Extended-release dalfampridine in the management of multiple-sclerosis-related walking impairment

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Carrie Hersh and Alex Rae-Grant

Abstract: Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system that causes neurological impairment in young adults. As part of the disease, ambulation remains one of the most disabling features of multiple sclerosis. Extended-release dalfampridine is a long-acting form of 4-aminopyridine that has been shown in two phase III trials to increase ambulation speed in a subset of patients with multiple sclerosis (timed walk responders). The primary endpoint of these studies was 'responder status', analyzing difference in the proportion of timed walk responders between extended-release dalfampridine and placebo groups. Extended-release dalfampridine exerts its effects by inhibiting voltage-activated K^+ channels and has been previously demonstrated to improve action potential propagation in demyelinated nerve fibers *in vitro*. Side effects of extended-release dalfampridine include increased urinary tract infections, insomnia, headache, asthenia, dizziness, back pain, and paresthesias. Rare seizure events are also reported on the approved dose of 10 mg every 12 h. In this review we will summarize the results of key phase II and phase III trials of extended-release dalfampridine, its safety, and potential use in patients with multiple sclerosis.

Keywords: 12-Item Multiple Sclerosis Walking Scale, ambulation, extended-release dalfampridine, Lower Extremity Manual Muscle Test, multiple sclerosis, potassium-channel blocker, Timed 25-Foot Walk test

Introduction

Multiple sclerosis (MS) is a relapsing or progressive inflammatory demyelinating disorder of the central nervous system (CNS). It is a major cause of neurological impairment and disability in young adults, particularly women. There are a variety of genetic and environmental influences, but the specific cause is not known [Frohman *et al.* 2006]. The relapsing–remitting form tends to affect women more than men in a 2.3:1 ratio [Alonso and Hernan, 2008] and generally presents itself clinically in the second to fourth decades [Confavreux and Compston, 2005]. MS can cause a wide array of neurological symptoms including visual loss or double vision, muscle weakness, paresthesias, sensory loss, fatigue, cognitive disruption, gait imbalance, incoordination, and bladder dysfunction [Tremlett *et al.* 2006]. As part of the disease, impaired ambulation remains one of the most feared and disabling symptoms of MS [Bever and Judge, 2009].

Ambulation is frequently affected by MS [Swingler and Compston, 1992]. It is affected early in the disease in many patients, even when clinical measures of disability are minimally altered [Martin *et al.* 2006]. Ambulation is important to patients with MS, and they perceive it as a major issue for their health [Heesen *et al.* 2008]. Its limitations have an impact on activities and participation, emotional status, quality of life, and health status [Zwibel, 2009]. At present, interventions specific to ambulation are limited in MS to physical therapy measures, and in an acute setting, steroid therapy or plasmapheresis. None of the standard disease-modifying therapies specifically

Correspondence to:
Alex Rae-Grant, MD, FRCP(C)
U-10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
rae-gra@ccf.org

Carrie Hersh, DO
Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

address improving ambulation as a therapeutic target.

4-Aminopyridine (4-AP) is a broad-spectrum inhibitor of voltage-activated K^+ (Kv) channels and has been demonstrated to improve action potential propagation in demyelinated nerve fibers *in vitro* [Judge and Bever, 2006]. There have been several hypotheses about the underlying mechanism of 4-AP's effect on action potential transmission. These include as a direct result of broad-spectrum inhibition of the Kv channel, repolarization delay, prolonging the duration of the action potential, which results in a larger influx of $Ca2^+$, thus increasing the efflux of neurotransmitter; and directly triggering high-voltage activated $Ca2^+$ channels independent of Kv channels [Espejo and Montalban, 2011]. While 4-AP's actions are not specific to ambulation, as a therapeutic target this is more objectively measurable than other functional measures such as fatigue and cognition. Extended-release dalfampridine (previously known as fampridine – sustained release) is a long-acting form of 4-AP with a similar physiological action but longer half life.

