

Review

# Understanding Tremor in Multiple Sclerosis: Prevalence, Pathological Anatomy, and Pharmacological and Surgical Approaches to Treatment

Andrés Labiano-Fontcuberta<sup>1,2</sup> & Julián Benito-León<sup>1,2,3\*</sup>

<sup>1</sup> Department of Neurology, University Hospital “12 de Octubre”, Madrid, Spain, <sup>2</sup> Department of Medicine, Complutense University, Madrid, Spain, <sup>3</sup> Centro de Investigación, Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain

## Abstract

**Background:** Given that tremor is one of the most prevalent and disabling features of multiple sclerosis (MS), we will review the most significant milestones in tremor in this disease in recent years, focusing on prevalence, clinical features, anatomical basis, and treatment.

**Methods:** Data for this review were identified by searching MEDLINE with the search terms “multiple sclerosis” and “tremor”. References were also identified from relevant articles published between January 1966 and May 2012.

**Results:** The predominant type of MS tremor is a large-amplitude, postural, and kinetic tremor, which most commonly affects the arms, although tremor can also involve head, neck, vocal cords, and trunk. Involvement of the tongue, jaw, or palate has not been reported. Although the anatomical basis underlying tremor in MS is poorly understood, the link between the cerebellum and the MS-related tremor is supported by clinical and experimental studies. Currently available medication is often unsuccessful in most cases. Surgical treatment can be a satisfactory alternative to treat severe and disabling tremor.

**Discussion:** Tremor in MS patients could be considered as an advanced consequence of the disease and its presence suggests a more aggressive course. MS tremor can be severe and very disabling for a small group of patients. Treatment of MS tremor remains a great challenge. Recent studies suggest that dissociating tremor from cerebellar dysfunction using selected clinical tests would be the key issue to successful surgical treatment. Understanding the pathophysiology and biochemistry of tremor production in MS may lead to new therapeutic approaches.

**Keywords:** Tremor, multiple sclerosis, review

**Citation:** Labiano-Fontcuberta A, Benito-León J. Understanding tremor in multiple sclerosis: prevalence, pathological anatomy, and pharmacological and surgical approaches to treatment. *Tremor Other Hyperkinet Mov* 2012;2:2: <http://tremorjournal.org/article/view/109>

\*To whom correspondence should be addressed. E-mail: [jbenitol@meditex.es](mailto:jbenitol@meditex.es)

**Editor:** Elan D. Louis, Columbia University, United States of America

**Received:** June 2, 2012 **Accepted:** July 6, 2012 **Published:** September 14, 2012

**Copyright:** © 2012 Labiano-Fontcuberta et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original author(s) and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

**Funding:** Dr. Benito-León is supported by NIH R01 NS039422 from the National Institutes of Health, Bethesda, MD, USA.

**Financial Disclosures:** None.

**Conflict of Interest:** The authors report no conflict of interest.

## Introduction

Tremor is an involuntary, rhythmic, muscle movement involving oscillations of one or more parts of the body, resulting from repeated contraction and relaxation of opposing muscle groups.<sup>1–3</sup> Multiple sclerosis (MS) is a common chronic inflammatory disease of the central nervous system; it most frequently appears in early adulthood.<sup>4–6</sup> Action tremor was for a long time considered to be a common feature of MS. In fact, the French neurologist Jean-Martin Charcot described tremor as one of the defining features of MS, together with nystagmus, and scanning speech.<sup>7</sup>

Given that tremor is one of the most prevalent and disabling features of MS,<sup>8</sup> we will describe the most significant recent milestones

that relate to MS tremor, focusing on prevalence, clinical features, anatomical basis, and treatment.

## Review criteria

Data for this review were identified by searching MEDLINE (in May 2012) with the search terms “multiple sclerosis” and “tremor”. References were also identified from relevant articles published between January 1966 and May 2012.

## Prevalence of tremor in multiple sclerosis

Studies have provided estimates of the prevalence of tremor in the MS population that range widely, between 25% and 58% (Table 1).<sup>8</sup>

In a 3-year-follow up study, Weinshenker et al.<sup>9</sup> reported that cerebellar deficits of functional importance were present in one-third of 259 MS patients. Two more recent studies have assessed the prevalence of tremor in MS.<sup>10,11</sup> Alusi et al.<sup>10</sup> described upper limb tremor in 58% of 100 patients randomly selected from a London MS unit. The tremor was minimal in 27%, mild in 16%, and moderate to severe in 15% of patients.<sup>10</sup> However, as that study was conducted from a specialty clinic, the relatively high prevalence and severity of tremor might be due to selection bias. In a community-based study involving 200 MS patients in Olmsted County, Minnesota, Pittock et al.<sup>11</sup> noted tremor in 25.5% of patients, and severe tremor in 3% of patients. This community-based study probably provides a more realistic estimate of the prevalence of MS-related tremor.

Despite these estimated figures, the prevalence of tremor in MS remains very difficult to establish accurately for three reasons. First, because of the complex natural history of MS, there is a transience of neurological signs, which may occur only during the relapsing and remitting phase of the disease. Second, there is the problem of distinguishing intention tremor from dysmetria.<sup>12</sup> Finally, the Kurtzke Expanded Disability Status Scale (EDSS),<sup>13</sup> the gold standard in assessing physical disability in MS, does not assess tremor.

**Clinical features**

Tremor is defined as a rhythmical, involuntary oscillatory movement of a body part<sup>14</sup> and can be classified according to the consensus statement of the Movement Disorder Society.<sup>14</sup> Tremor at rest is separated from action tremor, which is produced by voluntary muscle contraction. Action tremor includes postural, isometric, and kinetic tremors, and the last form includes intention tremor.<sup>14</sup>

MS tremor is manifested on action as postural tremor (tremor present while voluntarily maintaining a position against gravity) and/or intention tremor (occurring during target-directed movement where tremor amplitude increases during visually guided movements towards

the target).<sup>15</sup> MS tremor typically involves the upper limbs, although tremor can also involve head, neck, vocal cords, and trunk.<sup>15</sup>

Involvement of the tongue, jaw or palate has not been reported.<sup>15</sup> In the two main prevalence studies,<sup>10,11</sup> tremor was most commonly found in the arms. According to the study by Alusi et al.<sup>10</sup> the body parts affected by tremor varied among the patients, with the most common pattern being bilateral arm involvement (36 patients) followed by unilateral arm tremor (nine patients) and tremor of the head and arms (five patients). In every case, tremor was of an action type (postural, kinetic, or both).<sup>10</sup>

Titubation is defined as nodding head tremor with a frequency of 3–4 Hz and may be seen in midline cerebellar disease.<sup>16</sup> This type of tremor can occur in isolation or combined with a postural tremor elsewhere, especially in the arms.<sup>16</sup> Titubation can be seen in 9% of the MS patients.<sup>10</sup>

True rest tremor (tremor present in a body part that is not voluntarily activated and is completely supported against gravity) and Holmes (or “rubral”) tremor are extremely uncommon in patients with MS. Rest tremor was observed only in 1% of the MS patients from the Olmsted County survey,<sup>11</sup> whereas Holmes tremor has not been encountered in recent prevalence studies.<sup>10,11</sup> Task-specific tremors (for example, primary writing tremor) have not been documented in MS.<sup>10,11</sup> Similarly, simple kinetic tremor, which occurs during voluntary non-target-directed actions—for example, opening and closing a fist—has not been observed in MS patients in these studies.<sup>10,11</sup>

Despite the fact that the basal ganglia are relatively frequently involved by MS plaques<sup>17</sup> and that almost any neurological symptom or sign can appear with the disease, movement disorders other than tremor are quite uncommon in MS. Moreover, movement disorders can be observed in patients with MS in the absence of basal ganglia involvement.<sup>18</sup> Tranchant et al.,<sup>18</sup> in the largest review of movement disorders in MS, concluded that paroxysmal dystonias, ballism, chorea, and palatal myoclonus could be caused by demyelinating lesions, whereas parkinsonism, dystonia, and other types of myoclonus often seemed to be coincidental.

