

# Upper Limb Intention Tremor in Multiple Sclerosis

## An Evidence-Based Review of Assessment and Treatment

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**Background:** *To present the current knowledge on the characteristics, assessment, and treatment of upper limb intention tremor to inform and improve future intervention studies in patients with multiple sclerosis (MS), we conducted a literature review for articles on upper limb intention tremor in patients with MS.*

**Methods:** *Two reviewers conducted searches in PubMed, Web of Science, and MEDLINE (Ovid). Relevant articles, sorted on inclusion criteria, were examined for descriptions and assessments of upper limb intention tremor, and intervention studies were evaluated based on treatment type.*

**Results:** *Eight descriptive studies were found reporting on the incidence and severity of tremor, impairments, and lesion load. Ten studies focused on measurement of tremor using various assessments. Intervention studies included eight articles using a diverse set of noninvasive techniques mainly showing transient reduction in tremor amplitude and temporary increase in function. Eighteen studies on pharmacologic interventions were found, with most displaying positive outcomes and mediation of tremor; others showed little to no benefit. Surgical interventions included 17 studies on thalamotomy and 20 on deep brain stimulation. Most studies showed tremor improvement after surgery; however, most sample sizes were small, and interventions were highly invasive, with potential adverse effects resulting from surgery.*

**Conclusions:** *The literature on upper limb intention tremor in MS is relatively sparse. More studies are required to determine mechanism of action and to provide more suitable and sustainable interventions to decrease upper limb intention tremor and improve quality of life of individuals with MS. Int J MS Care. 2018;20:211-223.*

**M**ultiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that causes demyelination and axonal loss and results in increasing physical impairment over time.<sup>1</sup> Herein, we focus on upper limb intention tremor in the context of MS. Owing to the complex interactions of multiple tremor types that can be observed in MS, it is important to have a precise definition when defining this particular phenotype. A 1998 consensus statement by the Movement Disorder Society on tremor defines action tremor as “any tremor that is produced

by voluntary contraction of muscle, including postural, isometric, and kinetic tremor.” The consensus report also states that intention tremor is considered a form of kinetic tremor related to action tremor (as opposed to a rest tremor).<sup>2</sup> Intention tremor is categorized as “target-directed movements” and is described as “[the tremor] amplitude increases during visually guided movements towards a target at the termination of the movement where the possibility of position-specific tremor or postural tremor produced at the beginning or end of a movement is excluded.”<sup>2(p4)</sup>

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Previous studies have offered variable reports on the prevalence of tremor in MS, suggesting that approximately 25% to 60% of patients may display some form of tremor depending on the population studied.<sup>3-5</sup> The different forms of MS-associated tremor can be very complex to decipher because some components of action tremors can occasionally blend together.<sup>6</sup> For example, a particular study may describe action tremor without determining the specific components of action tremor, namely, kinetic and intention.<sup>2</sup> Furthermore, because MS is a multifocal disease with lesions appearing in various brain regions, it can compound the difficulties in locating the sources of tremor.<sup>7-9</sup> Further compounding the difficulty of tremor assessment in MS is overlap with other involuntary movement conditions, such as ataxia. In a recent study examining patients with MS with or without visible tremor on clinical examination, it was observed that patients with visible tremor showed more ataxia and dysfunction of the cerebellum than patients with MS without visible tremor.<sup>10</sup> Ataxia is thought to be observed separately from tremor by the unnecessary contraction of muscle groups not associated with the goal-directed movement.<sup>6</sup> Tremor is also associated with other debilitating symptoms, such as anxiety and depression,<sup>11</sup> which are known comorbidities in patients with MS.

Upper limb intention tremor is a common cause of disability in MS, affecting up to 25% of patients.<sup>12</sup> Patients with MS with intention tremor have increased difficulty with a variety of daily activities,<sup>3,13,14</sup> such as eating, writing, dressing, and bathing. The purpose of this review was to provide a report on the current literature surrounding upper limb intention tremor in patients with MS. We examine pharmacologic and nonpharmacologic treatments as reported in the literature, provide descriptions of severity, and present the methods that have been used to evaluate upper limb intention tremor in past studies. We aimed to address whether there is a consensus on treatment paradigms or methods of evaluating upper limb intention tremor in the literature. We also critically examined the literature to inform and improve future studies on the assessment and treatment of upper limb intention tremor in patients with MS.

## Methods

In October 2014, we searched Web of Science, PubMed, MEDLINE (Ovid), and MS-related journals that were not included in the databases. For the initial search, a qualified librarian helped provide the most

effective search strategy. The search terms were *tremor*, *intention tremor*, *action tremor*, and *multiple sclerosis*. Two reviewers (J.K.M. and J.A.R.) independently performed the search using the same search strategy. The independent search results were then merged, and duplicates were removed. The inclusion criteria were English-language articles, non-conference proceedings, research articles, human studies, and articles that included MS-related intention or action tremor. The two reviewers independently applied the inclusion criteria to article titles and then to abstracts, and any disagreements or questionable articles were resolved and decided on by discussion. Standardized data extraction tables created a priori by the senior author (S.J.F.) were completed by both reviewers. Four tables were created summarizing literature related to noninvasive interventions, pharmacology, thalamotomy, and deep brain stimulation (DBS). Data collected on interventions included study design, intervention type, sample size, measurements, main results, and mechanisms of action, as well as adverse effects for pharmacologic and surgical interventions (Tables 1-4).

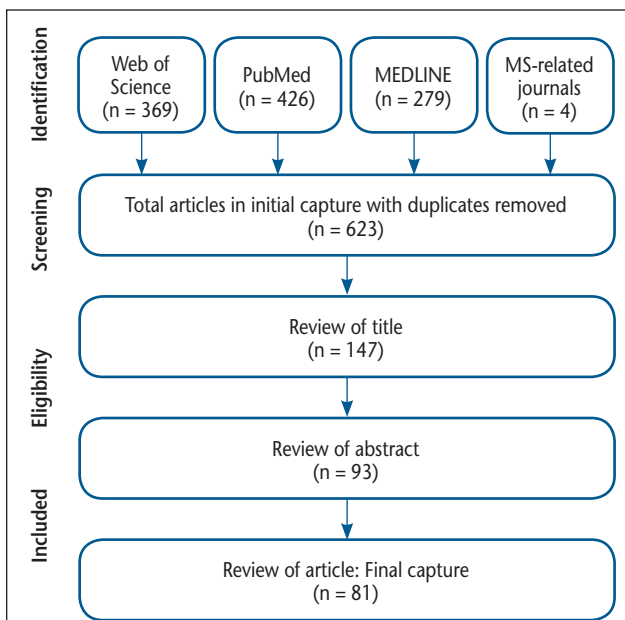
## Results

### Search Results

The initial search in each database yielded the following results: Web of Science (n = 369), PubMed (n = 426), MEDLINE (Ovid) (n = 279), and additional MS-related journals (n = 4). After removing duplicates, the initial search yielded 623 articles. After applying the inclusion criteria, a final capture of 81 articles<sup>8,9,12,14-71,73-92</sup> was used for data extraction (Figure 1).

