

## LETTERS TO THE EDITORS

### TO THE EDITORS

In the article by Marshall et al<sup>1</sup> there are several design flaws that tend to render the results far less useful than the authors conclude.

The comparison of a scheduled narcotic for chronic pain with a similar medication for breakthrough pain only is not a clinically relevant comparison. Chronic pain should always be treated with a combination of chronic and immediate release (IR) medications. The question that should have been asked is whether a short half-life drug scheduled every 4 hours provided better relief than a scheduled drug every 6 hours or a sustained-release (SR) drug lasting 12 hours, each patient having the same opportunity for treatment of breakthrough pain.

The oxycodone-acetaminophen group only took their medications on an as-needed basis, rather than on a set schedule, whereas patients in the oxycodone SR group received medication around the clock. Administration of medications on only an as-needed basis has been shown in other studies and clinical guidelines to clearly result in suboptimum outcomes because patients have the tendency to wait until they are in pain before taking the next dosage.<sup>2,3</sup> As-needed administration of drugs will frequently leave patients with the perception that the pain is not being well managed with the medication.

In addition, the study by Marshall et al is biased in favor of the oxycodone SR group by allowing patients in this group 5 mg of oxycodone IR whenever requested. However, in the oxycodone-acetaminophen group, patient intake of drugs was limited in several ways. Because of the acetaminophen content, the doses per day were limited to less than the maximum; in fact some patients in the oxycodone-acetaminophen group could not even receive the full oxycodone IR every 4 to 6 hours because they were on other acetaminophen products (not a limiting factor in the oxycodone SR group). Moreover, the administration of 5 mg oxycodone in the oxycodone-acetaminophen group, unlike the administration in the oxycodone SR group, was available only at the discretion of the prescriber. The easier solution would have been to provide both groups with oxycodone IR as needed for breakthrough pain with no or low amounts of acetaminophen, thereby allowing patients whatever amount of oxycodone IR they needed.

The measure of improvement was done using a scale that measured multiple variables through the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and the Health Utilities Index 3 (HUI3) scale; the latter contains 8 components. It is unrealistic to suggest that changes in that scale can be attributed solely to the treatment and relief of pain

without considering the confounders that may have acted on the other variables measured. For example, Marshall et al fail to consider the baseline characteristics of patients' arthritis, emotional state, or progression of their disease in which "improvement" would be based on much more than satisfaction with pain. These factors would affect not only the quality-adjusted life-years (QALYs) calculation (which was adjusted for in HUI3), but also the WOMAC score, the basis for determining "improvement."

The measure of pain relief by QALYs could be translated in a form much more useful for a decision maker than by comparing it to the arbitrary and standby standard used by many authors: \$50 000 to \$100 000 per year.

Assuming the data and results are valid, 0.0105 QALY equates to about 4 days of "wellness." A better question for decision makers is whether it is worth about \$800 over 4 months (or about \$6 more each day) to have patients who can describe their pain as improved noticeably in 4 of those 120 days, or about \$200 each month for 1 extra day in the month of improved pain.

Last, it was completely unnecessary for the article to refer to the sustained-release version by the brand name other than to bias the reader in favor of the product made by the study's sponsor. This product is available as a generic version and at a lower price than the branded version cited in the study.

Readers who still think the design by Marshall et al is valid should look more closely at the lower cost per QALY they can obtain by the use of the generic version of sustained release oxycodone.

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### RESPONSE TO LETTER TO THE EDITOR

We appreciate the opportunity to respond to the comments and questions raised by Dr Basskin regarding our study. The stated objective of the study was to evaluate controlled-release (CR) oxycodone q12h compared with

standard therapy (oxycodone-acetaminophen as needed) for the management of moderate to severe osteoarthritic pain of the hip or knee in a naturalistic setting. Subjects were allowed to continue their platform of usual care including the use of over-the-counter analgesics, herbal supplements, and nonpharmacologic interventions.

Dr Basskin expressed concern regarding the choice of comparator. We agree that one of the critical considerations in designing pharmacoeconomic studies is the selection of a comparison therapy that is clinically relevant. Our study was designed to reflect common practice/usual care in a naturalistic setting to obtain suitable data to conduct pharmacoeconomic analyses. To maximize external validity, the selection of a comparator should be dictated by prevailing standards of care. In that regard, one of the strengths of our study is that it compared CR oxycodone prescribed every 12 hours to one of the most commonly prescribed regimens for this type of chronic nonmalignant pain: oxycodone-acetaminophen prescribed as needed. As such, the study assesses the incremental benefit of treatment with CR oxycodone compared to standard treatment with oxycodone-acetaminophen, providing data of “real world” relevance.

