Arch Neurocien (Mex)
Vol. 18, No. 4: 171-181; 2013

Artículo original

Economic evaluation of duloxetine in the treatment of chronic low back pain in Mexico

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ABSTRACT

Objective: to compare the costs and efficacy results of duloxetine 60 mg QD/BID (DUL) and the fixed combination of tramadol/paracetamol 37.5/325 mg every 4 to 6 hours (TMD/PCM) in the pharmacological treatment of chronic low back pain (CLBP) from the perspective of public and private healthcare systems in Mexico. *Material and methods:* we performed a systematic search of all the multicenter, double-blind, randomized and placebo-controlled studies evaluating DUL and TMD/PCM in CLBP. By using the adjusted indirect comparison, we determined the likelihood of achieving satisfactory response (defined as pain relief ≥30 and ≥50% -compared to baseline) and early withdrawal. The time horizon of the study was 3 months. All the drugs acquisition costs, intolerable adverse event attention costs and medical management according to response type, were analyzed and expressed in Mexican pesos. Information sources included official listings and published literature. The sensitivity analysis was deterministic and probabilistic. *Results:* for both perspectives public and private, DUL resulted to be a dominant option (less costly, more effective) than TMD/PCM. Mean savings in patient receiving DUL were $203 pesos (1.5%) and $1,545 pesos (8.6%) for public and private perspectives, respectively. This means that for every 10,000 patients treated with DUL there would be a gain of 3 quality-adjusted life years (QALY). The model remains robust and DUL was the preferred choice in 59% (public perspective) and 90% (private perspective) of the generated simulations. *Conclusion:* DUL offer important savings in the management of LBP and represents a more-convenient regimen for patients.

Key words: economic evaluation, duloxetine, low back pain, Mexico.

Evaluación económica de la duloxetina en el tratamiento del dolor de espalda crónico en México

Objetivo: comparar costos y resultados de la eficacia asociadas de duloxetina 60 mg QD/BID (DUL), combinación fija de tramadol/paracetamol 37.5/325 mg cada 4 a 6 horas (TMD/PCM) en el tratamiento farmacológico del dolor de espalda crónico (DLC) desde la perspectiva de los sistemas de salud públicos y privados de México. *Material y métodos:* se realizó una búsqueda sistemática de todos los estudios multicéntricos, doble ciegos, aleatorizados y controlados con placebo que evaluaron DUL y TMD/PCM en el DLC. Mediante el uso de la comparación indirecta ajustada, a fin de determinar la probabilidad de lograr una respuesta satisfactoria (definida como el alivio del dolor[3] 30 y 50 %[3] en comparación con la basal) y el abandono de tratamiento. El horizonte temporal del estudio fue de 3 meses. Todos los costos de adquisición de medicamentos, eventos adversos grado 3/4, atención de eventos y atención médica de acuerdo al tipo de respuesta, fueron analizados y expresados en pesos mexicanos. Las fuentes de información incluyen listados oficiales y publicados en la literatura. El análisis de sensibilidad fue determinístico y probabilístico. *Resultados:* para ambas perspectivas pública y privada, DUL resulto ser una opción dominante (menos costosa, más eficaz) comparada con TMD/PCM. El ahorro promedio en los pacientes que reciben DUL fue $ 203 pesos (1.5 %) y $ 1.545 pesos (8.6 %) para las perspectivas públicas y privadas, respectivamente. Esto significa que por cada 10,000 pacientes tratados con DUL habría una ganancia de 3 años de vida ajustados por calidad (AVAC). El modelo sigue siendo robusto y DUL era la opción preferida en 59 % (perspectiva pública) y 90 % (punto de vista privado) de las simulaciones generadas. *Conclusión:* resultados del presente estudio, sugieren que

DUL podría ofrecer importantes ahorros en el tratamiento del dolor lumbar y lograr más años de vida con calidad para el paciente.

Palabra clave: evaluación económica, duloxetina, dolor lumbar, México.

Low back pain (LBP) is a lumbo-sacral pain, located at the level of the iliac ridge or lower, which can irradiate down to the knee[1]. LBP is a complex and heterogeneous medical condition which includes a great variety of symptoms[2]. The etiological factors include changes in the central nervous system such as neuronal hyperactivity, membrane excitation, inhibitory-system dysfunction, sensitization and expression of new genes which modulate inflammatory factors[3]. In the general population, up to 16% of LBP cases can be attributable to psychological factors such as anxiety[4].

Around 60-80% of people will present a LBP episode on their lifetime[1,5,6]. The LBP prevalence reported in literature varies from 1.0 to 58.1%, with a mean value of 18.1% (median 15.0%)[5]. In Mexico, LBP prevalence has been reported in a range from 5.8 to 6.3%[7,8]. LBP presents spontaneous resolution within 1-3 months in most of the cases. However, up to 15% of patients show persistent pain 1 year after the initial episode[3]. Indeed, LBP is recognized as one of the most frequent causes of non-oncologic pain[9]. The list of potential risk factors to undergo chronicity includes several aspects such as demographical, environmental and lifestyle, including smoking, obesity, manual activity occupations, driving vehicles for long periods and job dissatisfaction and stress[3,5].

Due to its high prevalence and the risk to become chronic, LBP entails a considerable economic impact at personal, family and social levels. It is estimated that all back pain (including LBP) consume nearly one fifth of the health expenses, which is equivalent to 1.5% of the gross domestic product[10]. The mean total cost of patients with chronic LBP (CLBP) tends to be twice as high compared to the respective cost for acute LBP[11]. A typical patient with CLBP in the United States has 7,500 USD of direct medical costs every 6 months[2]. It is also known that LBP constitutes one of the main reasons of medical consultation at the first-level (i.e., family medicine) in Mexico. Sánchez-Hernández *et al.* reported that the mean cost for every LBP case ranges from 7,896 to 13,237 Mexican pesos (2006 values)[12]. Literature data shows that the indirect costs related to loss of labor productivity caused by LBP are generally higher than the direct medical costs, representing between 46 to 85% of total cost[13-16]. Evidence also shows that the economic impact of LBP is related to its severity, duration and the age at presentation, among other factors[16,17]. The components with greater load for direct medical cost are physiotherapy sessions, medical treatment and hospitalization time[16,18]. The health-related quality of life (HRQoL) in patients with CLBP tends to be low due to the pain and its effect on the sleeping patterns[19], and also because people affected with this condition generally present mood disorders, with frequent episodes of stress and anxiety[20,21].