**Anatomical basis**

The anatomical basis underlying tremor in MS is poorly understood, mostly because MS is a multifocal disease, and therefore tremor occurrence often cannot be directly linked to a specific neuroanatomical lesion.<sup>15</sup>

The link between the cerebellum and the MS-related tremor is supported by clinical and experimental studies. In MS patients, tremor severity has correlated with the degree of dysarthria, dysmetria, and dysdiadochokinesia.<sup>10</sup> However, no correlation was found between the severity of tremor and cognitive function, the Barthel disability profile, or grip strength, which provides strong evidence to support a specific defective cerebellar function rather than just with diffuse cerebral damage.<sup>10</sup> In addition, the high occurrence of bilateral, symmetrical tremor may be explained by the presence of multifocal damage to the cerebellum and its connections.<sup>8</sup> Several animal studies

**Table 1.** Main Prevalence Studies of Tremor in Multiple Sclerosis

Reference	Sample	Prevalence
Weinshenker et al. <sup>9</sup>	259 patients selected from a regional multiple sclerosis clinic (Ontario, USA)	33%
Alusi et al. <sup>10</sup>	100 patients randomly selected from a London multiple sclerosis unit	58% (Severe in 15%)
Pittock et al. <sup>11</sup>	200 patients selected from a community-based study (Minnesota, USA)	25.5% (Severe in 3%)

have been undertaken to help understand the anatomical structures involved in the production of MS tremor.<sup>19</sup> Experimental studies from the 1930s showed that transection of the superior cerebellar peduncle caused intention tremor in monkeys.<sup>19</sup> This is consistent with the case described by Nakamura et al.,<sup>20</sup> who, using magnetic resonance imaging (MRI) in a single case, showed that a plaque in the superior cerebellar peduncle resulted in severe postural tremor. Additionally, intention tremor can also be induced by reversible cooling of the dentate nucleus (the origin of most cerebellar efferents) in monkeys.<sup>19</sup> Interestingly, Carpenter and Hanna<sup>21</sup> reported that tremor induced by transection of the superior cerebellar peduncle can be diminished by a second lesion in the lateroventral or centromedian thalamus. Taken together, these results strongly suggest that damage to cerebellar efferents (through lesions of the dentate nucleus or superior cerebellar peduncle) may cause disinhibition of thalamic nuclei, which are the main producers of intention tremor. The findings of these primate experiments are supported by newer MRI and/or pathological studies that have further studied the involvement of the cerebellum in MS patients.<sup>22–26</sup>

Cerebellar grey matter atrophy appears to be more prominent and clinically relevant than white matter atrophy.<sup>25</sup> This cerebellar grey matter damage has been associated with clinical cerebellar dysfunction, including patients who have presented with clinically isolated syndromes.<sup>27</sup> A pathological study of Kutzelnigg et al.<sup>26</sup> found widespread demyelination in the cerebellar cortex in patients with MS, which was more pronounced in patients with progressive disease than those with the relapsing–remitting form. Furthermore, the authors suggested that this cerebellar demyelination may be more prominent than that seen in the cerebrum.<sup>26</sup>

The absence of rest tremor argues against an involvement of the basal ganglia in the production of MS tremor. However, there are some data which suggest that cerebellar tremors seen in MS might actually be generated by the basal ganglia. Foote et al.<sup>28</sup> reported the satisfactory results in one patient with MS tremor who underwent placement of two thalamic deep brain stimulation (DBS) electrodes (one at the ventralis intermedius nucleus (VIM)/ventralis oralis posterior nucleus border and one at the ventralis oralis anterior/ventralis oralis posterior border). Ventralis oralis posterior is known to be the basal ganglia output nucleus.<sup>28</sup>

In the 1980s, several studies showed the susceptibility of cerebellar tremor amplitude and frequency to peripheral factors, such as mechanical loads, which implied the involvement of stretch-elicited peripheral feedback mechanisms in the manifestation of cerebellar tremor.<sup>29,30</sup> Hence, cerebellar tremor is thought to be modulated through increased long latency stretch reflexes.<sup>31</sup> In support of this view, load-compensating tasks, evoking sudden stretch, induced an increase in tremor in cerebellar patients.<sup>32</sup>

On the other hand, MS intention tremor may be modulated by sensory information.<sup>33</sup> This supports the notion that the cerebellum is involved in the production of tremor because the proprioceptive information about the direction, velocity, and amplitude of movements is mainly generated by muscle spindles, and additionally by tendon

organs, joint, and cutaneous receptors, and enters into the cerebellum via the spinocerebellar pathway.<sup>33</sup>

Patients with cerebellar deficits show a specific difficulty in using visual information to control arm and hand movements.<sup>34,35</sup> In the study of Feys et al.<sup>36</sup> movement accuracy during slow wrist tracking tasks decreased significantly more in MS patients with tremor than in healthy controls when visual feedback was absent, which is consistent with prior studies.<sup>37</sup> Feys et al.<sup>36</sup> postulated that tremor amplitude could specifically relate to deficits in online proprioceptive processing, leading to an increased visual dependence during sensorimotor tasks.

The excitability of muscle spindles,<sup>38–40</sup> which are an essential part of the reflex loop, and the velocity of peripheral nerve conduction are temperature dependent.<sup>41</sup> Thus, decreasing the stretch sensitivity of the muscle spindles and therefore also the long latency stretch reflexes, by means of cooling, may have an important effect on tremor.<sup>41</sup> In line with this assumption, several studies have manipulated the sensory input to the central nervous system.<sup>42–44</sup> A reduction of cerebellar tremor during handwriting has been found after the application of an ischemic block to the arm.<sup>42</sup> In two additional experimental studies, cooling of the arms markedly reduced intention tremor severity in patients with MS.<sup>43,44</sup> Moreover, the effect on tremor seemed to be proportional to the intensity of the cooling.<sup>44</sup> Feys et al.<sup>44</sup> argue that this effect might have been partly due to decreased muscle spindle function and decreased nerve conduction velocity, which in turn resulted in decreased sensory input into tremor producing cerebellar circuits. In contrast, overall tremor amplitude increased during memory-guided movements when muscle spindles were artificially activated by means of tendon vibration.<sup>45</sup> Following previous data suggesting that MS intention tremor is modulated by sensory information, Feys et al.<sup>46</sup> have recently studied the contribution of peripheral reflexes to the generation of MS intention tremor by measuring tendon reflexes, demonstrating that MS patients with tremor have a greater latency of brachioradialis, biceps, and triceps tendon reflexes than healthy controls and MS patients without tremor.