### Descriptive Literature

Overall, there were eight articles that analyzed descriptive characteristics of intention tremor in MS.<sup>8,9,14-19</sup> These articles used a combination of behavioral measurements, neuroimaging, and questionnaires as measures to determine associated descriptors of intention tremor. Across all studies there were 180 patients with MS with upper limb intention tremor and 96 controls. The types of studies included cohort cross-sectional controlled (n = 3), cohort cross-sectional (n = 3), and case studies (n = 2). Characteristics of intention tremor reported on by the studies related to the incidence and severity of tremor, abnormal eye movements, impairment in the extremities of patients, and lesion load. One article studied 100 patients with MS to determine the prevalence of intention tremor and found that 58% of the patients had tremor, and six patients had intention



**Figure 1. Search strategy**

The initial capture included 623 articles. After excluding duplicates, conference proceedings, and non-English-language articles, 147 articles remained. After excluding articles based on relevance of title, 93 articles remained. Articles were then reviewed based on their abstracts, and 81 articles remained, which was the final capture. MS, multiple sclerosis.

tremor.<sup>15</sup> Moreover, Feys and colleagues<sup>14</sup> investigated the level of disability in patients with MS and found that 94% had a moderate-to-severe cerebellar impairment and 81% experienced tremor while writing. Descriptive characteristics of abnormal eye movements as they relate to upper limb intention tremor included abnormal saccadic eye coupling<sup>16</sup> and increased size of fixational eye movements.<sup>17</sup> These studies suggested that imprecise eye movements may contribute to the abnormal hand movements in intention tremor. Measures of impairment in the extremities included delayed tendon reflexes<sup>18</sup> and the influence of central oscillations on voluntary movements.<sup>19</sup> These studies indicated that the action of intention tremor is influenced by multiple mechanisms, including pathologic control at a supraspinal level, possibly due to lesions in the cerebellar system, or slowed nerve conduction velocity.<sup>18,19</sup> Two studies investigated lesion load, with one study finding that lesion load was highest in the pons and cerebellum, with a significant correlation between tremor amplitude and lesion load in the contralateral pons,<sup>8</sup> suggesting that the lesions in the pons may be associated with tremor. Although the previous study examined the infratentorial regions of the brain, a series of case studies looking at upper limb intention tremor and ataxia in five patients observed that

these patients did not show cerebellar-associated lesions but rather lesion load in the per-central sulcus region in the five patients examined.<sup>9</sup> Other areas of investigation by the two studies included the midbrain and the medulla oblongata, and the results suggest that intention tremor is primarily caused by lesions in the afferent and/or efferent pathways of the cerebellum.<sup>8,9</sup>

### Assessment Literature

A multitude of assessments are used in the measurement of tremor in MS, including, but not limited to, performance-based assessments (including clinician-rated tests [ie, tremor rating scales] and objective tests [ie, the Nine-Hole Peg Test]) and patient-reported outcomes, such as quality-of-life questionnaires (for a review on assessments, see the study by Panicker and Pal<sup>20</sup>). The search found ten articles that were specifically focused on assessments, which were applied to and verified for use in upper limb intention tremor. Of the ten articles, four demonstrated the application of existing assessments to tremor, including the visually guided tracking task<sup>21-23</sup> and the Stewart-Holmes maneuver.<sup>24</sup> Five studies examined the validity and reliability of assessments. One study examined the comparative reliability and validity of rating upper limb intention tremor using the finger-to-nose task, spiral drawing, and handwriting by correlating them to finger tapping, the Nine-Hole Peg Test, and the activities of daily living questionnaire.<sup>25</sup> The study used three blinded examiners and found that all three ways of rating tremor in patients with MS were proved to be valid.<sup>25</sup> Another study confirmed the validity and reliability of digitized circle and square drawing for quantifying intention tremor severity and related disability in patients with MS.<sup>26</sup> The reliability of the Fahn Tremor Rating Scale (FTRS) was also examined in patients with MS.<sup>27</sup> Overall, the results of this study demonstrated good intrarater and interrater reliability.<sup>27</sup> A single-item questionnaire, the Tremor and Coordination Scale (TACS), was also assessed for criterion and construct validity.<sup>28</sup> The TACS was assessed using correlations with multiple measures, including the Expanded Disability Status Scale, the Nine-Hole Peg Test, age, and body mass index. The findings from this study supported the criterion and construct validity of the TACS.<sup>28</sup> Last, one study examined the reliability, validity, and use of a tool called the Multidimensional Assessment of Tremor (MAT).<sup>29</sup> The MAT characterizes many dimensions of tremor in MS,

including subjective descriptions on how tremor affects daily life and a person's psychosocial life, as well as an objective and clinician-rated measure of tremor severity.<sup>29</sup> The reliability, criterion validity, and clinical utility of the MAT were supported.<sup>29</sup> In general, all the assessments were proved to be reliable and valid for use in MS tremor.

