Outcomes of Sword Swallowing and Pharmaceutical Step-Therapy Interventions

Witcombe and Meyer found that sword swallowers experience side effects. While this outcome is perhaps not surprising, outcomes research was necessary to determine if there were factors related to the side effects. The research showed that esophageal tears were more likely when the swallow was (a) distracted or (b) swallowed an unfamiliar sword.

Like sword swallowing, step-therapy interventions that require prior use of a lower-cost therapy with effectiveness that is equivalent to a higher-cost therapy would, on their face, appear to have certain self-evident outcomes. However, research is necessary to answer questions such as the magnitude and durability of drug cost savings and whether drug cost savings are offset or overwhelmed by undesirable service outcomes or administrative costs. In an article published in JMCP in mid-2006, Dunn et al. showed that the cost per day for all antidepressant drug therapy was reduced by 9% as the result of a step-therapy intervention that required use of a generic selective serotonin reuptake inhibitor (SSRI) prior to coverage of a brand-name antidepressant, producing pharmacy benefit savings of $0.36 per member per month (PMPM) in 2005 dollars.

In the current issue of JMCP, Yokoyama et al. found that a step-therapy intervention that required use of an angiotensin-converting enzyme inhibitor (ACEI) prior to coverage of an angiotensin II receptor blocker (ARB), saved 13% in direct drug cost for all antihypertensives versus the comparison group without the ARB step-therapy intervention. The authors estimated that drug cost savings were $0.03 PMPM across the population of approximately 1 million members. However, while this $0.03 PMPM estimated savings was calculated over 12 months of follow-up, the identification period was only 6 months. Additionally, the study population was limited to continuously enrolled members, who represented only 76% of patients fulfilling all other study criteria. Therefore, actual drug cost savings may be $0.06 PMPM or more if extended to a full 12 months of ARB step-therapy intervention and to both continuously and noncontinuously enrolled members.

For a managed care organization population of 1 million members, the annual savings in drug costs from this ARB step-therapy intervention is at least $360,000 or as much as $720,000, in 2002-2003 dollars. While these cost savings are impressive, the authors acknowledge that potentially offsetting costs in the administrative time required in physician offices and pharmacies were not assessed, and a return on investment could not be calculated because the administrative costs incurred by the pharmacy benefits manager in administering the intervention were not measured.

While the direct drug cost savings of $0.06 PMPM or more from the ARB step-therapy intervention may be offset somewhat by administrative or provider personnel costs, the drug cost savings may be underestimated by Yokoyama for another reason. The absolute rates of initiation of either ACEI or ARB therapy were 2.4 times higher in the comparison group versus the intervention group, 2.2% of approximately 2 million members in the comparison group versus 0.9% in the intervention group. After application of the selection criterion of at least 15 months of continuous eligibility, the 2.4 times higher rate of initiation of either an ACEI or ARB remained the same in the comparison group (1.7%) versus the intervention group (0.7%). We don't know the reason(s) for this difference, but there are at least 3 plausible contributing factors.

Some might lump the sentinel effect with the “hassle factor” for providers in managed care. Yet, research on the rigor of step therapy suggests that not only is the cost of the hassle factor overwhelmed by cost savings in the target therapy but the step therapy intervention can also produce favorable clinical outcomes. Population-based observational research reported by Mamdani et al., for the period from January 1996 to November 2002, showed that a restrictive, step-therapy intervention in British Columbia that placed cyclooxygenase 2 (COX-2) inhibitors as fourth-line therapy after at least 3 non-steroidal anti-inflammatory drugs (NSAIDs) was associated with a 25% increase in prevalence of use of NSAIDs, including COX-2 inhibitors (from 8.7% to 10.9%) in persons aged 66 years or older. In Ontario, where step therapy was also recommended, the intervention was not as restrictive as in British Columbia, where “special authority approval” was required for use of a COX-2 inhibitor, and there was a larger, 51% increase in the prevalence of use of NSAIDs (from 10.9% to 16.5%). Putting aside the clinical and cost outcomes of adverse cardiovascular events associated with the use of COX-2 inhibitors, the rate of hospital admissions due to gastrointestinal (GI) hemorrhage increased significantly in Ontario, by about 16%, or a rate of 2 admissions per 10,000 older adults above the expected value (P<0.01). There was no increase in hospital admissions per 10,000 older adults in British Columbia, with its more restrictive step-therapy intervention for COX-2 inhibitors, a lower overall absolute rate of use of all NSAIDs, and lower rate of increase in the use of all NSAIDs following the market introduction of the COX-2 drugs.