The main objective of CLBP treatment is to prevent, reduce, or (if possible), eliminate the pain. Concomitant objectives include improvement of quality of life, functional capacity and ability to recover independence[22]. Therapeutic approach for CLBP must be individualized, with a multidisciplinary scope and comprised by pharmacological and non-pharmacological strategies[1,22-25]. Non pharmacological strategies include education, orientation, cognitive-behavioral therapy, exercise, physiotherapy, multidisciplinary intensive rehabilitation, acupuncture, spinal manipulation, yoga and progressive relaxation[1,22-26]. Pharmacological treatment of CLBP includes the use of several agents such as paracetamol, NSAIDs, tricyclic antidepressants, serotonin selective reuptake inhibitors (SSRI), serotonin and noradrenaline selective reuptake inhibitors (SNRI), benzodiazepines, tramadol and opioid analgesics[1,22-25,27-29].

Duloxetine and the fixed combination of tramadol 37.5 mg/paracetamol 325 mg (TMD/PCM) provide effective analgesia in patients with pain of varying degrees caused by diverse pathologies, including LBP[29-33]. The objective of the present study is to compare the costs and health outcomes of duloxetine and TMD/PCM in the treatment of CLBP from the public and private healthcare perspectives in Mexico.

MATERIAL AND METHODS

A complete cost-utility evaluation was performed[33].

Competitive strategies

The comparative analysis was performed for (i) daily doses of duloxetine (DUL) 60mg for 7 weeks (all patients) and 60 mg (in responders with pain relief of at

Recibido: 25 abril 2013. Aceptado: 8 de mayo 2013.

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least 30% from baseline after 7 weeks of therapy) or 120 mg (in non-responders) from week 8 to end of treatment, and (ii) TMD/PCM administered in the following dosage: 1-2 tablets every 4-6 hours according to response (pain relief) with a maximum of 8 tablets per day. Both drugs are orally administered and the dosages were established according to the recommendations found in the Pharmaceutical Specialties Dictionary (DEF, 2012 edition) in Mexico[34].

Target population

Adult patients with diagnosis of CLBP, eligible to receive duloxetine or TMD/PCM. These usually include patients who were non-responders to paracetamol or another NSAID or patients in which NSAIDs are contraindicated[29,35].

Perspective

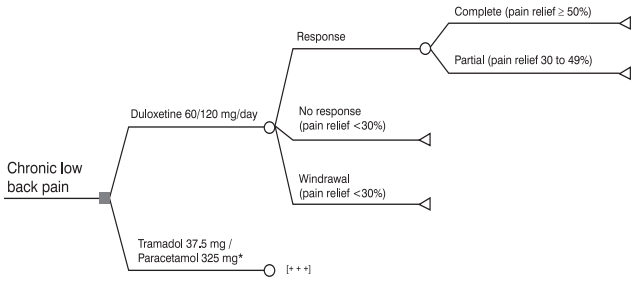
The analysis was performed from two different perspectives: (i) public healthcare system in Mexico; (ii) private healthcare system in Mexico.

Time horizon

The time horizon for this study was set at 3 months, reasonable time period concordant with other clinical studies of interest[29-32]. Because of the time horizon is less than 1 year, it was not necessary to apply any discount rate to reflect the intertemporal preferences of the population[36,37].

Decision model

Figure 1 shows a simplified structure of the analytical decision model used in this study. At the beginning of the study, the patients were assigned to either therapeutic alternative considered in this study. Because some patients withdraw study treatment prematurely, we assumed that this dropout occurs around the middle of the treatment period (approximately 1.5 months) and that such patients do not achieve a satisfactory response with the given drug (therapy). Those patients who completed 3 months of therapy had the possibility of achieving pain relief of 30% to 49% and even ≥ 50% from baseline.



* Fixed dose combination; [+ + +] indicates repeated node of duloxetine 60/120 mg/day.
Note: The percentage of pain relief refers to the change at three months versus baseline.

Figure 1. Simplified structure of the decision model: management of chronic LBP.

Systematic review

With the aim of identifying all relevant clinical information in terms of efficacy and withdrawal rates concerning the agents used in this study, we performed a systematic search in the PubMED/Medline website. The strategy consisted in the following searching chain: *(«Duloxetine» [Supplementary Concept] OR «Tramadol» [Mesh] AND «Acetaminophen»[Mesh]) AND «Low Back Pain» [Mesh].* The search was limited to human-population studies published in English or Spanish. Sixteen references were obtained. When selecting the studies who evaluated the drugs of interest in patients with CLBP, reporting efficacy and safety at three months, a total of 5 studies were selected as potentially relevant. Finally, to guarantee more comparability among the competitive strategies, we selected only those studies with flexible dosage. For that reason, two studies with fixed doses of duloxetine and performed by Skljarevski *et al*. were excluded[38,39]. The study led by Peloso[40] was also excluded because of the results reported for the placebo group were substantially different from the other 2 selected studies, situation that may implicate consi-

Table 1. Design and patient characteristics of the clinical studies selected for analysis.

Characteristics	Skljarevski, *et al.* (2010a) [41]	Ruoff, *et al.* (2003) [42]
Study design	DB-R-PC-MS	DB-R-PC-MS
Localization of participating centers	Brazil, France, Germany, Mexico and Netherlands	United States
Active treatment	Duloxetine 60/120mg [a]	TMD/PCM[b]
Treatment duration	3 months	3 months
Pain measuring scale	Brief Pain Inventory (BPI)	Pain Visual Analogue Scale (VAS)
Number of patients	236	318
Age (mean)	51 years	54 years
Female (%)	61%	63%
Caucasian /white	75%	90%
Baseline pain score	BPI = 6 [c]	Pain VAS = 70.0 [d]

DB-R-PC-MS: Double blind, randomized, placebo-controlled, multicenter study; TMD/PCM: Fixed dose combination of tramadol 37.5mg and paracetamol 325mg.
a. Initial daily dose was 30mg during the first week; then the dose was adjusted to 60mg per day. Those patients not showing pain relief ≥30% after 7 weeks of treatment were given 120mg per day from week 8.
b. Initial daily dose was 1 to 4 tablets for 10 days; then, the dose was adjusted up to a maximum of 8 tablets per day, according to the needs of every patient.
c. Mean value of the severity score reported in the BPI (weekly mean value). Comprising 11 categories (0-10) with 0 representing "no pain" and 10 representing the "worst imaginable/possible pain". Inclusion criteria baseline BPI score ≥4.
d. Pain score corresponding to mean value during 48 hours. Scores reorted by the patient by pointing or marking on a VAS, 100mm length where 0mm corresponds to "No Pain" and 100mm corresponds to the "Maximum pain". Inclusion criteria: VAS ≥40mm at baseline.

derable bias when attempting to make a placebo-adjusted indirect comparison. Both selected clinical studies[41,42] were comparable in terms of design and demographic characteristics of the patients enrolled (table 1).

