Parkinsonism and Related Disorders xxx (2015) 1–12

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review

# Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program

P. Odin [a, b, *, 1], K. Ray Chaudhuri [c, 1], J.T. Slevin [d], J. Volkmann [e], E. Dietrichs [f], P. Martinez-Martin [g], J.K. Krauss [h], T. Henriksen [i], R. Katzenschlager [j], A. Antonini [k], O. Rascol [l, m], W. Poewe [n], On behalf of the National Steering Committees

[a] Department of Neurology, Lund University Hospital, 221 85 Lund, Sweden
[b] Klinikum-Bremerhaven, D-27574 Bremerhaven, Germany
[c] King's College London, and National Parkinson Foundation Centre of Excellence, Dept of Neurology, King's College Hospital, London, UK
[d] Department of Neurology, University of Kentucky College of Medicine, Kentucky Clinic L-445, 740 South Limestone Street, Lexington, KY 40536-0284, USA
[e] Department of Neurology, University Hospital of Würzburg, 97080 Würzburg, Germany
[f] Department of Neurology, Oslo University Hospital and University of Oslo, N-0424 Oslo, Norway
[g] National Center for Epidemiology and CIBERNED, ISCIII, Avenida Monforte de Lemos 5, 28029 Madrid, Spain
[h] Department of Neurosurgery, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany
[i] University Hospital of Bispebjerg, Bispebjerg Bakke 23, 2400 København, NV, Denmark
[j] Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders, Sozialmedizinisches Zentrum Ost – Donauspital, 1220 Wien Langobardenstraße 122, Austria
[k] Parkinson and Movement Disorders Unit, IRCCS Hospital San Camillo, Venice, Italy
[l] Clinical Investigation Center 1436 and Department of Clinical Pharmacology, INSERM and University Hospital of Toulouse, Toulouse University, 37 alées Jules Giesde, 31000 Toulouse, France
[m] Clinical Investigation Center 1436 and Department of Neurosciences, INSERM and University Hospital of Toulouse, Toulouse University, 37 alées Jules Giesde, 31000 Toulouse, France
[n] Innsbruck Medical University/University Hospital, Anichstrasse 35, A-6020 Innsbruck, Austria

ARTICLE INFO

*Article history:*
Received 23 December 2014
Received in revised form
20 May 2015
Accepted 22 July 2015

*Keywords:*
Parkinson's disease
Device-aided therapies
Motor fluctuations
Dyskinesias
Non-motor symptoms

ABSTRACT

Navigate PD was an educational program established to supplement existing guidelines and provide recommendations on the management of Parkinson's disease (PD) refractory to oral/transdermal therapies. It involved 103 experts from 13 countries overseen by an International Steering Committee (ISC) of 13 movement disorder specialists. The ISC identified 71 clinical questions important for device-aided management of PD. Fifty-six experts responded to a web-based survey, rating 15 questions as 'critically important;' these were refined to 10 questions by the ISC to be addressed through available evidence and expert opinion. Draft guidance was presented at international/national meetings and revised based on feedback. Key take-home points are:

- Patients requiring levodopa >5 times daily who have severe, troublesome 'off' periods (>1–2 h/day) despite optimal oral/transdermal levodopa or non-levodopa-based therapies should be referred for specialist assessment even if disease duration is <4 years.
- Cognitive decline related to non-motor fluctuations is an indication for device-aided therapies. If cognitive impairment is mild, use deep brain stimulation (DBS) with caution. For patients who have cognitive impairment or dementia, intrajejunal levodopa infusion is considered as both therapeutic and palliative in some countries. Falls are linked to cognitive decline and are likely to become more frequent with device-aided therapies.

* Corresponding author. Department of Neurology, Skane University Hospital, SE-221 85 Lund, Sweden.
*E-mail addresses:* per.odin@med.lu.se, per.odin@klinikum-bremerhaven.de (P. Odin).
[1] Joint first authors.

http://dx.doi.org/10.1016/j.parkreldis.2015.07.020
1353-8020/

• Insufficient control of motor complications (or drug-resistant tremor in the case of DBS) are indications for device-aided therapies. Levodopa-carbidopa intestinal gel infusions or subcutaneous apomorphine pump may be considered for patients aged >70 years who have mild or moderate cognitive impairment, severe depression or other contraindications to DBS.



