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Objective and subjective measures of dalfampridine efficacy in clinical practice

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Abstract

Background: Multiple sclerosis affects mobility in over 80% of patients. Dalfampridine is the only approved treatment for walking impairment in multiple sclerosis. We assessed dalfampridine utilization in our practice and investigated response using timed 25 foot walk (T25FW) improvement and a patient-reported ambulation inventory.

Methods: Chart review identified patients with multiple sclerosis for whom dalfampridine was prescribed. T25FW data were extracted from medical records. Participants completed a dalfampridine-specific version of the multiple sclerosis walking scale (dMSWS-12) to assess the qualitative impact of dalfampridine on ambulation. We evaluated two responder categories: liberally defined as any improvement in T25FW; and over 20% T25FW improvement.

Results: The dMSWS-12 questionnaire was completed by 39 patients. Eighteen patients (46%) did not show any T25FW improvement. Of the 21 patients (54%) with T25FW improvement, four patients (11%) showed improvement greater than 20%. Analysis of dMSWS-12 scores showed a median score of 40 (range 12–60). Eleven patients (28%) showed no improvement (dMSWS-12 score $\leq$36). In contrast to objective T25FW improvement (54%), 28 patients (72%) reported improvement in walking ability (dMSWS-12 score $\geq$37).

Conclusion: Our results suggest that T25FW alone might not be sufficient for response characterization and that adding patient-reported measures may further elucidate the therapeutic response.

Keywords: Multiple sclerosis, gait, dalfampridine, treatment response, timed 25 foot walk, outcome measurement

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Background

Multiple sclerosis (MS) is a leading cause of non-traumatic disability in young adults[1] and affects mobility in more than 80% of patients. Intact ambulation is one of the most highly ranked quality of life indicators[2] and decreased mobility negatively affects both patients and their caregivers.[3] Befitting the importance of walking for the livelihood and independence of people with MS, many therapeutic strategies have focused on this target. To date, dalfampridine is the only US Food and Drug Administration approved agent for walking impairment in multiple sclerosis. Dalfampridine is a broad spectrum potassium channel blocker, which selectively blocks voltage-sensitive potassium channels. The proposed mechanism of action in MS is the prolongation of action potentials in demyelinated axons and improved conduction.[4]

The efficacy of dalfampridine was demonstrated in two randomized, placebo-controlled phase III trials involving 540 patients with MS. Analyzing the difference in the proportion of responders in treatment and placebo groups, both trials demonstrated a significant improvement in walking speed, derived from the timed 25 foot walk (T25FW), in 35% and 43% of patients in active arms, respectively. Responders, defined as patients with consistent

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improvement of T25FW speed during treatment period, manifested an average speed improvement of 25%.[5,6] The sustainability of dalfampridine response beyond 14 weeks was later demonstrated in long-term, open-label extensions of both studies. Despite the fact that walking speed declined from its peak during the duration of the extension trials, walking speed in the responders remained better than the pre-dalfampridine baseline speed.[7]

In the post-approval setting, dalfampridine efficacy was evaluated in smaller clinical studies, both open label and placebo controlled, showing concordant results.[8,9] However, only very few were performed in a clinical care practice setting utilizing real-world data.[10,11] We hypothesized that real-world dalfampridine efficacy could be better assessed through patient-reported outcomes utilized in clinical practice as compared with objective measures of T25FW speed employed in clinical trials. We assessed dalfampridine utilization in our practice setting and investigated the magnitude of response using both an objective measure (T25FW time improvement) and a patient-reported inventory of ambulatory function.

Methods

This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and all participants provided informed consent.

Participants

Research participants were enrolled at the Corinne Goldsmith Dickinson Center for Multiple Sclerosis at Mount Sinai. Retrospective chart review identified all patients with a confirmed diagnosis of MS[12] for whom dalfampridine was prescribed from March 2010 to August 2013. Only patients with dalfampridine treatment for 3 months or longer were included to ensure adequate drug exposure and to match the length of the clinical trials of this agent. Participants with at least two T25FW time measurements within 2 years pre and post-dalfampridine treatment initiation were included in the analyses.