Probabilities of achieving satisfactory response and withdrawal of therapy

Given that none of the selected studies reported a direct comparison of DUL and TMD/PCM, it was necessary to make an indirect-adjusted comparison[43] to determine the probabilities of reaching partial or complete response and therapy withdrawal with every treatment evaluated. In this case, the common comparator corresponds to the placebo group in the study performed by Skljarevski (2010a)[41]. Such study refers that 46 (40%) out of the 115 patients in the placebo group evaluated with the BPI instrument achieved an improvement ≥ 30% in pain intensity from baseline, including 31 (27%) patients who achieved an improvement ≥ 50%. The authors also reported that 7 (5.8%) of the 121 patients assigned to the placebo group had early withdrawal due to intolerable adverse events (AE)[41]. After determining the probabilities of achieving pain relief ≥ 30% and ≥ 50% from baseline and of therapy withdrawal due to AE with the common comparator (i.e., the placebo group in the DUL study), we then calculated the risk ratio or relative risk (RR) for each treatment intervention with their respective placebo groups (table 2). The probabilities of achieving pain relief ≥ 30 and ≥ 50% (*vs* baseline) and withdraw therapy with DUL or TMD/PCM (due to intolerable AE), were determined as the result of the probability with the common comparator (placebo) multiplied by the RR value, according to every treatment of interest (table 2). For example, when multiplying 27% by 1.36 we obtained the probability of reaching pain relief ≥ 50% from baseline in the TMD/PCM.

Table 2. Relative risk (RR) for achieving satisfactory response and early withdrawal with every treatment intervention.

DUL group			PBO group			RR: DUL vs. PBO		
N	PR	PR	N	PR	PR	Base	LL	UL
109	58	53.2	115	46	40.0	1.33	1.00	1.77
N	CR	CR	N	CR	CR	Base	LL	UL
109	42	38.5	115	31	27.0	1.43	0.97	2.10
N	WAE	WAE	N	WAE	WAE	Base	LL	UL
115	16	13.9%	121	7	5.8%	2.40	1.03	5.63
TMD/PCM group			**PBO group**			**RR: TMD/PCM vs. PBO**		
N	PR	PR	N	PR	PR	Base	LL	UL
161	88	54.7	157	62	39.5	1.38	1.09	1.76
N	CR	CR	N	CR	CR	Base	LL	UL
161	71	44.1	157	51	32.5	1.36	1.02	1.80
N	WAE	WAE	N	WAE	WAE	Base	LL	UL
161	30	18.6	157	9	5.7	3.25	1.60	6.62

DUL: Duloxetine 60/120mg per day; PBO: Placebo; TMD/PCM: Fixed dose combination of tramadol 37.5mg and paracetamol 325mg (up to 8 tablets per day); RR: Relative risk; N: Number of evaluable patients; PR: Partial response (pain relief from 30 to 49% at three months vs. baseline); CR: Complete response (pain relief ≥50% at three months *vs* baseline); WAE: Withdrawal due to adverse events; LL and UL indicate lower limit and upper limit of the 95% confidence intervals, respectively.

Resource usage and unitary costs

Only direct medical costs comprising the acquisition cost of study drugs, the cost of medical care due to intolerable AE and the cost of routine management associated with every type of response were analyzed. The cost of duloxetine in the public healthcare perspective was obtained directly from the manufacturer; the cost of TMD/PCM was obtained from the public bids for 2013 in the Mexican Social Security Institute (IMSS) purchase website[44]. In the analysis performed for the private healthcare perspective, the drug prices correspond to the values reported as «normal price» in the «*paciente plus*» website[45]. According with a document presented by Eli Lilly and Company to the FDA, 27 (23.48%) patients assigned to duloxetine required dose augmentation from the 8 week of study[46]. These patients received 120mg per day until the end of the study[41,46]. In the other hand, Ruoff *et al*[42] reported that the mean number of daily tablets of TMD/PCM per patient was 4.2. We assumed that patients in the public healthcare system presenting intolerable AE attend to the «family medicine» medical visit service. The unitary cost of this medical visit was obtained from the cost listings of the IMSS[47] and was updated to 2013 values considering the cumulative inflation between December 2011 and December 2012 in Mexico[48]. It was also assumed that the cost of a general practitioner (GP) medical visit in the private healthcare system is 10% higher. Regarding the drug consumption, it was determined that patients who withdrew due to intolerable AE received treatment only for the half of the treatment period (i.e., first 6.5 weeks).

The cost for every non-responder patient (i.e., pain relief < 30% at three months *vs.* baseline) was determined based on the results presented by Sánchez-Hernández *et al*[12] and updated to 2013 values considering the cumulative inflation between December 2006 and December 2012[48]. The costs per patient associated to complete and partial response were estimated with the information published by Beard *et al*[49]. According to this publication, patients with fibromyalgia who achieved pain relief from 30 to 49% at three months of treatment (*vs* baseline) presented costs 19% lower than patients not reaching even 30% of pain relief. Thus, in an analogous way, patients with pain relief ≥ 50% presented costs 35% lower than patients with pain relief under 30% (*vs* baseline)[49]. As it happened with the GP medical visit, we assumed that the cost of the chronic LBP management in the private

healthcare system is 10% higher (with respect to the public system).

Health outcomes

As intermediate effectiveness outcomes we considered the proportion of patients with partial response and complete response, defined as pain relief from 30 to 49% and ≥ 50% at three months (*vs.* baseline), respectively. The quality-adjusted life years (QALY) was the measure used in the cost-utility analysis. Because we did not find specific data for the evaluated responses such as percentage of pain relief in patients with CLBP, we made an adjustment to the utility scores published by *Beard, et al* [49]. In order to make such adjustment, we used the baseline values of HRQoL and pain intensity from the DUL group in the study by Skljarevski *et al (2010a)*[41], identified in the *«Clinical Study Website»* of the USA government[50]. When comparing the baseline HRQoL scores in patients with chronic LBP (BPI score =6)[50] with the same scores in patients with fibromyalgia[49], we observed similarity, and the value for chronic LBP was 5.8% lower than the fibromyalgia value (0.49 *vs* 0.52).

