Appl Health Econ Health Policy (2013) 11:555–557
DOI 10.1007/s40258-013-0049-6

LETTER TO THE EDITOR

Authors' Reply to Liedgens and Henske: "Cost-Utility Analysis of Duloxetine in Osteoarthritis: A US Private Payer Perspective"

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Published online: 2 August 2013

Dear Editor,

Thank you for giving us the opportunity to respond to the letter from Liedgens and Henske [1] concerning our cost-utility analysis of duloxetine in osteoarthritis (OA) [2]. Our analysis spanned multiple drug classes, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and an antidepressant. We were surprised by the reaction of Dr. Liedgens and Henske and are pleased to address their concerns. We do so below, using the same order and numbering as those used in their letter.

1) In their letter, Liedgens and Henske focus on pain levels. The basis of the treatment-specific utilities in our model was Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores, not exclusively pain scores. Total WOMAC scores incorporate function and stiffness, as well as pain. WOMAC scores have been mapped to health-related quality of life utilities by several studies [3–5] and have been used in pharmacoeconomic models such as that produced for the UK National Institute for Health and Clinical Excellence OA guideline [6]. The inclusion criteria for nearly all OA trials, regardless of treatment, specify pain of at least 4 on a 0–10 scale, i.e. at least moderate pain. Moreover, tapentadol trials have not reported baseline WOMAC scores, so there is no basis to assume that the severity of OA in those trials was greater than that in trials of other treatments. We believe that the continuum of treatments from NSAIDs to opioids represent relevant comparators to duloxetine and therefore they are appropriately represented in our analysis.

2) Liedgens and Henske note that our article did not make it clear which formulation of tapentadol was being compared. We concede that we could have been more specific; however, the assumptions we made for tapentadol were not made to enhance the position of duloxetine, but were made because of the unclear reporting of WOMAC scores in tapentadol trials (see response #9 below) and to be conservative in our estimation of the cost of tapentadol. The makers of tapentadol have conducted clinical trials of both immediate release (IR) [7] and extended release (ER) [8–10] formulations of tapentadol in OA populations. To be conservative in our analysis, the tapentadol IR formulation was used for costing because it is cheaper in the USA. Therefore, tapentadol IR dosing was also used.

3) Liedgens and Henske incorrectly state that an oxycodone daily dose of 10–30 mg was used in our model. The model's dosage was 10–30 mg twice daily (see Table 1 in our article) [2]. The range of tapentadol dosing in the model was the same as that in the tapentadol IR study conducted by Hale et al. [7]. The average tapentadol IR daily dose used in the model was 450 mg, not the 600 mg stated by Liedgens and Henske.

4) Liedgens and Henske incorrectly state that the utility for tapentadol in our model was the same as that for tramadol. In fact, tapentadol was assigned the same utility as oxycodone—the highest efficacy-based, treatment-specific utility assigned in the model (see Table 1 in our article).

In addition, the initial 3-month discontinuation rates for tapentadol IR and ER are very similar (44.0 % for tapentadol ER in the analysis performed by Lange et al. [11]

This reply refers to the article available at doi:10.1007/s40258-013-0031-3 and doi:10.1007/s40258-013-0048-7.

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and 43.4 % for tapentadol IR in the study conducted by Hale et al. [7]).

5) Contrary to the assertion by Liedgens and Henske, the rate of proton pump inhibitor (PPI) usage associated with opioids in the model was less than half that for the NSAID naproxen (see Table 1 in our article). This PPI usage rate by US opioid users was documented by Kelly et al. [12] and further supported by Williams et al. [13].

6) Liedgens and Henske pose several questions concerning discontinuation costs. The discontinuation cost listed in Table 1 in our article was not the cost for each patient treated in the model—rather, it was the cost per patient who discontinued. We estimated that cost as being the drug cost while tapering off the opioid. (The need for tapering to reduce withdrawal symptoms is clearly stated in the tapentadol prescribing information.) For dosages during tapering, we relied on the Washington State Medicaid opioid tapering calculator [14], which generally specified a 10 % dosage reduction per week. Liedgens and Henske are correct that, as in the model, the discontinuation rate is lower for tapentadol than for oxycodone. The probability of discontinuation, however, is unrelated to the cost per patient who discontinues. The cost of discontinuation plays a minor role in the model; even if we set the cost of discontinuation for tapentadol to zero, tapentadol remains over US$1,000 more expensive per patient than any other comparator.

