An expert opinion: Optimisation of pharmacological management of multiple sclerosis related spasticity

Abstract
Spasticity is a frequent symptom in people with Multiple Sclerosis. Whilst many respond to first line therapies it is estimated that 30-40% will have suboptimal treatment response requiring more specialised management. Such strategies include combination of oral medications, botulinum toxin, nabiximols and consideration of intrathecal therapies: baclofen or phenol. Early expert intervention as outlined in this review can have a positive impact on functional ability and quality of life for people with MS.

Multiple sclerosis (MS) is one of the leading causes of non-traumatic acquired disability in young people affecting more than 120,000 people in the UK and about 2.5 million people worldwide. Significant advances have been made in MS disease modifying therapies (DMTs) including the progressive phase. However, many people live with troublesome symptoms related to the disease. The North American Research Committee on MS (NARCOMS) Registry has identified 11 key symptom domains that are commonly affected in MS: mobility, hand function, tremor/coordination, vision, pain, fatigue, bowel/bladder function, sensory, spasticity, cognition, and depression. More than 80% of respondents reported spasticity during their disease course and spasticity severity was reported as moderate or high by between 35% and 54% of respondents. This was associated with stiffness, spasms, and/or pain, mainly in the lower limbs. Key aspects of managing MS-related spasticity are understanding the pathophysiology of spasticity, use of appropriate outcome measures and a personalised approach to pharmacological treatment in the context of the patient’s activities and quality of life.

Spasticity is defined by Lance as “a motor disorder characterised by a velocity dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the Upper Motor Neuron syndrome”. It is clinically important to differentiate between neural and non-neural components of stiffness to inform management. Optimum management requires a multidisciplinary team approach including a Neurologist or Rehabilitation Medicine Physician, Physiotherapist, Specialist Nurse and access to occupational therapy and splinting.

Assessment and outcome measures
Thorough assessment of the impact of spasticity on the individual is key. This involves accurate history taking as to the symptoms the individual experiences, diurnal variation, trigger factors including infections, bladder and bowel dysfunction, skin breakdown, suitability and fit of splints, and impact on walking and other activities. Generic and disease specific outcome measures can be used. A combination of objective (hands on) and patient reported outcome measures is essential to understand the degree of spasticity experienced and to monitor response to any intervention. The most commonly used measure is the Ashworth or modified Ashworth scales which are easy to administer in clinical practice. There are conflicting reports, however, regarding the validity and reliability of these measures. The Tardieu scale, commonly used in cerebral palsy and stroke, has not been validated for use in MS spasticity. The MS spasticity scale (MSSS-88) is an 88 item patient-based interval level scale which evaluates the symptoms the patient experiences and how spasticity affects their daily life. The numerical rating scale for spasticity (NRS) is a 0-10 point scale where the individual will rate the severity of their spasticity over the previous 24 hours. There is concern, however, that the individual might rate other symptoms such as weakness or pain, rather than spasticity in isolation, however this may additionally reflect quality of life. Other measures which might be useful in clinical practice include a spasm score or functional measures such as timed walking tests (25 foot walk, 10 metre walk) or measures of upper limb function (9 hole peg test).

Current pharmacological treatments
The basis of pharmacological treatment of MS spasticity remains with the use of first line agents: Baclofen, Tizanidine and Gabapentin (pregabalin). Whilst many will respond to such treatment about one third will continue to experience problematic symptoms. Addition of second line agents such as benzodiazepines (e.g. diazepam and clonazepam) may be helpful but are frequently associated with side effects including CNS depression, memory impairment are common as is dependence and withdrawal syndrome if stopped abruptly. Although there are distinct mechanisms of actions, many of these agents may serve to hyperpolarise neurons, such as through opening of chloride channels (benzodiazepines) or potassium channels and blockage of calcium channels (baclofen and cannabinoids), to block hyperexcitability, to quell the spastic response. Dantrolene is unique in its mode of action impacting the contractile mechanism of skeletal muscle by decreasing the release of calcium. Its use is limited by frequent side effects including gastrointestinal symptoms, weakness,
sedation and dizziness. The risk of hepatotoxicity is a major limiting factor and requires monitoring of liver function prior and during therapy. In a Cochrane review of antispasticity agents for MS the conclusions were that there was in general low quality evidence of the efficacy of these agents to treat MS related spasticity and that better outcome measures are required in trials to reflect efficacy and impact on quality of life.\textsuperscript{21}

Cannabinoids and MS spasticity

Cannabis has been used recreationally and medicinally by people with MS for many years prompting a research programme investigating utility of cannabis-based medicinal products (CBMPs) in MS.\textsuperscript{12,14} Biologically there is evidence that cannabis-based products modulate spasticity via CB1 receptors.\textsuperscript{22} The whole plant extract contains hundreds of chemical entities, however the two components of greatest interest are delta 9 tetrahydrocannabinol (THC) and cannabidiol (CBD) as the major psychoactive and non-psychoactive ingredients of cannabis that has been recently approved for some epilepsy conditions, respectively. Studies investigating synthetic THC, whole plant extracts, smoked cannabis and THC-CBD (Nabiximols) have been reported.\textsuperscript{12,15-18} In 2010 TH-CBD (Nabiximols) was licensed for moderate to severe MS related spasticity having shown a significant improvement in patient reported spasticity on the NRS as compared with placebo.\textsuperscript{19} In this pivotal trial the patients received intrathecally delivered THC/CBD in a programmable, subcutaneously implanted drug delivery system, delivering low doses of THC and CBD for focal treatment via an intrathecal catheter and fibrosis of the nerve which is largely irreversible.\textsuperscript{20} Similarly low dose alcohol has an anaesthetic effect and high dose (>50%) is neurolytic. Following phenol treatment, partial nerve regeneration and sprouting occurs so that the clinical effect may ‘wear off’ in about 30%. In our experience intrathecal phenol is a highly effective treatment in carefully selected subjects. It will usually impair bowel, bladder and sexual function and management plans must be in place in this regard. At the NHNN over a 12 year period 2006-2018, 45 people underwent ITP successfully with a reduction in spasticity on the Ashworth scale, pess spasms and higher levels of comfort. Due to its destructive and potentially irreversible nature ITP remains a last resort.

Discussion

Spasticity remains a problematic symptom in people with advanced MS and when sub-optimally treated leads to significant impairment and distress. Unlike the DMT options for MS there are limited new drugs for spasticity, nabiximols being the only recently licensed option, with severely restricted access. People with MS should be treated with at least two first line agents commencing at low doses and escalating the dose frequently until effect is gained. Side effects appear or the maximum dose is reached. Second line agents should then be added for additional effect. Botulinum toxin or focal nerve blocks are useful for localised problematic areas. In people, including those who remain ambulatory, who have failed 1st and 2nd line systemic agents, intrathecal therapies are reasonable options and they should be referred to specialised multidisciplinary service for optimal management.

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REFERENCES