VALUE IN HEALTH 16 (2013) 334–344

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

The Cost-Effectiveness of Duloxetine in Chronic Low Back Pain: A US Private Payer Perspective

Ronald C. Wielage, MPH[1,], Megha Bansal, MA[1], J. Scott Andrews, PharmD[2], Madelaine M. Wohlreich, MD[2], Robert W. Klein, MS[1], Michael Happich, PhD[3]*

[1]*Medical Decision Modeling Inc., Indianapolis, IN, USA;* [2]*Eli Lilly and Company, Indianapolis, IN, USA;* [3]*Lilly Deutschland GmbH, Bad Homburg, Germany*

ABSTRACT

Objective: To assess the cost-effectiveness of duloxetine in the treatment of chronic low back pain (CLBP) from a US private payer perspective. **Methods:** A cost-utility analysis was undertaken for duloxetine and seven oral post–first-line comparators, including nonsteroidal anti-inflammatory drugs (NSAIDs), weak and strong opioids, and an anticonvulsant. We created a Markov model on the basis of the National Institute for Health and Clinical Excellence model documented in its 2008 osteoarthritis clinical guidelines. Health states included treatment, death, and 12 states associated with serious adverse events (AEs). We estimated treatment-specific utilities by carrying out a meta-analysis of pain scores from CLBP clinical trials and developing a transfer-to-utility equation using duloxetine CLBP patient-level data. Probabilities of AEs were taken from the National Institute for Health and Clinical Excellence model or estimated from osteoarthritis clinical trials by using a novel maximum-likelihood simulation technique. Costs were gathered from Red Book, Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project database, the literature, and, for a limited number of inputs, expert opinion. The model performed one-way and probabilistic sensitivity analyses and generated incremental cost-effectiveness ratios (ICERs) and cost acceptability curves. **Results:** The model estimated an ICER of $59,473 for duloxetine over naproxen. ICERs under $30,000 were estimated for duloxetine over non-NSAIDs, with duloxetine dominating all strong opioids. In subpopulations at a higher risk of NSAID-related AEs, the ICER over naproxen was $33,105 or lower. **Conclusions:** Duloxetine appears to be a cost-effective post–first-line treatment for CLBP compared with all but generic NSAIDs. In subpopulations at risk of NSAID-related AEs, it is particularly cost-effective.

Keywords: chronic low back pain, cost-effectiveness, cost-utility analysis, duloxetine, pharmacoeconomic model.

Introduction

Low back pain (LBP) is the second most common cause of disability in the United States, exceeded only by arthritis and rheumatism [1]. During a 3-month period, 28.1% of US adults experience a day or more of LBP [2]. An estimated 70% to 80% of the population will experience LBP in their lifetimes [3] of whom 10% will progress to chronic LBP (CLBP). Although studies estimating the economic burden to the US economy have varied in methodology, they agree that the cost of LBP is large: $12 to $90 billion is incurred annually in direct costs, with indirect costs perhaps three times higher [4]. Few studies differentiate the cost of CLBP versus nonchronic or acute LBP.

CLBP has been variously defined but typically is described as LBP that is present longer than 3 months [5,6]. In North America, the prevalence of CLBP is estimated at 9% to 10.2% and appears to be increasing, up from 3.9% in 1992 [7,8]. Approximately 74.4% of the CLBP population suffers moderate to severe pain [8]. CLBP is often a mixed pain syndrome with nociceptive, neuropathic, and hyperalgesic components [9].

Few clinical trials of oral treatments for CLBP have been conducted. A 2011 review of pharmacological treatments for CLBP found only four studies of nonsteroidal anti-inflammatory drugs (NSAIDs), five of antidepressants, and eight of opioids; moreover, the review found that the quality of the evidence as of publication was low [10]. A 2009 review of pharmacotherapy for chronic pain reported no treatments with good-quality evidence of substantial benefit in LBP [11].

Cost-effectiveness analyses (CEAs) have been recognized as a pressing need [12]. Even so, few have been conducted [13]. The National Institute for Health and Clinical Excellence (NICE) reported that no economic models could be located for NSAIDs, opioids, or antidepressants for its 2009 guideline for LBP [14].

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, has demonstrated analgesic effects in CLBP in three 13-week randomized controlled trials (RCTs) [15–17]. Long-term efficacy has been demonstrated in an open label extension trial of 41 weeks [18]. A pooled analysis of duloxetine RCTs completed through 2008 reported that most treatment emergent adverse events (AEs) tended to be mild to moderate in severity

* Address correspondence to: Ronald C. Wielage, Medical Decision Modeling Inc., 8909 Purdue Road, Suite 550, Indianapolis, IN 46268, USA.

E-mail: rwielage@mdm-inc.com.

1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2012.12.006

and transitory in nature [19]. In November 2010, the US Food and Drug Administration approved duloxetine for chronic musculoskeletal pain [20]. By using the relative wealth of data available for duloxetine, we parameterized a pharmacoeconomic model to compare the cost-effectiveness of duloxetine and seven oral post–first-line comparators in CLBP treatment, including NSAIDs, weak and strong opioids, and an anticonvulsant.