### Noninvasive Interventions

Eight articles were categorized as noninvasive interventions (Table 1). Noninvasive interventions are generally administered to reduce tremor and allow for compensation to improve functionality. The main results were a transient reduction in tremor amplitude and a temporary increase in function using noninvasive techniques. Diverse interventions included visually guided techniques,<sup>30-32</sup> tendon vibration,<sup>33</sup> peripheral cooling,<sup>34</sup> weighting extremities,<sup>35</sup> proximal positioning, manual techniques,<sup>12</sup> positioning techniques, and the administration of electromagnetic fields.<sup>36</sup> One clear benefit of noninvasive interventions was the lack of adverse effects, where only minor inconveniences were mentioned, such as one intervention in which patients with MS reported that the given splints were obtrusive or fit poorly,<sup>12</sup> or a peripheral cooling intervention that was reported by some to be uncomfortable.<sup>34</sup>

### Pharmacologic Interventions

Eighteen articles were categorized as pharmacologic interventions (Table 2). Eleven pharmacologic drugs were investigated, including isoniazid,<sup>37-40</sup> botulinum toxin A,<sup>41,42</sup> cannabis,<sup>43,44</sup> levetiracetam,<sup>45,46</sup> primidone,<sup>47,48</sup> 4-amino-pyridine,<sup>49</sup> ethanol,<sup>50</sup> glutethimide,<sup>51</sup> natalizumab,<sup>52</sup> ondansetron,<sup>53</sup> and topiramate.<sup>54</sup> Pharmacologic interventions were used because of their ability to increase inhibitory action on the central nervous system and afferent nerve activity in the peripheral nervous system. Overall, isoniazid was the most studied pharmacologic drug and was successful in approximately 60% to 80% of patients. Ondansetron was the only pharmacologic drug that was found to have no effect on tremor severity. Several of the pharmacologic drugs investigated revealed conflicting outcomes, with most studies finding some positive results and approximately one-quarter of the studies showing null findings, sometimes in the same study. The most relevant adverse effects across all pharmacologic interventions were fatigue and weakness. An overall methodological limitation in the pharmacologic studies included a lack of controlled trials, and, therefore, blinded studies.

## Surgical Interventions

### Overview

Surgical interventions for upper limb intention tremor were composed of two categories: thalamotomy and DBS. In both cases, the surgical targets are the thalamus; although specific targets in the thalamus vary by patient, they commonly include the ventrolateral nucleus or the ventral intermediate nucleus.

### Thalamotomy

Thalamotomy is a process by which an area of the thalamus is ablated by various methods. There were 17 articles that fell under the category of thalamotomy as their main intervention (Table 3). Two of the studies<sup>55,56</sup> used a radiofrequency method, which limits the invasiveness of the surgery. Thalamotomy was generally effective in most groups, although some patients experienced a relapse of tremor often 1 year or more after surgery. Two articles in the search included control groups,<sup>57,58</sup> although one of the articles was retrospective and included information from patients in the first study. Some studies were older and included only physicians' descriptions as outcomes.<sup>59-62</sup> Spelman and van Manen<sup>63</sup> proposed a tremor rating scale for severity of arm intention tremor, which was used in a later study by another group.<sup>64</sup> Of the remaining studies, three were case studies,<sup>65-67</sup> three compared thalamotomy and DBS,<sup>68-70</sup> and one included the use of magnetic resonance imaging (MRI)- and computed tomography-guided thalamotomy.<sup>71</sup> In general, studies showed tremor improvement after surgery; however, outcome measures were varied because there was no standard evaluation method. Sample sizes in studies tended to be small. Although thalamotomy is overall effective in treating upper limb intention tremor in patients with MS, it is a highly invasive procedure and has a risk of damaging areas outside of the therapeutic target, leading to serious postoperative complications. Some potential adverse effects resulting from surgery can include weakness and fatigue, seizures, or increased paresis.

### Deep Brain Stimulation

Deep brain stimulation is a more recently developed surgical technique for treating tremor and involves the implantation of electrodes in the brain.<sup>72</sup> These electrodes are implanted and battery operated to stimulate the target area. Twenty studies met the criteria for DBS and upper limb intention tremor in MS (Table 4). None of the studies contained a control group. Multiple studies reported improvement of tremor after surgery as a

Table 1. Noninvasive interventions used to investigate intention tremor in MS

Study	Design	Intervention type	Participants, No.	Measurements	Data points	Main results	Mechanisms	
Feys et al., <sup>30</sup> 2003	Controlled cross-sectional cohort	Assessing IT and movement accuracy in response to visual conditions	Gr 1: 18 IT in MS, 6 M/12 F; Gr 2: 15 controls, 7 M/8 F	Visually guided technique			MS group had pronounced tremor when full vision was available; When vision was partially occluded, tremor decreased and tracking remained reasonably accurate	It is suggested that part of the error of the hand may be caused by inaccurate eye movements and that abnormal eye movement causes hand errors. Dysfunction of cerebellum and brainstem and its afferent and efferent structures may be source of interaction.
				Performed guided step-tracking task under 5 visual conditions. Measures: Finger-to-nose test	1			
Feys et al., <sup>31</sup> 2003	Controlled cross-sectional cohort	Assessing IT and simultaneous eye movement during aiming tasks and goal-directed movement	Gr 1: 16 IT in MS, 6 M/10 F; Gr 2: 16 controls, 5 M/11 F	Visually guided technique			MS group performed aiming tasks slower, had delayed peak movement velocity, and showed reduced accuracy; Initiation time for eye and hand movement for MS group was slower	
				Performed aiming task under 3 conditions (eye-hand, hand only, and loaded eye-hand); Collected eye data under 2 conditions (eye-hand, loaded eye-hand). Measures: Finger-to-nose test, pouring water and lifting telephone receiver, NHPT and finger tapping, ataxia rating scale of Trouillas	1			
Feys et al., <sup>32</sup> 2006	Controlled cross-sectional cohort	Changing visual feedback of hand movement	13 IT in MS; 14 controls	Visually guided technique			Reduced tremor amplitude during visually guided tracking tasks when visual feedback of the hand was changed	
				Used 4 visual conditions. Measures: Eye and hand movements recorded using a combined eye-hand tracker, hand-step tracking	1			
<b>Peripheral manipulations</b>								
Feys et al., <sup>33</sup> 2006	Controlled cross-sectional cohort	Tendon vibration	Gr 1: 20 IT in MS, 11 M/9 F; Gr 2: 19 MS no tremor, 9 M/10 F; Gr 3: 16 controls, 7 M/9 F	Peripheral manipulations			Vibration induced decrease in movement amplitude, with smallest effect in MS tremor group (28%) vs. those without tremor (50%)	Interventions have been designed to isolate or provide resistance to tremor. Adding momentum of moving limb increases tension on the antagonists and readily excites their succeeding contraction. Cooling or tendon vibrations are thought to effect proprioceptive afferents.
				Vibration to wrist extensor muscles during memory-guided slow wrist step-tracking task. 3 intervals consisting of 12 memory-guided tracking movements in vibration and no-vibration conditions were recorded. Measures: Finger-to-nose test and step-tracking task, spirometry	1			
Feys et al., <sup>2005</sup> <sup>34</sup>	Cross-sectional cohort	Peripheral cooling	18 IT in MS, 8 M/10 F	Peripheral manipulations			Reduced tremor amplitude and frequency during then 3- to step-tracking task after different intensities of 10-min sustained forearm cooling; Results persisted for 30 min after removal of cooling application	
				Cooling of forearm was achieved by a cryomantlet: 25°C and 18°C for deep and moderate cooling, respectively. Measures: Finger-to-nose test, step-tracking task, pouring water and spirometry, finger tapping and step-tracking task, finger tapping task	Before; then 3- to 10-min intervals after cooling			
Hawes et al., <sup>2010</sup> <sup>12</sup>	Cross-sectional cohort	Sequenced behavioral interventions: Manual splinting, weighting, combined techniques	6 IT in MS, 2 M/4 F	Peripheral manipulations			Some beneficial behavioral strategies; Earlier therapy rather than self-discovery could decrease frustration; Splints had low acceptance due to obtusiveness or poor fit; Most useful was proximal stabilization	
				Sequential introduction, education, training, performance and evaluation of techniques. Measures: MAT, qualitative reports, self-perceived efficacy	Before; daily for 1 wk; 1 mo later			
Hewer et al., <sup>1972</sup>	Cross-sectional cohort	Weighted wrist	50 IT in MS (10 with MS), 22 M/28 F	Peripheral manipulations			Tremor was reduced in 58%, therapeutic reduction in after; 6 mo later MS had objective reduction in tremor	
				Used lead weights consisting of 0.24-2 kg during activity. Measures: Finger-to-nose test, repetitive tapping, drawings, tremor records (photographic method)	Before; after; 6 mo later			
<b>Electromagnetic fields</b>								
Sandyk, <sup>36</sup> 1996	Case reports	Brief applications of alternating-current pulsed electromagnetic field	3 IT in MS	Measures: Finger-to-nose test, Archimedes circle, drinking a cup of water	Before; after; up to 5 d later	Able to drink without spilling; Improvement in Archimedes circle and finger-to-nose test	Electromagnetic fields may alter spontaneous electrical activity in reticular formation and cerebellar molecular layer.	