According to Skljarevski *et al. (2010a)*[41] and Ruoff *et al*[42] we established that a 6.5 score in the baseline BPI can be considered as adequate for our study population. *Beard et al*[49] reported that patients in the categories of 30-49% and ≥ 50% pain relief had an average reduction of 38 and 70% their level of pain intensity (*vs* baseline), respectively, and for patients with response < 30%, no improvement was observed. Thus, for a baseline BPI score of 6.5, we estimated that patients with partial or complete response would have final BPI values of approximately 4.0 and 2.0, respectively, whereas patients with no response (non-responders) would remain in the same value as baseline. Taking into account the previously mentioned information and based in the table 4, presented in the study by Beard, *et al*[49] which associates some HR-QOL scores to some BPI scores, we determined the utility values for patients with chronic LBP according to response-type. For this, we multiplied the scores of 0.46 (mean 0.40-0.52) in patients with fibromyalgia and no response, scores of 0.63 in patients with fibromyalgia and partial response and 0.74 in patients with fibromyalgia and complete response by a fixed factor of 0.942 (equal to 1-0.058) in order to obtain the respective HR-QOL scores in patients with chronic LBP. We included the disutility (loss of utility) caused by adverse events.

Incremental analysis

According to the recommendations of the General Health Council, the threshold for the incremental cost-utility ratio was fixed 144,052 Mexican pesos, this value is equivalent to the Gross Domestic Product (GDP) *per capita*, projected for 2013 in Mexico[51].

Sensitivity analysis

To evaluate the robustness of the results seen with the base-case we conducted an exhaustive

Table 3. Base case model parameters (range) and probability distribution.

Parameter	Base case value	Range	Distribution	Reference
Probability of reaching pain relief = 30% with placebo	40.00%	31.05% – 48.95%	Beta	[41]
RR of reaching pain relief = 30% with:			Log-Normal	
DUL vs. Placebo	1.33	1.00 – 1.77	Log-Normal	[41] [a]
TMD/PCM vs. Placebo	1.38	1.09 – 1.76		[42] [a]
Probability of reaching pain relief = 50% with placebo	26.96%	18.85% – 35.07%	Beta	[41]
RR of reaching pain relief = 50% with:				
DUL vs. Placebo	1.43	0.97 – 2.10	Log-Normal	[41] [a]
TMD/PCM vs. Placebo	1.36	1.02 – 1.80	Log-Normal	[42] [a]
Probability of early withdrawal due to adverse events with placebo	5.79%	2.36% – 11.56%	Beta	[41]
RR of early withdrawal with:				
DUL vs. Placebo	2.40	1.03 – 5.63	Log-Normal	[41] [a]
TMD/PCM vs. Placebo	3.25	1.60 – 6.62	Log-Normal	[42] [a]
Acquisition cost in public healthcare system in Mexico ($):				
DUL 60mg, 14-tablet package	292.86	BCV ± 10%	Uniform	Eli Lilly
TMD/PCM, 20tablet package	123.55	BCV ± 10%	Uniform	[44]
Acquisition cost in private healthcare system in Mexico ($):				
DUL 60mg, 14-tablet package	574.00	BCV ± 20%	Uniform	[45]
TMD/PCM, 20tablet package	309.00	BCV ± 20%	Uniform	[45]
Percentage of patients treated with DUL needing to adjust their daily dose to 120mg [b]	23.48	15.73 – 31.23	Beta	[46]
TMD/PCM daily tablets (mean)	4.2	---	---	[42]
Mean treatment duration in those withdrawing due to adverse events	6.5 weeks	---	---	Calculated
"Family Medicine" additional medical visits due to AE	1	---	---	Caclulated
Cost per medical visit (public sector)	499.21	BCV ± 10%	Uniform	[47, 48]
Cost per medical visit (private sector)	549.13	BCV ± 10%	Uniform	Calculated[c]
Quarterly cost of chronic LBP management according to response: (public system):				
No response	13,579	10,147 – 17,011	Gamma	[12, 48] [d]
Partial response	10,973	8,199 – 13,746	Gamma	Calculated[d]
Complete response	8,786	6,565 – 11,006	Gamma	Calculated[d]
Quarterly cost of chronic LBP management according to response: (private system):				
No response	14,936	11,161– 18,712	Gamma	Calculated[c]
Partial response	12,070	9,019 – 15,121	Gamma	Calculated[c]
Complete response	9,664	7,222 – 12,107	Gamma	Calculated[c]
Annual utility/savings according to response:				
No response	0.43	BCV ± 10%	Beta	[49, 50] [e]
Partial response	0.59	BCV ± 10%	Beta	[49, 50] [e]
Complete response	0.70	BCV ± 10%	Beta	[49, 50] [e]
Disutility (loss of utility) due to intolerable adverse events (%) [f]	10	5 – 15	Uniform	[65]

BCV: Base case value; RR: Relative risk; DUL: Duloxetine 60/120mg/day; TMD/PCM: Fixed combination of tramadol 37.5mg and paracetamol 325mg; AE: Adverse events. a: see table 2; b: from week 8; c: it was assumed that this value is 10% higher in the private system; d: it was assumed that the cost reported by Sánchez-Hernández et al. [12] corresponds to those cases with no response (updated by the inflation rate), and patients with partial response and complete response report 19% and 35% lower costs than patients with no response, respectively.[49]; e: Calculated by our investigators (see text); f: Refers to the lost utility attributable to intolerable adverse events.

sensitive analysis process. First, we generated a univariate deterministic sensitivity analysis. Then, we performed a probabilistic sensitivity analysis using a second-order Monte Carlo simulation with 10,000 interactions, which results are presented as acceptability curves. Table 3 shows the parameters used for the base case and sensitivity analysis. The gamma distributions were approximated with the mean and the standard deviation, calculated with the range data. All the analysis was performed using the TreeAge Pro 2013 software (TreeAge Software Inc., Williamstown, MA, USA).

RESULTS

Base case

From the public healthcare system perspective in Mexico, the use of DUL led to net savings of 203 pesos per patient (table 4); this number is equivalent to reducing 1.5% the average cost per patient receiving TMD/PCM. From the private healthcare system perspective, savings attributable to DUL reach 1545 pesos per patient (table 4); this figure is equivalent to reducing 8.6% the average cost per patient receiving TMD/PCM. With both treatment drugs and for all analysis perspectives, the most important expense-heading corresponds to the routine management of CLBP, followed by the acquisition cost of study medications and the cost of treating adverse events. Nonetheless, the difference in the acquisition costs of DUL and TMD/PCM was the main factor which determined the absolute difference in the mean total costs per patient with each treatment strategy evaluated. As a matter of fact, in the private healthcare sector, the study medication costs were 40% higher in the TMD/PCM group with respect to DUL group, whereas in the public healthcare system these costs were 10% higher in the TMD/PCM group compared to DUL group.