## 1. Introduction

Parkinson's disease (PD) is characterized by motor symptoms, such as bradykinesia, rigidity, tremor and postural instability. In its early stages, treatment with oral dopaminergic therapies is usually effective; however, as the motor disease progresses these therapies no longer provide adequate control of symptoms which range from motor and non-motor fluctuations to dyskinesias. At this stage, it is important to ensure timely referral of patients to a movement disorder specialist before deterioration in quality of life (QoL) and development of complications of advancing disease [1,2]. It may be appropriate to consider device-aided treatments when motor fluctuations become refractory to adjustments in oral/transdermal medication, and when these adjustments are typically complicated by the emergence (or worsening) of dyskinesias [2].

Three device-aided treatments are available:

- subcutaneous (SC) apomorphine pump [3];
- levodopa-carbidopa intestinal gel (LCIG) [4] infusions [5,6];
- deep brain stimulation (DBS) [7].

Alongside motor symptoms, people with PD also experience non-motor symptoms (NMS) such as: pain, drooling; choking/swallowing difficulties; constipation; bladder dysfunction; cognitive impairment; hallucinations; depression/anxiety; sexual dysfunction; insomnia, which occur from disease onset [8]. Non-motor symptoms contribute to severe disability, impaired QoL, and institutionalization [9], and can be more troublesome and disabling for the patient than motor complications [10]. Recent work suggests some NMS are treatable using device-aided therapies [11,12] since they are often dopaminergic in origin. Furthermore, some NMS specifically complicate motor fluctuations, and are treatable by strategies that attenuate fluctuations [13].

Current guidelines provide recommendations based on randomized placebo-controlled studies providing level 1 evidence of treatment. Such evidence is often not available for a range of non-motor issues as well as some motor phenomena. This leads to a lack of pragmatic real-life instruction on how to treat patients with device-aided therapies when oral/transdermal medications no longer effectively control their symptoms [14,15]. Despite multiple evidence-based guidelines, there remain clear gaps in knowledge, which, in clinical practice, are addressed through expert judgment and experience.

To supplement current clinical guidelines, a pan-European educational program, 'Navigate PD', was established to identify the key unresolved issues in the management of PD refractory to oral/transdermal therapies and explore questions commonly raised by clinicians about the optimal use of device-aided treatment. Here we propose approaches for the management of clinically important unresolved issues in PD based on the experience and expert opinion of over 100 experts in the field of PD/neurology.

A total of 103 experts from 13 countries worldwide participated in the Navigate PD program (Working Group members excluding authors of this paper are listed in Acknowledgments). Each country had its own National Steering Committee and the program was overseen by an International Steering Committee (ISC) of 13 specialists from Europe and chaired by two authors of this paper (PO and KRC). The lead authors were contacted and suggested the Steering Committee. AbbVie then contacted a leading MD specialist in each of the participating countries, who could then suggest the specialists participating from each country. The main criteria for participation was to be an internationally recognized movement disorder specialist with well-documented experience with advanced PD therapies.

The objectives of the program were:

- to identify and address the most important questions relating to device-aided management of PD;
- to provide practical answers based on available evidence and the clinical experience of participants; and
- to develop pan-European guidance for PD management beyond oral/transdermal therapy that clearly defines the patient and treatment choices available.

The multi-step program took place between April 2012 and July 2013 and involved numerous international and national meetings attended by neurologists, geriatricians and MD specialists representing many countries. The process is outlined in Fig. 1.

The ISC identified areas of clinical focus and developed 71 key questions (Appendix 1), which were ranked in a web-based survey by the experts. Based on this ranking, the ISC prioritized questions via informal debate, then prepared draft guidance for each based on available evidence from literature reviews combined with expert opinion where evidence gaps existed. The draft guidance was presented and discussed at national and international meetings and revised based on the feedback obtained. This was not a formal consensus or Delphi process; the program aimed to achieve answers on which all participants had reached broad agreement.

Fifty-six completed web-based prioritization questionnaires were returned. Of 71 questions, 15 were rated as 'critically important' by at least one-quarter of respondents. These were further refined by the ISC to 10 questions to be addressed through literature search and expert opinion.

## 2. Practical guidance on device-aided management of PD derived from discussions of navigate PD

### *2.1. How do I recognize and refer for specialist assessment a patient in whom the dosage and adjustment of oral/transdermal therapies cannot further improve mobility and quality of life?*

Non-invasive therapies may be judged insufficient when QoL becomes inadequate due to motor fluctuations with or without dyskinesias, and the clinician and patient agree that non-invasive therapy alone is no longer effective. Adequate trial of non-invasive therapies includes levodopa and, unless contraindicated, dopamine agonists, monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors. Broadly, referral to a specialist should be considered if levodopa is required $\geq$5 times daily, although the number of doses is not relevant if tolerated by the patient and an adequate reduction in 'off' time is achieved.

Please cite this article in press as: P. Odin, et al., Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.07.020