Abbreviations: F, female; Gr, group; IT, intention tremor; M, male; MAT, Multidimensional Assessment of Tremor; MS, multiple sclerosis; NHPT, Nine-Hole Peg Test.

**Table 2. Pharmacologic interventions used to investigate intention tremor in MS**

Study	Design	Participants, No.	Measurements	Data points	Main results	Mechanisms
<b>Isoniazid</b>						
Bozek et al., <sup>37</sup> 1987	Randomized, double-blind, single-crossover trial	10: 6 M/4 F	General neurologic examination, EDSS, tremograms (visual-tracking task)	Every week for 8 wk	6 patients showed minimal improvement; Beneficial for postural tremor as opposed to intentional tremor	It is suggested that part of error of hand may be caused by inaccurate eye movements and that abnormal eye movement causes hand errors.
Duquette et al., <sup>38</sup> 1985	Open-label controlled study	13: 10 M/3 F (9 with IT)	Subjective evaluation, clinical evaluation, standardized neurologic evaluation	Before; during and 1 mo after therapy	10 patients tremor improved in 1 or more method of evaluation (5 with IT); 1 patient opted to continue taking isoniazid	Dysfunction of cerebellum and brainstem and its afferent and efferent structures may be source of interaction.
Morrow et al., <sup>39</sup> 1985	Case series	5: 2 M/3 F	Qualitative (drawing a line between 2 crosses, building a brick tower)	18-mo follow-up	4 patients improved; 3 developed ability to drink from a glass; 2 ate independently	
Francis et al., <sup>40</sup> 1986	Pilot study	5: 1 M/4 F	Polarized light goniometry, EDSS	Before and after	Twofold to threefold reduction of tremor in patients	
<b>Botulinum toxin A</b>						
Van Der Walt et al., <sup>41</sup> 2012	Randomized, double-blind, controlled crossover trial	26: 9 M/17 F	Clinical evaluation, writing and motor tasks, QOL questionnaire	Every 6 wk over 6 mo	Treatment significantly improved tremor severity	Botulinum toxin A may interfere with afferent nerve fiber activity from injected limb and thereby have a central effect that, in turn, ameliorates tremor.
Clarke, <sup>42</sup> 1997	Open pilot study	5: 3 M/2 F	Validated clinical rating, writing and spirometry, ADL questionnaire	Baseline; 2 and 8 wk after	No significant improvement occurred in tremor in injected upper limb	(AE: weakness.)
<b>Cannabis</b>						
Fox et al., <sup>43</sup> 2004	Randomized, double-blind, placebo-controlled crossover trial	14: 6 M/8 F	Clinical rating scale, spiral drawings, NHPT, finger tapping task, frequency of tremor	Every 2 wk for 3 wk	Orally administered cannabis extract had no significant positive effect on upper limb tremor	Cannabinoids release (and block reuptake of) serotonin and may elevate acetylcholine. Cannabis may also cause subjective effect on tremor (mood, mental state).
Meinck et al., <sup>44</sup> 1989	Case report	1 M	Muscle tone and reflex, electromagnetic recording of a tremor	Before and after	Improvement in action tremor hours after administration	(AEs: drowsiness, light-headedness, memory disturbance, dysphoria, euphoria.)
<b>Levetiracetam</b>						
Feys et al., <sup>45</sup> 2009	Randomized, double-blind, placebo-controlled crossover trial	18: 7 M/11 F	FTRS, ADL questionnaire, wrist step-tracking task, spirometry	Over 18 wk; 0-, 4-, 6-, 9-, 13-, and 15-wk assessments	Did not find significant decrease in tremor severity or improvement in functionality	Levetiracetam is an antiepileptic drug shown to have reversible, saturable, and stereospecific binding to synaptic membrane sites, including hippocampus, cortex, and cerebellum.
Striano et al., <sup>46</sup> 2006	Open-label study	14: 6 M/8 F	Tremor rating scale, finger-to-nose test, spiral drawings, ataxia score	Before and after	Significant reduction in tremor rating scale	(AEs: fatigue, stomach ache, headache, dizziness, irritability, 1 epileptic insult, sedation, somnolence, agitation)