Timed 25 foot walk

T25FW data were extracted from the electronic medical records. This measure is obtained during each clinical visit and performed as described in the Administration and Scoring Manual published by the National Multiple Sclerosis Society.[13] The average time between T25FW assessments was 3 months. To address possible within-subject fluctuations in T25FW, and establish a more stable pre and post-dalfampridine T25FW values for each patient, the mean T25FW time was calculated using data from at least two separate clinical visits. T25FW measures captured after the initiation of dalfampridine were acquired while patients remained on this treatment.

Modified multiple sclerosis walking scale

All participants in the dalfampridine database were asked to complete a dalfampridine-specific version of the multiple sclerosis walking scale (dMSWS-12) to assess the qualitative impact of dalfampridine on ambulation. The MSWS-12 is a validated and reliable self-report qualitative measure of the impact MS has on ambulation.[14] Building on this platform, our dalfampridine-specific version of the MSWS-12 assessed the patient-reported impression of the effect of dalfampridine on overall ambulation including gait-related features such as walking distance, effort to walk and walking speed. In particular, we asked the patients to rate the change (positive, negative or none) in walking since starting dalfampridine. Congruent with the MSWS-12, the dMSWS-12 also consists of 12 questions with Likert scale-type responses ranging from significantly worsened (1) to significantly improved (5). The minimum score of 12 represents significantly worsened ambulation, a score of 36 represents no improvement and a score of 60 indicates maximally improved ambulation during dalfampridine treatment. Mean impact scores for individual gait-related features were also calculated using previously published methodology.[15]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 22 (Chicago, IL, USA). Basic demographic characteristics, T25FW time analysis and dMSWS-12 data analysis were performed using descriptive statistics. The distribution of data was tested using the Shapiro–Wilk normality test. We evaluated two T25FW responder categories: liberally defined as any improvement in T25FW; and as defined by Schwid et al. as greater than 20% T25FW improvement.[16]

Results

Chart review identified 221 patients for whom dalfampridine treatment was prescribed. Dalfampridine was shipped to 174 patients, 12 of whom never began therapy. Thirty patients discontinued dalfampridine in under 3 months due to lack of subjective benefit. Sixty-seven patients had insufficient visits or documentation during the time window, and six

patients treated with dalfampridine were non-ambulatory at baseline.

The dMSWS-12 questionnaire was distributed to 59 eligible patients. The response rate was 66% and yielded a sample of 39 patients with 26 women (67%). Twenty five patients had a progressive form of MS (64%) and mean disease duration was 12.2 years (range 1.3–28.9 years). The median dalfampridine pre-treatment T25FW was 9.7 seconds (range 3.6–66.3 seconds) (Table 1).

Variable degrees of T25FW improvement were seen (Figure 1). The median dalfampridine post-treatment T25FW time was 6.65 seconds (range 4.15–48.09 seconds). Eighteen patients (46%) did not show any improvement. Of the 21 patients (54%) who showed T25FW improvement, only four patients (11%) showed improvement greater than 20%. The distribution of T25FW values is shown in Figure 2(a).

Regarding the continuation of dalfampridine, our records showed that 34 patients (87%) continued dalfampridine treatment at the time of the last follow-up visit and dMSWS-12 assessment.

Analysis of dMSWS-12 (Table 2) scores demonstrated a median score of 40 (range 12–60). Eleven patients (28%) reported no improvement (dMSWS-12 score $\leq$36). Twenty-eight patients (72%) reported improvement in walking ability (dMSWS-12 score $\geq$37). The distribution of dMSWS-12 scores are shown in Figure 2(b).

To examine further the impact of dalfampridine on individual gait-related components of the dMSWS-12, we calculated mean impact scores for each gait-related characteristic.[15] Dalfampridine showed the highest impact on patient-reported walking ability (impact score 3.85), walking distance (3.54), effort to walk (3.54) and walking speed (3.49).

