Identifying priority outcomes that influence selection of disease-modifying therapies in MS

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Abstract

Background

Persons with multiple sclerosis (MS) may now choose from a broad array of approved disease-modifying treatments (DMTs). The priority that patients and practitioners assign to specific clinical outcomes is likely to influence the MS DMT selection process.

Methods

We invited 9,126 participants in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry and 18 members of the American Academy of Neurology MS DMT guideline development panel to complete a brief survey prioritizing outcomes of importance to MS DMT selection. The frequency of outcomes ranked as first, second, or third priority by respondents were compared across groups.

Results

A total of 2,056 of 9,126 (23.6%) NARCOMS participants and all 18 members of the MS DMT guideline development panel (100%) completed the survey. Reduced disability progression was identified as a priority by a majority of respondents in both groups. Guideline panelists tended to be more likely than persons with MS to prioritize relapse rate reduction ($p = 0.055$). Respondents from both groups commonly cited the "selection of therapies most likely to lead to improvements in quality of life measures, MS symptoms, and preservation of cognition" as top priorities in DMT selection; however, these priority outcomes were reported in fewer than 20% of clinical trials used to inform MS DMT guideline development.

Conclusion

Specific outcomes were defined by similar proportions of persons with MS and guideline panelists as priority outcomes influencing MS DMT selection. Several of these priority outcomes were not routinely reported in clinical trials, identifying areas for future evidence development.

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Shared decision-making (SDM) requires clinicians and patients to weight the evidence for and against specific treatments to jointly arrive at a decision that best integrates expressed values, preferences, and circumstances. This process is increasingly recognized as key to the delivery of high-quality health care,[1] of importance in regulatory decision-making[2] and reimbursement,[3] and integral to navigating uncertainty in clinical decision-making.[4] The benefits of SDM are most evident when multiple efficacious treatments options are available, where the best option is the one that aligns with the patient's individual values and goals of care.[4] For this reason, multiple sclerosis (MS) serves as an exemplar disease state when considering the potential challenges and benefits of SDM.

Identifying outcomes of importance to patients and practitioners is essential to promoting SDM, as these outcomes are the most likely to influence the decision-making process. Yet few, if any, studies have systematically considered patient- and practitioner-specified priority outcomes in MS. Those that have tended to independently evaluate how patients with MS[5–9] and their physicians[10,11] weight factors in therapeutic decision-making, rather than comparing responses. These studies emphasize the relative importance that patients' perceptions exert on the DMT selection process, and the challenges faced by practitioners who must translate limited clinical trial data to address outcomes relevant to clinical decision-making. Ultimately, the patient- and practitioner-defined priority outcomes that guide MS DMT selection remain unclear.

In 2015, the American Academy of Neurology (AAN) approved the development of an evidence-based guideline regarding MS DMT prescribing.[12] In determining key outcomes for inclusion in the guideline, the guideline panel leadership sought to determine how persons with MS and guideline panelists prioritized outcomes potentially affected by DMTs. Priority rankings were compared across groups in the interest of defining outcomes of greatest importance to stakeholders. The frequency with which these outcomes were measured and reported in clinical trials was also evaluated to identify clinically relevant gaps in outcome evaluation and reporting.

Methods

Participants in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry and MS DMT guideline panelists were asked to prioritize outcomes important to DMT selection. The NARCOMS Registry is a self-report registry for persons with MS. Participants report sociodemographic and clinical information relevant to their disease at enrollment and twice annually thereafter. Prior studies have demonstrated the validity of self-reported diagnoses of MS, and outcome measures used by the registry.[13–15] In 2015, the AAN approved the development of a guideline regarding MS DMT prescribing.[12] As per the 2011 AAN guideline manual,[16] the guideline development panel consisted of content experts; members of the AAN Guideline Development, Dissemination,

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and Implementation subcommittee; patient representatives; and an evidence-based medicine methodologist, who was not directly involved in recommendation development. Conflicts of interest were assessed according to AAN policy[16]; the majority of panel members were considered nonconflicted.