Pharmacology, pharmacokinetics, and mechanism of action

4-AP is a derivative of pyridine with an amino group substitution at the 4-position, developed and marketed by Phillips Petroleum in 1963 [DeGrazio *et al.* 1971]. In its unionized form it is able to cross the blood–brain barrier due to its lipid-soluble nature, and is thus able to interact with various channels on the cytoplasmic side of neuronal membranes within the CNS [Bever and Judge, 2009]. The pharmacokinetics has been studied in animal and human models. In humans, oral doses are rapidly and completely absorbed with a bioavailability of about 95%, reaching peak-serum concentration in about 80 min and a half life of approximately 4 h [Evenhuis *et al.* 1981; Hayes *et al.* 2003; Uges *et al.* 1982]. The drug is primarily metabolized through the kidney and excreted relatively unchanged in the urine [Blight and Henney, 2009].

4-AP exerts its inhibitory effects by binding to a wide variety of Kv channels that are located on the intracellular membranes of various CNS cell types, including neurons, microglia, and oligodendrocytes [Judge and Bever, 2006; Espejo and Montalban, 2012]. In addition, it exerts its effects by binding to several cell types in the immune system, including T cells, B cells, dendritic cells, and macrophages [Espejo and Montalban, 2012]. After gaining entrance into the intracellular space due to its lipid solubility, it binds to the open mouth of the channel transmembrane pore region, delaying repolarization of the neural cell, and thus prolonging the duration of the action potential [Bever and Judge, 2009; Judge and Bever, 2006]. This allows for a greater influx of $Ca2^+$ into the presynaptic ending, resulting in an increased release of transmitter into the synaptic cleft [Lemeignan and Lechat, 1967; Sherratt *et al.* 1980, Thomsen and Wilson, 1983]. This action increases the postsynaptic response. In this manner, 4-AP is able to improve conduction in demyelinated nerve fibers. The method in which 4-AP is able to do this has been demonstrated in immunohistochemical studies that showed that a high concentration of sodium channels are mainly located in the nodal regions of the neural axon, while a higher concentration of potassium channels are distributed underneath the myelin sheath [Rasband, 2005; Waxman, 1982]. During conduction of a normally myelinated axon, the action potential is propagated in a saltatory manner, appearing to jump from node to node. This results in a faster and more cohesive, concentrated action potential because the myelin sheath is able to insulate the sodium channels and thus reduce radial dispersion of the electrical activity. However, in the demyelinated axon, the action potential is 'spread out' and is unable to conduct in such an effective manner, slowing down the propagation [Dunn and Blight, 2011]. 4-AP's mechanism of action is able to restore some of the 'lost current'. It actively binds to and inhibits the open Kv channels that have been uncovered by the loss of myelin and increase the duration of the action potential, essentially making up for quality by quantity of the AP. However, it has not yet been specifically demonstrated how increased synaptic transmission and neurotransmitter release is able to compensate therapeutically for the clinical effects of demyelination in patients with MS [Dunn and Blight, 2011].

Development of 4-aminopyridine and extended-release dalfampridine

The first clinical trial to investigate the clinical impact of 4-AP on MS was an open-label, placebo-controlled trial, conducted by Jones and colleagues in 1983 [Jones *et al.* 1983]. This study assessed 10 patients, five with chronic stable deficits due to MS with spinal cord involvement and

five patients with thermal-sensitive visual impairments. It showed that with 60 mg/day of 4-AP there were statistically significant improvements in visual symptoms, but only two of the patients in the first group noted any clinical improvements – one in sensation and another in ambulation.

In 1994, Bever and colleagues conducted a randomized, double-blind, placebo-controlled, serum-controlled study that investigated the effects of 4-AP in patients with MS who reported Lhermitte equivalent (temperature sensitive) phenomena [Bever *et al.* 1994]. This study monitored the serum concentration of 4-AP in those patients enrolled, and the dosages were adjusted accordingly to meet a predetermined average serum concentration. Based on the data collected, Bever and colleagues were able to correlate the concentration of drug with level of clinical improvement. In addition, they were able to determine that clinical improvements were related to the total 4-AP exposure, and adverse side effects (i.e. nausea, paresthesias, and seizures) were related to the peak serum dose. Along with several other studies conducted by van Diemen and colleagues [Diemen *et al.* 1993], Bever and colleagues set the stage for a longer acting formulation of 4-AP designed to limit peak-dose side effects [Bever *et al.* 1994]. This longer-acting form is now known as extended-release dalfampridine (trade name Ampyra, Acorda Therapeutics, NY).

