**LETTERS**

### Consensus Statements from a Panel of U.S. Managed Care Pharmacists and Physicians for Management of Multiple Sclerosis Agents

Miller et al. ("Approaches to the Management of Agents Used for the Treatment of Multiple Sclerosis: Consensus Statements from a Panel of U.S. Managed Care Pharmacists and Physicians") published in the January/February 2012 issue of *JMCP* present the results of a modified Delphi panel regarding formulary management of disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS). The authors have noted that none of the participants had clinical practice experience treating MS patients, yet emphasized that all participants were considered experts in managed care. We commend the authors in consolidating and communicating prevailing opinions among U.S. payers in the management of access to MS therapies, however the explicit absence of MS expert clinical input renders the conclusions less robust.

Given the complexity and heterogeneity of MS, we question the clinical validity and appropriateness of the panel’s opinion, particularly when the consequences of such decisions may have a significant effect on the health of plan members. To that end we wish to call attention to several concerns regarding the panel’s process and methods related to interpretation of the existing literature, which appears to be biased against fingolimod.

- Funding for the project by Biogen Idec, a manufacturer of 2 of the products under consideration, is adequately described, but there is no description of the manufacturer’s role in reviewing the questions, survey data, or attendance at the live meeting. We would appreciate fuller transparency in this matter to resolve any issues relating to conflict of interest.

- A “platform therapy” is any DMT “that can be initiated and continued on a long-term basis.” Fingolimod was not considered a “platform therapy” in the research despite published 1- and 2-year pivotal studies, demonstrating the safety and efficacy in extended use, supplemented by published 3-year follow-up data. Although long-term real-world data do not exist on fingolimod, as with any newly approved agent, all of these publications support inclusion of fingolimod as a platform therapy and were available at the time the project was initiated. It would be worthwhile to clarify the definition used by the authors for inclusion under “platform therapy.”

- The panel reached consensus that “if efficacy and safety are judged comparable among agents, then cost and contracting should be considered.” Fingolimod demonstrated superior efficacy to weekly intramuscular interleukin beta-1a in a randomized, double blind, double dummy, controlled clinical trial, reducing annualized relapse rates by 38%-52% versus the active comparator. Yet because it was inappropriately excluded from the platform therapy category, it was subsequently not considered as an alternative to low-dose/low-frequency interferons. Hence, by default or design fingolimod was relegated to a “comparable” efficacy category without direct comparison of the available data.

- Questions regarding combination therapy with interferons or glatiramer acetate were applied only to fingolimod despite the absence of any clinical data of fingolimod use in combination or FDA indication, suggesting that this was evidence-based or even a consideration among clinicians. This inherently creates a bias against fingolimod by positioning it as the only DMT with the “potential” to be used in combination with other platform therapies in the absence of any data supporting this conjecture.

- Cladribine, an oral immunosuppressant with demonstrated efficacy in MS, was not discussed nor mentioned despite the fact that the manufacturer’s submission was still under review by the FDA at the time of this exercise. Subsequently, cladribine was rejected by the FDA in March 2011 for the MS indication and received negative reviews in Europe; and hence might not have been included in the publication. However, clarity should be provided whether it was considered in the panel discussion.

- The paper defines consensus as a mean score of 3.3 on a 4.0 point Likert scale or 100% of panelists either “strongly agree” or “agree,” but the literature does not define consensus in a Delphi process. Moreover, one of the recommendations of the panel is that “prior authorizations should be utilized by health plans to manage patient access to fingolimod” even though the panel failed to reach consensus (3.1/4.0) based on the pre-specified definition. More precise definitions of consensus are needed to interpret the panel’s findings.

In summary, we agree with the authors’ conclusions that “payers are challenged to make management decisions in the MS category without clinical consensus” but disagree that, in the absence of treatment guidelines, such decisions can be responsibly made without the counsel of clinical experts in the management of MS. We believe that this panel would have been more informative if conducted with such input in a more balanced manner. Furthermore questions around the panel’s processes and data interpretation raise questions around bias and conflict of interest which require explanation.

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**DISCLOSURES**
Kern, Grinspan, and Kim are employed by Novartis Pharmaceuticals Corporation, manufacturer of fingolimod.

**REFERENCES**


To the Editor:
I read with interest the recent article in JMCP by Miller et al., “Approaches to the Management of Agents Used for the Treatment of Multiple Sclerosis: Consensus Statements from a Panel of U.S. Managed Care Pharmacist and Physicians.” As an experienced neurologist and multiple sclerosis (MS) specialist, I believe that consensus commentary can be very relevant in these increasingly complex times in MS therapeutics, especially in view of very limited evidence-based treatment guidelines. Whereas I feel that most of the consensus comments (Table 3) are in keeping with modern MS practices, I have a concern pertaining to consensus comment 21 (regarding dalfampridine use).

Consider the following, not-infrequent clinical scenario: a patient with either secondary-progressive MS without relapses or primary-progressive MS who, because of his or her nonrelapsing status, is not or is no longer taking one of the U.S. Food and Drug Administration (FDA)-approved disease-modifying agents (DMAs; none have clearly demonstrated benefits in nonrelapsing forms of MS). This individual may very likely demonstrate significant ambulation limitations due to MS, and therefore could be a good candidate for symptomatic ambulation improvement with dalfampridine—quite independent of whether or not that individual is concurrently receiving an approved DMA. Taken at face value, consensus statement 21 would disapprove of such an individual receiving possible symptomatic improvement with dalfampridine.