**Table 2. Pharmacologic interventions used to investigate intention tremor in MS (continued)**

Study	Design	Participants, No.	Measurements	Data points	Main results	Mechanisms
Henkin and Herishanu, <sup>47</sup> 1989	Case series	2 F	Qualitative	Primidone Variable	Reduced tremor in both patients	Primidone's major metabolite is phenobarbital and is a potent anticonvulsant. Primidone also increases inhibitory GABA-mediated chloride flux.
	Pilot study	10: 2 M/8 F	ADL questionnaire, NHPT, FTRS	Baseline; up to 6 and 12 wk of administration follow-up	Improved IT in patients with MS after 6 wk of administration	(AEs: drowsiness, vertigo, nausea, and fatigue)
Schnepp et al., <sup>49</sup> 2013	Case report	1 F	NHPT, tremor questionnaire, surface EMG	4-amino-pyridine		
				24 h and 18 mo after	Improvement in NHPT; Improved tremor questionnaire; Decreased EMG recordings	4-amino-pyridine is a reversible potassium-channel blocker that improves cerebellar dysfunction.
Hammond and Kerr, <sup>50</sup> 2008	Case report	1 M	Written letter	Ethanol		
				1 time point	Reduction in tremor (more legible writing) with alcohol consumption	Ethanol or alcohol reduces cerebellar hyperactivity and may be mediated through GABAergic mechanisms.
Aisen et al., <sup>51</sup> 1991	Open-label study	6: 4 M/2 F	Keyboard test, hoop test, FTRS, pursuit-tracking task, power and magnitude	Glutethimide		
				Before; 7 and 14 d after stable dose was achieved	Improved functional testing in 5 patients; Abstract testing in 4 patients improved; 3 patients chose to continue use	Glutethimide is structurally similar to phenobarbital, sharing its sedative and anticonvulsant effects. (AEs: sedation, fatigue)
Rinker et al., <sup>52</sup> 2014	Survey-based case-control study	202 (natalizumab), 229 controls	Tremor-related ADL questionnaire, tremor handicap, visual analog scale, tremor and coordination scale, ataxia rating scale	Natalizumab		
				Retrospective	Treatment may improve the changes of a reduction in tremor severity over time	Natalizumab is a humanized monoclonal antibody and is in class of selective adhesion molecule inhibitors. It is believed to prevent immune cells from crossing blood-brain barrier.
Gbadamosi et al., <sup>53</sup> 2001	Open-label prospective controlled study	14: 5 M/9 F	NHPT, star copying, spiral drawing, free writing	Ondansetron		
				Before; 1 h after	No significant change in tremor measured as functional outcome score and patient's subjective response rating	Ondansetron is a highly selective competitive 5-HT <sub>3</sub> receptor antagonist.
Schroeder et al., <sup>54</sup> 2010	Case report	1 F	Focus on walking distance but mention fine motor skills	Topiramate		
				From 4 d to 2 y	Patient's walking distance dramatically improved as well as fine motor skills	Topiramate is a sulfamate-substituted monosaccharide with anticonvulsant properties. It antagonizes a subtype of glutamate receptors, stabilizing hyperexcited neuronal membranes.

Note: Articles are sorted first by number of studies in each treatment, by design (most reproducible), and then by alphabetical order of treatment.

Abbreviations: ADL, activities of daily living; AE, adverse effect; EDSS, Expanded Disability Status Scale; EMG, electromyography; F, female; FTRS, Fahn Tremor Rating Scale; GABA,  $\gamma$ -aminobutyric acid; IT, intention tremor; M, male; MS, multiple sclerosis; NHPT, Nine-Hole Peg Test; QOL, quality of life.