The opportunity for cost savings from step therapy for COX-2 inhibitors was identified 4 years ago when Cox et al. showed that 65% of patients new to COX-2 therapy did not have an indicated risk for GI hemorrhage, 68% did not have evidence of prior use of first-line therapy with another NSAID, and a combined 45% of new users of COX-2 inhibitors did not have either a possible indication of GI risk or prior use of first-line therapy. Subsequent research showed that the cost savings were $0.29 PMPM in 2002-2003 dollars in a 20,000-member pharmacy benefit plan with
step-therapy intervention for COX-2 inhibitors.8

In this issue of JMCP, Gleason compares some of the cost savings reported by step-therapy interventions and outlines the opportunities for which we do not yet have results from outcomes research, including step therapy for cholesterol management, allergy, and attention-deficit/hyperactivity disorder.9 The present article by Yokoyama et al. is the first peer-reviewed, published report of the cost and utilization outcomes associated with an ARB step-therapy intervention. However, Gleason et al. reported recently in a poster abstract the results of an ARB step-therapy intervention that reduced the direct drug cost for antihypertensive drug therapy by $0.11 PMPM in the first 4 months of follow-up across an entire health plan of 65,524 members.10 The larger savings reported by Gleason et al. may be attributable, to the lack of a control group as well as to the nature of the intervention. In both the Yokoyama et al. and Gleason et al. interventions, the health plans required a trial of an ACEI or a prior-authorization request before permitting coverage of an ARB. In Gleason et al., the step-therapy program was more stringent: only generic ACEIs were considered first-line therapy, and the health plan required a generic ACEI trial or a prior-authorization request submitted by fax before a brand ACEI or ARB was covered.

The magnitude of the effect on cost outcomes associated with step therapy would appear to be proportional to the restrictiveness of the intervention. The difference in magnitude of cost savings in the ARB step-therapy interventions described by Gleason et al. versus Yokoyama et al. and the magnitude of difference in the increase in NSAID use and hospitalization outcomes reported by Mamdani et al. associated with the more restrictive COX-2 step therapy in British Columbia versus Ontario support this hypothesis. In Ontario, the “Limited Use” system requires the prescriber to merely write a code number (“316” for osteoarthritis or “317” for rheumatoid arthritis) on the prescription to permit coverage and payment for a COX-2 inhibitor, signifying that the patient has failed an adequate trial of acetaminophen (e.g., acetaminophen 1 gram 4 times daily for several weeks) and has had a history of a documented, clinically significant ulcer or GI bleed or failure or intolerance with at least 3 listed NSAIDs.11 In British Columbia, coverage of a COX-2 inhibitor requires prior use of at least 3 listed NSAIDs or submission of a prior-authorization request through a paper-based system.12

These observations should remind us that not all step-therapy interventions are “created equal,” and it is important to qualify step-therapy interventions when investigating clinical, service, and cost outcomes and when reporting the results of these investigations. Perhaps it is time to propose a categorical system to rate step-therapy interventions by the degree of restrictiveness. There are at least 2 dimensions of step-therapy restrictiveness: (a) the medium-process itself (e.g., hand-written code number, automated voice response, or FAX submission form), and (b) the specificity of the exception criteria (e.g., signature of the physician vs. open-ended request for clinical justification). This categorical system for rating restrictiveness may be helpful in interpreting the results of these population-level evaluations of step-therapy interventions.

