1698 Post Road East, Suite 1A • Westport, CT 06880
Phone: 203-517-4785
Fax: 203-517-4786
www.realendpoints.com

RealEndpoints

People with MS value therapies differently than do physicians or payers

By Beth Nash, MD, Stacy Mowry, MA, R. Brett McQueen, PhD, Roger Longman

Introduction and Methodology

When it comes to the practical decisions of using and paying for specialty drugs, the dominant voices belong to physicians and payers, whose preferences around specific drugs are reflected in their prescribing and formulary choices. Pharmaceutical companies certainly make themselves heard about the value of their own products. And patient advocacy organizations may participate in discussions about opening access to all drugs, but less often to influence a decision about a specific one.

In most prescribing and coverage decisions, the patient's voice is the quietest. And for good reason: faced with a complex, serious disease, most patients take their doctors' advice, which is itself based on that physician's experience with other patients and his or her reading of the clinical literature – and often filtered by the coverage rules of the patient's insurer.

But for a variety of reasons, getting the patient involved in the decision is increasingly important. In the first place, the patient is paying an increasingly large part of the bill – and should therefore have a seat at the decision-makers table. In the second, patients have different points of view on their diseases and how they should be treated – different from each other and different from their physicians. And regulators increasingly want to hear from them. The 21st Century Cures bill specifically adds patient-reported outcomes to a regulatory approval agenda which is otherwise dominated by clinical endpoints important to physicians and researchers.

The challenge: what do patients want – and does what patients want differ meaningfully from the preferences of payers and physicians? To begin to answer these questions, Real Endpoints (RE) undertook both a broad literature review and a survey of patient, physician and payer preferences. To keep the project manageable, we limited its scope to multiple sclerosis therapy. The project was funded by the Pharmaceutical Research Manufacturers Association.

The literature review focused on three subjects:

- Heterogeneity of disease, predictability of its course, and patient response to therapy
- Costs of therapy – direct, indirect and quality-of-life
- Variability in patient preferences in treatment

The survey attempted to define preferences among three stakeholder groups: patients with MS, neurologists who treat MS, and payers.

We performed a systematic search of the literature using PubMed, focusing on research from the prior 10 years, where possible. We reviewed over 300 titles, and selected the most relevant for additional analysis. We then procured and reviewed the full-text of these studies and developed summaries (literature review and bibliography is attached).

The survey was based around RE's RxScorecard drug-value assessment framework, a fully transparent, evidence-based tool that comparatively "scores" drugs that treat a particular disease. All drugs in the category are scored on the same set of efficacy, safety, ease-of-use and economic elements. Our "base case" analysis weights elements according to the points of view of payers in the RE network.

In this survey, RE aimed to define the weightings of people with MS and treating neurologists as well as payers. Using the elements from the MS RxScorecard and additional elements suggested by our literature review, we created a survey, using best/worst-case scaling as described by Kremer IEH, et al, of thirty people with MS, 30 payers, and 30 neurologists who treat MS.

Indeed, one key difference between the review and the survey: the role of payers. There is a very small body of literature reviewing payer preferences in MS, an important gap the current RE survey begins to fill.

The literature review and survey was led by Beth Nash, MD, RE's chief medical officer, working with RE staff, in particular Stacy Mowry, our statistician. Brett McQueen, PhD, a health economist and outcomes researcher at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of Colorado assisted in the survey development, and reviewed our work and its conclusions, suggesting some important procedural changes and editorial modifications.

Findings

1. MS is a heterogeneous, costly disease

MS affects over 2 million people worldwide but the condition remains poorly understood. It's an extremely heterogeneous disease. And predicting its course in any individual patient, or the response to any specific treatment, has been challenging. Numerous studies have tried to predict responders vs. non-responders to a particular agent, especially interferon (IFN). None has definitively succeeded. Likewise, researchers have also tried to predict which patients would experience a more benign disease course vs. an aggressive or malignant course in order to target potentially more effective but also more toxic therapy to those at greatest risk of severe disease or disability. Again, there were significant disagreements – around the importance of age of onset, for example.