**Table 3. Surgical intervention thalamotomy used to treat intention tremor in MS**

Study	Participants, No.	Measurements	Data points	Main results	Adverse effects
Alusi et al., <sup>57</sup> 2001	24: 13 TS, 11 controls	Finger-to-nose test, handwriting, Archimedes circle, finger tapping task, NHPT	Preop, 3 and 12 mo postop	11 showed improvement; Significant improvement in kinetic tremor score to 12 mo postop	Contralateral hemiparesis, dysarthria, seizure of person with epilepsy, fatigue, reduced bladder and bowel function, depression
Jahanshahi et al., <sup>58</sup> 2008	11: 6 TS, 5 controls	Cognitive tests	Preop, 3 mo postop	Significant tremor reduction; Cognitive changes in digit span, verbal fluency, and MMSE	Not reported
<b>Cohort studies: long-term</b>					
Cooper, <sup>61</sup> 1960	6: 2 MS	Physician and patient reports	Preop, 3 and 12 mo postop	Improvement of IT	Not reported
Cooper, <sup>60</sup> 1967	32	Physician evaluation	1-8 y postop	25 had complete disappearance of IT, although recurred in 2; 6 had improvement of IT; 1 had no change	Spastic hemiparesis worsening, transient speech and swallowing problems, seizures
Critchley and Richardson, <sup>64</sup> 1998	24	Scale by Speelman and van Manen (1984), EDSS, ADL questionnaire	Preop, immediately postop, 6 wk postop, 6 mo postop, most recent postop (mean, 2.2 y)	Improvement in 79% at 6 mo; 58% had sustained improvement at late follow-up	Mild hemiparesis, worsening of dysarthria, seizures, nocturnal confusion
Hassan et al., <sup>68</sup> 2012	9: 6 TS, 3 DBS	TFS scale, EDSS, physician evaluation	Surgery was 12 y earlier	All experienced improved tremor; At 12 mo, 3 patients had excellent results, 3 were unchanged, and 3 had poor results; Longest tremor suppression: 5 y with TFS of 4.3%	Not reported
Mathieu et al., <sup>55</sup> 2007	6	Finger-to-nose test, Archimedes circle, writing	Follow-up: 5 mo to 1 y	Significant improvement postop; 2 had recurrence of tremor	Progressive hemiparesis
Matsumoto et al., <sup>69</sup> 2001	9: 6 TS, 3 DBS	Clinical tremor rating scale, quantitative movement analysis created by authors, FIM, Functional Assessment of MS Scale, box and block test	2 time points preop, 3 and 12 mo postop	Significant improvement postop, although was not retained to 12 mo	Weakness, worsening gait
Niranjan et al., <sup>56</sup> 2000	11: 3 MS	Handwriting and drawing	Preop, 2-11 mo postop	Improvement in tremor postop; Action tremor improved in 3 patients with MS	Weakness, dysarthria
Speelman and van Manen, <sup>63</sup> 1984	11	Developed rating scale for IT severity and arm function impairment	Preop, 3-9 mo postop, >1.5 y for 9 patients	8 patients had good results to reduce IT, 1 had moderate results, and 2 showed no change; 6 patients had good results for improved arm function, 3 had moderate results, and 2 showed no change	Somnolence, frontal lobe syndrome, speech disorders, fixed gaze to side of operation, hemiparesis and hemihyphesthesia, micturition disturbances
Whittle and Haddow, <sup>71</sup> 1995	9	Tremor rated by video, clinical review, CT and MRI	Preop, 4 wk and 3 and 12 mo postop	8 showed improved IT postop; 1 had no improvement and had minimal IT preop	Psychomotor slowing, confusion, transient urinary dysfunction, depression
<b>Cohort studies: pre/post outcomes</b>					
Bittar et al., <sup>70</sup> 2005	20: 10 TS, 10 DBS	Finger-to-nose test, Evaluation of arms outstretched, bat-wing position	Preop, 1 to >4 y postop	All had improvement in tremor; IT was reduced by 72% in TS group and 36% in DBS group	6 TS (seizures, confusion, paresis, and dysarthria), DBS (monoparesis and wound infection)
Cooper, <sup>62</sup> 1960	12: 6 MS	Motion picture studies, referring physician report	Preop and postop	10 patients had improvement in IT	Not reported
<b>Case studies/series</b>					
Braeger and Fog, <sup>67</sup> 1962	4	Finger-to-nose test, daily living ability, physician report	Preop, 1-6 mo postop	Decreased IT, although 1 patient died shortly after surgery	Dysmetria
Krayenbuhl and Yasargil, <sup>59</sup> 1962	4	Physician report of daily activities	Preop, up to 6 mo postop	4 patients improved	Increased paresis, difficult urinating, right side weakness, confusion
Laitinen et al., <sup>65</sup> 1974	1	Daily activities	Preop, 1 d postop, 6 mo postop, 3 y postop	Able to eat, write, and smoke postop; Able to walk and drive car 3 y postop	Not reported
McCabe et al., <sup>66</sup> 1998	1	Results despite postop GBS adverse event	Preop, 13 and 18 d postop, 3 mo postop	Tremor was reduced	Weakness 13 d postop, progressed at 18 d to clinical diagnosis of GBS, GBS symptoms resolved at 3 mo postop

Abbreviations: ADL, activities of daily living; CT, computed tomography; DBS, deep brain stimulation; EDSS, Expanded Disability Status Scale; FIM, Functional Independence Measure; GBS, Guillain-Barre syndrome; IT, intention tremor; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MS, multiple sclerosis; NHPT, Nine-Hole Peg Test; postop, postoperatively; preop, preoperatively; TFS, tremor-free survival; TS, thalamic stimulation.



Table 4. Surgical intervention DBS used to treat intention tremor in MS

Study	Participants, No.	Measurements	Data points		Main results	Adverse effects
			Cohort follow-up	Preop, 2 and 12 mo postop (QOL: 3 and 22 mo postop)		
Berk et al., <sup>80</sup> 2002	12	FTRS, QOL questionnaire	Preop, 2 and 12 mo postop (QOL: 3 and 22 mo postop)	Significant improvement in tremor up to 12 mo postop; Improved ability to feed independently	Severe infection and thus electrodes removed, minor infection, mild transient paresthesia, transient urine retention	
Hamel et al., <sup>81</sup> 2007	11: 2 MS	FTRS	Preop, 3 and 12 mo postop	All patients showed decreased tremor rating at follow-up	Not reported	
Herzog et al., <sup>82</sup> 2007	21: 11 MS	Electrode placement, modified FTRS, reach-to-grasp movement	Preop, at least 4 mo postop	Significant improvement correlated in all patients but was more pronounced when electrodes were in contact with anterior/posterior commissure line than ventral intermedius nucleus	Not reported	
Hooper et al., <sup>76</sup> 2002	10	Modified FTRS, Jebsen Hand Function Test, QOL questionnaire	Preop and 1, 3, 6, and 12 mo postop	Significant reduction in tremor at all postop points; Significant improvement in Jebsen Hand Function Test and QOL measures	Transient upper limb paresthesia, seizures, hematoma, weakness, infection	
Hooper and Whittle, <sup>88</sup> 2003	10	Modified FTRS, Jebsen Hand Function Test, QOL questionnaire, cost implications of surgery (using patients from Hooper et al. 2002)	Preop and 1, 3, 6, and 12 mo postop	Significant improvement in hand function and tremor 12 mo postop (as reported by Hooper et al. 2002); High initial costs as well as high costs postop; Excessive costs provide little benefit	Depression, decreased bladder function, dysarthria, generalized psychomotor slowing, hematoma, seizures	
Hosseini et al., <sup>83</sup> 2012	9	FTRS, 36-item Short Form Health Status Survey QOL, manual capacity scale	Preop and 1, 3, and 6 mo postop	Improvement in all patients	Aggravated dysarthria, progression of tremor	
Montgomery et al., <sup>74</sup> 1999	15	Clinical tremor rating scale (rest tremor), sustained posture with hands at shoulders (postural tremor), finger-to-nose test and cup task (action tremor)	Preop, <3 mo to 1 y postop	Action tremor improved in finger-to-nose test and cup task	Intercerebral hematoma	
Nandi and Aziz, <sup>92</sup> 2004	10: 14 limbs with tremor	Computer-controlled, visually guided arm-tracking tasks; EMC recordings	Preop, various postop (mean, 1.5 mo)	36% improved from preop mean score	Hemiparesis, transient seizure, dysarthria, infection	
Schulder et al., <sup>89</sup> 2003	9	Bain-Finchley tremor scale, EDSS, MRI, neuropsychological test	Range, 9-48 mo	Tremor mean score of 5.4 preop was improved to 2.1 at late follow-up; 3 maintained ability to eat and/or drink	Not reported	
Thevathasan et al., <sup>77</sup> 2011	11: 16 limbs with tremor	Clinical Rating Scale, Archimedes circle	Preop, within 12 mo postop, >3 y postop as late time point	Mean tremor improvement of 44% (range, 0%-86%); Late follow-up showed 10 limbs with permanent tremor reduction	Seizures, scalp erosion over extension cables	
Torres et al., <sup>73</sup> 2010	10	FTRS	Preop and 3, 6, and 12 mo postop	At 1 y, 50% showed improvement; At 3 y, 30% continued to benefit	Seizure during operation, infection	
Zakaria et al., <sup>84</sup> 2013	16	FTRS, Bain-Finchley Tremor Rating Scale, QOL questionnaire	Preop, 6 and 12 mo postop	5 showed a 50% reduction in tremor; 11 showed a 30% reduction in tremor on Bain-Finchley Tremor Rating Scale	Infection	
Mandat et al., <sup>87</sup> 2010	5	Spirography, modified ADL questionnaire	Preop, 3 mo postop	At 3-mo follow-up, showed a mean 40% improvement, 5%-75% improvement on spirography, and 18% improvement on ADL	Not reported	
Brice and McLellan, <sup>75</sup> 1980	3	Observation of reduction of tremor	Preop, up to 6 mo postop	Anecdotally all improved	Dysarthria	
Hyam et al., <sup>79</sup> 2007	6	Medical Research Council grading, upper limb tremor scores	Preop, at least 3 y postop	5 patients improved at 4 y postop; 1 patient showed increased tremor	Weakness	
Kocabacak et al., <sup>85</sup> 2013	1	FTRS, NHPT, Trail Making Test	Preop, up to 6 mo postop	Tremor improved by 51%; Able to perform NHPT with right hand (previously unable) and improved with left hand; Able to eat and drink independently	Not reported	
Lim et al., <sup>86</sup> 2007	1	FTRS, patient reports	Preop, up to 9 mo postop (first surgery), 10 mo postop (second surgery)	Tremor improved; Able to drive with left hand and drink from a cup with right hand	Not reported	
Marmosu et al., <sup>90</sup> 2005	1	EDSS, KRS	Preop, 12 mo postop (settings changed), 3 mo after change	3 mo after settings change in KRS was 28/40 and 24/40 compared with 35/40 at baseline	Not reported	
Moringlane et al., <sup>78</sup> 2004	1	Finger-to-nose test	4 y postop	Although battery had died, improvement remained at level 1	Not reported	
Nandi et al., <sup>91</sup> 2002	1	Visual tracking task	Preop, 1 wk postop, up to 12 mo postop	Ability to drink from a cup, write name, and draw a crude spiral; Tremor control remained 1 y postop	Not reported	

