Measuring Value in the Treatment of Symptoms of Allergic Rhinitis With Nasal Steroids

Patients' willingness to pay (WTP) is a subject of interest, particularly in these times of consumer-directed health care and benefit designs that involve multiple copayment tiers. Since tiered copayment products have been found to reduce premium costs, the continued proliferation of tiered copayment benefits can be expected.

Wasserfallen et al. found that parents were willing to pay up to 0.71% of monthly income to avoid the pain experienced by their children in the medical procedure of blood sampling, with a median WTP of 25 CHF (Swiss francs) for a prescription drug to reduce the stress of this experience. These researchers found that it was difficult to assess parents' WTP in an outpatient setting. Economists Whynes, Frew, and Wolstenholme studied the elicitation formats used in WTP research, finding that the technique is controversial and the relative merits of rival interventions will be predicted, in part, by the elicitation format used in the WTP research. Other researchers have suggested that the WTP method may not be capable of determining precise WTP because of the prominence effect in which subjects may select prominent values (e.g., $5, $10, $20, $50), while others have combined WTP with the relative merits of rival interventions will be predicted, in part, by the elicitation format used in the WTP research.

The WTP method seems to be ideal for demonstrating that most patients are willing to pay something to obtain a desirable attribute or to avoid an undesirable attribute. The controversy appears to surround the degree to which the WTP method can produce reliable WTP amounts. In this context, the results of WTP research can often appear to be intuitive. For example, Guelyard et al., in a telephone survey of 562 parents of children who had been treated for an episode of acute otitis media (AOM), found that they had a median WTP in 2002 dollars of Can $31.66 for a single dose of an antibiotic to resolve the AOM or Can $26.63 for a once-daily dosing regimen for 3 days to resolve the AOM. Regression analysis showed that the amount parents were willing to pay increased with the amount of household annual income, the number of AOM episodes experienced in the previous year, and if adverse effects were experienced from antibiotic treatment. Also not surprising, patients with diabetes expressed a WTP about 3 times more out of pocket for inhaled antibiotic treatment. Also not surprising, patients with diabetes expressed a WTP about 3 times more out of pocket for inhaled antibiotic treatment. Also not surprising, patients with diabetes expressed a WTP about 3 times more out of pocket for inhaled antibiotic treatment. Also not surprising, patients with diabetes expressed a WTP about 3 times more out of pocket for inhaled antibiotic treatment.

The present study by Mahadevia et al. in this issue of JMCP, report the results obtained from assessment of preferences for desirable and undesirable characteristics of the use of nasal steroids for the treatment of the symptoms of allergic rhinitis among 113 patients. These authors previously reported, in 2004, that among these same 113 patients, 28% selected aftertaste as the most important of 6 attributes assessed, followed by taste (19%), throat rundown (18%), nose runout (12%), smell (11%), and feel of the spray (7%). So, how does the present article inform managed care pharmacists, and what other relevant research has been performed previously?

A query of MEDLINE for “willingness to pay” yielded 825 references. Refining the query to include “allergy” resulted in 16 references, only one of which was specific to the use of the WTP method in a manner that appears to be relevant to the research performed by Mahadevia et al. Keith et al. reported, in 2000, that patients who received intranasal budesonide delivered by Turbuhaler (i.e., dry as 400 mcg) or aqueous spray (256 mcg) once daily for 4 weeks were willing to spend an average of $15.89 (in 1999 dollars) to alleviate the problems of seasonal ragweed rhinitis. The mean WTP for the drug used during a subsequent ragweed season was $12.95 per week. This research did not assess sensory attributes specifically but found no difference in WTP between the dry versus aqueous delivery methods for budesonide nasal spray.

The present study by Mahadevia et al. in this issue of JMCP
affirms our intuition that (a) patients can discern among specific sensory attributes of intranasal steroid products, (b) some attributes have higher economic value in their avoidance (e.g., no aftertaste versus strong aftertaste), and (c) the absolute WTP amount is higher for some attributes (i.e., a lot of throat rundown and nose runout) for persons with higher household income. It may also be reasonable to extrapolate these findings to the conclusion that physicians and patients should be discussing product attributes, particularly for patients who will be using intranasal steroids on a regular basis due to persistent symptoms.