Indeed, treatment itself may be part of the problem in understanding the disease and appropriate drugs: widespread early therapy itself makes it difficult to define the natural course of the disease – and therefore identify the most appropriate treatments and design clinical trials.

But one thing is crystal clear about MS: it is a very costly disease – more expensive than most other chronic conditions -- with significant burdens on quality-of-life and on employers. The disease starts early so lifetime costs are high. Because most MS patients are working, their employers have to deal with significant and expensive issues of absenteeism and presenteeism (working, but unproductively, due to illness). The impact on caregivers varies, but the more severe the disease, the higher the caregiver costs. Drug therapy is itself a significant part of the cost – but studies disagree over cost-effectiveness, at least in part because they use different methodologies. But they all agree that while the newer disease-modifying therapies provide significant clinical benefit, they are more expensive than standard of care and their prices have risen faster than medical inflation.

2. Patient preferences around therapies are highly varied – but also different than preferences of physicians and payers.

Despite the costs – and in particular the costs for patients – patient preferences are neither well documented nor, when they are, much taken into account. For instance, one study by Lin, PJ et al. (see 22 in the attached bibliography) assessed the value respondents put on treating specific MS symptoms by asking them to choose between two scenarios with different symptoms and treatments. The researchers used a bidding game approach to assess respondents' willingness to pay for the treatments (or in the case of the neurologists, the predicted willingness of their patients). MS patients valued certain symptoms over

others but their preferences were different than predicted by physicians. For example, MS patients were willing to pay the most to treat mobility and upper limb function ($525/month) whereas neurologists thought patients would be willing pay the least for this combination of symptoms ($177/month).

Ignoring patient preferences is more than a merely social or fairness problem (i.e., if the patient is paying a healthy part of the cost, shouldn't she have some say in what she gets?): listening to patients' points of view might also improve adherence to therapy, according to one study by Kremer IEH, et al. (see 37 in the bibliography).

To be fair, understanding patient preferences isn't easy. Both the existing literature and the RE survey demonstrate a broad diversity of opinion among patients. Part of the challenge in defining value is that patients at different points in their disease value different things. Lynd et al. [10], for example, found that, in general, experienced patients valued avoidance of serious side effects most strongly, while those who had recent symptom exacerbations tended to value symptom relief more strongly. Some studies showed patients willing to sacrifice efficacy for avoidance of side-effects (Wicks et. al., 16); others showed that route of administration was more important than avoiding side effects (e.g., Utz et. al., 18)…and another found, more or less, the opposite (Kremer et. al., 37).

The RE survey likewise reflected a significant heterogeneity in preferences among patients with MS. In almost all categories, patient opinions were more heterogeneous than those of physicians and payers. Such a finding makes intuitive sense: physicians are trained to look at MS in similar ways; payer policies generally follow medical practice – which is to say the practices that physicians have been taught to follow. Patients go through much more individualized training – the training taught by living with the disease itself.

But despite the diversity, the RE survey and the literature review showed strong and particular patterns of patient preference. Most importantly, in the RE survey, patients ascribe highest value to a drug's effect on MS symptoms, such as fatigue and ability to walk; payers and physicians are more concerned with disease progression, effect on relapse rate and effect on severity of relapses. There are many possible explanations for the dichotomy. One such explanation, for example, might be that patients are more concerned about the ongoing features of the disease, e.g., living with fatigue all day every day. Physicians tend to focus on the episodic nature of the information available to them: has walking deteriorated since the last patient visit? Does the MRI show more lesions? Has visual acuity gotten worse?

Likewise the survey – in accordance with studies from the literature review as well -- found that patients were more concerned about a drug's safety characteristics (e.g., severity of side-effects, interactions with other medications) than were payers or physicians.

And finally – and intuitively -- payers were less concerned about patients' out-of-pocket costs for a particular drug than were patients themselves – and more concerned about the drug's effect on healthcare services needed to treat MS.

Still, even if physicians or payers had a good methodology for understanding patient preferences – which they don't – matching drug and preference wouldn't be straightforward. One major reason: the outcomes studied in clinical trials do not generally reflect the outcomes most important to patients – like reduction in symptoms and avoidance of adverse drug reactions, although these are less emphasized in studies.