In summary, clinical observation as well as animal and experimental studies strongly point to the cerebellum and its connections as the major source of intention tremor production, but further research is needed to better understand the pathophysiologic model underlying the production of tremor in MS.

### Assessment of tremor in multiple sclerosis

In MS tremor, a valid, precise, and reliable scale is required if the efficacy of different interventions is to be assessed accurately. Moreover, it would ideally take into account the ataxic elements, which usually complicate the clinical picture. Most tremor rating scales deployed in therapeutic trials involving patients with MS have not been tested for their reliability and sensitivity.<sup>47–49</sup>

There are only two published studies examining the reliability of a clinical scale for scoring tremor in MS.<sup>50,51</sup> Hooper et al.<sup>50</sup> developed a modified version of the Fahn–Tolosa–Marin Tremor Rating Scale<sup>52</sup> to accommodate goal-directed tremor and studied its reliability in patients with MS. However, they failed to assess the validity of the

scale.<sup>50</sup> Alusi et al.<sup>51</sup> examined the validity and comparative reliability of the 0–10 tremor severity scale devised by Bain et al.,<sup>53</sup> which had already been validated in other tremulous conditions. The authors concluded that this scale represents a valid and reliable way of assessing tremor in these patients.<sup>51</sup> The most reliable test was shown to be scoring tremor on posture, whereas kinetic tremor and associated ataxic deficits were more difficult to score reliably.<sup>51</sup> Despite its reliability, the scale has so far only been used in a few clinical studies.<sup>10,54,55</sup>

### Outcome of tremor in multiple sclerosis

According to Alusi et al.,<sup>10</sup> the median latency from disease onset to the development of tremor is 11 years. Hence, tremor in MS patients could be considered as an advanced consequence of the disease.

Patients who exhibit clinical signs of cerebellar damage early in the disease course tend to develop severe disability more quickly.<sup>56</sup> Although in the majority of MS patients the severity of the tremor is mild, tremor can be severe and very disabling for a small group of patients.<sup>10</sup> In the two main prevalence studies,<sup>10,11</sup> tremor was associated with greater disability. The study of Alusi et al.<sup>10</sup> showed that 27% of the patients had tremor-related disability and 10% had incapacitating tremor. Moreover, patients with severe tremor were more likely than those without tremor to be wheelchair dependent and have a worse EDSS.<sup>10</sup> In the Olmsted County study, patients with tremor of any severity were more likely to be unemployed or to have retired early because of disability, and they had on average a 2-point higher EDSS.<sup>11</sup> Other studies have shown that intention tremor severity seriously affects many activities of daily living, such as drinking, handwriting, or personal computer interaction.<sup>57,58</sup>

## Treatment

### General considerations

As with other chronic diseases, it is important to consider the psychological and social impact of illness on patients. MS patients may be unable to continue full-time work, and financial problems may rise. Physicians should coordinate care with other healthcare professionals in order to address these social and psychological issues. The impact of the disease on the patient's family should also be taken into account. It may be beneficial for MS patients to bring their spouse or partner to a consultation, to help them better understand the disease and to discuss their difficulties and concerns.

Patient-centered associations may be of help in offering individual and group support, education and advice. Through such interactions, patients may benefit by learning ways to cope with the many practical day-to-day difficulties that arise for those living with this disease.

There are physical aids as well as certain lifestyle changes that may be helpful in patients with mild tremor. Electromagnetic fields, limb cooling, physiotherapy, weight bracelets, orthoses, and specialized software may offer some symptomatic relief. For example, physiotherapeutic approaches, such as arm cooling, appear to reduce tremor severity.<sup>44,59</sup> The effect of peripheral sustained cooling on intention tremor was first described by Albretch et al.;<sup>59</sup> in their study, patients

achieved significantly better results on a clinical testing battery after sustained cooling of the tremulous forearm in ice water. In a similar study, Feys et al.<sup>44</sup> described a clear reduction of overall tremor amplitude and frequency during the step-tracking task after two different intensities of sustained cooling of the arm. Although the effects of cooling on intention tremor are probably temporary, both studies showed that they persist for at least 30 minutes.<sup>44,59</sup> This sustained benefit led the authors to argue that cooling of the arm may be useful before performing activities of daily life, such as applying make-up, eating a meal, or writing and signing documents.<sup>44,59</sup>

Reduction of intention and postural tremor in three MS patients was achieved with pulsed electromagnetic fields,<sup>60</sup> although further trials are needed to support this finding.

The use of a mouse-driven computer system was evaluated by Feys et al.<sup>58</sup> These researchers found significant improvement in the time needed to complete some basic mouse-driven computer operations using specialized software developed to aid computer use in 36 tremulous MS patients included in their study.<sup>58</sup> Furthermore, some patients may experience modest benefits from relaxation methods aimed at alleviating the anxiety or stress that may exacerbate tremor. Lifestyle changes may be of benefit in some patients. These changes include restricting caffeine intake or other stimulants that may increase symptoms.

Although there is no cure for tremor in MS, several therapies can ease the condition for some patients (Table 2). The issue is that such treatments for tremor in MS have side effects, and it is important to carefully consider in each patient whether the benefits outweigh any side effects. Medications should be used to reduce functional disability or embarrassment and to improve health-related quality of life.<sup>61,62</sup> Hence, treatment generally begins when the tremor begins to interfere with the patient's ability to perform daily activities, or if the tremor is embarrassing to the patient. Surgery should be limited to those disabling cases that fail to benefit from several different medications.

### Pharmacological agents

Tremor in MS patients is difficult to manage and often frustrating because drug treatment with currently available medication is unsuccessful in most cases. Some clinical relief has been reported for a range of drugs, including primidone,<sup>63</sup> glutethimide,<sup>64</sup> intrathecal baclofen,<sup>65</sup> and isoniazid.<sup>66</sup> However, most of the published literature on medical treatment consists of case reports and uncontrolled open label studies characterized by small patient size and short duration of drug intake.<sup>8</sup> Some functional relief was noticed with glutethimide, an hypnotic-sedative drug, in six of eight tremulous MS patients included in an open label study.<sup>64</sup> Weiss et al.<sup>65</sup> reported an alleviation of tremor with intrathecal baclofen in a single patient with bilateral arm tremor. The tremor amplitude decreased nearly linearly with increasing intrathecal baclofen dosage, and disappeared completely at a dose of 250 µg/day.<sup>65</sup>

Controlled clinical trials have been published on the use of propranolol,<sup>47</sup> ethanol,<sup>47</sup> isoniazid,<sup>47,67,68</sup> carbamazepine,<sup>49</sup> ondansetron (5-hydroxytryptamine type 3 receptor antagonist),<sup>69</sup> dolasetron,<sup>70</sup> and