The implications of the research on WTP for sensory attributes beyond these conclusions are less clear. The graphs (Figure 1) in the article by Mahadevia et al. are remarkably similar in slope and clustering except for aftertaste (Figure 1C). Second, at $50 per prescription, the sensory attributes have little differentiation. (Readers are encouraged to examine the Choice Set in Table 3 of the article to make their own inferences.) Based upon the actual costs of the 7 therapeutic alternatives in 2005 (Table 1 page 168), there is only an absolute difference of $5 per month between budesonide, mometasone, triamcinolone, and fluticasone.

Members of pharmacy and therapeutics (P&T) committees are challenged in decision making by the absence of information about sensory attributes in the labeling for intranasal steroids. But, Kaliner found, in a telephone survey of 503 patients with seasonal and perennial allergic rhinitis, that 86% of the patients reported that they had not complained to their physician about sensory attributes in the labeling for intranasal steroids.13 Since the work by Kaliner was performed 6 years ago, this research, if conducted today, may find that patients are more outspoken. On the other hand, perhaps sensory attributes of intranasal steroids are important to only a small proportion of the population that suffers from allergic rhinitis. One wonders how important the sensory attributes of intranasal steroids should be in clinical and P&T committee decision making. The one apparent opportunity for quality improvement is in increasing, to more than 7%, the proportion of physicians that base their choice of a nasal steroid on patient preference14 for sensory attributes.

### What Is the Future of Thiazolidinediones (TZDs)
#### After Market Introduction of Inhaled Insulin?
The U.S. Food and Drug Administration (FDA) approved inhaled insulin (INH) under the trade name Exubera on January 27, 2006, for use in adult patients with type 1 and type 2 diabetes.15 Exubera is an inhalable, powdered form of insulin delivered by a device developed by Nektar Therapeutics. Earlier in January 2006, Pfizer agreed to acquire the world-wide rights to Exubera from sanofi-aventis for $1.3 billion.16

One of the clinical trials that favored FDA approval of INH was a multicenter clinical trial that randomized 145 persons with uncontrolled type 2 diabetes (with glycosylated hemoglobin [A1c] in the range of 8%-11%) to either INH before meals or rosiglitazone (Avandia) 4 mg twice daily.17 The mean A1c values at baseline were 9.5% in the INH group versus 9.4% for the rosiglitazone group. After 12 weeks of the therapy, the INH group (71 of 76 randomized patients completed the trial) achieved a mean A1c of 7.2% versus 8.0% for the 63 of 69 patients who completed the rosiglitazone treatment arm, yielding 64% greater reduction in A1c (-2.3 absolute points vs. -1.4 absolute points) for INH compared with rosiglitazone, with an adjusted treatment group difference of -0.89, 95% confidence interval [CI], -1.23 to -0.55.18 At 12 weeks of treatment, 82.7% of the INH group achieved A1c of 8% or less versus 58.2% for rosiglitazone, adjusted odds ratio (OR), 7.14; 95% CI, 2.48-20.58; P <0.001. By the American Diabetes Association standard of <7.0% A1c, the proportion achieving the primary end point was more than twice the proportion for rosiglitazone, 44.0% for INH vs. 17.9% for rosiglitazone, (adjusted OR, 4.43; 95% CI, 1.94-10.12). According to the guidelines of the American Association of Clinical Endocrinologists (A1c ≤5.5%), the success rate was even higher for INH versus rosiglitazone, 28.0% vs. 7.5% (OR, 5.34; 95% CI, 1.83-15.57).