The timing of these first reports in the literature by Yokoyama et al. and Gleason et al. (as a poster abstract) on the cost and utilization outcomes of ARB step-therapy interventions coincides with a recent report on the comparative effectiveness of ACEIs and ARBs in treating hypertension as determined by the Effective Health Care Program of the Agency for Health Research and Quality in January 2007.13 This AHRQ report sought to determine if ACEIs and ARBs are effectively equivalent in treating hypertension as assumed by most clinicians by evaluating the literature on intermediate outcomes (e.g., blood pressure control, rate of use of a single hypertensive agent [monotherapy]), and endpoint outcomes, including all-cause mortality and cardiovascular disease-specific mortality. In addition to comparative therapeutic effectiveness, AHRQ sought answers to the question of comparative safety outcomes (e.g., withdrawal from therapy due to adverse events) and the incidence of adverse events such as angioedema, cough, weight gain, and impaired renal function. The evidence showed no advantage of ARBs over ACEIs in intermediate outcomes (e.g., blood pressure control, effect on lipid values, left ventricular mass index, or ejection fraction) or in endpoint outcomes (e.g., all-cause mortality, disease-specific mortality, quality of life, or cardiac events such as myocardial infarction [MI]). The ARBs were found to have a lower risk of cough compared with ACEIs, pooled odds ratio 0.341, representing a difference of 5.7 percentage points based on clinical trials, which specifically query subjects regarding symptoms, but a difference of only 1.3 percentage points for cohort studies. Thus, the AHRQ report notes that the numbers of patients needed to treat with ARBs to prevent 1 patient with cough are 18 based on the clinical trial data or 76 using cohort data. The latter number would have more clinical relevance.

The AHRQ report on comparative effectiveness also found no reliable difference between ACEIs and ARBs in the intermediate outcomes of persistence and adherence. In the translation of outcomes from randomized controlled trials (RCTs) to the real world, in which drug therapy is discontinued for many reasons, including adverse events or perceived ineffectiveness, assessment of medication adherences helps provide the glue to connect RCTs with population health. In research not considered in the AHRQ report of comparative effectiveness, Shrank et al. found, in their examination of 6 drug classes including ARBs and ACEIs, that adherence with therapy was 6.6% greater for patients prescribed generic drugs versus nonpreferred (nonformulary) brand drugs (P<0.001). Adequate adherence was also more common for generic drugs compared with nonpreferred drugs (odds ratio [OR]: 1.62, 95% confidence interval [CI], 1.39-1.89.14 Out-of-pocket cost
may be an important factor in these findings since generic drugs have the lowest out-of-pocket cost (member copayment). A mail survey of nearly 18,000 adult senior respondents found that about 25% reported not taking prescribed medication due to cost.\(^5\) Fortunately for health plans and for patients, all of the ACEIs except ramipril are available by generic name and most, including the former blockbusters enalapril (Vasotec), lisinopril (Zestril), and benazepril (Lotensin), are available at a total cost before member cost share of less than $0.60 per day of therapy.\(^6\) And for ramipril, recent evidence appears to close the book on any remaining questions regarding a class effect of the ACEIs on endpoint outcomes; Tu et al. found no difference in the combined endpoint of death or hospital readmission for acute myocardial infarction (AMI) in a 2-year follow-up of AMI patients who used ramipril versus enalapril (adjusted hazard ratio [HR], 0.95; 95% CI, 0.79-1.15), vs. lisinopril (HR, 1.02; 95% CI, 0.84-1.25), or compared with other ACEIs (HR, 1.08; 95% CI, 0.88-1.32).\(^7\)

Finally, it is not yet clear that ARBs are as safe and effective as ACEIs in long-term use, as noted in the AHRQ report on comparative effectiveness. Publication of the results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in 2004 raised concern about the possible relative risk of ARBs, particularly in patients at high risk of cardiovascular events.\(^8\) An outcome of the VALUE trial was not cited in the abstract was that the ARB valsartan produced a statistically significant 19% relative increase in the prespecified secondary endpoint of MI (fatal and nonfatal) compared with amlopidine. Verma and Strauss in an editorial in the British Medical Journal posited that (a) the results of the VALUE trial should be acknowledged in the context that ARBs may increase the risk of MI and (b) perhaps it is time to consider informing patients of this apparent increased risk.\(^9\) However, McDonald et al. in a subsequent systematic review concluded that there was not an increased risk of MI compared with placebo (OR, 0.94; 95% CI, 0.75-1.16) or compared with ACEIs (OR, 1.01; 95% CI, 0.87-1.16).\(^10\)

There is much that we do not know. Outcomes research is necessary whether the intervention is sword swallowing or step therapy to manage population health care. In the present article by Yokoyama et al., the drug cost savings appear to be underestimated, but the potential costs in patient or provider dissatisfaction and the personnel costs incurred in pharmacy and physician offices were not assessed. Thus far, the evidence shows that step-therapy interventions can help steer patients to the therapy with the greatest value.

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REFERENCES


16. Analysis of pharmacy claims for dates of service for the 3 months from October 1, 2006, through December 31, 2006, for a pharmacy benefit manager for more than 2,000 small employers throughout the United States.