With regard to additional therapeutic interventions with a potential influence on mobility, 23 patients (59%) had documented continuous physical therapy or independent exercise routine during the pre and post-T25FW assessment period. To evaluate for confounders, we assessed if physical therapy/exercise was associated with dMSWS-12 score or either definition of T25FW responder status, and we found no independent association.

Discussion

This study explored the profile of objective and subjective dalfampridine impact on ambulation in clinical practice, and added to the small number of

Table 1. Baseline demographics.

Study participants	*N*=39
Sex	Female 67% (26) Male 33% (13)
Age	Mean 55.5 years (range 35–69 years)
Disease course	RRMS 36% (14) SPMS 36% (14) PPMS 15% (6) Progressive MS not specified: 13% (5)
Disease duration	Mean 12.1 years (range 1.3–28.9 years)
Pre-treatment T25FW	Median 9.70 seconds (range 3.6–66.30 seconds)
Post-treatment T25FW	Median 6.65 seconds (range 4.15–48.09 seconds)
Current dalfampridine treatment	87% (34 patients)
Concurrent physical therapy/home exercise	59% (23 patients)
dMSWS-12 score	Median 41 (range 12–60)

RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; MS: multiple sclerosis; T25FW: timed 25 foot walk; dMSWS-12: dalfampridine-specific version of the multiple sclerosis walking scale.

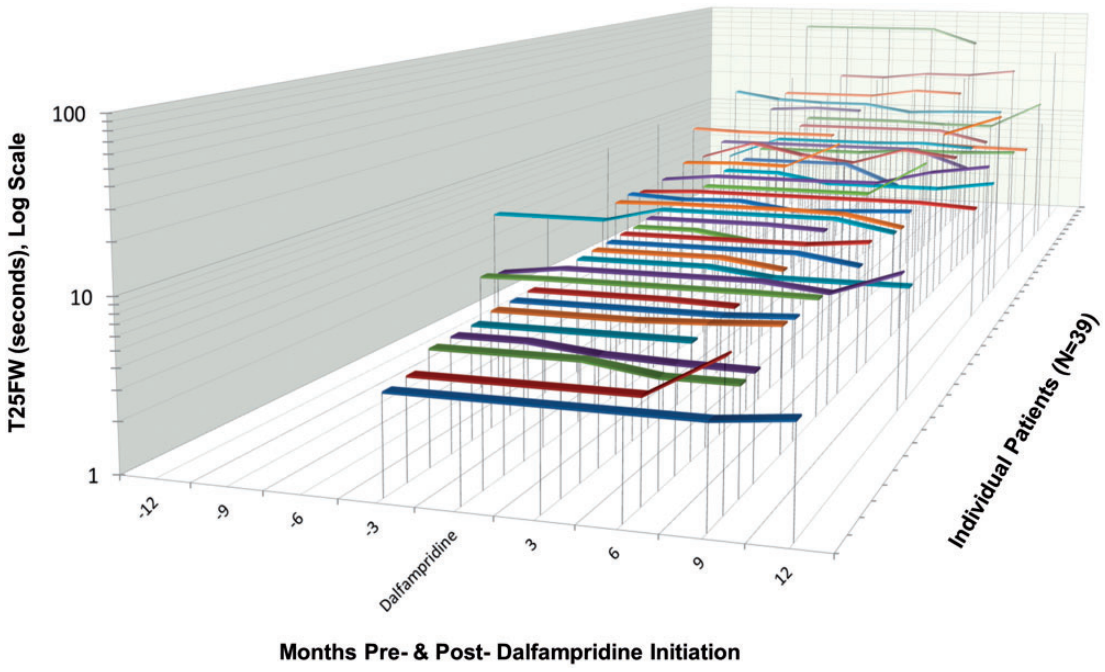

Figure 1. Plot of individual patients' T25FW times pre and post-dalfampridine initiation. Graph depicts inter and intrapersonal variability and walking speed trends over time. Patients are shown in ascending order of pre-treatment walking speed. Note the *Y* axis is the log scale of T25FW times, best to depict a broad range of 3.6–66.3 second pre-dalfampridine walking speeds.

studies evaluating dalfampridine performance in this setting.