Abbreviations: ADL, activities of daily living; DBS, deep brain stimulation; EDSS, Expanded Disability Status Scale; EMC, electromyography; FTRS, Fahn Tremor Rating Scale; GBS, Guillain-Barre syndrome; IT, intention tremor; KRS, Klockgether Rating Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NHPT, Nine-Hole Peg Test; postop, postoperatively; preop, preoperatively; QOL, quality of life.

result of a thalamotomy-like effect before initiations of stimulation.<sup>73-76</sup> Also, several studies reported continued benefit in patients after the electrodes were turned off.<sup>77-79</sup> As in thalamotomy, there were no standard outcomes across studies, making it difficult to compare results, although multiple studies used the FTRS.<sup>73,80-87</sup> Others used the modified FTRS,<sup>76,88</sup> a clinical tremor rating scale,<sup>74,77</sup> the Bain-Finchley Tremor Rating Scale,<sup>89</sup> the Expanded Disability Status Scale,<sup>90</sup> the finger-to-nose test,<sup>78</sup> and a novel visual tracking task.<sup>91,92</sup> Similar to the studies that included the FTRS, most of these studies also included other outcome measures. Also similar to thalamotomy articles, the *n* values tended to be small in these studies, likely due to the invasiveness of the surgery. Although DBS has the advantage of being able to stimulate a brain region instead of simply ablating it, it is still a complex neurosurgery, which imposes increased risks to the patient's health after surgery. Potential adverse effects resulting from surgery can include postoperative infection, seizures, hematoma, or dysarthria.

## Discussion

Although there have been previous reviews on MS-related tremor,<sup>5,12</sup> overall this review provides the most comprehensive overview of upper limb intention tremor in MS related to the descriptive literature, the assessment literature, and the intervention literature, including noninvasive, pharmacologic, and surgical interventions. The literature on noninvasive interventions included a diverse set of strategies to investigate tremor, with studies mostly achieving a transient reduction in tremor amplitude and a temporary increase in function. The suggested mechanism being investigated by interventions using visually guided techniques for upper limb intention tremor was that of inaccurate and abnormal eye movements.<sup>30-32</sup> The source of this interaction may be dysfunction in the cerebellum and brainstem and its afferent and efferent structures. Interventions using peripheral manipulations have been designed to isolate or provide resistance to tremor.<sup>33,35</sup> The suggested mechanism of these manipulations is based on adding momentum of the moving limb to increase the tension on the antagonists, which readily excites their succeeding contraction.

Regarding the pharmacologic literature, many studies had small samples of patients. Most pharmacologic interventions had outcomes with some participants displaying positive results and mediation of tremor and others having little to no benefit from the intervention. Overall, isoniazid was the most common pharmacologic

agent investigated and was successful in approximately 60% to 80% of patients. Isoniazid was investigated due to its inhibition of  $\gamma$ -aminobutyric acid aminotransferase that leads to an increase in  $\gamma$ -aminobutyric acid.<sup>38</sup> However, all of these studies were conducted before the 1990s; therefore, a follow-up study, even if it is retrospective, may be beneficial. On the other hand, ondansetron was the only pharmacologic agent that was found to have no effect on tremor severity. Ondansetron is a highly selective and competitive 5-HT<sub>3</sub> receptor antagonist, and it has previously been suggested that the heterogeneity of patients with MS makes this type of pharmacologic intervention inappropriate.<sup>53,56</sup> Along with the limitation of the pharmacologic literature having an uncharacteristically small number of participants, there was also a lack of controlled trials. A previous review of tremor in MS similarly found that the published studies on medical treatment of MS-related tremor consisted mostly of case reports and uncontrolled open-label studies, or a scarce number of small randomized controlled trials.<sup>5</sup> Follow-up studies on some pharmacologic agents that showed potential, such as glutethimide and 4-amino-pyridine, would be warranted. Larger controlled studies, even if retrospective, may benefit this area of research.