The percentage distribution of patients according to response type resulted very similar in both strategies. The proportion of patients showing response to treatment (relief ≥30% in pain intensity at three months *vs.* baseline) was slightly higher in the TMD/PCM group (55.4 *vs* 53.2%). However, the proportion of patients with complete response (relief ≥ 50% in pain intensity at three months *vs.* baseline) was higher in patients treated with DUL (38.6%) compared to those patients who received TMD/PCM (36.7%). When transforming these efficacy results into HRQoL indicators, the number of estimated QALYs for every 10,000 patients is superior for DUL than for TMD/PCM (table 4). Thus, in pharmacoeconomic terms, DUL constitutes a dominant healthcare intervention (i.e., less costly and with gain in QOL, compared to TMD/PCM). This latter is true for both the public and private healthcare systems in Mexico.

Table 4. Cost-utility analysis: DUL *vs* TMD/PCM (base case).

Public healthcare perspective analysis					
Intervention	Cost	Δ cost	QALY *	Δ QALY*	CUIR
DUL	13,368	Reference	1,379	Reference	Reference
TMD/PCM	13,571	203	1,376	3	Dominated
Private healthcare perspective analysis					
Intervention	Cost	Δ cost	QALY *	Δ QALY *	CUIR
DUL	16,380	Reference	1,379	Reference	Reference
TMD/PCM	17,925	1,545	1,376	3	Dominated

DUL: Duloxetine 60/120mg/day; TMD/PCM: Fixed combination of tramadol 37.5mg and paracetamol 325mg; QALY: Quality adjusted life years; Δ denotes incremental; CUIR: Cost-utility incremental ratio. *Data for every 10,000 patients.

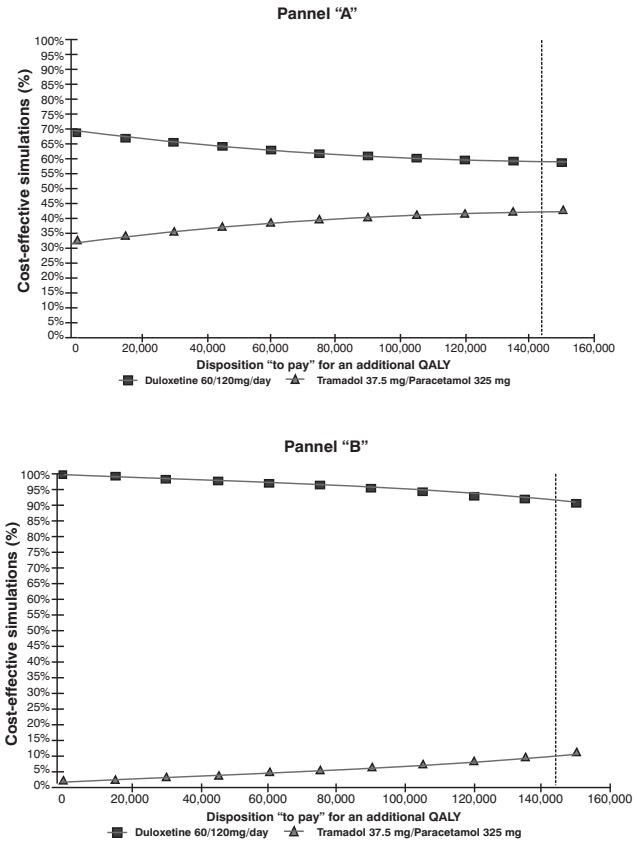
Sensitivity analysis

According to the deterministic sensitivity analysis, the five parameters generating more uncertainty regarding the results in both perspectives (public and private) were: the usual cost of CLBP management in non-responder patients; the probability of pain relief ≥30% in the reference -placebo- group; the RR of achieving pain relief ≥30% with DUL; the utility score assigned to complete response; and the cost of CLBP management in patients with complete response.

Figure 2 show the acceptability curves for the cost-utility analysis, derived from the probabilistic sensitivity analysis. This analysis shows that the probability of treatment with DUL to be less costly than treatment with TMD/PCM is 69% for the public healthcare system and 99% for the private healthcare system in Mexico. Also, the probabilistic sensitivity analysis indicates that the probability for DUL to be the preferred alternative (i.e., more cost-effective strategy, taking 1 GDP [in Mexico] as the maximum limit of acceptability) is approximately 59% for the public healthcare system and 90% for the private healthcare system in Mexico.

DISCUSSION

The present study evaluated the use of pharmacologic therapy for the treatment of CLBP from two different perspectives in Mexico: the public healthcare system and the private healthcare system. The available evidence shows that the financial burden associated with chronic LBP is rising. Even when the cost associated with drug treatment not always represents the greatest in LBP management, it does represent one of the most relevant because its



Pannel A shows the analysis of the public healthcare perspective in Mexico. Pannel B shows the analysis of the private healthcare perspective in Mexico. QALY: Quality-adjusted life years. Vertical lines indicate the estimated value of the gross domestic product for 2013 ($144,052 Mexican pesos).

Figure 2. Acceptability curves: cost-utility analysis.

important role in the evolution of patients, thus generating important impact on the costs[52]. In a context of scarcity of medical resources it is important to identify favorable and convenient treatment strategies for public healthcare institutions and general population. Both duloxetine and fixed combination of tramadol 37.5mg and paracetamol 325mg are agents used for the treatment of different types of moderate-severe pain, including musculoskeletal pain. Nevertheless, only duloxetine has the approved indication for LBP treatment in the Pharmaceutical Specialties Dictionary (DEF, 2012 edition) in Mexico[34].

Strictly speaking, the results obtained in the present study suggest that duloxetine in a dominant healthcare intervention for both perspectives. Net savings of using DUL instead of TMD/PCM for a maximum period of 3 months were $ 203.00 and $1,545.00 per patient from the public and private healthcare perspectives, respectively. This is equivalent to a 1.5% (public system) and 8.6% (private system) reductions in total cost per patient receiving TMD/PCM. The great majority of savings are just evident, because they come from the difference in acquisition costs and the average daily consumption. In the public healthcare system and taking into account the rate of early withdrawal due to intolerable adverse events (before three months of treatment), mean daily cost of giving duloxetine 60/120 mg was 21.42 pesos per patient. This same cost was 23.50 pesos for TMD/PCM, almost a 10% difference in favor of DUL. For the private healthcare system, the mean daily cost of giving TMD/PCM was nearly 40% higher than for duloxetine 60/120 mg per day. The other heading where duloxetine showed several advantages was the treatment of intolerable adverse events, although absolute advantages were of reduced magnitude.