Randomized clinical trials are the gold standard for the determination of treatment efficacy but the ideal conditions of a trial differ from routine clinical practice. In contrast, studies performed in a real-world setting offer a more pragmatic approach and the results are often pertinent in clinical decision-making. Unlike the dalfampridine clinical trials, which evaluated treatment response in an immediate time period after treatment start,[5,6] we chose to evaluate the T25FW response in the timeframe reflective of therapeutic expectations in everyday clinical practice (at >3 months of dalfampridine treatment and up to 2 years post-treatment initiation). In addition, the use of the qualitative tool dMSWS-12 supplemented the T25FW data by evaluating not just short distance walking speed observed in the office, but patient-reported walking ability more comprehensively.

Our clinical practice cohort demonstrated a lower rate and magnitude of T25FW improvement than was seen in clinical trials in which 35% and 43% of dalfampridine-treated patients demonstrated an average T25FW speed improvement of 25%. Unlike the pivotal trials, we used T25FW time as an objective measure of treatment response. We chose this approach because T25FW time, rather than speed, is the measure typically used in real-world clinical practice and provides pragmatic and relatable information for clinicians. Our results are concordant with work by German authors who examined dalfampridine responders while assessing the predictive value of motor-evoked potentials for dalfampridine response. Similar to our results, the authors found only 15% of patients with greater than 20% T25FW time improvement. The response rate increased to 45% after liberalization of response criterion to over 10% of T25FW improvement.[11]

Our results also suggest that T25FW when used alone might be an insensitive measurement tool for patient-perceived therapeutic response to dalfampridine. The reliability of T25FW in the MS population has been validated previously but it can be offset by differences in administration and day-to-day performance variability, especially in patients with greater disability.[17,18] Despite the low rate and magnitude of dalfampridine response on the T25FW in our cohort, the majority (87%) of patients continued the treatment and 72% of patients reported benefits not only for walking speed but also for walking distance and effort. It is possible that the use of different assessment tools with higher sensitivity for walking