Standard protocol approvals, registrations, and patient consents

All NARCOMS participants agree that their de-identified information may be used for research purposes. NARCOMS enrollment and update surveys are reviewed and approved by the University of Alabama at Birmingham institutional review board. In addition, an existing institutional review board–approved protocol allows anonymous polls of NARCOMS participants through the NARCOMS website. The Washington University School of Medicine Human Research Protection Office reviewed the overall project and determined that publication of anonymous survey data and aggregate participant information was not subject to institutional review board oversight.

Survey design and participant selection

Outcomes included in the survey were selected following literature review. Five outcomes were consistently reported in high-quality (Class I or II) studies of DMTs selected via the AAN MS DMT guideline review process[12]: relapse rate, disability progression, adverse events leading to discontinuation of treatment due to adverse events, neuroimaging changes, and serious adverse events (threatening life or organ). Three additional outcomes were identified through literature review targeting studies reporting on patient preferences for MS DMT selection,[5,9,17] including preservation of cognition, improvement in MS symptoms (e.g., fatigue, pain, urinary incontinence), and improvement in quality of life. Survey questions (table) were developed in consultation with MS DMT guideline leadership and NARCOMS steering committee members. All respondents were asked to rank outcomes "in order of importance to you when choosing an MS treatment."

All NARCOMS participants with an email address who completed NARCOMS enrollment or a semiannual survey in the prior 2 years were invited to complete this anonymous online survey via an electronic link provided by email. The poll was open from January 6–11, 2016, reflecting the time constraints of the project. Summary information was available for invited participants concerning demographic (age, education, sex) and clinical characteristics (duration of symptomatic disease, disease

Table Survey questions distributed to persons with multiple sclerosis (MS) from the North American Research Committee on Multiple Sclerosis registry and American Academy of Neurology MS disease-modifying treatment guideline panelists

Request to survey respondents
Please order the following statements in order of importance to you when choosing an MS treatment (number 1 = most important, number 8 = least important).
A. Ability of treatment to prevent relapses due to MS
B. Ability of treatment to decrease long-term disability due to MS
C. Ability of treatment to prevent changes in memory and thinking due to MS
D. Ability of treatment to prevent brain changes seen on MRI due to MS
E. Ability of treatment to improve overall quality of life
F. Ability of treatment to improve symptoms of MS (e.g., fatigue, pain, numbness)
G. Safety of the treatment (e.g., risk of death associated with treatment)
H. Side effects of the treatment (e.g., fevers, chills, muscle aches associated with taking the medicine)

activity). Due to the anonymous nature of the survey, data were not available from respondents at an individual or group level (i.e., respondents vs nonrespondents). A separate link to the survey was provided to MS DMT guideline panelists, with responses collected from December 18, 2015, to January 11, 2016. Respondent and panel responses were fully anonymized, and consent assumed by survey completion.

Statistical analyses

Priority outcomes were defined as those rated as first, second, or third priority by survey respondents, and comprised the main outcome measure. This approach was believed to most reflect a clinical approach to decision-making, accepting that patients and practitioners often balance multiple priorities when discussing and selecting drug therapies, rather than basing decision-making on one priority. Priority outcomes were summarized by respondent groups (NARCOMS participants, guideline panelists) and response rates were compared across groups using the 2-tailed Fisher exact test (version 24.0, SPSS Statistics; IBM, Armonk, NY), unless otherwise specified. Statistical significance was defined as $p < 0.05$. Aggregate information from NARCOMS participants was collected in JMP Pro 12 (SAS Institute, Cary, NC).

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on request.