**Table 2.** Treatment Options for Multiple Sclerosis Tremor

<b>Surgical treatment</b>	
Deep brain stimulation thalamotomy	Both are comparable procedures for tremor suppression
<b>Pharmacological agents</b>	
<i>Insufficient evidence to support or refute the efficacy. Possibly effective</i>	
Topiramate	
Riluzole	
Rituximab	
Isoniazid	
Carbamazepine	
Gluthetimide	
Intrathecal baclofen	
Botulinum toxin type A	
<i>They probably do not reduce multiple sclerosis tremor</i>	
Levetiracetam	
Propranolol	
Ondansetron	
<i>It should not be considered for treatment of multiple sclerosis tremor</i>	
Cannabis	

levetiracetam.<sup>71</sup> Koller et al.<sup>47</sup> evaluated the effect of propranolol, isoniazid and ethanol on tremor in three tremulous MS patients in a double blind crossover trial and did not find beneficial effect for any of the treatments. Although no further trials with propranolol have been published, it should be emphasized that two tremulous MS patients were excluded from a thalamotomy trial because they had achieved functional improvement after propranolol use.<sup>54</sup>

Two double-blind placebo-controlled trials using isoniazid have been published.<sup>67,68</sup> In the first study, alleviation of tremor was achieved in six of eight patients,<sup>67</sup> assessing functional improvement in four of them. In the second study, measurable tremor reduction was achieved in all six patients, although no functional improvement was noticed.<sup>68</sup> Despite this clinical improvement, doses of isoniazid used to treat MS-related tremor are usually very high (up to 1200 mg a day) and consequently this may lead to significant adverse effects such as anorexia, nausea,<sup>72</sup> drowsiness, dysphagia, and increased bronchial secretions.<sup>73,74</sup>

A successful improvement of tremor was found in seven patients in a small single-blind placebo-controlled trial with carbamazepine.<sup>49</sup>

However, no functional improvement was mentioned.<sup>49</sup> In a placebo-controlled, double-blind, crossover study using a single intravenous dose of ondansetron, tremor reduction was described in 12 of the 16 tremulous MS patients, with functional improvement in nine of them.<sup>69</sup> However, no positive effects were described in another study using the same intervention and doses.<sup>75</sup> In the same way, a newer small clinical trial has failed to show beneficial effects on cerebellar ataxia with dolasetron, another 5-HT<sub>3</sub> receptor antagonist.<sup>70</sup>

Despite the growing interest in cannabis as a possible therapeutic agent in MS, no positive effect has been found in several well-conducted randomized controlled trials with orally administered cannabis extracts<sup>76-78</sup> or oral D9-tetrahydrocannabinol.<sup>76</sup>

Levetiracetam, which has been suggested to have beneficial effects on cortical myoclonus or post-ischemic Holmes' tremor,<sup>79-81</sup> appeared effective for cerebellar tremor in both a case series study and an open-label trial with tremulous MS patients. Likewise, a crossover study showed a modification of kinematic parameters although without functional improvement in most of the six MS tremulous patients included.<sup>82</sup> However, a randomized, placebo-controlled, double-blind, crossover study neither found a significant decrease in tremor severity nor an improvement in functionality in 14 patients with MS-related tremor.<sup>71</sup> Therefore, the clinical relevance of levetiracetam in the treatment of MS tremor remains unclear.

Topiramate may be a new therapeutic option to treat cerebellar tremor and ataxia in patients with MS.<sup>83-85</sup> A small, open-label study of topiramate in patients with cerebellar tremor showed improvement in clinical and electrophysiological indices of limb tremor.<sup>83</sup> The authors hypothesized a net inhibitory effect on the cerebello-thalamo-cortical pathways due to facilitation of gamma-aminobutyric acid (GABA)ergic transmission, and antagonism at the AMPA/kainate receptor.<sup>83</sup> Similarly, topiramate have been reported to provide relief in cerebellar signs in two recent case reports.<sup>84,85</sup>

More recently, a pilot trial with riluzole suggested benefits in patients with cerebellar tremor.<sup>86</sup> Alternatively, Chansakul et al.<sup>87</sup> reported a dramatic resolution of head tremor with rituximab. These newer studies postulate that aggressive treatments should be considered in the presence of a recently developed tremor secondary to MS.

Recently, in a study of 23 MS patients with tremor, there was a significant improvement after botulinum toxin compared with that after placebo treatment in the Bain score for tremor severity at 6 weeks ( $p=0.0005$ ) and 12 weeks ( $p=0.0001$ ), writing at 6 weeks ( $p=0.0001$ ) and 12 weeks ( $p=0.0003$ ), and Archimedes spiral drawing at 6 weeks ( $p=0.0006$ ) and 12 weeks ( $p=0.0002$ ).<sup>88</sup> This study provides Class III evidence that targeted injection of botulinum toxin type A is associated with significant improvement in MS-related upper limb tremor.<sup>88</sup>

### **Surgical treatment**

Advances in surgical interventions offer patients an alternative treatment modality when pharmacotherapy is inadequate. The surgical treatment options for tremor in MS are stereotactic thalamotomy and DBS, which both can be a satisfactory alternative

to treat severe and disabling tremor. In the majority of the reported cases, the surgical target for DBS implantation is the VIM.

Stereotactic thalamotomy has been performed for the alleviation of MS tremor since 1960.<sup>89</sup> More recently, thalamic DBS has been deployed effectively. Although Niranjan et al.<sup>90</sup> described marked improvement of tremor in all three tremulous MS patients using gamma-knife thalamotomy, no further studies have been published to evaluate this non-invasive alternative. There are three trials in which thalamotomy and DBS have been compared in MS patients.<sup>55,91,92</sup> Schuurman et al.<sup>91</sup> did not find significant differences between thalamotomy and DBS in functional outcome for a subgroup of MS patients. In a non-randomized study conducted by Bittar et al.,<sup>55</sup> thalamotomy was a more efficacious surgical treatment for intractable MS tremor (78% tremor reduction for postural tremor and 72% for intention tremor) than the DBS group (64% tremor reduction for postural tremor and 36% for intention tremor) after a mean follow-up period of 15–16 months. However, the incidence of persistent neurological deficits was also higher in patients receiving lesional surgery.<sup>55</sup> In a more recently study, Yap et al.<sup>92</sup> concluded that both thalamotomy and thalamic DBS were comparable procedures for tremor suppression and that adverse effects occurred with both procedures. Although larger clinical trials comparing both interventions are needed, currently DBS is widely accepted as the preferred surgical strategy.

Lack of objective measurements of tremor in MS and post-surgical efficacy are the main reasons that may explain why VIM DBS has not been established yet as a recommended general therapeutical option.<sup>54,93–95</sup> Although sophisticated tools and mathematic models have been created to make pre-surgical qualification and post-surgical evaluation more objective, they have not been widely accepted, mostly because of their complexity and poor standardization.<sup>53,91–93</sup> Furthermore, the possibility of progression of the disease makes the objective evaluation of the surgery even more difficult. This may explain conflicting results. Indeed, older studies suggest a disappointing prognosis with progressive disability in most patients,<sup>96,97</sup> however, a recent DBS study reported 5-year permanent tremor relief.<sup>98</sup>

In MS tremor, there is a variable contribution of ataxia to the overall tremor phenotype.<sup>37,99</sup> Ataxic tremor responds poorly to both stimulation and lesioning, which may explain why MS tremor responds so variably to stimulation. According to many authors, dissociating tremor from cerebellar dysfunction using selected clinical tests would be the key issue to successful treatment.<sup>93,94,100</sup> In line with this assumption, in a recent prospective study Hosseini et al.<sup>101</sup> have confirmed the higher efficacy of VIM DBS treatment of kinetic tremor in the subgroup of MS patients with minor or absent cerebellar dysfunction.