A dose-ranging study of extended-release dalfampridine was reported by Goodman and colleagues in April 2007 [Goodman *et al.* 2007]. This was a randomized, double-blind, placebo-controlled study that occurred over a 14-week treatment period, using extended-release dalfampridine in 37 patients with MS at four centers (active medication $n = 25$, placebo $n = 11$, one discontinued prior to randomization, intent to treat analysis) in doses from 10 to 40 mg twice daily taken orally. In the prospectively planned analysis the change from baseline in the Timed 25-Foot Walk (T25FW) test did not achieve significance on the repeated measures analysis ($p = 0.28$). A *post hoc* analysis showed clinical improvements in walking speed in 38.4% of patients who were in the treatment group compared with 8.3% who improved in the placebo-controlled group ($p < 0.0004$). In addition to quantitative measurements of improved ambulatory dysfunction, there was also a subjective improvement in quality of walking among the responders, measured by the 12-Item Multiple Sclerosis Walking Scale (MSWS-12). Other secondary measures investigated in this trial included assessment of leg strength using the Lower Extremity Manual Muscle Test (LEMMT), spasticity using the Ashworth scoring system, manual dexterity and speed using the 9-hole peg test, Clinician Global Impression (CGI), and Subject Global Impression (SGI). The authors framed this study as primarily a safety analysis. No new tolerability issues or safety profile data were identified in this study. The most common treatment-emergent adverse events on extended-release dalfampridine were dizziness, insomnia, paresthesia, asthenia, nausea, headache, and tremor, all of which exceeded rates in the placebo group. Most adverse events were mild or moderate and transient. Severe treatment-emergent adverse events occurred only at doses greater than 25 mg twice a day.

In 2009, Goodman and colleagues reported a phase III randomized, double-blind, placebo-controlled trial in 301 patients using a fixed dose regimen (extended-release dalfampridine 10 mg twice daily, $n = 229$; placebo twice daily, $n = 72$) (MS-F203 trial) [Goodman *et al.* 2009]. A responder/nonresponder analysis was used based on the T25FW test as the primary endpoint. This was a novel design for MS studies. The primary efficacy analysis was 'responder status' based on consistent improvement in timed walk measures over multiple visits. A 'timed walk responder' was defined as a patient with a faster walking speed for at least three of four visits during the double-blind treatment period than the maximum speed for any of the first five off-drug visits (four prior to double-blind phase and one 2 weeks after discontinuation of treatment). This study demonstrated that the number of patients who met the responder criterion was 78/224 in the extended-release dalfampridine group (35%) and 6/77 (8%) in the placebo group [$p < 0.001$, Mantel–Haenszel odds ratio 4.75; 95% confidence interval (CI) 2.08–10.86]. Further, there was also significantly improved leg strength in responders ($p < 0.028$). A secondary measure was MSWS-12, which was used to validate the patient perspective on ambulatory disability. Average changes in MSWS-12 during treatment were significantly improved in responders *versus* nonresponders ($p = 0.0002$). Treatment-emergent adverse events were similar to the Goodman 2007 trial. Of note, 11 patients (5%) in the extended-release dalfampridine group were withdrawn from the study during the double-blind phase due to adverse events. In eight cases,

these began during the double-blind phase (sepsis, ankle fracture, balance disorder, confusional state, dizziness, headache, and anxiety) [Goodman *et al.* 2009]. One patient in the placebo arm was lost to follow up but none were removed for adverse events.

In 2010, Goodman and colleagues conducted a 39-center, double-blind trial in patients with definite MS of any course type, randomized to 9 weeks of treatment with extended-release dalfampridine (10 mg twice daily, $n = 120$) or placebo ($n = 119$) [Goodman *et al.* 2010]. Response was defined as consistent improvement in the T25FW, with percentage of timed walk responders (TWRs) in each treatment group as the primary outcome. The study showed that the proportion of TWRs was significantly higher in the extended-release dalfampridine group (51/119, 42.9%) compared with the placebo group (11/118, 9.3%; $p < 0.0001$). The average improvement in walking speed among TWRs in the extended-release dalfampridine-treated group during the 8-week efficacy evaluation period was 24.7% from baseline (95% CI 21.0–28.4%). Adverse event rates were similar to the prior studies [Goodman *et al.* 2010].

