Tremor in Multiple Sclerosis: An Area of Unmet Need and Opportunity

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Introduction

- Tremor in multiple sclerosis (MS) is common and contributes to disability.
- Little is known about its pathophysiology, imaging correlates, characteristics, and treatment.
- We developed a draft of an MS-tremor-specific patient reported outcome (PRO) tool.

Aims and Hypothesis

1. Review what is currently known about tremor in MS (i.e., characterization, treatment) through a systematized review.
2. Identify knowledge gaps of tremor in MS.

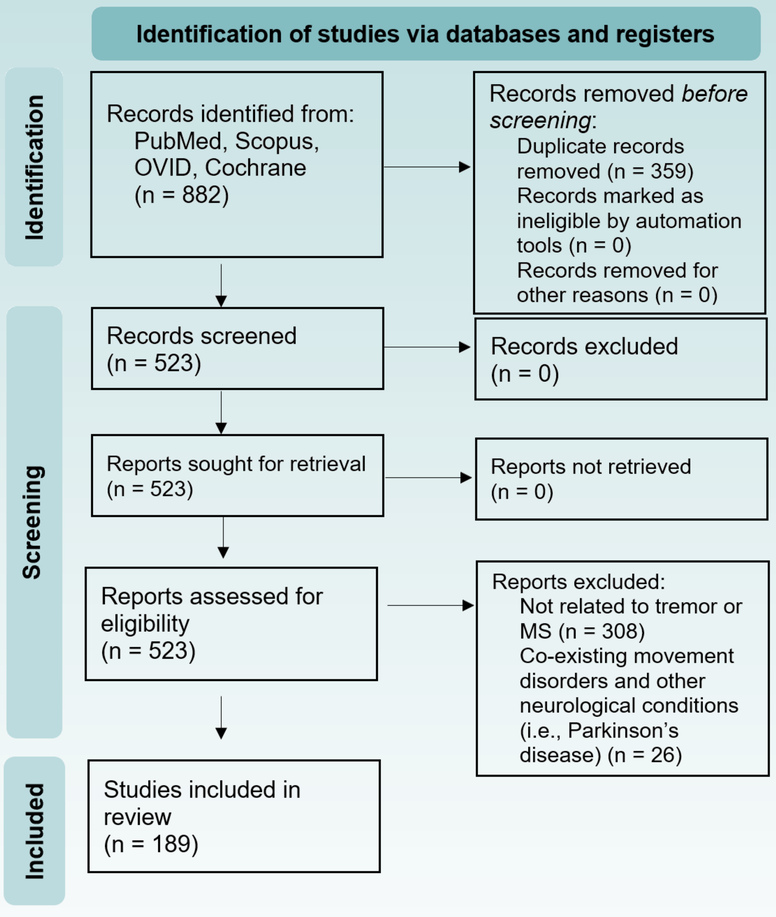
Hypothesis: Tremor in MS is an under-researched area and several gaps in knowledge exist.

Methodology

Information Sources and Search Strategy:

- Four databases (PubMed, Scopus, Cochrane and OVID) were searched. Keyword: "multiple sclerosis tremor," filtered for studies of the adult population (over 18 years old) and English language publications.
- Search filtering was based on the PICO-based inclusion criteria (adults over 18 years old and no treatment intervention), with two authors (C.I. and A.Z.O.).
- A separate search was performed for the pediatric population (keyword: "multiple sclerosis tremor," and filtered by 18 years and younger), yielding no results.
- Therefore, we kept only the adult population citations.
- Excluded studies of co-existing neurologic disease.
- The four databases were accessed on 6/25/2021, and the filtering criteria were based on the information provided in the inclusion and exclusion criteria.

Figure 1. PRISMA Flowchart describing the screening process for eligible studies.



MS-Tremor Specific PRO Tool Development

We created a preliminary draft of an MS-tremor specific patient reported outcome (PRO) tool.

Examples of MS-Specific Questions:

Daily Activities (Yes/No Response):

1. My tremor interferes with reaching for an object (like reaching a book on a table).
2. I am unable to keep my balance because of my tremor.

Scoring to be determined, with the help of a psychometrician.

Results

Pathophysiology:

- *Current Research:* No definite answer on the pathogenesis of MS tremor (possible cerebellar-thalamic pathology).
- *Gaps:* Many types of tremor observed in MS patients, factors that may explain the complexity of MS tremor clinical presentation.
- *Future Directions:* More research is needed to determine pathophysiology of tremor types in MS. Lesion distribution could explain different tremor types.

Characterization:

- *Current Research:* Actively researched topic (incorporating technology and using general scale metrics).
- *Gaps:* There is a lack of unique scale metrics used for tremor in MS.
- *Future Directions:* New scale metrics geared towards MS tremor should be developed in future research.

Treatment:

- *Current Research:* DBS is heavily researched, pharmacological treatment is less studied. Table 1 summarizes published treatments.
- *Gaps:* No best pharmacological approach to treat MS tremor
- *Future Directions:* More studies are needed on a diverse patient population

Disability and Pediatrics:

- *Current Research:* No studies done on children with MS tremor, some research on accessibility tools (wheelchair) for disabled MS patients.
- *Gaps:* Few studies on social identities and how this impacts the life of a person living with MS tremor
- *Future Directions:* Studies need to address disability and age as factors in MS tremor experience.

Table 1. The current pharmacological treatments researched for MS tremor including number of studies, designs, and general outcome.

Drug Name	Number of Studies	Study Design(s)	General Outcome
Onabotulinum toxin A (Botox)	2	Randomized	Possible therapy
Isoniazid	3	Randomized, Double Blind	Mixed results
Levetiracetam	3	Randomized, Double Blind	Mixed results
Primidone	1	Randomized	Possible therapy
Topiramate	1	Case study	Possible therapy
Glutethimide	2	Randomized, Double Blind	Mixed results
Cannabis	3	Case study, Randomized	Mixed results

Conclusion

- We support our hypothesis that tremor in MS has several knowledge gaps in pathophysiology, treatment, and characterization.
- Current treatments for MS-tremor are inadequate.
- Current studies fail to explain the different experiences of tremor depending on disability level and age.
- There is a lack of MS-specific patient reported tool for tremor.

Next Steps

- Quantify characterization of MS tremor through accelerometry tools.
- Further develop the preliminary patient reported outcome measure that is MS-tremor-specific.
- Implement the MS-tremor specific PRO tool to quantitively characterize tremor.

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