EDITORIALS

Decision Analytic Modeling and NSAID Gastropathy

Could We Be More Sensitive?

The widespread use of prescription and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) exposes millions of individuals to a well-documented increased risk of gastrointestinal adverse events. Although the probability is low that any NSAID user will experience a drug-related complication,¹ the fact that 2 million Americans regularly use these agents makes NSAID gastropathy an important problem from clinical and economic perspectives. It is estimated that over 100,000 hospitalizations and 10,000 to 20,000 deaths each year in the United States can be attributed to NSAID-related complications.² While the costs of excess hospitalizations have been estimated at \$4 billion annually,³ these expenditures greatly underestimate the societal impact of NSAID gastropathy, in that indirect costs such as lost productivity tend not to be included.

Controversy remains among clinicians on how best to weigh the potential clinical benefits of NSAIDs against the possibility of adverse events associated with their use. Until the recent availability of equally effective anti-inflammatory agents with decreased propensity for gastrointestinal injury (i.e., COX-2 selective inhibitors), the most common clinical approach to reduce NSAID toxicity was the prescription of additional “protective” pharmaceutical agents. Despite the fact that misoprostol is the only FDA approved drug indicated to prevent NSAID-related adverse events, numerous different agents are used for this purpose. A dearth of outcomes data combined with the lack of head-to-head trials among available therapies have added to the confusion. The study by Ko and Deyo⁴ in this issue of the *Journal* used decision analysis to estimate the cost-effectiveness of 6 available prophylactic strategies compared to no preventive measures in an elderly population requiring 3 months of NSAID use.

Decision analysis is a well chosen methodology to evaluate this issue, given the number of controlled trials that have evaluated endoscopic outcomes, the need for data from numerous sources, and uncertainty regarding several key clinical inputs. Modeling allows important clinical and economic outcomes for each strategy to be explicitly compared to others in a transparent and reproducible manner. Through the use of extensive sensitivity analyses, Ko and Deyo make an important contribution by identifying the key future research questions. However, uncertainties regarding specific inputs do not allow the confident acceptance of the principal case results.

Decision analysis may not be viewed as a particularly

rigorous method to alter clinical practice, largely due to common criticisms surrounding the selection of specific clinical and cost inputs and the generalizability of the findings to an individual decision-maker. To overcome these limitations, the strength of the evidence behind the selection of the inputs used in the principal case and sensitivity analyses must be defended explicitly. Maybe more importantly, the natural history of the disease under study—the “engine” of the model—must be programmed to mimic community practice, as opposed to that found in a research trial.

Specific to the modeling of NSAID gastropathy, 3 points can illustrate how departing from the clinical trial model and programming the “real world” may add credence to the methodology. First, although clinical trials are usually of 3-month duration, the risk of NSAID gastropathy is related to the duration of NSAID exposure so a model that extends beyond 90 days may provide more insight into the outcome of cost per life-year saved. Second, since patients requiring NSAIDs may fail therapy or experience persistent symptoms after treatment is prescribed, the clinical and cost consequences of different prophylactic strategies depend upon the subsequent diagnostic and treatment decisions that occur over the entire natural history of disease. Clinicians frequently switch NSAIDs and/or add an anti-secretory agent. Patients who get pain relief from their NSAID often do not stop their drug on first symptomatic event, but instead have an anti-secretory agent prescribed to relieve their symptoms. Therefore, economic analyses that compare two regimens against each other in an exclusive fashion (e.g., histamine-2 receptor antagonist vs. proton pump inhibitor), may not reflect actual clinical practice since available alternatives are often used in sequence (histamine-2 receptor antagonist then proton pump inhibitor). Thus, the most cost-effective initial prophylactic strategy depends on the variation in patients' symptomatic response and resultant likelihood of future health care expenditures. Third, the difference between endoscopic ulcers and symptomatic events must be distinguished. Clinical history and physical examination are poor predictors of the presence or absence of ulcers/erosions in symptomatic NSAID users. Since symptoms are imperfectly related to the presence of an endoscopic lesion, progression through the model should be symptom-driven. We applaud the authors for considering this important distinction in their model.

We Can Be More Sensitive

One of the biggest advantages of decision analytic modeling is the performance of sensitivity analysis to assess the validity of the results. By allowing one or any combination of the clinical and cost inputs to be varied over a selected range, dependence/independence of the results on a particular assumption/input can be determined. When key inputs are unknown or uncertain, sensitivity analyses should be highlighted, not the base case results. Since several critical inputs are uncertain in the Ko model, if the results were to focus on sensitivity analyses and not the base case results, the findings would be more useful and limitations regarding generalizability could be downplayed. We used such an approach when assessing the potential role of *H. pylori* eradication to prevent gastric cancer, because the most critical input—whether *H. pylori* cure lowered the increased cancer risk attributable to the infection—was unknown.⁵ Since a similar controversy exists regarding the impact of *H. pylori* cure on the NSAID ulcer rate (a critical input in the Ko model) the sensitivity analysis is more informative than the highlighted base case results.

In situations such as this one, where sensitivity analyses reveal that results change as key inputs differ, journal editors should allow—perhaps recommend—a presentation style highlighting sensitivity analyses and downplaying prin-

cipal case results. If such a publication strategy was adopted, the best attributes of this powerful, developing methodology could be demonstrated and its usefulness to decision makers showcased.—**A. MARK FENDRICK, MD**, Consortium for Health Outcomes, Innovation, and Cost-Effectiveness Studies (CHOICES), and Division of General Medicine, University of Michigan, Ann Arbor, Mich, and **JAMES M. SCHEIMAN, MD**, Consortium for Health Outcomes, Innovation, and Cost-Effectiveness Studies (CHOICES), and Division of Gastroenterology, University of Michigan, Ann Arbor, Mich.

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