7) Our manuscript was submitted in September 2012, which was prior to the November/December 2012 publication by Dart et al. [15] mentioned in the letter from Liedgens and Henske.

8) Tapentadol and oxycodone are both listed as Schedule II controlled substances by the US Drug Enforcement Administration, meaning that they have a high potential for abuse [16]. Even if we reduce the opioid abuse rate for tapentadol to zero in our model, tapentadol remains over US$1,300 more expensive per patient than any other comparator.

9) Liedgens and Henske take our statement regarding the lack of tapentadol trials out of its context with regard to efficacy. Our analysis of efficacy and our estimation of treatment-specific utilities were based on the availability of total WOMAC scores. Since Hale et al. [7], Lange et al. [11] and Wild et al. [17] had patient populations spanning both OA and chronic low back pain, WOMAC scores (which are specific to OA) were not outcomes in those trials. Total WOMAC changes from baseline scores were reported by two tapentadol ER trials (ClinicalTrials.gov identifiers NCT00421928 [8, 9] and NCT00486811 [10]). The numbers of patients analyzed for WOMAC scores in both the NCT00421928 and NCT00486811 trials were much lower than the numbers randomized, placing these WOMAC scores in doubt. Moreover, Afilalo et al. [8] did not specify the scale of the WOMAC scores that were reported. The description of changes from baseline total WOMAC scores in the ClinicalTrials.gov entry for the NCT00421928 trial states that the total WOMAC is a "…measure with a Likert ordinal scale from 0–4…" [9]. This is clearly erroneous, as each item in the WOMAC is on a 0–4 Likert scale, with the total score being on a 0–96 scale [18]. While WOMAC scores in the literature have been reported using unconventional scales, reporting the total WOMAC score on a 0–4 scale would be very rare and perhaps unprecedented [19].

Given the above, no tapentadol studies were available that reliably reported WOMAC scores for estimation of efficacy and utilities. We made the conservative assumption (conservative for duloxetine, and favourable for tapentadol) that the difference between tapentadol and placebo in the change from the baseline total WOMAC score ($\Delta\Delta$) would be equivalent to the efficacy of oxycodone controlled release (CR) in the study by Markenson et al. [20]. Markenson et al. reported a $\Delta\Delta$ value of 17.5, while the NCT00421928 trial (the tapentadol ER trial reporting better WOMAC scores) reported a $\Delta\Delta$ value of 0.3 [9]. Even if the NCT00421928 trial score was reported on a 0–4 scale, once converted to a 0–96 scale, the $\Delta\Delta$ value is only 7.2. Thus we assumed a treatment effect over twice that seen in the NCT00421928 trial, using the most generous interpretation possible. We did so on the basis of the statistically non-significant difference in total WOMAC scores between tapentadol ER and oxycodone CR in the NCT00421928 and NCT00486811 trials [9, 10].

We acknowledge that the formulation of tapentadol could have been specified in our article. Nonetheless, our analysis was conservative. For tapentadol, we assumed both the cost of the lower-priced tapentadol IR formulation and a level of efficacy possibly more than twice as high as that reported in tapentadol ER trials. In preparation for our response to the Liedgens and Henske letter, we performed an additional analysis using ER pricing and assuming that the WOMAC scores reported in the NCT00421928 and NCT00486811 trials were on a 0–4 scale. That analysis was less favourable to tapentadol than the one we published. We stand by our research, analysis and published conclusions.

Conflicts of interest Funding to perform this research was provided by Eli Lilly and Company, Indianapolis IN, USA. Mr Wielage is an employee of Medical Decision Modeling, a contract research organization and vendor to Eli Lilly and Company. Ms Bansal is a past employee of Medical Decision Modeling. Dr Andrews is an employee of Eli Lilly and Company. Mr Klein is a principal and employee of Medical Decision Modeling. Dr Happich is an employee of Lilly Deutschland GmbH.

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