Although dalfampridine is typically prescribed to a person with MS who happens also to be taking a DMA, the 2 are independent treatments with independent benefits that are not related to or dependent on each other. Importantly, at the point where a person with nonrelapsing MS may no longer be an optimal candidate for an approved DMA treatment, that same person may still be an optimal candidate for FDA-approved use of dalfampridine.2,3,4

Given the limitations inherent in any questionnaire process, the respondents to the consensus survey may not have considered the latter, less frequent, but nonetheless very important scenario. Nonetheless, consensus statement 21 makes a sweeping recommendation that, for reasons outlined above, is not universally accurate or necessarily appropriate. Exercising consensus statement 21 could, perhaps inadvertently and unintentionally, deprive a significant number of patients with MS an important, often beneficial, and FDA-approved symptomatic treatment option.

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The author reports receiving speaker or consulting honoraria from Acorda, Biogen Idec, Genzyme, Novartis, Sanofi-Aventis, and Teva.

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The Authors Respond:
We thank Kern et al. and Phillips for their constructive critiques of our article. While they have highlighted the inherent limitations of developing consensus statements by payers for payers, we feel that they have slightly, but importantly, misinterpreted the purpose of our work. As stated in our article, the multiple sclerosis (MS) consensus statements were intended “to serve as a practical reference tool for health plans, to be used in conjunction with clinical evidence, when designing benefits and coverage policies for MS agents.” We appreciate the not-infrequent clinical scenario described by Phillips and the feedback concerning the limitations of consensus statement 21. We agree that a patient with either secondary-progressive MS without relapses or primary-progressive MS who is no longer taking 1 of the disease-modifying agents needs a symptomatic treatment option. However, the consensus statements published in our article were never meant to be used by managed care decision makers in the absence of clinical judgment, and nowhere in our article is it implied that they were. In addition, the claim by Kern et al. that our article implies that management decisions in the MS category should be made “without the counsel of clinical experts” is not valid. In fact, we noted in the Limitations section of the article that “practicing neurologists and the specialists who treat patients with MS may have different opinions than pharmacy and medical directors of health plans.”

While we agree and acknowledge in our article that the consensus statements do not incorporate MS expert clinical input, we disagree that this fact renders the conclusions less robust. Additionally, we wish to further inform readers about the work that is in progress to bridge the gap between clinical and payer resources in MS. As stated in the last sentence of our article: “Future opportunity exists to seek commentary on this reference from neurology experts and to update the statements as new agents enter the market.” Specifically, the organization.

that sponsored our work plans to continue to convene this group of managed care decision makers, as well as a provider panel of clinical experts in the treatment of MS, as new agents used for the treatment of MS enter the market and as new data become available on the existing agents used for the treatment of MS.

The letter by Kern et al. raised several concerns regarding potential biases against fingolimod that we would like to address:

1. Kern et al. questioned the exclusion of fingolimod from the category of platform therapies in our study. The decision to incorporate fingolimod as a stand-alone topic, rather than aggregate it with existing platform therapies, was based on the timing of the availability of the fingolimod prescribing information relative to the initiation of our study. The fingolimod prescribing information was not yet available at the time survey 1 was developed, and fingolimod had only been available for 3 months at the time of the live panel. Therefore, the panelists chose to address fingolimod singularly, rather than grouping it with agents that have been in use for several years. Payers also had questions regarding the safety of fingolimod and the monitoring requirements at the time of this study. In light of the potential safety issues related to fingolimod that have been recently reported to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, their concerns did not prove to be unfounded.

2. Kern et al. highlighted a clinical trial by Cohen et al. that demonstrated superior efficacy for fingolimod versus the active comparator of intramuscular interferon beta-1a. Our study was not intended to be a review of clinical trial data or a comparative effectiveness study. Therefore, we are perplexed by the statements by Kern et al. that fingolimod was not considered as an alternative to low-dose/low-frequency interferons and that “fingolimod was relegated to a ‘comparable’ efficacy category without direct comparison of the available data.” Our article made no attempt to directly compare the safety and efficacy of any of the agents used for the treatment of MS.

3. Kern et al. questioned the following statement: “Access to combination therapy with fingolimod and an injectable disease-modifying therapy should be restricted until safety and efficacy data are available.” We agree that there are no data supporting or advocating for the use of fingolimod in combination therapy with an injectable disease-modifying therapy. The consensus statement was included as a result of the following panelist concerns: (a) the potential for some prescribers to attempt to use fingolimod in combination despite the lack of data since it is the first oral agent approved for MS; and (b) the safety profile of fingolimod. The panelists did not have these concerns for other agents and, therefore, did not develop similar statements for other agents.

4. Kern et al. comment that we published a consensus statement for which consensus was not reached. However, this comment is erroneous because Kern et al. apparently mistakenly transposed the score from statement 4.1 in Table 2 (which refers to step therapy and did not reach consensus) to statement 16 in Table 3 (which refers to prior authorization and did reach consensus).

Addressing the other concerns by Kern et al.:

1. Biogen Idec, which provided financial support for this research, did not provide input either on the questions for survey 1 or survey 2 or on the questions presented at the live meeting. Representatives from Biogen Idec did attend the live meeting to observe the commentary but did not participate in the discussion.

2. Although cladribine was under consideration by the FDA at the time of this study, it was not considered in the panel discussion because the panel considered only agents that were FDA-approved for the treatment of MS either prior to or during the study.

We appreciate Kern et al. and Phillips for providing their letters with commentary on our article and agree with some of the points made regarding the limitations of the study; however, we feel that our study was methodologically sound and provides an excellent first step toward providing resources to payers for the management of agents used for the treatment of MS.

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**REFERENCES**


