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Evidence for treatment of spasticity in motor neuron disease

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See Articles page 155

Motor neuron disease is a relentlessly progressive disease. Expert consensus guidelines have been developed for key care concerns in patients with motor neuron disease, including respiratory management, nutrition, and palliative care.[1] Because there is no cure, symptom control to maintain quality of life is the mainstay of treatment. Spasticity is one of the defining characteristics of primary lateral sclerosis, but occurs to a variable degree in patients with amyotrophic lateral sclerosis.[2] Spasticity, however, is usually not the focus of management in patients with motor neuron disease. Notably, a Cochrane review[3] for treatment of spasticity in motor neuron disease identified only one randomised controlled trial of moderate-intensity, endurance-type exercise versus usual activities in 25 patients with amyotrophic lateral sclerosis. The authors of this Cochrane review concluded that further research was needed.[3] Available antispasticity drugs—ie, baclofen, dantrolene, benzodiazepines, gabapentin, and levetiracetam—have been reported to reduce spasticity in patients with amyotrophic lateral sclerosis,[4] but no controlled studies have been done. Additionally, these medications can be associated with increased muscle weakness or fatigue.

In *The Lancet Neurology*, Nilo Riva and colleagues report the results of a multicentre, randomised, double-blind, placebo-controlled phase 2 trial[5] of the safety and efficacy of nabiximols, a *Cannabis sativa* extract, on spasticity symptoms in patients with motor neuron disease (CANALS). After positive results for, and the subsequent regulatory approval of, cannabinoids for symptomatic treatment of spasticity in patients with multiple sclerosis,[6] Riva and colleagues initiated their proof-of-concept study at four tertiary motor neuron disease centres in Italy. Eligible patients had amyotrophic lateral sclerosis or primary lateral sclerosis. Patients were randomly assigned (1:1) to either a standardised oromucosal spray containing a defined combination of delta-9-tetrahydrocannabinol and cannabidiol (nabiximols) or to placebo for 6 weeks.

The primary endpoint was the change in Modified Ashworth Scale (MAS) scores, assessed at baseline and at the end of treatment. In the nabiximols group the MAS score improved by a mean of 0·11 (SD 0·48), whereas in the placebo group the score deteriorated by a mean of 0·16 (0·47). The difference between groups was significant (adjusted effect estimate –0·32 [95% CI –0·57 to –0·07]; p=0·013). Nabiximols was well tolerated, and no participants withdrew from the blinded phase of the study. Adverse events were mild to moderate and included asthenia, somnolence, vertigo, and nausea. However, substantially more adverse events occurred in the nabiximols group than in the placebo group. With respect to secondary outcomes, significant improvements were noted in scores on the pain numeric rating scale and in participants' global impression of change in the nabiximols group compared with the placebo group. No significant improvements were noted on various other secondary outcome measures, such as the upper motor neuron score and spasms and spasticity numeric rating scales. However, sample size might have been a limitation in this respect.

After 6 weeks of masked treatment, all participants were given the opportunity to enrol in an open-label phase. Two patients did not enter the open-label extension study, and seven withdrew during the open-label phase because of side-effects or disease progression. The mean MAS score of patients who had been assigned to the placebo group improved substantially during the open-label study.

The results of this study are promising, but the trial had several limitations. First, there was a bias towards patients

with exclusive or predominant involvement of upper motor neurons (n=16) in the nabiximols group, in whom spasticity is the prevailing symptom. These patients could have benefited more than the 13 patients with classic amyotrophic lateral sclerosis, which involves both upper and lower motor neurons. There are divergent opinions on the occurrence of spasticity in classic amyotrophic lateral sclerosis. Some authors reported that stiffness or spasticity were presenting symptoms only rarely in amyotrophic lateral sclerosis compared with in primary lateral sclerosis.[2] However, in a questionnaire-based study,[7] spasticity affecting quality of life was reported by roughly 80% of patients with amyotrophic lateral sclerosis (based on numeric rating scale spasticity responses). The authors of that study acknowledged that these findings were not validated by clinical examination, but they also questioned whether clinician assessment should be the gold-standard measure of spasticity. They did not detail the phenotypes of the included patients, so the proportion of patients with upper-motor-neuron-dominant amyotrophic lateral sclerosis is unknown.

Second, Riva and colleagues did not distinguish between upper and lower limb spasticity, or whether or not patients had bulbar spasticity. These patients could perhaps be differently affected by spasticity. Third, the MAS has been used in previous positive studies of the efficacy of other antispastic treatments but, as Riva and colleagues acknowledge, it lacked sensitivity in studies of the efficacy of cannabinoids in patients with multiple-sclerosis-related spasticity, and new spasticity numeric rating or visual analogue scales are being adopted.[8] A novel Rasch-based scale for patient-reported spasticity has been developed, but its responsiveness in amyotrophic lateral sclerosis has yet to be proven.[7] Finally, the fact that the number of adverse effects was substantially higher in the active treatment group than in the placebo group might have resulted in unblinding, which could have had a role in the significant findings.

Before regulatory approval of cannabinoids for symptomatic treatment of spasticity in patients with amyotrophic lateral sclerosis, further studies are needed to establish the frequency of spasticity in the various presentations of motor neuron disease, and also whether reductions in spasticity improve quality of life. Natural history studies including all subtypes of motor neuron disease and better outcome measures of spasticity are required. Riva and colleagues' data are encouraging, and larger multicentre randomised controlled trials should be done to identify which subgroups of patients derive clinically significant benefits from nabiximols.

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I declare no competing interests.

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The hunt for better treatments for Huntington's disease

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See **Articles** page 165

Huntington's disease is an autosomal dominant condition that typically presents in midlife as a combination of motor, cognitive, and psychiatric problems, along with sleep and metabolic abnormalities. Its clinical course runs over 15–20 years and eventually leads to death as patients develop dementia and become bed-bound. At present, no disease-modifying therapy is approved for patients with Huntington's disease. Although research on antisense therapies that target the huntingtin gene has generated much excitement, these therapies have not yet been shown to lead to measurable changes in disease progression.[1,2] Furthermore, given that they aim to modify and not cure the disease, adjunct symptomatic treatments would still be required. Symptomatic therapies