Editorial

Trials Are Short, Disease Long: Measuring Drug Utility Beyond Clinical Trials

In his first aphorism, Hippocrates said: "Life is short; art is long..."[1], suggesting to some that it was most difficult to master the "art" of medicine during the lifespan of an individual physician, even if that art were not constantly changing and the body of knowledge not continually expanding.

Clinical trials have been developed to provide a lifetime of experience in a shorter period of time and to avoid what Hippocrates called "delusive experience." Clinical trials have succeeded in providing a wealth of unbiased experience upon which to base rational treatment decisions. At the same time, it could also be said that "clinical trials are short; disease is long." Rheumatic diseases generally last a lifetime. It may not be possible to draw definitive conclusions about them from any study lasting 6 weeks, 6 months, or even a year. These diseases change over time and such changes cannot readily be captured by a brief glimpse of a moving target through a small window.

The other major limitation of clinical trials is the generalizability of the results. This has recently been underscored by Sokka and Pincus, who found that only 16% of patients seen in community practice would be eligible to participate in one clinical trial of anti-tumor necrosis factor therapy, and only 5% of another population would have qualified for another such trial[2]. Yet clinical decisions about all patients with rheumatoid arthritis are based upon the results of these studies. Whether such conclusions are valid has yet to be definitively determined. Longterm clinical trials, enrolling a broad spectrum of patients with multiple comorbid conditions, as in clinical practice, are simply not feasible. Other approaches are needed.

In this issue of *The Journal*, Wolfe and colleagues have used duration of use or survival time on drug as a means of assessing longer-term effectiveness and tolerability of nonsteroidal antiinflammatories in a much broader patient population than would be included in most clinical trials[3]. This method has been utilized previously but rarely with a population of the size reported here and infrequently with such analytical sophistication[4-8].

Wolfe used duration of use as a combined measure of efficacy and tolerability. The underlying hypothesis is that the longer the patient takes a particular medication the better that medication is for that patient, all other things being equal. One of the major advantages of this approach is that it balances and weighs efficacy and toxicity in an individual patient but also permits a global decision about the utility of the drug in a group of patients. In clinical trials, efficacy and toxicity are generally assessed independently and comparative conclusions drawn about each separately. In practice, all decisions are tradeoffs between effectiveness and toxicity. If a medication works and works well, then a patient is much more likely to continue the drug despite side effects than if the medication isn't particularly effective and produces the same adverse effects. In the former case, the drug has been of net benefit to the patient, as assessed by the patient and the physician. In the latter, the liabilities of the medication outweigh any benefits.

Unlike clinical trials, the patient population that can be studied with this and similar observational methods is inclusive rather than exclusive. All patients willing to participate are able to do so, regardless of disease severity, comorbid conditions, or use of concomitant medications. While patients may have to agree to participate and this may exclude some patients, the vast majority is eligible for this type of observational study, unlike most randomized controlled trials. The authors of the present study have also looked at differences between participants and nonparticipants in terms of demographics and disease severity, and found none, providing additional reassurance that the results will be applicable to the larger population of patients seen in community practice.

The drug survival method is not, however, without its limitations and requires thoughtful consideration and careful adjustment for potential confounding factors. Among those factors that may result in the premature termination of a medication are cost, change in insurance coverage or copayment, formulary status of a covered medication, intensity of advertising, recent introduction of a new product, concomitant medication administration, severity of disease and comorbid conditions, previous drug experience, and patient expectations.

Wolfe and coworkers do an excellent job of controlling

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for most of these potential confounders. One of the more important factors influencing drug utilization may be cost to the patient. There is a considerable difference in cost of the nonselective NSAID (NSNSAID) versus cyclooxygenase-2 selective NSAID (CSNSAID). In 2001, the average cost/prescription for Celebrex and Vioxx was $97.32 and $85.44, respectively, while the average cost for naproxen was $24.90 and that for ibuprofen was even less[9]. The prices for the CSNSAID have continued to increase. While this might not be an important consideration for some, for many it is the deciding factor, especially for older patients taking multiple brand-name medications. In their analysis, the authors have controlled for age, income, functional status, education, race, and sex. While they have not controlled directly for insurance status and medication coverage, the variables employed are likely correlated and should account for this influence. And, in response to a question from a reviewer, the authors confirm that insurance type did not influence the results, but point out that not all insurance plans have the same medication coverage. In addition, not all insurance plans have the same co-payments for similar CSNSAID. There are preferred and nonpreferred formulary CSNSAID, and financial disincentives have been put in place by some plans to influence medication choice. It is difficult, at best, to control for these influences. However, it could also be argued that financial disincentives would likely decrease the time on drug for CSNSAID (in general) in comparison to NSNSAID if out-of-pocket expenses for the former were significantly greater. But cost pressure could influence the decision as to which CSNSAID is chosen and how long that particular CSNSAID is taken.

It seems likely, although unproven, that advertising could influence duration of use. It appears to increase drug sales. There was a 24.6% increase in sales of the 50 most heavily advertised drugs versus 4.3% increase for all others drugs from 1999 to 2000. For Vioxx, the single most heavily advertised drug to consumers in the year 2000, with promotional expenditures of over $160 million, retail sales quadrupled from $329.5 million in 1999 to $1.5 billion in 2000[10].

I would agree with the authors that it may not be possible to precisely determine the magnitude of the effect, but the net result is undoubtedly an increase in prescriptions for CSNSAID. In many cases, a new prescription for CSNSAID results in the termination of an existing NSNSAID, which otherwise might not have been terminated, at least not at that time. The effect of advertising is to raise expectations of benefit. Most patients who came into my office after the approval of celecoxib and rofecoxib didn't ask for these medications because they heard they were safer; they requested them because they had been encouraged to believe that they were more effective. These expectations could influence duration of use.

Finally, the measurement of drug survival does not take into account or weigh the reasons for termination. These may be important and could change the fundamental risk/benefit equation. For example, not all side effects that result in discontinuation are equally significant. This method of analysis treats terminations for fatal gastrointestinal bleeds the same as those for a rash. If 2 drugs had the same average survival time, but one caused twice the number of deaths, one wouldn't necessarily conclude that the 2 were equivalent. Some measure of severity of toxicity is also required, such as the toxicity index proposed by Fries and colleagues[11].

The conclusions of the analysis reported here are clearly strengthened by the large number of subjects who have been recruited from a multitude of practices located across the country. The numbers of subjects and their heterogeneity may overcome some of the concerns listed above. If that were the case, then the questions that must now be asked are: do the differences detected represent a meaningful clinical difference; and, are those differences worth the cost?

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