It has been observed that tremor in MS can sometimes permanently decrease during the course of DBS.<sup>102</sup> This permanent tremor reduction has been attributed to limb weakness (occurring with MS progression) preventing the expression of tremor.<sup>102</sup>

Although a review of the reported cases suggests that chronic DBS produces improved tremor control in MS,<sup>103</sup> it should be emphasized

that most of the studies are small observational retrospective studies with predominantly short-term follow-up (1 year or less) and with a remarkable absence of standardized outcome measures or information on long-term functional outcome.<sup>103,104</sup>

It is interesting to note the recent study of Hassan et al.<sup>105</sup> reported a prospective 12-year follow-up of a cohort of nine patients with MS tremor, previously reported by Matsumoto and coworkers.<sup>106</sup> The study showed that the benefit of surgery (six patients underwent thalamotomy and three DBS) was overall short lived (median 3 months), with long-term poor prognosis.<sup>105</sup> Moreover, over half of the patients were dead by 7 years and survivors were severely impaired, which led the authors to conclude that when surgery is considered for MS, patients have already entered a disease trajectory with dismal prognosis. This contrasts with prior studies suggesting EDSS stability at 12–36 month follow-up.<sup>107,108</sup>

In summary, although the majority of published studies suggest a tremor reduction in almost all patients immediately after surgery, the short-term follow-up of the published series is insufficient to conclude whether surgery is a judicious strategy. Nonetheless, the 5-year permanent tremor reduction reported in a recent DBS study<sup>98</sup> encourages the pursuit of further DBS trials.

## References

1. Benito-Leon J, Louis ED. Essential tremor: emerging views of a common disorder. *Nat Clin Pract Neurol* 2006;2:666–678, <http://dx.doi.org/10.1038/ncpneu0347>.
2. Benito-Leon J, Louis ED. Clinical update: diagnosis and treatment of essential tremor. *Lancet* 2007;369:1152–1154, [http://dx.doi.org/10.1016/S0140-6736\(07\)60544-3](http://dx.doi.org/10.1016/S0140-6736(07)60544-3).
3. Benito-Leon J, Louis ED. Update on essential tremor. *Minerva Med* 2011; 102:417–439.
4. Benito-Leon J, Martin E, Vela L, et al. Multiple sclerosis in Mostoles, central Spain. *Acta Neurol Scand* 1998;98:238–242, <http://dx.doi.org/10.1111/j.1600-0404.1998.tb07302.x>.
5. Benito-Leon J. Multiple sclerosis: is prevalence rising and if so why? *Neuroepidemiology* 2011;37:236–237, <http://dx.doi.org/10.1159/000334606>.
6. Benito-Leon J. Are the prevalence and incidence of multiple sclerosis changing? *Neuroepidemiology* 2011;36:148–149, <http://dx.doi.org/10.1159/000325368>.
7. Rascol A, Clanet M. Multiple sclerosis from Charcot and Vulpian to the present time. *Rev Neurol (Paris)* 1982;138:921–930.
8. Koch M, Mostert J, Heersema D, De Keyser J. Tremor in multiple sclerosis. *J Neurol* 2007;254:133–145, <http://dx.doi.org/10.1007/s00415-006-0296-7>.
9. Weinschenker BG, Issa M, Baskerville J. Long-term and short-term outcome of multiple sclerosis: a 3-year follow-up study. *Arch Neurol* 1996;53:353–358, <http://dx.doi.org/10.1001/archneur.1996.00550040093018>.
10. Alusi SH, Worthington J, Glickman S, Bain PG. A study of tremor in multiple sclerosis. *Brain* 2001;124:720–730, <http://dx.doi.org/10.1093/brain/124.4.720>.