The results of the indirect comparison show that the analgesic effectiveness of both agents (DUL and TMD/PCM) is very similar. The proportion of patients with pain relief of at least 30% at three months of treatment from baseline was slightly higher with TMD/PCM (55.4%) compared to DUL (53.2%). On the other hand, the proportion of patients with the best analgesic response (relief ≥ 50% in pain intensity at three months *vs* baseline) was higher for DUL than for TMD/PCM (38.6 *vs* 36.7%). These numbers make the HRQoL comparable among both strategies. By incorporating quality of life deterioration due to adverse events it was possible to determine the number of QALY in every strategy. The results of the base case show that both DUL and TMD/PCM lead to almost identical HRQoL scores; for every 10,000 patients (in each group), there would be a gain of 3 QALY in favor of duloxetine treatment.

With the information mentioned above and speaking in pharmacoeconomic terms, it can be stated that duloxetine constitutes a dominant healthcare strategy over TMD/PCM, due to the important and considerable savings and the better quality of life offered. Because of the narrow difference in utility, another way of analyzing the results would be to determine that both strategies are comparable in terms of number of QALY they provide and thus, to base the results only in the comparison of costs. Either way –by making cost-utility evaluation or cost-minimization analysis- DUL would continue as the preferred strategy.

Besides the economic advantages over TMD/PCM, there are some other aspects favorable to DUL which are worth to mention. First, almost 75% of patients participating in the duloxetine clinical study used for the analysis,[41] remained in the 60 mg daily dose and only 25% required 120 mg. According to the study protocol[41], patients received 120 mg in one administration. In the other hand, the pharmaceutical specialties dictionary (DEF) mentions that daily 120 mg

dosage must be given in two 60mg administrations (every 12 hours)[34]. Either way, duloxetine administration results more convenient for patients in comparison with TMD/PCM, which has to be administered every 4-6 hours, which also means that patients can receive 4 or even 6 doses per day. It is widely demonstrated that patients with chronic diseases who are submitted to therapeutic approaches using fewer daily doses present higher compliance levels, situation which can also increase their effectiveness[53-55]. Because the analysis of the present study is based on the results of controlled clinical trials, it is possible to assume that –in the daily practice- the convenience of an easier dosage could also lead to better results in pain relief in favor of DUL *versus* TMD/PCM.

The safety profile of DUL seems to be better than TMD/PCM. In the clinical trials who evaluated duloxetine in musculoskeletal pain (osteoarthritis and chronic LBP), the adverse events reported with more frequency were nausea (13.9%), dry mouth (7.0%), constipation (6.9%), insomnia (6.6%), diarrhea (5.7%), dizziness (5.7%), somnolence (5.6%) and fatigue (5.0%)[56]. In the study by Ruoff *et al*[42] the more-frequently reported adverse events were nausea (13.0%), somnolence (12.4%), constipation (11.2%), headache (8.7%), dry mouth (8.1%), dizziness (7.5%), pruritus (6.8%), fatigue (6.8%), upper airway infection (5.6%) and sinusitis (5.0%). Whereas the incidence of adverse events (leading to treatment withdrawal) in the placebo groups of these clinical studies was almost identical (5.7% in the study by Ruoff[42] and 5.8% in the study by Skljarevski[41]), the incidence for TMD/PCM was higher than it was for DUL (18.6% *vs* 13.9%, non-adjusted values)[41,42]. Early withdrawal due to intolerable adverse events is usually accompanied by extra expenses generated by these events. Besides the HRQoL deterioration due to lack of efficacy (in this particular case, not achieving significant pain relief), the occurrence of intolerable adverse events provoke even more deterioration of their HRQoL. Another advantage of duloxetine is that it can be administered for long term periods. One clinical study with 41-week follow up showed that those patients who initially responded to duloxetine in the study by Skljarevsk*i et al* (2010a)[41], reported improved efficacy, good tolerability and non-occurrence of new adverse events[57].

The results of the present study contribute to the cumulative evidence about pharamcoeconomic advantages of duloxetine in the management of moderate-severe pain. Different publications underline that duloxetine is a cost-effective agent in the treatment of patients with peripheral diabetic neuropathy[52,58-60], osteoarthritis[61] and fibromyalgia[49,62]. One recently published study investigated 6 drugs which may be used for the second-line treatment of CLBP in Canada[63]. The results of this study show that duloxetine constitutes a dominant intervention (i.e., less costly, more effective) than hydromorphone, pregabalin and extended-release oxicodone, whereas amitriptyline was dominated by naproxen and celecoxib. Of the three non-dominated agents, naproxen was the less costly, followed by celecoxib and duloxetine. In the other hand, duloxetine resulted the most-effective intervention of all. The cost for every additional QALY provided by duloxetine *vs.* celecoxib was 43,437 Canadian dollars (2011 values) and being considered as a moderately cost-effective healthcare intervention. The results were more favorable for some population subgroups such as >65 years and patients with high risk of presenting cardiovascular or gastrointestinal adverse events. In these scenarios, the cost-utility ratios of using duloxetine *vs*. celecoxib were just 21,567 and 18,726 Canadian dollars for every additional QALY[63].

One of the main strengths of our study consisted of using statistic methods recommended in specialized literature to perform an indirect placebo-adjusted comparison[43]. This type of techniques is used to obtain standard estimations and minimize bias risk[64]. Also, the similarity of the results obtained in the placebo groups in the 2 analyzed clinical studies is a fact that increases confidence about these results. Another strength is the reliability of the sources where acquisition costs were obtained[44,45]. This is important because the main component of the difference between the total costs of DUL and TMD/PCM lies precisely in the acquisition cost of these agents. Finally, the exhaustive sensitivity analysis can be considered as other strength. The results of such analysis allow us to establish that the model is robust to parameter variations within a reasonable range. In the sensitivity analysis we observed that variables causing more uncertainty were the cost of managing CLBP in «non-responder» patients and in patients with complete response, the probability of reaching response with duloxetine and the utility score assigned to complete response. Duloxetine was dominant or at least cost-effective in 59% of the simulations performed as part of the probabilistic sensitivity analysis in the public healthcare perspective in Mexico. For the private healthcare perspective, 90% of the performed simulations showed that duloxetine was dominant or at least cost-effective.

The present study in not exempt of limitations. One is the lack of studies comparing directly DUL and TMD/PCM. Another limitation is that the analysis was based only in two clinical studies, excluding some other

publications. For example, the study by Peloso *et al*[40] has a similar design and patient characteristics to the study by Ruoff *et al*[42]. Nevertheless, the efficacy results in the placebo group in the study by Peloso *et al*[40] are significantly different from those in the study by Ruoff *et al*[42] and Skljarevski *et al* (2010a)[41]. In this case it was better not to incorporate results which can lead to bias rather than trying to increase the sample size. In the same way, two clinical studies led by Skljarevski[38,39] were not incorporated in the analysis because they included fixed doses, whereas the selected studies used flexible doses[41,42]. However, it must be mentioned that efficacy and withdrawal rates (due to AE) in the duloxetine 60 mg groups of the discarded studies[38,39], are consistent with the results reported in the flexible dose study (60/120 mg/day) [41].