Responder/nonresponder analysis has potential weaknesses that should be appreciated when one is studying such data [Snapinn and Jiang, 2007]. For example, there is a reduced power relative to analysis on the original scale due to the use of a threshold value in analysis rather than just rejection of the null hypothesis [Snapinn and Jiang, 2007]. There is also an issue with the arbitrary nature of the definition of a response. Such a definition needs validation against meaningful clinical measures to ensure that it is truly an appropriate endpoint. The T25FW *post hoc* analysis of data from the pivotal trials of extended-release dalfampridine appeared to confirm a correlation between change in T25FW speed and CGI. In addition, participants characterized 'minimally improved' by the CGI as a mean of 0.36 ft/s or a 17.2% relative change from average baseline walking speed of 2.1 ft/s. This study confirmed the clinical significance of the timed walk change in responders in these trials [Goodman *et al.* 2009, 2010; Coleman *et al.* 2012]. In 2011, Bethoux and Bennett described several methods in which to quantitatively measure ambulation status [Bethoux and Bennett, 2011]. In addition to the aforementioned T25FW and patient self-report MSWS-12, other instruments include the Dynamic Gait Index and the Timed Up and Go test that involve other aspects of mobility, including balance. Tests such as the 2- or 6-Minute Walk provide information on endurance and motor fatigue that may not be picked up on other measures. It is possible that other measures of walking under various conditions may more accurately predict a 'useful' or 'clinically meaningful outcome' with this medication and others in the pipeline.

Safety of extended-release dalfampridine

The clinical efficacy of 4-AP formulations is directly related to the total serum concentration (measured as area under the serum concentration curve), while toxicity and adverse side effects are directly related to the peak serum dose [Bever *et al.* 1994]. The average side effect profile was summarized in several pivotal trials, looking at both immediate-release and extended-release formulations, including the studies by Goodman and colleagues [Goodman *et al.* 2007, 2008, 2009, 2010] and van Diemen and colleagues [van Diemen *et al.* 1993]. Common side effects included headache, fatigue, dizziness, nausea, paresthesias, imbalance, urinary tract infections, insomnia, asthenia, and falls. However, the above side effect profile was reduced overall with the sustained release formulation and the 10 mg twice daily dosing regimen [Goodman *et al.* 2008]. The most serious adverse side effect was seizures (including generalized tonic–clonic seizures in two out of 23 patients with MS) in those treated for 6–32 months with 4-AP who were reported in the study by Polman and colleagues [Polman *et al.* 1994]. In addition, in recent studies reported by the Goodman investigators [Goodman *et al.* 2007], two out of 25 patients with MS on extended-release dalfampridine experienced one seizure each while enrolled in a 14-week treatment trial (taking 20 mg twice daily, and one accidentally overdosed). In general, there appeared to be a dose-related, increased risk of seizure development.

There are two major contraindications to the use of extended-release dalfampridine. Patients with moderate to severe renal impairment (creatinine clearance $\leq$ 50 ml/min) should avoid extended-release dalfampridine due to its renal excretion and risk of toxicity. Patients with mild to moderate renal impairment are at risk of higher plasma levels of extended-release dalfampridine approaching the 15 mg twice daily dosing levels in trials (Ampyra medication guide approved by US Food and Drug Administration). Patients with a seizure

history should also avoid extended-release dalfampridine due to the increased risk of seizures [Acorda Therapeutics, Inc., 2010].

At present, extended-release dalfampridine is only available in a 10 mg twice a day dose. This dose may not be exceeded, and pills may not be manipulated (split, crushed, etc.). Further trials are underway to assess lower dosing regimens. The safety of extended-release dalfampridine in pregnancy and breast feeding is unknown at present, and this medication should likely be avoided in these circumstances. Data on pediatric use (under age 18) and in older people (over 65 years of age) are lacking. In older people, a creatinine clearance should be obtained before considering the use of extended-release dalfampridine [Acorda Therapeutics, Inc., 2010].

