Symptomatic therapy in multiple sclerosis: Big pharma should do more – commentary

Michael Hutchinson

Management of an increasing burden of symptoms is the main preoccupation both of people with multiple sclerosis (MS) and their health care providers.1 One of the advantages of a multidisciplinary clinic is that the many diverse skills needed to address the complex needs of people with MS are available in one place and time. The difficulties that we face include (a) numerous, disparate symptoms in different organ systems, (b) limited therapeutic options, and (c) low-powered, poor-quality trials, often with qualitative subjective endpoints and few quantitative ‘hard’ outcome measures. There is the perception that the pharmaceutical industry is not interested in addressing this unmet need; there is more money in disease-modifying therapies (introduced or reintroduced older therapies modified in some way for the market). A recent paper and accompanying editorial in Neurology outlined clearly the burgeoning market in these therapies, especially in the United States (US).2

Pharmaceutical companies could, with some justification, reply that bringing a new therapy to market, particularly a new molecule, is a hugely expensive and slow process with high risks of failure and financial loss. The companies could also point out that there are numerous drugs already available which could be repurposed for use in symptom management. They might also point out that academic neurologists should conduct better trials. In a recent survey of clinical trials, there were a total of 1299 trials in MS, of these 55% were industry funded.3 The pharmaceutical industry does fund trials which have little or no financial interest for the industry; for example, of 26 vitamin D trials in MS trials, four are supported/funded by industry. If one examines trials for relief of pain in MS, 55% of 100 trials are industry funded. Similarly for bladder symptoms and MS, 13/23 (57%) trials are funded by industry.4 If one examines trials for relief of spasticity in MS, 112/273 (41%) of trials of putative therapies for spasticity are industry funded.5

In MS trials, four are supported/funded by industry. If one examines trials for relief of pain in MS, 55% of 100 trials are industry funded. Similarly for bladder symptoms and MS, 63/100 (63%) trials are funded by industry. Similarly for bladder symptoms and MS, there are 18/28 (64%) trials of putative therapies for cognitive problems in MS are funded by industry. It should, however, be acknowledged that a number of

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these symptoms are secondary or tertiary endpoints in trials involving disease-modifying therapies and that the particular symptom is not a primary endpoint. Despite that, overall I do not get the impression that the pharmaceutical companies are not pulling their weight in the field of symptomatic therapies. The usual scenario at present is that the pharmaceutical industry develops a new molecule (be it an anti-muscarinic, anti-convulsant or antidepressant); eventually it is shown to be effective in phase 3 studies and then its effects are studied in an MS population. Thus the MS population really benefits only after the drug has been proven in another clinic population (for example, a new antidepressant in patients with primary bipolar disorder).

Fampridine, however, a selective blocker of potassium channels, which restores saltatory conduction, was an old drug known to improve symptoms in a proportion of MS patients. In its new formulation, dalfampridine, it had a partial effect in about 30% of patients with walking difficulties in a clinical trial situation. One difficulty with symptomatic therapies is that there can be a mismatch between the perceived benefit to the patient/client and the objective measurement by the doctor. In a real-world situation, one-third of the patients were found to have improved (by greater than 20%) in their walking speed at four weeks and only 16% by six months. However, using the Multiple Sclerosis Walking Scale-12 (MSWS-12), two-thirds (66%) of patients reported improvement at four weeks and 60% at six months. This is one of the difficulties with the assessment of symptomatic therapies: The objective measurement (in this case the 25-foot timed walk test) showed only an improvement in one third of the patients at four weeks and in one sixth of patients at six months. The same patients, however, were reporting significant changes in a validated self-report measure (MSWS-12) in 60% of patients at six months. Thus, either there was a prolonged placebo effect (unlikely), or the MSWS-12 was measuring something that cannot be judged by the 25-foot walk test (more likely).

Three other symptoms prominent in MS include bladder symptoms, pain and fatigue. We are probably best at managing bladder symptoms in people with MS and reasonably good (working with a pain specialist unit) at managing pain; fatigue is the really difficult symptom which none of us feel we can manage adequately. In this case, I feel the problem is with the clinician. We academic neurologists need to address both the origins and pathophysiology of fatigue and develop reasonably objective measures of fatigue severity. Once we understand the patho-mechanisms of fatigue, then we can test appropriate therapies. One recent surprising report was the suggestion that vitamin D supplementation might alleviate fatigue; this needs to be replicated.6

In summary, I do not think that the pharmaceutical industry is dragging its heels in this area. We need more collaborative neurologist-led clinical trial research into novel therapies for specific symptoms in MS, the most prevalent and most difficult to treat being that of fatigue.

Conflicts of interest
Michael Hutchinson served on a medical advisory board for the CONFIRM study (BG00012) for Biogen-Idec; serves on the editorial board of the Multiple Sclerosis Journal; has received speaker’s honoraria from Novartis, Biogen-Idec and Bayer-Schering; and receives research support from Dystonia Ireland, the Health Research Board of Ireland and the European Dystonia Foundation.

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