One issue with studies conducted in upper limb intention tremor has been inconsistent outcome measures. More than 40 outcome measurements were used across all the literature reviewed. We found that the most commonly used measure of assessment was the FTRS (21 references), or individual functional assessments from within this scale (ie, finger-to-nose test, spiral drawing, pouring water, bat-wing; 37 references). The most frequent individual assessment from the FTRS was the finger-to-nose test (13 references). Subsequently, the most frequent measurements outside the FTRS were handwriting and drawing (ten references), the Nine-Hole Peg Test (seven references), and finger tapping (five references). For a useful review of these measurements, see the article by Lamers et al.<sup>93</sup> Note that subjective assessments, including qualitative assessments, physician reports, and self-perceived evaluations, were present in 18 articles. In a past review of surgical treatments for MS-related tremor, most studies provided basic, minimal information on the effect on functional status and tremor-associated disability causing great caution in making any comparisons across studies.<sup>5</sup> Similarly, in the present review, a comparison of decreased tremor amplitude due to DBS is impossible to compare with a study of thalamotomy that was evalu-

ated by Archimedes spiral. Furthermore, in studies using similar outcome measures, discrepancies can be observed based on instructions given to participants and variations of certain tests. For example, although the finger-to-nose test is commonly used, there are variations on how the test is administered, leading to potentially altered outcomes. For example, Feys et al.<sup>94</sup> examined the finger-to-nose test following four separate protocols for its administration and found that clinically observable tremor severity could be altered depending on whether an individual is required to touch his or her nose or hold a stable position. Nevertheless, given the wide use of the FTRS (or one of its individual functional tests) in past studies, with further studies of its psychometric properties and improved standardization techniques, it seems to be the most promising comprehensive measure of assessment for upper limb intention tremor. It is clear from the findings of this review that a consistent scoring system should be used across future studies in upper limb intention tremor. This, however, becomes more complicated depending on the research study questions being addressed. Advantages to a standardized testing protocol would be the ability for comparisons between studies where interventions have been used. An ideal test battery would assess multiple functions of both coordi-

nation and functional daily activity outcomes using a scale with the least amount of interexaminer variation and standardized quantification methods.

The mechanism by which tremor occurs is still not fully documented in upper limb intention tremor. The treatment of upper limb intention tremor in MS may be dramatically improved if there were clearer data on its mechanism. In surgical interventions, the area of the thalamus to be stimulated or lesioned is generally evaluated individually in patients. One emerging technology in future surgical interventions is focused ultrasound. Although two of the studies reviewed used gamma-knife radiosurgery,<sup>55,56</sup> MRI-focused ultrasound has improved the accuracy of the surgical target definition and may be useful in tremor.<sup>95</sup> This technology is already showing promise in the treatment of essential tremor when used for a thalamotomy procedure.<sup>96</sup>

In terms of strengths, this review provided a summary of evidence from studies conducted on MS-related upper limb intention tremor. Unfortunately, we were unable to perform a meta-analysis owing to high heterogeneity across study protocols and high variation in the measures of assessment. The review also highlighted some limitations in the literature that should be acknowledged. First, an overall limitation included a lack of randomized trials and a lack of controlled, blinded studies. Second, there was a lack of objective evaluation methods due to a variety of assessment tools used (with no universal scoring system used and, therefore, no consistent measurement of recovery). Moreover, there were a variety of physician-reported outcomes that led to contradictory information. Last, the studies were generally limited to a small sample population.

In this review, we were unable to find articles reviewing pathology in patients with MS with or without intention tremor. These types of studies may be beneficial in determination of partial causes of upper limb intention tremor because, for example, lesion location may be examined and correlated with upper limb intention tremor in patients with MS. Currently, it is unknown whether lesion location is directly responsible for the development of this condition. Besides postmortem studies, lesions in patients developing upper limb intention tremor may be evaluated and correlated using MRI. This would allow evaluation of patients with MS with and without upper limb intention tremor to perform a properly controlled MRI study looking at lesion sizes and locations.

Furthermore, the shortcomings of the study protocols and the use of small sample sizes could be improved by

## PRACTICE POINTS

- One of the debilitating physical manifestations in MS can be intention tremor, which in general consists of rhythmic, oscillatory movement of a body part produced involuntarily. This article offers a literature review of intervention studies focused on upper limb intention tremor specifically in patients with MS.
- The current literature on upper limb intention tremor in MS is relatively sparse, but a variety of studies were found in the following categories: surgical interventions (thalamotomy, deep brain stimulation), pharmacologic interventions, and noninvasive interventions.
- Owing to the heterogeneity in existing studies, it is currently not possible to compare and combine findings, which confirms the importance of and need for consistent outcome measures and larger multicenter studies to investigate and treat upper limb intention tremor. With a multidisciplinary approach (including physicians, specialists, and physical and occupational therapists), it may be possible to develop clear treatment paradigms for patients and improve their quality of life in the future.

future larger-scale multicenter studies. To address these limitations, future studies should be more proactive in their research design, including controlled studies and more objective methods of assessment. To improve the potential for a future meta-analysis of findings, future studies would benefit from more consistency in outcome measures because it is currently difficult to compare outcomes across studies.

In conclusion, after reviewing articles on upper limb intention tremor in patients with MS, a variety of studies were found; however, owing to design differences, lack of controls, and inconsistent outcome measures, it is currently not possible to compare many of the studies. This leaves physicians and health care professionals with a lack of specific guidelines on how to approach the treatment of upper limb intention tremor in patients with MS. What is clear from this literature is the importance of and the need for a multidisciplinary approach (including physicians, specialists, and physical and occupational therapists) to investigate and treat upper limb intention tremor. With more consistent outcome measures and larger multicenter studies, as well as improvements in technology and mechanisms of upper limb intention tremor in MS, we may be able to develop clear treatment paradigms for patients and improve their quality of life in the future. □

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