Conclusion

Extended-release dalfampridine has been found in several randomized, double-blind, placebo-controlled trials to significantly improve walking speed and likewise lower extremity motor strength, spasticity, and dexterity (secondary endpoints) in some patients (responders) with MS affecting walking speed. It primarily operates by blocking Kv channels along demyelinated axons, thus shortening the length of repolarization, and thereby prolonging the depolarization phase of the action potential. This ultimately increases the concentration of neurotransmitter available for release into the synaptic cleft, hence optimizing neurotransmission in an already compromised system due to autoimmune attack on the myelin sheaths. Multiple studies have also investigated the effects of extended-release *versus* immediate-release formulations on patients treated with dalfampridine. These trials demonstrated peak-dose side effects including gastrointestinal upset, dizziness, falls, and even seizures to a greater extent in patients taking 4-AP *versus* extended-release formulation. As demonstrated in the study by Coleman and colleagues, the CGI scale positively correlated with improvement in ambulation, measured as the T25FW [Coleman *et al.* 2012]. Ambulation is crucial for patients with MS. Extended-release dalfampridine may significantly affect gait in a minority of patients, potentially improving independence in some patients.

In future, it would be interesting to investigate the molecular mechanism attributed to responder *versus* nonresponder status in those exposed to therapeutic doses of dalfampridine. For instance, although not yet clearly defined in the literature, it would be interesting to speculate if the difference in response is related to potassium receptor polymorphisms or perhaps some other downward process in leading to increased transmitter release at the level of the synapse. Along the same lines, it would also be interesting to describe if in nonresponders the increased dalfampridine serum level would lead to a degree of response before causing seizures or if seizures are not likely to be triggered in patients who are nonresponders because of their lack of receptor sensitivity.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Acorda Therapeutics, Inc. (2010) Ampyra (package insert). New York: Acorda Therapeutics, Inc.

Alonso, A. and Hernan, M.A. (2008) Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology* 71: 129–134.

Bethoux, F. and Bennett, S. (2011) Evaluating walking in patients with multiple sclerosis: which assessment tools are useful in clinical practice? *Int J MS Care* 13: 4–14.

Bever, C.T. Jr and Judge, S. IV (2009) Sustained-release fampridine for multiple sclerosis. *Exp Opin Investig Drugs* 18: 1013–1024.

Bever, C.T., Young, D., Anderson, P.A., Krumholz, A., Conway, K., Leslie, J. *et al.* (1994) The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomized, placebo-controlled, double blind, concentration controlled crossover trial. *Neurology* 44: 1054–1059.

Blight, A.R. and Henney, H.R. (2009) Pharmacokinetics of 14C-radioactivity after oral intake of a single dose of 14C-labled fampridine (4-aminopyridine) in healthy volunteers. *Clin Ther* 31: 328–335.

Coleman, C.I., Sobieraj, D.M. and Marinucci, L.N. (2012) Minimally important clinical difference of the Timed 25-Foot Walk Test: results from a randomized controlled trial in patients with multiple sclerosis. *Curr Med Res Opin* 28: 1–8.

Confavreux, C. and Compston, A. (2005) The natural history of multiple sclerosis. In: Compston, A. (ed) *McAlpine's Multiple Sclerosis*. 4th edition. Philadelphia, PA: Churchill Livingstone, pp. 183–269.

DeGrazio, J.W., Besser, J.F., DeCino, T.J., Guarino, J.L. and Starr, R.I. (1971) Use of 4-aminopyridine to protect ripening corn from blackbirds. *J Wildl Mgmt* 35: 565–569.

Dunn, J. and Blight, A. (2011) Extended-release dalfampridine: a brief review of its mechanism of action and efficacy as a treatment to improve walking in patients with multiple sclerosis. *Curr Med Res Opin* 27: 1415–1423.

Espejo, C. and Montalban, X. (2012) Dalfampridine in multiple sclerosis: from symptomatic treatment to immunomoduluation. *Clin Immunol* 142: 84–92.

Evenhuis, J., Agoston S., Salt, P.J., Chir, B., De Lange, A.R., Wouthuyzen, W. *et al.* (1981) Pharmacokinetics of 4-aminopyridine in human volunteers: a preliminary study using a new GLC method for its estimation. *Br J Anesth* 53: 567–570.