Pharmacy and therapeutics (P&T) committees have an interesting question to debate in 2006: the relative value and need for the thiazolidinediones (TZDs) rosiglitazone (Avandia and Avandamet) and pioglitazone (Actos) now that clinicians and patients have access to INH, which has been found to be superior to rosiglitazone in the intermediate outcome of A1c. TZDs have a larger hole to crawl out of when relative safety is considered by P&T committees and clinicians. More than 2 years ago, at the end of 2003, the American Heart Association and the American Diabetes Association released a joint consensus statement warning that patients with moderate-to-severe congestive heart failure (CHF) should not be prescribed either rosiglitazone or pioglitazone.19 Analysis of administrative claims data reported in November 2003 by Delea found a 55% higher incidence of heart failure for 5,441 TZD patients compared with 28,103 control patients with diabetes (hazard ratio = 1.7, P <0.001); the adjusted incidence of heart failure at 40 months was 8.2% for TZD patients and 5.3% for control subjects (absolute difference 2.9%, relative difference 55%).20 The TZDs have a tendency to cause fluid retention and edema, particularly of the feet, a hallmark of CHF. The incidence of fluid retention and edema appear to be exacerbated by concomitant use of insulin and dose-related for both rosiglitazone21 and pioglitazone.22,23

The black cloud over TZDs does not end with fluid retention, edema, and heart failure. The first TZD, troglitzone (Rezulin), approved by the FDA for marketing in the United States in January 27, 1997,24 was withdrawn in March 2000 after its association with hepatotoxicity was no longer in doubt. By year-end 1998, the FDA had record of a total of 32 reported deaths and 4 liver transplants associated with the use of troglitzone.25 Prior to the market withdrawal of troglitzone, the manufacturer had distributed 2 warning letters to physicians, including a notice to
monitor liver enzymes monthly, and the United Kingdom had withdrawn troglitazone from the market more than 2 years earlier, in November 1999.26 For pioglitazone, introduced to the U.S. market in July 1999,27 the first death from liver failure associated with its use was reported in 2004.28 A “Dear Prescriber” letter dated April 26, 2002, highlighted changes in the precautions section of labeling of rosiglitazone regarding the potential for hepatic effects, even a rare case of hepatic failure, and, in other parts of product labeling, a possibility of weight gain.

Add to peripheral edema, weight gain, and possible hepatotoxicity an apparent increased risk of macular edema. In January 2006, the FDA notified health care professionals of reports of both new-onset and worsening cases of diabetic macular edema associated with the use of rosiglitazone, albeit reversible and apparently dose related.29

With an apparent black eye for safety and inferior to INH in efficacy for lowering A1c, the cost outcomes for theTZDs may offer a refuge in the storm. Kalsekar et al., in this issue of JMCP, found, from administrative claims data in a Medicaid fee-for-service population, that patients who started TZD therapy incurred 35% lower costs in a 12-month follow-up period in 2000-2001 for emergency room (ER) visits and hospitalization compared with patients who initiated therapy with insulin, an average of $3,727 versus $5,793, respectively (P < 0.01).30 For diabetes-related costs only, the 53% higher pharmacy costs in the TZD patients ($1,678) versus insulin patients ($1,096, P < 0.01) was offset by lower costs for emergency room (ER) visits and hospitalization ($2,855 vs. $5,090, P < 0.01), resulting in 25% lower total diabetes-related costs for the TZD group compared with the insulin group ($5,425 vs. $7,255, P < 0.05).

Limitations in the study by Kalsekar et al. are significant. Important among these limitations was the inability to measure disease severity. Lacking clinical values for A1c and blood glucose, the researchers attempted to assure the comparability of the 2 groups through the use of propensity matching. However, the propensity matching technique would tend to exclude patients with more-severe diabetes who were, therefore, using insulin and could not be matched to TZD patients. The magnitude of this limitation can be gleaned from the authors’ Table 1, which shows that 65% (n = 1,271) of otherwise study-eligible patients were excluded in the process of propensity matching, leaving only 690 patients in the final analyses: 345 patients with type 2 diabetes in the TZD group and 345 patients in the insulin group.