11. Pittock SJ, McClelland RL, Mayr WT, Rodriguez M, Matsumoto JY. Prevalence of tremor in multiple sclerosis and associated disability in the Olmsted County population. *Mov Disord* 2004;19:1482–1485, <http://dx.doi.org/10.1002/mds.20227>.
12. Sabra AF, Hallett M. Action tremor with alternating activity in antagonist muscles. *Neurology* 1984;34:151–156, <http://dx.doi.org/10.1212/WNL.34.2.151>.
13. Kurtzke JF. A new scale for evaluating disability in multiple sclerosis. *Neurology* 1955;5:580–583, <http://dx.doi.org/10.1212/WNL.5.8.580>.
14. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord* 1998;13(Suppl 3):2–23.
15. Alusi SH, Glickman S, Aziz TZ, Bain PG. Tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1999;66:131–134, <http://dx.doi.org/10.1136/jnnp.66.2.131>.
16. Proudlock FA, Gottlob I, Constantinescu CS. Oscillopsia without nystagmus caused by head titubation in a patient with multiple sclerosis. *J Neuro-ophthalmol* 2002;22:88–91, <http://dx.doi.org/10.1097/00041327-200206000-00004>.
17. Pirko I, Lucchinetti CF, Sriram S, Bakshi R. Gray matter involvement in multiple sclerosis. *Neurology* 2007;68:634–642, <http://dx.doi.org/10.1212/01.wnl.0000250267.85698.7a>.
18. Tranchant C, Bhatia KP, Marsden CD. Movement disorders in multiple sclerosis. *Mov Disord* 1995;10:418–423, <http://dx.doi.org/10.1002/mds.870100403>.
19. Wilms H, Sievers J, Deuschl G. Animal models of tremor. *Mov Disord* 1999;14:557–571, [http://dx.doi.org/10.1002/1531-8257\(199907\)14:4<557::AID-MDS1004>3.0.CO;2-G](http://dx.doi.org/10.1002/1531-8257(199907)14:4<557::AID-MDS1004>3.0.CO;2-G).
20. Nakamura R, Kamakura K, Tadano Y, et al. MR imaging findings of tremors associated with lesions in cerebellar outflow tracts: report of two cases. *Mov Disord* 1993;8:209–212, <http://dx.doi.org/10.1002/mds.870080218>.
21. Carpenter MB, Hanna GR. Effects of thalamic lesions upon cerebellar dyskinesia in the rhesus monkey. *J Compar Neurol* 1962;119:127–147, <http://dx.doi.org/10.1002/cne.901190202>.
22. Sepulcre J, Sastre-Garriga J, Cercignani M, Ingle GT, Miller DH, Thompson AJ. Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. *Arch Neurol* 2006;63:1175–1180, <http://dx.doi.org/10.1001/archneur.63.8.1175>.
23. Mesaros S, Rovaris M, Pagani E, et al. A magnetic resonance imaging voxel-based morphometry study of regional gray matter atrophy in patients with benign multiple sclerosis. *Arch Neurol* 2008;65:1223–1230, <http://dx.doi.org/10.1001/archneur.65.9.1223>.
24. Ceccarelli A, Rocca MA, Pagani E, et al. A voxel-based morphometry study of grey matter loss in MS patients with different clinical phenotypes. *NeuroImage* 2008;42:315–322, <http://dx.doi.org/10.1016/j.neuroimage.2008.04.173>.
25. Anderson VM, Fisniku LK, Altmann DR, Thompson AJ, Miller DH. MRI measures show significant cerebellar gray matter volume loss in multiple sclerosis and are associated with cerebellar dysfunction. *Mult Scler* 2009;15:811–817, <http://dx.doi.org/10.1177/1352458508101934>.
26. Kutzelnigg A, Faber-Rod JC, Bauer J, et al. Widespread demyelination in the cerebellar cortex in multiple sclerosis. *Brain Pathol* 2007;17:38–44, <http://dx.doi.org/10.1111/j.1750-3639.2006.00041.x>.
27. Henry RG, Shieh M, Okuda DT, Evangelista A, Gorno-Tempini ML, Pelletier D. Regional grey matter atrophy in clinically isolated syndromes at presentation. *J Neurol Neurosurg Psychiatry* 2008;79:1236–1244, <http://dx.doi.org/10.1136/jnnp.2007.134825>.
28. Foote KD, Seignourel P, Fernandez HH, et al. Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. *Neurosurgery* 2006;58:ONS-280–285; discussion ONS-285–286, <http://dx.doi.org/10.1227/01.NEU.0000192692.95455.FD>.
29. Flament D, Vilis T, Hore J. Dependence of cerebellar tremor on proprioceptive but not visual feedback. *Exp Neurol* 1984;84:314–325, [http://dx.doi.org/10.1016/0014-4886\(84\)90228-0](http://dx.doi.org/10.1016/0014-4886(84)90228-0).
30. Hore J, Flament D. Evidence that a disordered servo-like mechanism contributes to tremor in movements during cerebellar dysfunction. *J Neurophysiol* 1986;56:123–136.
31. Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. *Muscle Nerve* 2001;24:716–735, <http://dx.doi.org/10.1002/mus.1063>.
32. Richard I, Guglielmi M, Boisliveau R, et al. Load compensation tasks evoke tremor in cerebellar patients: the possible role of long latency stretch reflexes. *Neurosci Lett* 1997;234:99–102, [http://dx.doi.org/10.1016/S0304-3940\(97\)00681-2](http://dx.doi.org/10.1016/S0304-3940(97)00681-2).
33. Bosco G, Poppele RE. Proprioception from a spinocerebellar perspective. *Physiol Rev* 2001;81:539–568.
34. Day BL, Thompson PD, Harding AE, Marsden CD. Influence of vision on upper limb reaching movements in patients with cerebellar ataxia. *Brain* 1998;121:357–372, <http://dx.doi.org/10.1093/brain/121.2.357>.
35. Liu X, Ingram HA, Palace JA, Miall RC. Dissociation of ‘on-line’ and ‘off-line’ visuomotor control of the arm by focal lesions in the cerebellum and brainstem. *Neurosci Lett* 1999;264:121–124, [http://dx.doi.org/10.1016/S0304-3940\(99\)00165-2](http://dx.doi.org/10.1016/S0304-3940(99)00165-2).
36. Feys P, Helsen WF, Liu X, et al. Effect of visual information on step-tracking movements in patients with intention tremor due to multiple sclerosis. *Mult Scler* 2003;9:492–502, <http://dx.doi.org/10.1191/1352458503ms949oa>.
37. Liu X, Miall C, Aziz TZ, Palace JA, Haggard PN, Stein JF. Analysis of action tremor and impaired control of movement velocity in multiple sclerosis during visually guided wrist-tracking tasks. *Mov Disord* 1997;12:992–999, <http://dx.doi.org/10.1002/mds.870120624>.
38. Mense S. Effects of temperature on the discharges of muscle spindles and tendon organs. *Pflugers Archiv* 1978;374:159–166, <http://dx.doi.org/10.1007/BF00581297>.
39. Bell KR, Lehmann JF. Effect of cooling on H- and T-reflexes in normal subjects. *Arch Phys Med Rehabil* 1987;68:490–493.
40. Fischer M, Schafer SS. Temperature effects on the discharge frequency of primary and secondary endings of isolated cat muscle spindles recorded under a ramp-and-hold stretch. *Brain Res* 1999;840:1–15, [http://dx.doi.org/10.1016/S0006-8993\(99\)01607-8](http://dx.doi.org/10.1016/S0006-8993(99)01607-8).
41. Lee HJ, DeLisa JA, Bach JR. The effect of temperature on antidromic median sensory conduction. *Electromyogr Clin Neurophysiol* 1993;33:125–128.
42. Dash BM. Role of peripheral inputs in cerebellar tremor. *Mov Disord* 1995;10:622–629, <http://dx.doi.org/10.1002/mds.870100515>.
43. Quintern J, Immisch I, Albrecht H, Pollmann W, Glasauer S, Straube A. Influence of visual and proprioceptive afferences on upper limb ataxia in