Results

The survey invitation was distributed to 9,126 NARCOMS participants, of whom 5,487 (65.5%) had completed the fall 2015 update; the remainder had completed at least 1 survey in the prior 2 years. Nearly 24% (2,156) of invited NARCOMS participants and all 18 members of the MS DMT guideline development panel (100%) responded to the survey request. At the time of survey distribution, invited NARCOMS participants had a mean (SD) age of 58.2 (10.2) years, with age at MS symptom onset of 31.2 (10.2) years, and disease duration of 27.0 (11.9) years. Most invited participants were Caucasian (92.3%) women (80.5%) with an advanced educational background: 68.1% completed post-secondary education. A total of 4,650 invited participants provided information concerning income, with 58.2% reporting annual income greater than $50,000. Most participants attained MS care via a neurologist at a nonacademic center (54.2%), or within a specialized MS center (33.5%); 87.4% reported having used a DMT, with 67.3% taking a DMT in fall 2015. Seven guideline panelists were women (7/18, 39%). Panelists included 3 persons living with MS (cumulative symptoms, 75.3 years; cumulative DMT use, 44.3 years); 8 experts in clinical practice and research in MS (median [range] clinical/research experience, 18.5 [10–50] years); and 9 AAN Guideline Development, Dissemination, and Implementation Subcommittee members (median [range] guideline development experience, 9.0 [1.0–19.5] years). Two panelists served as both content experts and subcommittee members.

Specific outcomes were identified as priorities in therapeutic decision-making by similar proportions of persons with MS and guideline panelists (figure 1). Reduced disability progression was identified as a priority outcome by the majority of persons with MS and guideline panelists. More guideline panelists prioritized relapse rate reduction when selecting an MS DMT ($p = 0.055$, Fisher exact test; $p = 0.035$, Pearson χ^2). No significant differences were observed between respondents concerning other outcomes. Of interest, 46.9% of persons with MS and 33.3% of guideline panelists identified the selection of therapies most likely to lead to improvements in quality of life, MS symptoms, or preservation of cognition, as priority outcomes in DMT selection ($p = 0.34$). Reporting concerning these outcome measures was limited (figure 2), with data concerning one or more of these measures included in only 11/58 (19%) of clinical trials reviewed.

Discussion

Our findings suggest that treatment priorities are reasonably aligned between persons with MS enrolled in a large self-

> Clinicians should query patients' goals of care, including views on modification of disability and symptomatic care, and use this information to guide treatment strategies.

Figure 1 Outcomes of greatest importance to selection of a multiple sclerosis (MS) disease-modifying therapy (DMT), as defined by persons with MS and panelists engaged in MS DMT guideline development
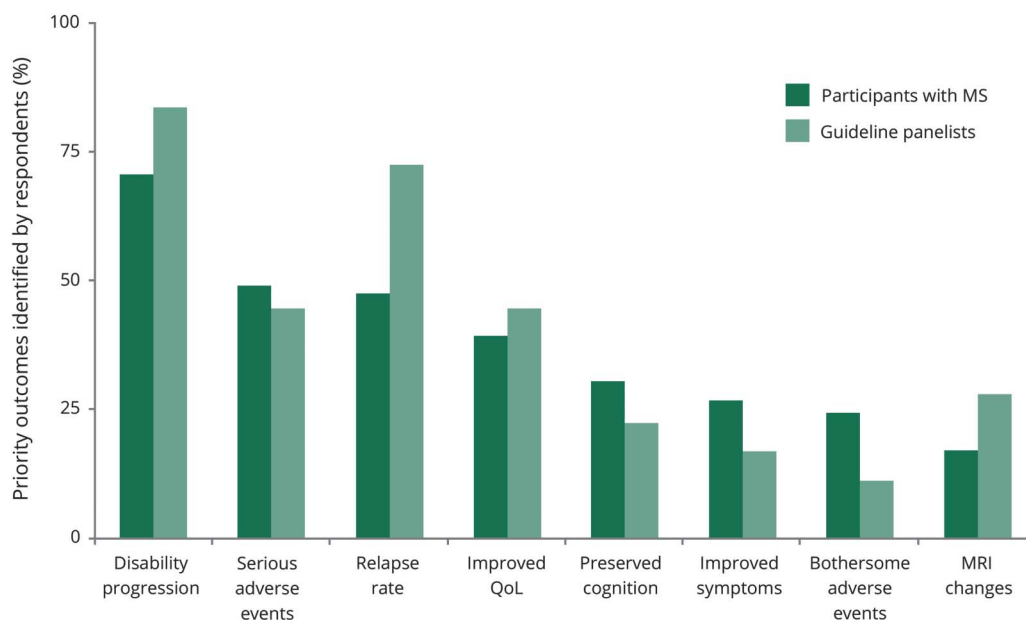

