

BMJ Open Non-lesional treatment options for tremor in idiopathic Parkinson syndrome: a protocol for a systematic literature review

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ABSTRACT

Introduction Idiopathic Parkinson syndrome (iPS) is one of the most common neurodegenerative disorders characterised by the triad of bradykinesia, rigidity and tremor. Tremor at rest predominantly at one side is often perceived by patients as severely disabling and yet ranges among the most difficult symptoms to treat. In medically refractory cases, lesional approaches have proven to be effective alternatives. However, to date, there is no comprehensive analysis of non-surgical therapies to manage iPS-patients' tremor. We therefore present a detailed study protocol for a systematic literature review assessing efficacy/effectiveness and safety of non-lesional treatments for tremor in iPS.

Methods and analysis We will search three electronic databases (MEDLINE, EMBASE and PsycINFO) using a combination of title/abstract keywords. Additionally, hand-searched reference and citation lists of key reviews identified through the search strategy will be screened. Eligible studies should investigate the efficacy/effectiveness and safety of therapeutic options for tremor in iPS excluding lesional interventions. Publications will be independently assessed for inclusion criteria by two investigators and study information summarised using a standardised template including quality assessment according to the QualSyst tool. We will provide a narrative synthesis of results and conduct a meta-analysis whenever possible.

Ethics and dissemination We commit to present contemporary evidence on the efficacy/effectiveness and safety of non-lesional interventions for tremor in iPS in a future publication. We aim to compile rich data of published studies to inform healthcare professionals in order to ultimately improve patient outcomes.

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INTRODUCTION

Tremor ranges among the most frequent movement disorders. A newly proposed classification of tremor syndromes recommends an assignment according to specific clinical characteristics and to its aetiology. Thus, tremor may be idiopathic, genetic or acquired.¹ Yet, tremor has become widely known in Parkinson syndromes as triad along with bradykinesia and rigidity² and in

Strengths and limitations of this study

- Our systematic review aims to gain a clear and comprehensive overview of available evidence on the treatment of tremor in idiopathic Parkinson syndromes.
- By broadening inclusion criteria beyond experimental study designs from interdisciplinary fields, we hope to acquire additional evidence on less common interventions.
- We will follow guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to ensure high quality reporting of our results.
- Despite the extensive search strategy, this systematic review may yet be affected by publication bias.

fact continues to be mistakenly considered pathognomic by some patients.

In medical examinations, the rhythmic and oscillatory movements within idiopathic Parkinson syndrome (iPS), that is, Parkinson's disease are typically unilateral and occur at rest or after sustained postural positions—termed therefore re-emergent tremor. Furthermore, it is of mild to moderate amplitude and shows frequencies around 4–8 Hz.^{1,3} Tremor in iPS is of particular clinical relevance not only given its high prevalence but especially as it strongly relates to loss of life quality during the course of the disease.⁴ Notwithstanding the high amount of disability,^{5,6} tremor often remains one of the most challenging symptoms to manage.^{7,8}

This is all the more surprising as alleviation of tremor was the first symptomatic treatment for iPS-patients as early as the 19th century.⁹ Since then, newly developed substances have enabled amelioration of bradykinesia, whereas being less effective reducing tremor.

Among the reasons for the difficulty in suppressing tremor to this day is a lack of understanding of its pathophysiology.

It was found that aberrant brain networks including basal ganglia, the cerebral cortex and the cerebellum are responsible for generating tremor and modulating its amplitude.^{10 11} In cases with insufficient symptom control, structural or functional lesions may be contemplated as they offer good efficacy at a moderate risk of side-effects.¹² Nevertheless, not all patients are suited or willing to undergo invasive treatments as they come at cost of possible risks such as haemorrhages, infections or psychiatric sequelae.^{13 14} Besides, invasive options are relatively expensive and require complex infrastructure which may not be available universally. In cases where lesional therapies are not eligible, iPS-patients with severe tremor often report years of odyssey by the healthcare system and exposure to medications that often lack beneficial effects.

We would like to present a protocol for a systematic literature review aiming at comparing the efficacy/effectiveness of non-lesional treatment options (eg, various orally/enterally administered drug substance groups, local botulinum toxin administration, physiotherapeutic interventions, etc.) for tremor in the context of iPS. To date, no systematic literature review exists on which treatment options are most effective. On the one hand, despite the heterogeneous presentation of iPS symptoms, the relatively new concept of stratification into subgroups¹⁵ has not yet found entrance into scientific and clinical routine. Otherwise, even though recognised as a cardinal symptom of iPS,¹⁶ there is still no consensus on how to adequately assess tremor. Tremor can thus be evaluated objectively by neurophysiological measures or by determining resulting disability. Moreover, subjective assessments by patients themselves through clinical rating scales are also gaining relevance. These different aspects may offer explanations for a heterogeneous data situation, so that a targeted review of available studies for the development of effective and safe therapy strategies for the subgroup of tremulous iPS patients may not only be scientifically appealing but also improve and individualise care. We specifically intend to answer the following questions: What is the efficacy/effectiveness of medications and non-medical interventions excluding lesional approaches on tremor in iPS? What are prevalences of side-effects of interventions according to published, peer-reviewed studies?