Methods

The authors developed a semi-Markov model from a US private payer perspective for oral treatments of CLBP in a post–first-line (post-acetaminophen [APAP]) place in therapy. We modeled duloxetine and comparators representing commonly used drug classes in the US market: a nonselective NSAID and a COX-2 inhibitor, strong opioids, weak opioid/monoamine reuptake inhibitors, an anticonvulsant as well as a combination product. Specifically, the model included naproxen, celecoxib, oxycodone extended release (oxycodone), tapentadol extended release (tapentadol), tramadol immediate release (tramadol), pregabalin, and oxycodone/APAP as comparators to duloxetine (Table 1).

CLBP and osteoarthritis (OA) are both chronic musculoskeletal conditions that are commonly treated with NSAIDs and opioids. In both conditions, these oral treatments are not disease modifying, but provide symptomatic improvement in pain associated with the condition. Therefore, in the absence of CEAs in CLBP, we referenced the 2008 OA economic model published by NICE as a framework. Appendix D of the NICE OA guidelines documents the model, with additional documentation of treatment-specific utilities in Appendix C [33]. The NICE LBP clinical guidance refers to the OA guidelines concerning treatment with NSAIDs [14].

Model Overview

The model is a discrete-state, time-dependent semi-Markov model with changing probabilities as the cohort ages. Treatment efficacy, AE profile, and discontinuation as well as concomitant proton pump inhibitor (PPI) usage are the clinical dimensions modeled. Economic inputs include drug costs and medical utilization for the management of AEs, titration, and discontinuation. The model includes two types of AEs: persistent and transient. Persistent AEs disrupt treatment, increase costs, and have a permanent effect on mortality and health-related quality of life (HRQoL). Transient AEs temporarily increase costs and lower HRQoL but have no permanent effect. Treatment-specific utilities represent treatment efficacy in the model. AE profiles are modeled with 3-month probabilities of incurring persistent or transient events. We modeled aging by using age-dependent relative risks of persistent AEs, age-specific general population utility weights, and increasing mortality. The model calculates cycle-specific utilities from the interaction between utilities/utility weights representing treatment efficacy, age, and AEs. Model inputs are parameterized from the NICE model, meta-analysis, the literature, and, for a small number of inputs, expert opinion.

Structure

We used a lifetime time horizon with 3-month cycles to the maximum length of treatment and annual cycles thereafter. This allows the model to accumulate the long-term effects of NSAID-related AEs. Health states include treatment, death, and 12 during- and post- persistent-AE states. In the treatment state, the patient experiences the increased HRQoL due to treatment, reductions to HRQoL due to transient AEs, and changes in HRQoL due to discontinuation and switch to a post-discontinuation basket of treatments (PDBT). The PDBT is composed of all comparators weighted by market share (days prescribed). Costs are incurred in the treatment state for treatment drugs, management of transient AEs, and medical services related to titration and discontinuation. Upon the end of the treatment period, the portion of the cohort still receiving each comparator discontinues and switches to the PDBT. In the base case, treatment is for the lesser of 1 year, until discontinuation, or until occurrence of a persistent AE and is followed by treatment from the PDBT until death.

Patients transition to other health states upon death or any of six persistent AEs. These health state transitions may take place during the original treatment period or after switch to the PDBT. The patient enters a 3-month during-AE health state followed by a post-AE state in which the patient continues until death. During these states, HRQoL, excess mortality, and cost are assessed as appropriate to the AE. The age of the cohort during each cycle determines the appropriate background mortality. Figure 1 is a simplified depiction of the model structure.

Adverse Events

Persistent AEs include cardiovascular (CV) and gastrointestinal (GI) AEs associated with NSAID treatment as well as fracture, an AE associated with opioid and anticonvulsant comparators (Table 2). Transient AEs included in the model occur at substantially different rates among the comparators, potentially having economic and HRQoL impacts (Table 3).

Transition Probabilities

We used the 3-month CV and GI AE probabilities from the NICE model for naproxen and celecoxib, and assumed equivalence to no treatment for other comparators [33]. The probabilities of fracture were derived principally from odds ratios calculated by Vestergaard and colleagues and applied to rates of fracture in the general population [35,36,46,52,62–65]. We examined duloxetine CLBP clinical trial reports for rates of fracture; fractures occurred at or below the rates found in the control arms [34,66,67]. Age-dependent relative risks from the literature were then applied to these probabilities [46,57,58].

The age-dependent probability of background mortality at each cycle is calculated from a US life table [68], while excess mortality associated with each persistent AE was derived from a variety of sources in the literature [33,46,51,53–56,69].

Transient AE and Discontinuation Probabilities

We conducted meta-analyses for most transient AEs and for discontinuation by using CLBP RCTs for duloxetine and OA RCTs for NSAIDs and opioids, as more OA RCTs were available. A 12-week minimum duration of treatment was among the inclusion criteria. Three-month probabilities of dyspepsia for naproxen and celecoxib were taken from the NICE model, and were assumed equivalent to no treatment for other comparators [33].

We used conventional techniques for the AE meta-analysis when possible. A maximum-likelihood simulation technique was used when an AE rate fell below the reporting threshold for one or more RCTs of a treatment. This technique assumed that all RCTs for that treatment experienced the AE rate within the same binomial distribution truncated by the publication reporting thresholds. In the case that no publications for a treatment reported a rate for an AE, a rate was assumed equal to that of another medication in the same class. AE rates for tapentadol were taken from the Nucynta package insert.

A meta-analysis of discontinuation rates from the OA RCTs above was used to calculate discontinuation probabilities in the first 3-month cycle of treatment for NSAIDs and opioids. Data were pooled from two RCTs in neuropathic pain for pregabalin