Frohman, E., Racke, M. and Raine, C. (2006) Multiple sclerosis: the plaque and its pathogenesis. *N Engl J Med* 354: 942–955.

Goodman, A.D., Brown, T.R., Cohen, J.A., Krupp, L.B., Schapiro, R., Schwid, S.R. *et al.* (2008) Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology* 71: 1134–1141.

Goodman, A.D., Brown, T.R., Edwards, K.R., Krupp, L.B., Schapiro, R.T., Cohen, R. *et al.* (2010) A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 68: 494–502.

Goodman, A.D., Brown, T.R., Krupp, L.B. Schapiro, R.T., Schwid, S.T., Cohen, R. *et al.* (2009) Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 373: 732–738.

Goodman, A.D., Cohen, J.A., Cross, A., Vollmer, T., Rizzo, M., Cohen, R. *et al.* (2007) Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose ranging study. *Mult Scler* 13: 357–368.

Hayes, K.C., Katz M.A., Devane, J.G., Hsieh, J.T.C., Wolfe, D.L., Potter, P.J. *et al.* (2003) Pharmacokinetics of an immediate-release oral formulation of fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. *J Clin Pharmacol* 31: 379–385.

Heesen, C., Böhm J., Reich, C., Kasper J., Goebel M. and Gold S.M. (2008) Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Mult Scler* 14: 988–991.

Jones, H.E., Heron J.R., Foster, D.H., Snelgar, R.S. and Mason, R.J. (1983) Effects of 4-aminopyridine in patients with multiple sclerosis. *J Neurol Sci* 60: 353–362.

Judge, S. IV. and Bever, C.T. (2006) Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharm Ther* 111: 224–259.

Lemeignan, M. and Lechat, P. (1967) Sur l'action anticurare des aminopyridines [On the anticurare action of aminopyridines]. *C R Acad Sci Paris Serie D* 264: 169–172.

Martin, C.L., Phillips B.A., Kilpatrick, T.J., Butzkueven, H., Tubridy, N., McDonald, E. *et al.* (2006) Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler* 12: 620–628.

Polman, C.H., Bertelsmann, F.W., van Loenen, A.C. and Koetseier, J.C. (1994) 4-Aminopyridine in the treatment of patients with multiple sclerosis: long-term efficacy and safety. *Arch Neurol* 51: 292–296.

Rasband, M.N. (2005). Potassium channel organization of myelinated and demyelinated axons. In: Waxman, S.G. (ed) *Multiple Sclerosis as a Neuronal Disease*. Amsterdam: Elsevier Academic Press, pp. 57–67.

Sherratt, R.M., Bostock, H. and Sears, T.A. (1980) Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. *Nature* 283: 570–572.

Snappin, S.M. and Jiang, Q. (2007) Responder analyses and the assessment of a clinically relevant treatment effect. *Trials* 8: 31.

Swingler, R.J. and Compston, D.A. (1992) The morbidity of multiple sclerosis. *Q J Med* 83: 325–337.

Thomsen, R.H. and Wilson, D.F. (1983) Effects of 4-aminopyridine and 3,4-diaminopyridine on transmitter release at the neuromuscular junction. *J Pharmacol Exp Ther* 227: 260–265.

Tremlett, H., Paty D. and Devonshire, V. (2006) Disability progression in multiple sclerosis is slower than previously reported. *Neurology* 66: 172–177.

Uges, D.R.A., Sohn, Y.J., Greijdanus, B., Scat, A.H.J. and Agoston, S. (1982) 4-Aminopyridine kinetics. *Clin Pharmacol Ther* 31: 587–593.

Van Diemen, H.A.M., Polman, C.H., Koetsier, J.C., Van Loenen, A.C., Nauta, J.J.P. and Bertelsmann, F.W. (1993) 4-Aminopyridine in patients with multiple sclerosis: dosage and serum level related to efficacy and safety. *Clin Neuropharmacol* 16: 195–204.

Waxman, S.G. (1982) Membranes, myelin, and the pathophysiology of multiple sclerosis. *N Engl J Med* 306: 1529–1533.

Zwibel, H.L. (2009) Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. *Adv Ther* 26: 1043–1057.