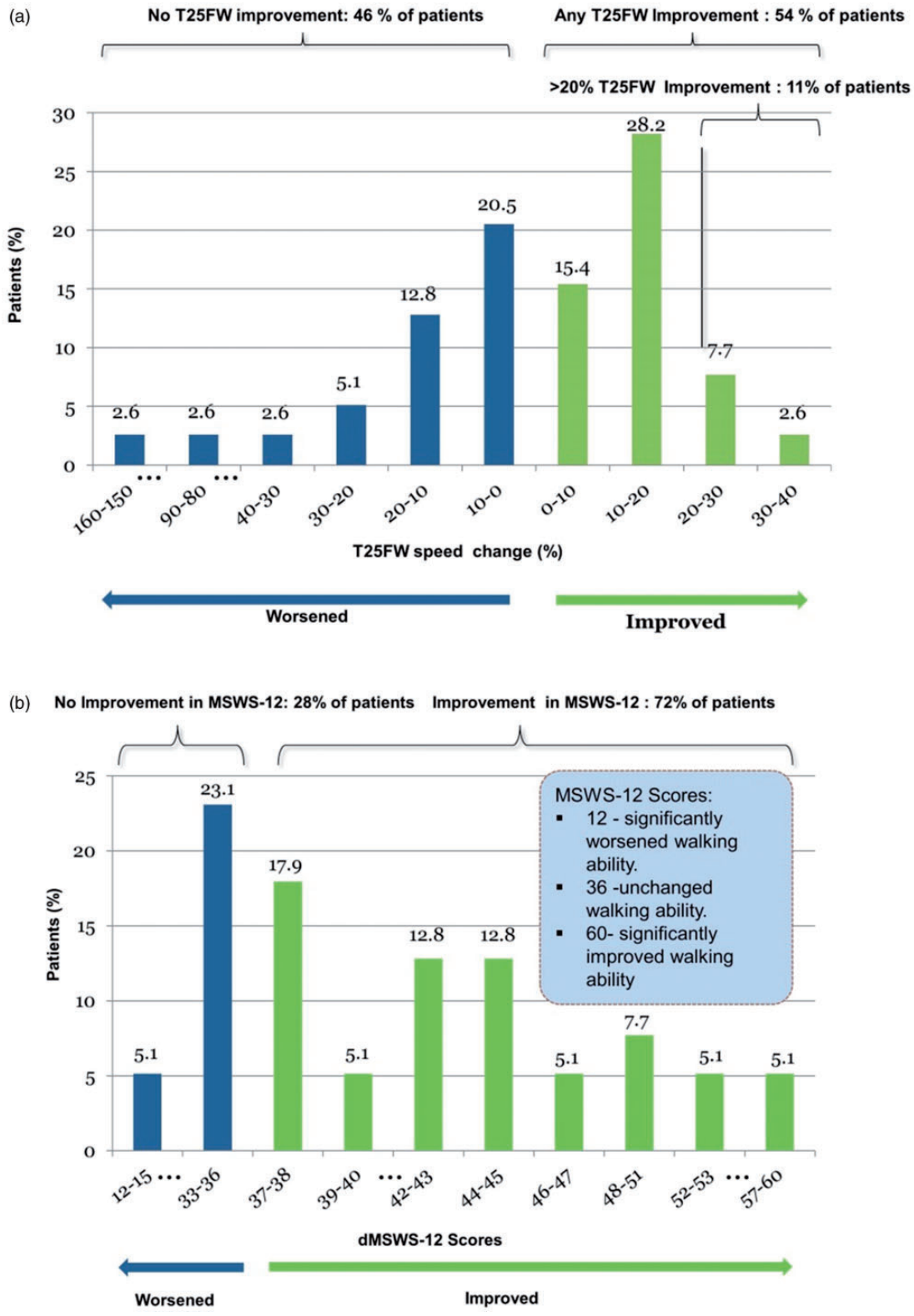

Figure 2. Objective and subjective response to dalfampridine. Graphs (a) and (b) depict the objective and subjective response to dalfampridine. A long tail of gait improvement is seen in the patient-reported measure despite a long tail of gait worsening as assessed by the T25FW, further underscoring the discordance between these two measures. (a) Objective response to dalfampridine (T25FW). (b) Subjective response to dalfampridine (dMSWS-12).

Table 2. Dalfampridine-specific multiple sclerosis walking scale (dMSWS-12).

Since starting Ampyra, has there been:	Worsened significantly	Worsened somewhat	Unchanged	Improved somewhat	Improved significantly
1) A change in your ability to walk?	1	2	3	4	5
2) A change in your ability to run?	1	2	3	4	5
3) A change in your ability to climb up and down stairs?	1	2	3	4	5
4) A change in your ability to stand while doing things?	1	2	3	4	5
5) A change in your balance when standing or walking?	1	2	3	4	5
6) A change in how far you are able to walk?	1	2	3	4	5
7) A change in the effort needed for you to walk?	1	2	3	4	5
8) A change in how necessary it is for you to use support when walking indoors (e.g. holding on to furniture, using a stick, etc.)?	1	2	3	4	5
9) A change in how necessary it is for you to use support when walking outdoors (e.g. using a stick, a frame, etc.)?	1	2	3	4	5
10) A change in your walking speed?	1	2	3	4	5
11) A change in how smoothly you walk?	1	2	3	4	5
12) A change in how necessary it is for you to concentrate on your walking?	1	2	3	4	5

Ampyra: dalfampridine.