The proportion of persons with MS (n = 2,156) and guideline panelists (n = 18) designating an outcome as first-, second-, or third-highest priority (priority outcomes) when selecting an MS DMT is depicted (rank-ordered from most to least common responses). QoL = quality of life. Published with permission from Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:777–788. doi: 10.1212/WNL.0000000000005347.

report registry and members of a guideline panel engaged in developing recommendations concerning MS DMT prescribing. Although panelists tended to be more likely than persons with MS to prioritize relapse rate reduction, 47.2% of persons with MS listed this measure within their top 3 priorities, alongside disability progression and the potential for medications to result in serious adverse events. These outcome measures were commonly reported within Class I and Class II studies evaluating DMT efficacy, reflecting regulatory requirements to establish efficacy and safety prior to drug approval (North America: Food & Drug Association, United States[18]; Canada: Health Canada[19]; Europe: European Medicines Agency, United Kingdom[20]). Interestingly, nearly one-half of persons with MS and one-third of guideline panelists identified maintenance of quality of life, minimization of MS symptoms, or preservation of cognition as priority outcomes when selecting DMTs. With notable exceptions,[21–23] data concerning these measures were not consistently reported in reviewed clinical trials. This underreporting likely reflects challenges inherent in the measurement of subjective outcomes (i.e., quality of life, MS symptoms) and detection of cognitive changes, which may require repeated monitoring beyond typical clinical trial timelines. Without evidence detailing the effect of MS DMTs on these priority outcomes, guideline developers cannot make evidence-based therapeutic recommendations that appropriately integrate these concerns. Likewise, practitioners cannot engage patients in discussions concerning drug efficacy and safety measures that incorporate evidence concerning patient-specified priorities, compromising SDM. Together these findings highlight the importance of directly measuring patient- and practitioner-specified priority outcomes, and the need to develop tools permitting assessment of outcomes that can be incorporated in future clinical trials of MS DMTs.

Aligning patient preferences with the evidence is not a trivial task. Discussing available evidence in the context of patients' values and preferences is the foundation of SDM, with implications for improving patient understanding, satisfaction, and trust in practitioners, which may in turn promote adherence with medical therapies.[24] While there is currently limited evidence that decision aids (structured instruments to support SDM) affect adherence in MS,[25] evidence shows that decision aids generally improve knowledge regarding options, reduce patients' decisional conflict related to feeling uninformed or uncertain of their own preferences, encourage patients to take a more active role in decision-making, and improve the accuracy of patients' perceptions of the risks associated with a specific therapy.[26] SDM models also suggest that the benefits of SDM may extend beyond patient care, with downstream effects on resource utilization, workforce modification, and the cost of delivering high-quality health care, factors that may convey positive benefits for practitioners and health systems.[27] With this in mind, clinicians should query patients' goals of care, including views on modification of disability and symptomatic care, and use this information to guide treatment strategies.