In Dr Basskin’s discussion regarding the use of 5 mg immediate-release (IR) oxycodone as rescue medication, we would like to address several misconceptions. As stated above, the study was designed, as much as possible, to reflect standard practice in a usual care setting. Dr Basskin suggests that oxycodone intake was limited in the oxycodone-acetaminophen group in multiple ways because of the acetaminophen content of the medication. This is an intrinsic limitation of this medication; the risks associated with high levels of acetaminophen intake have been well documented.

When CR opioid analgesics are used, it is a principle of pain management as well as common practice to also make an IR opioid available, to be taken by the patient on an as-needed basis for “breakthrough” pain. In this study, subjects in the CR oxycodone group could be prescribed 5 mg IR oxycodone every 4 to 6 hours as needed, with a maximum daily rescue dose of 15 mg. Dose adjustments for CR oxycodone were made at the discretion of the investigator. By nature of the prescribing instructions, subjects in the oxycodone-acetaminophen (5/325 mg) group were instructed to receive 5 mg IR oxycodone every 4 to 6 hours on an as-needed basis. Due to dose-limiting toxicities associated with acetaminophen ingestion, subjects who reached the maximum daily dose of acetaminophen were eligible to receive IR oxycodone (single entity) as rescue medication, at the discretion of the investigator.

In addition to the naturalistic character of this study, which compared treatments applied in routine clinical settings, another strength of our study design was the use of randomization. Dr Basskin suggests that it is unrealistic to suggest that changes in the Health Utilities Index 3 (HUI3) scale, which contains 8 components, can be attributed to treatment and relief of pain without controlling for confounding factors. First, although the HUI3 scale contains 8 components, it also, and most importantly, contains a single summary score that represents the utility of the health of the patient over the recall period. Second, as this study was a randomized trial, the difference in improvement and utility gain between the 2 treatment groups can be considered attributable to the intervention, not to confounders. The randomization aspect of the design is intended to balance the 2 treatment groups and is generally considered to be the gold standard in study design to control for confounding. Moreover, in a detailed statistical analysis plan specified *a priori*, the analysis for the primary outcome measure (improvement in Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain index) controlled for study site, and the number of quality-adjusted life-years (QALY) over the 4-month study period was adjusted for potential differences in utility at baseline.

As per standard analytical procedure, we did indeed examine and compare all subject characteristics at baseline by treatment group. With regard specifically to the subject’s emotional status, scores on the Beck Depression Inventory at baseline were similar between the groups: 9.31 (SD=7.831) for oxycodone-acetaminophen compared to 9.79 (SD = 8.467) for CR oxycodone, with a higher score indicating a higher level of depression. A table of baseline characteristics was included in the original manuscript, but was deleted due to space considerations. As indicated in the paper, this table is available on request from the authors.

The validity of the pharmacoeconomic results is further supported by clinical data described in a forthcoming manuscript. For example, during the 4-month study period, the CR oxycodone group showed significant improvement in the WOMAC composite pain score, the composite function score, and the composite stiffness score as well as significant reduction in sleep interference due to osteoarthritic pain compared with the oxycodone-acetaminophen group.

With regard to the interpretation of the measure of pain relief by QALYs, Dr Basskin proposes a format that differs from the standard approach of \$50 000 to \$100 000 per year. First, to clarify, the gain of 0.0105 QALY equates to about 4 days of being alive and healthy

(utility 1) rather than being dead (utility 0). An alternative scenario for presentation purposes is one of being completely healthy and pain free (utility 1) for 8 days versus being in significant arthritic pain and poor health (utility 0.5) for those 8 days annually. The question then becomes whether it is worth spending approximately \$800 over 4 months to achieve this gain or not. This might be a useful way to present the data for decision-making purposes, and we thank Dr Basskin for suggesting this kind of analogy. However, decision makers generally do not want these kinds of disease-specific value statements. Instead, they prefer a standard comparison of dollars per QALY gained to compare competing program options.<sup>1-5</sup> This is the rationale underlying QALY analyses.

Finally, Dr Basskin asserts that it was unnecessary to refer to the CR oxycodone product by its brand name, suggesting that in doing so the reader would be potentially biased in favor of the study sponsor's product. In fact, both study drugs in the trial were referred to by their brand names. The brand names for both study drugs were specified simply to disclose, in a transparent manner, the actual products administered in the study. We believe this to be standard practice in the context of describing study treatments and disclosure of results. Moreover, it is worth noting that during the study design and implementation period, only the branded version of CR oxycodone was available, and a generic version was still not available at the time that the study data were analyzed. As a result, the branded drug was used in the cost analysis. One of the main cost drivers in the cost-effectiveness analysis (Table 2) was the cost of prescription medication. Consonant with Dr Basskin's comment, if generic CR oxycodone had been substituted in the

analysis, the cost per QALY would have been even lower than that reported in our study results.

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