Another limitation is the time horizon, because it was restricted to the approximate duration of the double-blind and placebo-controlled analysis-phase of the selected clinical trials[41-42]. To broaden this horizon might need to define certain treatment sequences, being a difficult situation due to the multiple combinations which can be made with the available drugs and their different dosages[64,65]. In the other hand, the authors which have chosen to apply treatment sequences have assumed (necessarily), that the efficacy and safety of the therapeutic agents remains unaltered, regardless of their place in the sequence[49,61], this assumption is debatable.

Despite of being a very frequent chronic condition, there is scarse information related to the costs of routine management of CLBP. We found only one Mexican study which mentions the average cost for every case[12]. Unfortunately nor in that publication or any other reported in literature was possible to determine the real consumption of medical resources according to response type (pain relief <30%, 30 to 49% and ≥ 50%). In front of this situation we assumed that the average cost for every published case by Sánchez-Hernández *et al*[12] corresponds to the most-severe cases, this assumption seems reasonable because this were patients with prolonged incapacity and required medical rehabilitation services. Due to the lack of data, the costs related to the other responsetypes were configured according to the published data of other disorder (fibromyalgia)[49]. In addition, the cost attributable to intolerable adverse events was determined as the cost of a «family medicine» medical visit (in the public system) and the cost for the private system was adjusted according to the public system weighting. It is true that these parameters must be used with caution and most important is to mention that the vast majority of the differences in total costs per patient correspond to the acquisition costs and not to these items, whose really impact is minimal. All utility scores had to be estimated under several assumptions. We have also to underline that all HRQoL parameters were not collected in Mexican population, which also is another limitation. Nonetheless and because all health results are similar between both groups, the most important aspect for the decision-taking is the cost rather than quality of life.

CONCLUSION

The results of the present study suggest that duloxetine and TMD/PCM offer similar health outcomes in the treatment of chronic LBP, but duloxetine is associated to lower total costs, from both, the public healthcare system perspective and the private healthcare system perspective in Mexico. Duloxetine also presents a more convenient administration profile which can turn duloxetine into the preferred strategy.

DISCLAIMER

This study was sponsored by an unrestricted grant from Eli Lilly y Compañía de México S.A. de C.V., without any legal obligation or string concerning the results. At the moment of the study, Jocelyn Ramírez Gámez and Ignacio Ruíz were employees of Eli Lilly y Compañía de México S.A. de C.V.

REFERENCES

1. Diagnóstico, tratamiento y prevención de lumbalgia aguda y crónica en el primer nivel de atención. México: Secretaría de Salud. 2009.
2. Ivanova JI, Birnbaum HG, Kantor E, Schiller M, Swindle RW. Duloxetine use in chronic low back pain: treatment patterns and costs. *Pharmacoeconomics* 2012;30(7):595-609.
3. Atkinson JH. Chronic back pain: searching for causes and cures. *J Rheumatol* 2004:31(12):2323-5.
4. Croft PR, Papageorgiou AC, Ferry S, Thomas E, Jayson MI, Silman AJ. Psychologic distress and low back pain. Evidence from a prospective study in the general population. *Spine* 1995;20(24):2731-7.
5. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. *Best Pract Res Clin Rheumatol* 2010;24(6):769-81.
6. Manchikanti L. Epidemiology of low back pain. *Pain Physician* 2000;3(2):167-92.
7. Peláez-Ballestas I, Sanin LH, Moreno-Montoya J, Alvarez-Nemegyei J, Burgos-Vargas R. Epidemiology of the rheumatic diseases in Mexico. A study of 5 regions based on the COPCORD methodology. *J Rheumatol* Suppl 2011;86:3-8.
8. Cardiel MH, Rojas-Serrano J. Community based study to estimate prevalence, burden of illness and help seeking behavior in rheumatic diseases in Mexico City. A COPCORD study. *Clin Exp Rheumatol* 2002;20(5):617-24.
9. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81(9):646-56.
10. Phillips CJ. Pain management: health economics and quality of life considerations. *Drugs* 2003;63(2):47-50.
11. Becker A, Held H, Redaelli M, Strauch K, Chenot JF, Leonhardt