- patients with multiple sclerosis. *J Neurolog Sci* 1999;163:61–69, [http://dx.doi.org/10.1016/S0022-510X\(99\)00006-4](http://dx.doi.org/10.1016/S0022-510X(99)00006-4).
44. Feys P, Helsen W, Liu X, et al. Effects of peripheral cooling on intention tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005;76:373–379, <http://dx.doi.org/10.1136/jnnp.2004.044305>.
  45. Feys P, Helsen WF, Verschuere S, et al. Online movement control in multiple sclerosis patients with tremor: effects of tendon vibration. *Mov Disord* 2006;21:1148–1153, <http://dx.doi.org/10.1002/mds.20938>.
  46. Feys P, Helsen W, Ilsbrouck S, Meurrens T. Is MS Intention tremor amplitude related to changed peripheral reflexes? *ISRN Neurol* 2011;2011:192414.
  47. Koller WC. Pharmacologic trials in the treatment of cerebellar tremor. *Arch Neurol* 1984;41:280–281, <http://dx.doi.org/10.1001/archneur.1984.04050150058017>.
  48. Speelman JD, Van Manen J. Stereotactic thalamotomy for the relief of intention tremor of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1984;47:596–599, <http://dx.doi.org/10.1136/jnnp.47.6.596>.
  49. Sechi GP, Zuddas M, Piredda M, et al. Treatment of cerebellar tremors with carbamazepine: a controlled trial with long-term follow-up. *Neurology* 1989;39:1113–1115, <http://dx.doi.org/10.1212/WNL.39.8.1113>.
  50. Hooper J, Taylor R, Pentland B, Whittle IR. Rater reliability of Fahn's tremor rating scale in patients with multiple sclerosis. *Arch Phys Med Rehabil* 1998;79:1076–1079, [http://dx.doi.org/10.1016/S0003-9993\(98\)90174-5](http://dx.doi.org/10.1016/S0003-9993(98)90174-5).
  51. Alusi SH, Worthington J, Glickman S, Findley LJ, Bain PG. Evaluation of three different ways of assessing tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000;68:756–760, <http://dx.doi.org/10.1136/jnnp.68.6.756>.
  52. Stacy MA, Elble RJ, Ondo WG, Wu SC, Hulihan J, group TRSs. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in essential tremor. *Mov Disord* 2007;22:833–838, <http://dx.doi.org/10.1002/mds.21412>.
  53. Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. *J Neurol Neurosurg Psychiatry* 1993;56:868–873, <http://dx.doi.org/10.1136/jnnp.56.8.868>.
  54. Alusi SH, Aziz TZ, Glickman S, Jahanshahi M, Stein JF, Bain PG. Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study. *Brain* 2001;124:1576–1589, <http://dx.doi.org/10.1093/brain/124.8.1576>.
  55. Bittar RG, Hyam J, Nandi D, et al. Thalamotomy versus thalamic stimulation for multiple sclerosis tremor. *J Clin Neurosci* 2005;12:638–642, <http://dx.doi.org/10.1016/j.jocn.2004.09.008>.
  56. Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurolog Sci* 2000;21:S831–838, <http://dx.doi.org/10.1007/s100720070021>.
  57. Schenk T, Walther EU, Mai N. Closed- and open-loop handwriting performance in patients with multiple sclerosis. *Eur J Neurol* 2000;7:269–279, <http://dx.doi.org/10.1046/j.1468-1331.2000.00068.x>.
  58. Feys P, Romberg A, Ruutiainen J, et al. Assistive technology to improve PC interaction for people with intention tremor. *J Rehab Res Dev* 2001;38:235–243.
  59. Albrecht H, Schwecht M, Pollmann W, Parag D, Erasmus LP, Konig N. Local ice application in therapy of kinetic limb ataxia. Clinical assessment of positive treatment effects in patients with multiple sclerosis. *Nervenarzt* 1998;69:1066–1073, <http://dx.doi.org/10.1007/s001150050384>.
  60. Sandyk R, Dann LC. Weak electromagnetic fields attenuate tremor in multiple sclerosis. *Int J Neurosci* 1994;79:199–212, <http://dx.doi.org/10.3109/00207459408986081>.
  61. Benito-Leon J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. *Disabil Rehabil* 2003;25:1291–1303, <http://dx.doi.org/10.1080/09638280310001608591>.
  62. Mitchell AJ, Benito-Leon J, Gonzalez JM, Rivera-Navarro J. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *Lancet Neurol* 2005;4:556–566, [http://dx.doi.org/10.1016/S1474-4422\(05\)70166-6](http://dx.doi.org/10.1016/S1474-4422(05)70166-6).
  63. Henkin Y, Herishanu YO. Primidone as a treatment for cerebellar tremor in multiple sclerosis—two case reports. *Isr J Med Sci* 1989;25:720–721.
  64. Aisen ML, Holzer M, Rosen M, Dietz M, McDowell F. Glutethimide treatment of disabling action tremor in patients with multiple sclerosis and traumatic brain injury. *Arch Neurol* 1991;48:513–515, <http://dx.doi.org/10.1001/archneur.1991.00530170077023>.
  65. Weiss N, North RB, Ohara S, Lenz FA. Attenuation of cerebellar tremor with implantation of an intrathecal baclofen pump: the role of gamma-aminobutyric acidergic pathways. Case report. *J Neurosurg* 2003;99:768–771, <http://dx.doi.org/10.3171/jns.2003.99.4.768>.
  66. Sabra AF, Hallett M, Sudarsky L, Mullally W. Treatment of action tremor in multiple sclerosis with isoniazid. *Neurology* 1982;32:912–913, <http://dx.doi.org/10.1212/WNL.32.8.912>.
  67. Bozek CB, Kastrukoff LF, Wright JM, Perry TL, Larsen TA. A controlled trial of isoniazid therapy for action tremor in multiple sclerosis. *J Neurol* 1987;234:36–39, <http://dx.doi.org/10.1007/BF00314007>.
  68. Hallett M, Lindsey JW, Adelstein BD, Riley PO. Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. *Neurology* 1985;35:1374–1377, <http://dx.doi.org/10.1212/WNL.35.9.1374>.
  69. Rice GP, Lesaux J, Vandervoort P, Macewan L, Ebers GC. Ondansetron, a 5-HT<sub>3</sub> antagonist, improves cerebellar tremor. *J Neurol Neurosurg Psychiatry* 1997;62:282–284, <http://dx.doi.org/10.1136/jnnp.62.3.282>.
  70. Monaca-Charley C, Stojkovic T, Duhamel A, De Seze J, Ferrily D, Vermersch P. Double-blind crossover study with dolasetron mesilate, a 5-HT<sub>3</sub> receptor antagonist in cerebellar syndrome secondary to multiple sclerosis. *J Neurol* 2003;250:1190–1194, <http://dx.doi.org/10.1007/s00415-003-0176-3>.
  71. Feys P, D'Hooghe M B, Nagels G, Helsen WF. The effect of levetiracetam on tremor severity and functionality in patients with multiple sclerosis. *Mult Scler* 2009;15:371–378, <http://dx.doi.org/10.1177/1352458508099142>.
  72. Francis DA, Grundy D, Heron JR. The response to isoniazid of action tremor in multiple sclerosis and its assessment using polarised light goniometry. *J Neurol Neurosurg Psychiatry* 1986;49:87–89, <http://dx.doi.org/10.1136/jnnp.49.1.87>.
  73. Duquette P, Pleines J, du Souich P. Isoniazid for tremor in multiple sclerosis: a controlled trial. *Neurology* 1985;35:1772–1775, <http://dx.doi.org/10.1212/WNL.35.12.1772>.
  74. Morrow J, McDowell H, Ritchie C, Patterson V. Isoniazid and action tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1985;48:282–283, <http://dx.doi.org/10.1136/jnnp.48.3.282>.



