

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

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

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

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

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

4. Options for non-oral PD medication

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

5. Transdermal therapies

5.1. Rotigotine patch

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

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

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

5.2. Rivastigmine patch

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

5.3. Subcutaneous apomorphine

Apomorphine is a dopamine agonist that selectively acts at