distance and endurance can provide better characterization of dalfampridine treatment response and sustainability. Cameron et al.[10] evaluated dalfampridine response in veterans while using the T25FW, 2-minute timed walk test (2MTW) and MSWS-12 as assessment measures. Their results showed that while the effect of dalfampridine on T25FW was lost at 1 year follow-up, the 2MTW and MSWS-12 showed sustained significant improvement.[10] This again is similar to our findings, which showed subjective improvement in ambulation despite the lack of objective T25FW improvement, with a high patient-reported impact of dalfampridine on walking distance and walking endurance. When comparing the distributions of objective and subjective dalfampridine response depicted in Figure 2(a and b), respectively, there is a clear difference in the skew of these graphs. A long tail of gait improvement is seen in the patient-reported measure despite a long tail of gait worsening as assessed by the T25FW, further underscoring the discordance between these two measures. These results suggest that T25FW alone might not be sufficient for response characterization and that adding qualitative and other objective measures sensitive to other aspects of ambulation may further elucidate the therapeutic response to dalfampridine.

Our project has several limitations. This was a single center retrospective project with a modest sample size. The T25FW data were extracted from the medical records and a proportion of insufficient visits or documentation limited our sample. Dalfampridine response in patients who discontinued the drug in less than 3 months was not captured as these patients did not have adequate exposure to the treatment. Excluding those patients does not clearly bias our results in one direction, however, as this group may have comprised both T25FW responders and non-responders. Unlike in clinical trials, we used a longer timeframe and variable time points for T25FW acquisition. However, as we intended to evaluate dalfampridine efficacy in clinical practice, our parameters mirror standard of care more closely. Finally, the dMSWS-12, our modification of the MSWS-12 to identify the effect of dalfampridine

as a retrospective patient-reported outcome, is an assessment tool that has not been independently validated which poses a limitation on our project. The MSWS-12 was, however, modified only insofar as we are querying patient-reported gait experience while on this agent. The content of the questions and their answers and scoring have not been altered from the validated MSWS-12. This allowed us to focus on dalfampridine impact on ambulation, whereas the unmodified MSWS-12 itself would not sufficiently instruct patients on describing the relationship between dalfampridine and gait function that we aimed to evaluate. In addition, the single time point administration of dMSWS-12 could lead to recall bias. This is an inherent disadvantage for any retrospective patient-reported measure, and the results should be interpreted with caution and will require further replication in a prospective manner.

In conclusion, this project characterized the dalfampridine response profile in clinical practice, and our results suggest that the T25FW when used alone is an insensitive measure of dalfampridine response and supports the use of supplementary assessment tools such as dMSWS-12, further to uncover additional therapeutic benefits of this agent on ambulatory function.

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Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S Klineova has received compensation for advisory board work with Teva, Genentech and Biogen Idec and has given non-promotional lectures with Biogen Idec. R Farber has received compensation for advisory board work with Teva. FD Lublin has received compensation for consulting and advisory board work with Bayer HealthCare Pharmaceuticals, Biogen Idec, EMD Serono, Inc., Novartis, Teva Neuroscience, Actelion, Sanofi/Genzyme, Acorda, Questcor/Malinckrodt, Roche/Genentech, Celgene, MedImmune, Osmotica, Xenoport, Receptos, Forward Pharma, BBB Technologies, Akros, TG Therapeutics and Abbvie, and sources of funding for research from Biogen Idec, Novartis Pharmaceuticals Corp, Teva Neuroscience, Inc., Genzyme, Sanofi, Celgene, Transparency Life Sciences, NIH and NMSS. S Krieger has received compensation for consulting and advisory board work with Acorda Therapeutics, Bayer HealthCare, Biogen Idec, EMD Serono, Genentech, Genzyme, Mallinckrodt, Novartis, Teva and TG Therapeutics, and has given non-promotional lectures with Biogen Idec. C Farrell completed this work while working at Mount Sinai and now works for Novartis. J Friedman has nothing to disclose.

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