75. Gbadamosi J, Buhmann C, Moench A, Heesen C. Failure of ondansetron in treating cerebellar tremor in MS patients—an open-label pilot study. *Acta Neurolog Scand* 2001;104:308–311, <http://dx.doi.org/10.1034/j.1600-0404.2001.00075.x>.
76. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362:1517–1526, [http://dx.doi.org/10.1016/S0140-6736\(03\)14738-1](http://dx.doi.org/10.1016/S0140-6736(03)14738-1).
77. Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004;62:1105–1109, <http://dx.doi.org/10.1212/01.WNL.0000118203.67138.3E>.
78. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004;10:434–441, <http://dx.doi.org/10.1191/1352458504ms1082oa>.
79. Striano P, Coppola A, Vacca G, et al. Levetiracetam for cerebellar tremor in multiple sclerosis: an open-label pilot tolerability and efficacy study. *J Neurol* 2006;253:762–766, <http://dx.doi.org/10.1007/s00415-006-0112-4>.
80. Striano P, Coppola A, Pezzella M, et al. An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007;69:250–254, <http://dx.doi.org/10.1212/01.wnl.0000265222.24102.db>.
81. Striano P, Elefante A, Coppola A, et al. Dramatic response to levetiracetam in post-ischaemic Holmes' tremor. *J Neurol Neurosurg Psychiatry* 2007;78:438–439, <http://dx.doi.org/10.1136/jnnp.2006.103275>.
82. Solaro C, Brichetto G, Capello E, Abuarqub S, Sanguineti V. Activity, tolerability and efficacy of levetiracetam on cerebellar symptoms in multiple sclerosis patients: a pilot kinematic study. *Eur J Neurol* 2008;15:619–626, <http://dx.doi.org/10.1111/j.1468-1331.2008.02129.x>.
83. Sechi G, Agnelli V, Sulas FM, et al. Effects of topiramate in patients with cerebellar tremor. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:1023–1027, [http://dx.doi.org/10.1016/S0278-5846\(03\)00170-2](http://dx.doi.org/10.1016/S0278-5846(03)00170-2).
84. Kobylecki C, Marshall AG, Varma A, Kellett MW, Dick JP, Silverdale MA. Topiramate-responsive cerebellar axial postural tremor. *Mov Disord* 2008;23:1189–1191, <http://dx.doi.org/10.1002/mds.22068>.
85. Schroeder A, Linker RA, Lukas C, Kraus PH, Gold R. Successful treatment of cerebellar ataxia and tremor in multiple sclerosis with topiramate: a case report. *Clinical Neuropharmacol* 2010;33:317–318, <http://dx.doi.org/10.1097/WNF.0b013e3181f84a39>.
86. Ristori G, Romano S, Visconti A, et al. Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. *Neurology* 2010;74:839–845, <http://dx.doi.org/10.1212/WNL.0b013e3181d31e23>.
87. Chansakul C, Moguel-Cobos G, Bompreszi R. Head tremor secondary to MS resolved with rituximab. *Neurolog Sci* 2011;32:1157–1160, <http://dx.doi.org/10.1007/s10072-011-0600-x>.
88. Van Der Walt A, Sung S, Spelman T, et al. A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. *Neurology* 2012;79:92–99, <http://dx.doi.org/10.1212/WNL.0b013e31825dcd9>.
89. Cooper IS. Relief of intention tremor of multiple sclerosis by thalamic surgery. *JAMA* 1967;199:689–694, <http://dx.doi.org/10.1001/jama.1967.03120100051007>.
90. Niranjani A, Kondziolka D, Baser S, Heyman R, Lunsford LD. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. *Neurology* 2000;55:443–446, <http://dx.doi.org/10.1212/WNL.55.3.443>.
91. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000;342:461–468, <http://dx.doi.org/10.1056/NEJM200002173420703>.
92. Yap L, Kouyialis A, Varma TR. Stereotactic neurosurgery for disabling tremor in multiple sclerosis: thalamotomy or deep brain stimulation? *Br J Neurosurg* 2007;21:349–354, <http://dx.doi.org/10.1080/02688690701544002>.
93. Geny C, Nguyen JP, Pollin B, et al. Improvement of severe postural cerebellar tremor in multiple sclerosis by chronic thalamic stimulation. *Mov Disord* 1996;11:489–494, <http://dx.doi.org/10.1002/mds.870110503>.
94. Berk C, Carr J, Sinden M, Martzke J, Honey CR. Thalamic deep brain stimulation for the treatment of tremor due to multiple sclerosis: a prospective study of tremor and quality of life. *J Neurosurg* 2002;97:815–820, <http://dx.doi.org/10.3171/jns.2002.97.4.0815>.
95. Berk C, Honey CR. Bilateral thalamic deep brain stimulation for the treatment of head tremor. Report of two cases. *J Neurosurg* 2002;96:615–618, <http://dx.doi.org/10.3171/jns.2002.96.3.0615>.
96. Kandel EI, Hondcarian OA. Surgical treatment of the hyperkinetic form of multiple sclerosis. *Acta Neurolog* 1985;7:345–347.
97. Hooper J, Whittle IR. Long-term outcome after thalamotomy for movement disorders in multiple sclerosis. *Lancet* 1998;352:1984, [http://dx.doi.org/10.1016/S0140-6736\(05\)61329-3](http://dx.doi.org/10.1016/S0140-6736(05)61329-3).
98. Thevathasan W, Schweder P, Joint C, et al. Permanent tremor reduction during thalamic stimulation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2011;82:419–422, <http://dx.doi.org/10.1136/jnnp.2010.213900>.
99. Liu X, Aziz TZ, Miall RC, et al. Frequency analysis of involuntary movements during wrist tracking: a way to identify MS patients with tremor who benefit from thalamotomy. *Stereotact Funct Neurosurg* 2000;74:53–62, <http://dx.doi.org/10.1159/000056464>.
100. Romanelli P, Bronte-Stewart H, Courtney T, Heit G. Possible necessity for deep brain stimulation of both the ventralis intermedialis and subthalamic nuclei to resolve Holmes tremor. Case report. *J Neurosurg* 2003;99:566–571, <http://dx.doi.org/10.3171/jns.2003.99.3.0566>.
101. Hosseini H, Mandat T, Waubant E, et al. Unilateral thalamic deep brain stimulation for disabling kinetic tremor in multiple sclerosis. *Neurosurgery* 2012;70:66–69, <http://dx.doi.org/10.1227/NEU.0b013e31822da55c>.
102. Hyam JA, Aziz TZ, Bain PG. Post-deep brain stimulation—gradual non-stimulation dependent decrease in strength with attenuation of multiple sclerosis tremor. *J Neurol* 2007;254:854–860, <http://dx.doi.org/10.1007/s00415-006-0433-3>.
103. Wishart HA, Roberts DW, Roth RM, et al. Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports. *J Neurol Neurosurg Psychiatry* 2003;74:1392–1397, <http://dx.doi.org/10.1136/jnnp.74.10.1392>.
104. Torres CV, Moro E, Lopez-Rios AL, et al. Deep brain stimulation of the ventral intermediate nucleus of the thalamus for tremor in patients with multiple sclerosis. *Neurosurgery* 2010;67:646–651; discussion 651, <http://dx.doi.org/10.1227/01.NEU.0000375506.18902.3E>.

105. Hassan A, Ahlskog JE, Rodriguez M, Matsumoto JY. Surgical therapy for multiple sclerosis tremor: a 12-year follow-up study. *Eur J Neurol* 2012;19:764–768, <http://dx.doi.org/10.1111/j.1468-1331.2011.03626.x>.

106. Matsumoto J, Morrow D, Kaufman K, et al. Surgical therapy for tremor in multiple sclerosis: an evaluation of outcome measures. *Neurology* 2001;57:1876–1882, <http://dx.doi.org/10.1212/WNL.57.10.1876>.

107. Hooper J, Taylor R, Pentland B, Whittle IR. A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. *Br J Neurosurg* 2002;16:102–109, <http://dx.doi.org/10.1080/02688690220131769>.

108. Schulder M, Sernas TJ, Karimi R. Thalamic stimulation in patients with multiple sclerosis: long-term follow-up. *Stereotact Funct Neurosurg* 2003;80:48–55, <http://dx.doi.org/10.1159/000075160>.