Second, Medicaid patients, particularly those not enrolled in managed Medicaid, are most likely not representative of the general population of patients with type 2 diabetes, and discontinuous eligibility contributes to discontinuous care in this population.31 A hint of the problem of discontinuous care might be found in the 75% of patients identified with a diagnosis of type 2 diabetes who were excluded from the study because of the absence of a pharmacy claim for TZD or insulin plus another 12% of patients who did not have continuous eligibility during the study period. LaFleur, in a previous issue of JMCP, provided a comprehensive and useful review of the limitations of administrative claims data specific to the measurement of costs of care for patients with type 2 diabetes.32

Third, the time period for the administrative claims used in the analyses by Kalsekar et al. is confounded by the TZD market disruption caused by the withdrawal of troglitazone in March 2000, in the middle of their 1999-2001 study period. While troglitazone patients were excluded from the 12-month follow-up period, 12.8% of the TZD patients and 13.0% of the insulin patients in the final analysis received troglitazone in the preperiod (Table 3 in Kalsekar et al.). One wonders why the outpatient costs, which included office visits and laboratory tests for liver enzymes, were not higher in the preperiod for both groups and why the outpatient costs were similar ($177 mean difference, $1,070 for the insulin group compared with $893 for the TZD group, P = 0.458 for the comparison) in the postperiod, particularly since there was considerable media attention to the market withdrawal of troglitazone at the time. Consumer groups, represented by Public Citizen, petitioned the FDA in early 2000 to revise the product labeling for all 3 TZDs to describe the adverse effects that include liver toxicity and heart failure.33

Fourth, a threat to validity seems inherent in the premise that higher drug costs for TZDs are offset by lower costs for ER visits and hospitalizations, in only 12 months of administrative claims data. For diabetes-related costs, the insulin group had a higher average number of physician office visits, but the average outpatient costs (including physician office visits) were not different between the 2 groups over 12 months of follow-up. However, the contribution of the $177 mean difference ($1,070 for the insulin group vs. $893 for the TZD group, P = 0.458 for the comparison) may have contributed to the $1,830 difference ($153 per month) in total diabetes-related costs ($7,255 for the insulin group vs. $5,425, P = 0.022 for the comparison). Stephens et al. provide a useful context for interpreting these absolute and relative values in their summary of the literature on economic studies in this issue of JMCP, including their Table 1, showing the breakdown of total direct costs for managed care organization (MCO) enrollees with diabetes.34

The place in therapy for TZDs in type 2 diabetes is summarized clearly and succinctly in the NICE (National Institute for Clinical Excellence) appraisal released in November 2002. TZDs are third-line therapy in type 2 diabetes after sulfonylureas and metformin have proved unsuccessful when used as monotherapy and in combination to achieve glycemic goals.35 NICE concluded that “the use of glitazone combination therapy with either metformin or sulphonylurea is not likely to be cost effective when compared with the combination of metformin and sulphonylurea.”

So, much of the market future of TZDs may have to do with
relative cost. In previous research reported in JMCP, Shetty et al. found that patients with type 2 diabetes maintained at target A1c (≤7%) had 24% lower total diabetes-related medical costs compared with patients who were above target A1c (>7%). The actual daily direct drug costs for INH are not yet known. What is known is that the TZDs are not inexpensive. Based upon MCO pharmacy claims for the fourth quarter of 2005, the average direct drug cost, including pharmacy dispensing fees, was $4.34 per day ($130 per month) for Avandia, $4.55 per day ($136 per month) for Avandamet, and $5.13 ($154 per month) for Actos. The evidence presents a classic conundrum for P&T members: a product—INH—with superior efficacy and safety but (probable) higher direct drug cost compared with TZDs. Still, the market introduction of INH in February 2006 seems likely to knock pioglitazone and rosiglitazone from their status in the top 12 drugs by expenditure at year-end 2005.

_Frederic R. Curtiss, PhD, RPh, CEBS_  
Editor-in-Chief  
fcurtiss@amcp.org

REFERENCES


Letters to the Editor

JMCP welcomes letters that serve to clarify subjects published in previous issues of the Journal or regarding subject matter of interest to managed care pharmacists. Letters in JMCP are not peer reviewed but are subjected to editorial review. Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net. See www.amcp.org for details.