There is probably good reason that clinical trial endpoints and patient preferences don't match up. Clinical development programs follow pathways defined primarily by regulatory requirements, which are in large part driven by clinical opinion – the same opinion that informs physician and payer preferences. Thus most MS drugs' evidence packages are not fully equipped to define relative benefits or disadvantages for patients. Moreover, drug companies may have focused on relapse modification as a primary endpoint for pragmatic reasons: it's faster and possibly less expensive to report than many more-patient-centered endpoints (although endpoints more meaningful to patients have been examined as secondaries).

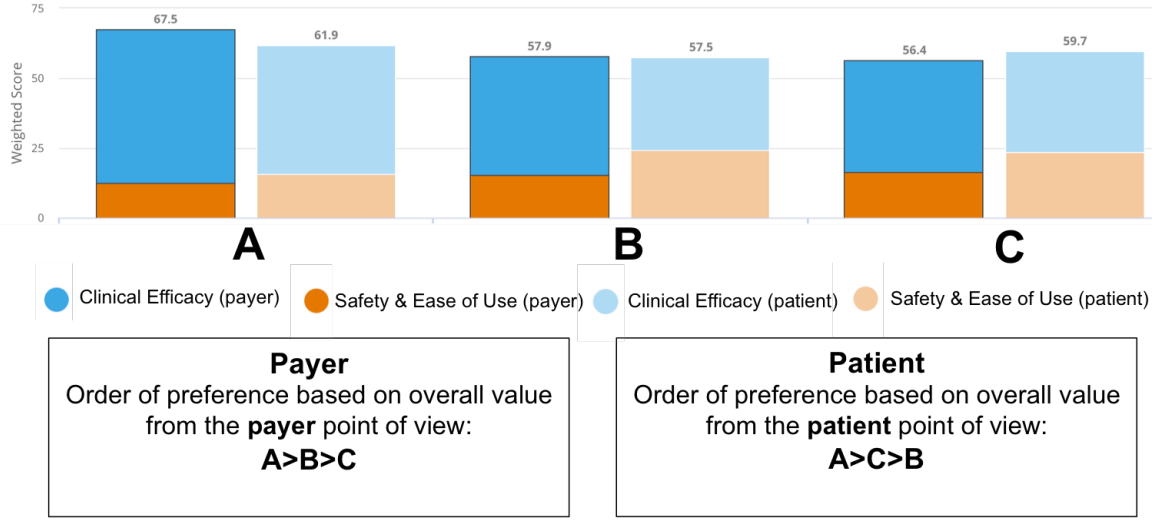
This situation could change with the patient-oriented alterations supported by the 21st Century Cures Act – for example, encouraging the use of patient-reported outcomes. But even if the clinical data reflecting endpoints of importance to patients becomes available – which will take years – physicians will still have to learn to solicit preferences from their patients, and perhaps to accept real-world evidence to inform patient preferences. They certainly lack training to do so; they don't have the requisite tools – and it's not clear they have the time or space within their workflow to do it.

3. Patient preferences can change drug evaluations

Nonetheless, if physicians and payers did take patient preferences into account, it's very possible that drug choices would change.

RE ran several scenarios with its RxScorecard evaluation tool to show how these preferences could alter assessments of three drugs that are used to treat MS.

In the chart below, we show how three MS therapies – A (an infused agent), B (an oral) and C (an injectable), one of which is still under development, have different overall values depending on the point of view. In the left (darker) graphs, we've weighted the elements based on our survey results of payers. The graphs to the right (lighter) reflect the weightings from the patient point of view in our survey.