METHODS AND ANALYSIS

This systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁷ The protocol was prospectively registered in the International Prospective Register of systematic reviews (PROSPERO) in order to document our commitment to transparency in research.

Eligibility criteria

A systematic literature review will be conducted including studies with adult participants in any setting diagnosed

with iPS. Mixed populations will only be considered if at least 80% of participants were diagnosed with iPS or separate results are available for this specific patient population. Moreover, at least 10 participants must be included in the investigation to be considered while there is no obligation of a specific control group. Eligible studies should examine the efficacy/effectiveness and safety of therapeutic options for tremor. All experimental and quasi-experimental study designs will be contemplated. Review articles, letters, editorials and conference abstracts will be excluded. In addition to a recent systemic review on neurosurgical interventions for the treatment of tremor,¹² we would like to focus on all treatment options except for lesional interventions such as Deep Brain Stimulation or focussed ultrasound. Primary outcomes will be the scores for items 2.10 and 3.15 to 3.18 of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)¹⁸ or items 2.16, 3.20 and 3.21 of the UPDRS.¹⁹ Secondary outcomes will be other measures in relation to clinical and tremor-related endpoints such as tremor amplitude and frequency, subjective outcomes such as satisfaction with treatment and adverse events.

Search strategy and study selection

Three electronic databases (MEDLINE, EMBASE PsycINFO) will be searched using a combination of title/abstract keywords and MeSH-terms (cf. online supplemental data for the Ovid Medline search strategy). Since the UPDRS, a recognised and well-established instrument serving as our primary outcome, was not introduced into neurological research until 1987,¹⁹ we will restrict our literature search to publication dates from 1987 onwards. Our search strategy includes hand-searching references and citation lists of key reviews in order to identify further original articles. Two authors will select eligible studies after independently screening titles and abstracts. Full text will be retrieved if any uncertainty about eligibility remains. If consensus about inclusion cannot be achieved, remaining uncertainties will be resolved with a third researcher via discussion. Non-English-language articles will be assessed for inclusion, and data will be extracted by a fluent speaker if relevant. According to the PRISMA guidelines, a flow diagram will be created to illustrate the selection process.

Data collection process

For each included study, detailed information will be extracted by one author using a standardised data form covering following points:

- ▶ Study details: title, first author publication details.
- ▶ Study characteristics: aim/objectives, study design, start/end date, recruitment procedure, setting country.
- ▶ Eligibility criteria
- ▶ Sample characteristics
- ▶ Comparators
- ▶ Outcome data/results
- ▶ Time to follow-up

► Statistical methods.

To ensure rigour, a random 10% sample of data forms will be checked by a second author. Any potential disagreement between these two review authors will be resolved through discussion with a third researcher. Aggregate data on preinterventional and postinterventional tremor severity will be extracted from publications. Measures of central tendency and dispersion measures will be calculated if not already available. Reasons for exclusion of papers after full-text review will be documented.

Quality assessment

By including a multitude of study designs beyond randomised controlled trials, we hope to identify a broad spectrum of interventions, which will certainly need to be critically examined and discussed from a quality perspective. Methodological quality will be appraised using the QualSyst tool (*Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields*), a validated tool designed to systematically assess quality of research in a variety of study designs.²⁰ On a checklist with 14 items (*checklist for assessing the quality of quantitative studies*), scores up to 28 points can be obtained. A second author will assess a random 10% sample. Scores diverging by >10% will be discussed within the research team until consensus is reached.

Measures of treatment effect and synthesis of results

For all available results, central tendency along with dispersion measurements will be provided for all tested groups preintervention and postintervention. In case of insufficient data provided, data extraction method will be contemplated²¹ or authors will be contacted directly. Whenever possible, standardised mean value differences will be estimated using Hedge's *g*, in view of assumed heterogeneous results and according to its advantages for small sample sizes.²² Furthermore, random effects meta-analysis will be applied when possible as well as sensitivity analyses to explore heterogeneity. If possible, specific effects for gender and age will be determined. We will provide a narrative synthesis of results structured by intervention type. Forest plots will serve for better visualisation. Prevalences of adverse events shall be summarised descriptively. Analogous to continuous data, random-effects models are assumed for non-continuous variables. In these cases, ORs will be determined where possible and weighted according to the sample sizes to estimate effects. Results will further be discussed in the context of quality assessment and study design.

Patient and public involvement

Patients or public were not involved in the development of the research protocol.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis aim at critically appraising peer-reviewed literature on the efficacy/

effectiveness and safety of non-lesional interventions for the treatment of iPS-patients' tremor. Despite being a hallmark symptom of Parkinson-syndromes, tremor amelioration remains among the most challenging tasks. Regardless of effective lesional approaches, we consider it imperative to analyse the available data to inform health-care practitioners on alternative, beneficial and safe treatment options. Results of this work should hopefully help to draw conclusions to ultimately improve patient care and reveal ideas for future work. We aim to disseminate results of our investigation in a peer-reviewed journal in order to make our implications publicly available. To increase transparency, we will present the data extracted from the original studies in a table format. The registration of our study protocol with PROSPERO as well as the present publication demonstrate our commitment to provide detailed and candid information about the different phases of our research project. As our work is based on published articles, this research is exempt from ethics approval.

Contributors AJPC and DJP are responsible for the conception of the systematic review. AJPC, DJP and FM were involved in writing the study protocol.

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