Figure 2 Primary and secondary outcomes reported in multiple sclerosis (MS) disease-modifying therapy (DMT) clinical trials
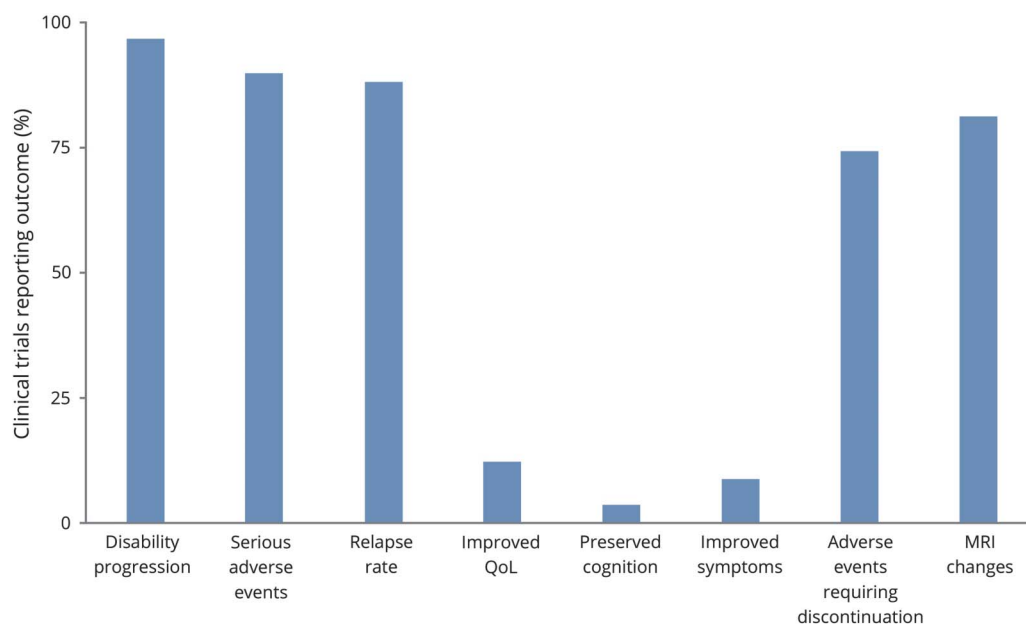
The frequency of reporting of primary and secondary outcome measures in 58 MS DMT clinical trials used to inform MS DMT guideline development are depicted (ordered as in Figure 1). QoL = quality of life. Published with permission Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90;777–788. doi: 10.1212/WNL.0000000000005347.

Evidence from MS DMT studies may then be framed in this context, including results pertaining to disability progression and lack of evidence regarding other key outcomes. In the absence of good quality evidence concerning specific patient-prioritized outcomes, practitioners and patients may mitigate uncertainty by developing strategies that permit monitoring of priority outcomes while on treatment, with the potential to use this information to inform future treatment decisions.

Beyond implications for clinical trial design and individual SDM, our findings provide direct evidence that patient treatment priorities may be assessed efficiently and cost-effectively through the use of existing databases and patient registries (e.g., NARCOMS). The patient survey was accessible for 6 days following distribution of the invitation—a prespecified timeline necessary to ensure timely progression of the guideline development process. Despite the limited timeframe, over 2,000 persons with MS responded. In light of the protracted response period, the response rate (23.6%) is encouraging, suggesting that persons with MS are interested and willing to contribute information concerning priority outcomes. Surveying affected patients is one important consultation strategy in guideline development,[28] and may be a feasible means of identifying and prioritizing outcome measures, with subsequent applications in clinical trial design. Such findings may also affect development of evidence-based treatment recommendations. In the context of the AAN MS DMT guideline, this survey prompted the panel to include quality of life, MS symptoms, and

preservation of cognition in the questions addressed by the guideline.[12] Although recommendations regarding these outcomes were tempered by the paucity of available clinical trial evidence, inclusion of these questions calls attention to evidence gaps that may be addressed through future studies. Incorporating patient preferences in drug development is key to informing development of clinical practice guidelines, and advancing SDM in the clinic environment.

We acknowledge several limitations pertinent to interpretation of the study results. Outcomes of interest were selected following a review of relevant literature, and respondents were asked to rank-order these prespecified outcomes. Accordingly, potentially important outcomes may have been overlooked. In addition, surveyed persons with MS were drawn from a single self-report registry (NARCOMS), and guideline panelists from a selected group of individuals (including patient advocates, clinicians, and content experts). As a result, our results do not likely reflect the breadth of patients' and practitioners' perspectives that would be captured by a population-based survey soliciting responses from greater numbers of persons with MS and practitioners. Similarly, the use of an online-only survey, completed over a limited time period, may have biased respondent selection, favoring responses from motivated and technologically adept participants who may possess disease characteristics that distinguish them from nonrespondents. This potential selection bias may limit generalizability of results to clinical populations. However, as clinical trial populations are

frequently composed of highly motivated individuals, we suggest that this bias is less likely to compromise application of findings to the design and conduct of future clinical trials. Finally, our study design did not allow respondent-specific demographic or disease characteristics to be collected. Future studies may obtain this information through direct discussion with patients and practitioners, allowing the influence of patient- and disease-specific factors on the full spectrum of priority outcomes to be determined.