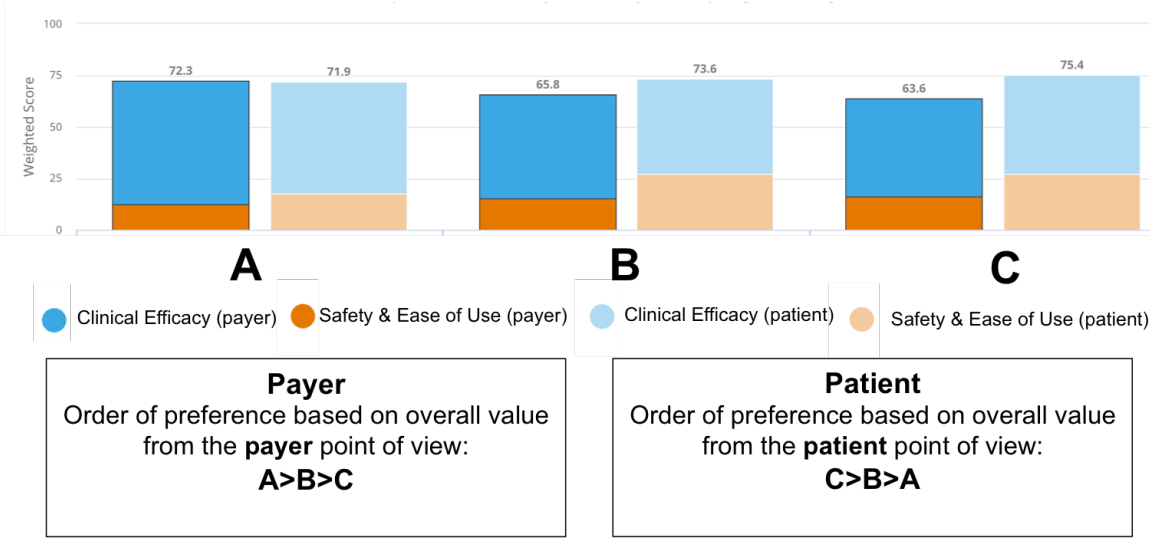


While Drug A, based on their preferences, was the highest-valued agent for both payer and patient preferences, they disagreed about the next most valuable choice: Drug B for payers and Drug C for patients. Also of note, when comparing overall value from the patient point of view to overall value from the payer point of view, Drug A decreased in value, Drug B stayed about the same and Drug C increased in value.

In our original MS RxScorecard, we did not include several elements of value that are, or could be, important to patients. The most notable of these was a drug's effect on MS symptoms (such as fatigue, numbness, etc.), an element we didn't include simply because we found little clinical trial data on that endpoint to date, but that may be changing with the development of more sophisticated metrics.

The survey allowed us to recognize that effect on MS symptoms was the most important element of value from the patient's perspective. In the chart below, we show how the same 3 drugs compare if the effect on MS symptoms were included in the RxScorecard, and if all 3 drugs significantly improved MS symptoms. The order of preference based on overall value would now completely reverse between the payer and patient points of view. Of note, effect on MS symptoms may mean different things to patients than to physicians or payers. For example, a physician or payer may be more focused on long-term effect on MS symptoms (reflected in their preferences for effect on disease progression) whereas a patient may be

more focused on short-term effect on MS symptoms. This will need to be explored in more detail in future work.



Future Directions

The RxScorecard scenario analysis above would be hypothetical even if we had the data on elements like symptom reduction. Indeed, to really understand patient preferences, we need to better understand the preferences of specific subpopulations – for example, those in the earliest stages of the disease and those who have had the disease for many years. We should also do more substantial testing of economic issues. In their chapter "Consumer Demand and Health Effects of Cost-Sharing in the Oxford Handbook of the Economics of the Biopharmaceutical Industry, Dana P. Goldman and Geoffrey F. Joyce find evidence that patients are less price sensitive to specialty drugs such as infusions, as compared to oral agents, for treating complex, progressive chronic diseases. And the RE survey more or less concurred – economics was *not* a major preference issue for patients. However, roughly half of the respondents did not have significant co-pay expense. How would their preferences for infusions vs. oral agents change if their out-of-pocket costs did?

Just as importantly, preferences don't always correspond with decision-making. Payers, for example, weight a drug's ability to slow disease progression more heavily than they weight it's effect on relapse rate. Do their formularies and utilization management policies reflect those preferences? Likewise, does physician prescribing align with their expressed preferences? It would be a useful exercise to find out.

We recognize this project only scratches the surface of a major new medical opportunity – one that, appropriately pursued, could benefit all stakeholders in healthcare…and simultaneously personalize a system that still, today, revolves more around process than patients.