C, *et al*. Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976)* 2010;35 (18):1714-20.
12. Sánchez-Hernández MA, Ibarra-Ramírez CT, Vilchis-Aguado M del R. Impacto del servicio de rehabilitación en el primer nivel de atención. *Rev Med Inst Mex Seg Soc* 2008;(4):391-6.
13. Juniper M, Le TK, Mladsi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. *Expert Opin Pharmacother* 2009;10(16):2581-92.
14. Wieser S, Horisberger B, Schmidhauser S, Eisenring C, Brügger U, Ruckstuhl A, *et al*. Cost of low back pain in Switzerland in 2005. *Eur J Health Econ* 2011;12(5):455-67.
15. Becker A, Held H, Redaelli M, Strauch K, Chenot JF, Leonhardt C, *et al*. Low back pain in primary care: costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976)* 2010;35(18):1714-20.
16. Ekman M, Jönhagen S, Hunsche E, Jönsson L. Burden of illness of chronic low back pain in Sweden: a cross-sectional, retrospective study in primary care setting. *Spine (Phila Pa 1976)* 2005;30(15):1777-85.
17. Depont F, Hunsche E, Abouelfath A, Diatta T, Addra I, Grelaud A, *et al*. Medical and non-medical direct costs of chronic low back pain in patients consulting primary care physicians in France. *Fundam Clin Pharmacol* 2010;24(1):101-8.
18. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;8(1):8-20.
19. Jain R. Pain and the brain: lower back pain. *J Clin Psychi* 2009; 70(2):e41.
20. Keeley P, Creed F, Tomenson B, Todd C, Borglin G, Dickens C. Psychosocial predictors of health-related quality of life and health service utilisation in people with chronic low back pain. *Pain* 2008;135(1-2):142-50.
21. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA* 2010;303(13):1295-302.
22. Witte AP. Treatment options in managing chronic low back pain. Disponible en http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/107595/
23. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, *et al*. Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007;147(7):478-91.
24. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, *et al.* COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15 Suppl 2:S192-300.
25. National Collaborating Centre for Primary Care. NICE clinical guideline 88: Low back pain. Early management of persistent non-specific low back pain. London: National Institute for Health and Clinical Excellence. 2009.
26. Chou R, Huffman LH, American Pain Society, American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147(7):492-504.
27. Chou R, Huffman LH, American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147(7):505-14.
28. Kuijpers T, van Middelkoop M, Rubinstein SM, Ostelo R, Verhagen A, Koes BW, *et al*. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J* 2011;20(1):40-50.
29. Smith HS, Smith EJ, Smith BR. Duloxetine in the management of chronic musculoskeletal pain. *Ther Clin Risk Manag* 2012;8:267-77.
30. Pergolizzi JV Jr, Raffa RB, Taylor R Jr, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract 2012 Jun 21. doi: 10.1111/j.1533-2500.2012.00578.x.*
31. Dhillon S. Tramadol/paracetamol fixed-dose combination: a review of its use in the management of moderate to severe pain. *Clin Drug Investig* 2010;30(10):711-38.
32. Pergolizzi JV Jr, van de Laar M, Langford R, Mellinghoff HU, Merchante IM, Nalamachu S, *et al*. Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain. *J Pain Res* 2012;5:327-46.
33. Drummond MF, O´Brien BJ, Stoddart GL, Torrance GW. Métodos para la evaluación económica de los programas de atención de la salud. Ed. Díaz de Santos. S.A. España 1991.
34. Diccionario de especialidades farmacéuticas PLM Thompson 2012. Disponible en http://www.facmed.unam.mx/bmnd/dirijo.php?bib_vv=6
35. National Horizon Scanning Centre. Duloxetine (Cymbalta) for chronic somatic pain. University of Birmingham and National Institute for Health Research. 2010.
36. Consejo de Salubridad General. Guía para la conducción de estudios de evaluación económica para la actualización del Cuadro Básico de Insumos del Sector Salud en México. México, D.F. Agosto 2008. Disponible en http://www.csg.salud.gob.mx/descargas/pdfs/cuadro_basico/GUxA_EVAL_ECON 25082008_ 2_ech.pdf
37. International Society for Pharmacoeconomics and Outcomes Research. Pharmacoeconomic Guidelines Around The World. Available at http://www.ispor.org/peguidelines/index.asp
38. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S, *et al*. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol* 2009;16(9):1041-8.
39. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, *et al*. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010;11(12):1282-90.
40. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N, Protocol TRP-CAN-1 Study Group. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol* 2004;31(12):2454-63.
41. Skljarevski V, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, *et al*. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine (Phila Pa 1976)* 2010;35(13):E578-85.
42. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M, Protocol CAPSS-112 Study Group. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 2003;25(4):1123-41.
43. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50(6):683-91.
44. Portal de compras del Instituto Mexicano del Seguro Social. Disponible en http://compras.imss.gob.mx/

45. Portal de paciente plus. Disponible en http://www.pacienteplus.com/tienda/index.php
46. Eli Lilly and Company. Duloxetine for the management of chronic pain. Disponible en http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM225311.pdf
47. Instituto Mexicano del Seguro Social. Costos unitarios por nivel de atención médica para el año 2012. Diario Oficial de la Federación, Miércoles 9 de mayo de 2012.
48. Instituto Nacional de Estadística y Geografía. Calculadora de inflación. Disponible en http://www.inegi.org.mx/sistemas/indiceprecios/CalculadoraInflacion.aspx
49. Beard SM, Roskell N, Le TK, Zhao Y, Coleman A, Ang D, *et al.* Cost effectiveness of duloxetine in the treatment of fibromyalgia in the United States. *J Med Econ* 2011;14(4):463-76.
50. Portal de ensayos clínicos del gobierno de Estados Unidos de América. Disponible en: http://www.clinicaltrials.gov/ct2/show/results/NCT00424593?term=duloxetine+AND+chronic+ low+back+pain&rank=4
51. International Monetary Fund. World Economic Outlook Database, October 2012. Available at http://www.imf.org/external/pubs/ft/weo/2012/02/weodata/index.aspx
52. Asche CV, Kirkness CS, McAdam-Marx C, Fritz JM. The societal costs of low back pain: data published between 2001 and 2007. *J Pain Palliat Care Pharmacother* 2007;21(4):25-33.
53. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23(8):1296-310.
54. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care* 2009;15(6):22-33.
55. Coleman CI, Limone B, Sobieraj DM, Lee S, Roberts MS, Kaur R, *et al*. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012;18(7):527-39.
56. Skljarevski V, Zhang S, Iyengar S, D'Souza D, Alaka K, Chappell A, *et al*. Efficacy of duloxetine in patients with chronic pain conditions. *Curr Drug ther* 2011;6(4):296-303.
57. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med* 2010;11(5):648-57.
58. Wu EQ, Birnbaum HG, Mareva MN, Le TK, Robinson RL, Rosen A, *et al*. Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain. *J Pain* 2006;7(6):399-407.
59. O'Connor AB, Noyes K, Holloway RG. A cost-utility comparison of four first-line medications in painful diabetic neuropathy. *Pharmacoeconomics* 2008;26(12):1045-64.
60. Beard SM, McCrink L, Le TK, Garcia-Cebrian A, Monz B, Malik RA. Cost effectiveness of duloxetine in the treatment of diabetic peripheral neuropathic pain in the UK. *Curr Med Res Opin* 2008;24(2):385-99.
61. Elizondo-Cano M, Carlos F, Ramírez-Gámez J, Dueñas H. Evaluación económica del uso de duloxetina en el tratamiento del dolor causado por osteoartritis en el sistema privado de salud en México. Manuscrito enviado a publicación en la revista *PharmacoEconomics-Spanish Res Art.*
62. Carlos-Rivera F, Ramírez-Gámez J, Ruiz I, Ortiz-Escalante K. Costo-efectividad del uso de duloxetina en el tratamiento farmacológico de fibromialgia en México. Manuscrito que será enviado a publicación a la Revista de *Archivos de Neurociencias.*
63. Wielage R, Bansal M, Wilson K, Klein R, Happich M. The cost-effectiveness of duloxetine in chronic low back pain: a Quebec Societal Perspective. *Spine (Phila Pa 1976). 2012 Dec 17. [Epub ahead of print]*.
64. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. *Int J Technol Assess Health Care* 2008;24(2):170-7.
65. Carlos F, Ramírez-Gámez J, Dueñas H, Galindo-Suárez RM, Ramos E. Economic evaluation of duloxetine as a first-line treatment for painful diabetic peripheral neuropathy in Mexico. *J Med Econ* 2012;15(2):233-44.