Conclusions

Reduced disability progression, perceived risk of serious adverse events, and effect on relapse rate were rated as top priorities when choosing a MS DMT by persons with MS and guideline panelists. Several additional priority outcomes were not routinely measured or reported in clinical trials, limiting the ability of patients and practitioners to weight these factors in informed decision-making concerning MS DMT. High-quality evidence concerning patient- and practitioner-prioritized outcomes is critical to advancing the development of relevant, informed, and effective treatment guidelines, and to facilitating effective SDM in the clinic environment. The results of this study may be used to inform the design and execution of future MS DMT clinical trials, prioritizing measurement and reporting of outcomes of greatest importance to the patients who use MS DMTs and the practitioners who prescribe them.

Author contributions

G.S. Day participated in study design and conduct, acquisition and interpretation of data, statistical analysis, and drafting, revision, and finalization of the manuscript. A. Rae-Grant participated in study design and conduct and drafting, revision, and finalization of the manuscript. M.J. Armstrong participated in study design and conduct and finalization of the manuscript. T.M. Pringsheim participated in study design and conduct and finalization of the manuscript. S.S. Cofield participated in acquisition and interpretation of data and revision and finalization of the manuscript. R.A. Marrie participated in study design and conduct, acquisition and interpretation of data, and revision and finalization of the manuscript.

Disclosure

G.S. Day is involved in clinical trials of antiamyloid agents (sponsored by Eli Lilly); serves as an ad hoc editor for *DynaMed*; receives research support from Avid Pharmaceuticals, Barnes Jewish Hospital Foundation, American Brain Foundation (Clinical Research Training Fellowship), and Eugene M. Johnson, Jr. (Weston Brain Institute Postdoctoral Fellowship); and holds stocks in ANI Pharmaceuticals. A. Rae-Grant is involved in a clinical trial of biotin for multiple sclerosis with MedDay (no personal remuneration); is a member of the level of evidence editorial board for *Neurology*®; receives publishing royalties for *Handbook of Multiple Sclerosis* (Springer Healthcare, 2010), *Comprehensive Review of Clinical Neurology* (Wolters Kluwer, 2012), *5-Minute Consult in Neurology* (Wolters Kluwer, 2012), *Comprehensive Review of Clinical Neurology, 2nd edition* (LWW, 2016), *Ultimate Review of Neurology* (DEMOS, 2016), and *Multiple Sclerosis and Related Disorders* (DEMOS, 2014); serves as an ad hoc editor for *DynaMed*; and receives research support from NIH (CO-PI 4% effort FMRI as an imaging biomarker for preclinical Alzheimer's disease). M.J. Armstrong serves as an evidence-based medicine methodology consultant for the American Academy of Neurology guideline program; is a member of the level of evidence editorial board for *Neurology* and related publications; holds a career development award from the Agency for Healthcare Research and Quality (AHRQ K08HS24159) investigating the effect of engaging patients in evidence-based guideline development; receives publishing royalties for *Parkinson's Disease: Improving Patient Care* (Oxford University Press, 2014); has received writing/speaking honoraria from Medscape CME; and receives research support from TBI Endpoints Development Initiative. T.M. Pringsheim serves on editorial boards of *Neurology: Clinical Practice* and *Canadian Journal of Psychiatry*; and receives research support from Canadian Institutes of Health Research, Sick Kids Foundation, and Alberta Mental Health Strategic Clinical Network. S.S. Cofield serves on scientific advisory boards for MedImmune, Orthotech Biotech, and US Department of Defense; serves as a consultant for Oxford University Press and American Shoulder and Elbow Society; and receives research support from Pfizer, American College of Rheumatology, and Consortium of MS Centers. R.A. Marrie serves on the editorial boards of *Neurology* and *Multiple Sclerosis Journal*; has received research support from Canadian Institutes of Health Research, Research Manitoba, Waugh Family Chair in Multiple Sclerosis, Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Multiple Sclerosis Scientific Foundation, Consortium of Multiple Sclerosis Centers, Rx & D Health Research Foundation, and Crohn's and Colitis Canada; and has conducted clinical trials funded by Sanofi-Aventis. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

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