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Original article

Economic evaluation of duloxetine as a first-line treatment for painful diabetic peripheral neuropathy in Mexico

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Abstract

Objective:
To perform an economic evaluation of duloxetine, pregabalin, and both branded and generic gabapentin for managing pain in patients with painful diabetic peripheral neuropathy (PDPN) in Mexico.

Research design and methods:
The analysis was conducted using a 3-month decision model, which compares duloxetine 60 mg once daily (DUL), pregabalin 150 mg twice daily (PGB), and gabapentin 600 mg three-times daily (GBP) for PDPN patients with moderate-to-severe pain. A systematic review was performed and placebo-adjusted risk ratios for achieving good pain relief (GPR), adverse events (AE), and withdrawal owing to intolerable AE were calculated. Direct medical costs included drug acquisition and additional visits due to lack of efficacy (poor pain relief) or intolerable AE. Unit costs were taken from local sources. Adherence rates were used to estimate the expected drug costs. All costs are expressed in 2010 Mexican Pesos (MXN). Utility values drawn from published literature were applied to health states. The proportion of patients with GPR and quality-adjusted life years (QALY) were assessed.

Results:
Branded-GBP was dominated by all the other options. PGB was more costly and less effective than DUL. Compared with branded-GBP and PGB, DUL led to savings of 1.01 and 1.74 million MXN (per 1000 patients). The incremental cost per QALY gained with DUL used instead of generic-GBP was $102 433 MXN. This amount is slightly lower than the estimated gross domestic product per capita in Mexico for 2010. During a second-order Monte Carlo simulation, DUL had the highest probability of being cost-effective (61%), followed by generic-GBP (25%) and PGB (14%).

Limitations:
Study limitations include a short timeframe and using data from different dosage schemes for GBP and PGB.

Conclusions:
This study suggests that DUL provides overall savings and better health outcomes compared with branded-GBP and PGB. Administering DUL rather than generic-GBP is a cost-effective intervention to manage PDPN in Mexico.

Introduction

Pain is the most common reason for healthcare visits worldwide and can be broadly classified on the basis of the pathophysiology into four categories: nociceptive, inflammatory, neuropathic, and functional[1]. The International Association for the Study of Pain (IASP) defines neuropathic or neurogenic

pain as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system'[2]. Neuropathic peripheral pain occurs when the lesion or dysfunction affects the peripheral nervous system. Painful diabetic peripheral neuropathy (PDPN) is a chronic neuropathic pain condition that affects patients with diabetes mellitus and can be manifested as either mononeuropathy or polyneuropathy. The main symptoms of PDPN typically include aching, burning, stabbing or tingling sensations which generally begin in the feet and are often worse at night[3,4]. The prevalence of pain in the diabetic population has been estimated at 8–25% and reaches 40–50% in those patients with diabetic neuropathy[5–9]. Epidemiological data indicates that PDPN is more frequent in type 2 than in type 1 diabetes mellitus[3,10].

PDPN imposes a substantial economic and social burden. Patients suffering from this condition experience poor health-related quality-of-life and show a functional capacity level lower than would normally be expected for his/her age[1,11,12]. Pain disrupts sleep patterns causing anxiety, depression, and disability[3,12–15]. The presence of PDPN in the diabetic population is associated with more comorbidities, a notorious increase in the consumption of medical resources, and significantly higher treatment costs[1,7,16,17].

The treatment of such a complex entity along its different etiologies besides the high impact of this condition on both diabetes evolution and patient functionality warrant medical pathways to be taken following an evidence-based approach on analgesic effect. There are several consensus documents and guidelines recently published that aimed to inform healthcare professionals about the sequential management of PDPN and the rational for using a polypharmacy strategy in some cases[3,18–20].

A wide range of pharmacological agents from different therapeutic classes are commonly used to treat neuropathic pain. These classes include selective serotonin and noradrenaline re-uptake inhibitors (SNRI: duloxetine and venlafaxine); tricyclic antidepressants (TCA: amitriptyline, imipramine, desipramine, nortriptyline and clomipramine); anticonvulsants (gabapentin, pregabalin, valproic acid, topiramate, carbamazepine, oxcarbazepine and lamotrigine); and opioids (morphine, oxycodone and tramadol). However, only two drugs (duloxetine and pregabalin) are formally approved for the treatment of PDPN in Europe as well as in the US[9,21].

The Neuropathic Pain Special Interest Group of the IASP recommended TCA, SNRI, calcium channel alpha(2)-delta ligands (i.e., gabapentin and pregabalin), and topical lidocaine as first-line treatment options for neuropathic pain[18]. The French-speaking Society of Diabetology stated that TCA, anticonvulsants, and SNRI are of equal value in treating PDPN[3]. Another evidence-based guideline developed by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation included pregabalin (level A), duloxetine (level B), and gabapentin (level B) into their list of recommended drugs to treat PDPN[19]. The National Institute for Health and Clinical Excellence (NICE) in England and Wales has recently published a guideline for the pharmacological management of neuropathic pain in adults. Based on aspects such as efficacy, tolerability, and cost-effectiveness, NICE recommends duloxetine to be offered as the preferred option for first-line treatment of PDPN[20].

Three clinical randomized and placebo-controlled trials have demonstrated duloxetine to be both well-tolerated and effective in reducing levels of neuropathic pain[22–25]. A recently published meta-analysis suggests that duloxetine provides comparable efficacy and tolerability to gabapentin and pregabalin in PDPN[21]. The once daily dosing of duloxetine represents a potential advantage over pregabalin and gabapentin, which in contrast need to be administered two and three times every day, respectively[26]. A less frequent dose may improve compliance and can be more convenient for patients[27,28].

Examining the pharmacoeconomic profile of newer drugs is necessary to make an optimal allocation of available resources and to maximize the clinical and economic benefits to society[29]. The aim of the present study was to evaluate the cost-effectiveness of duloxetine as a first-line treatment of PDPN from the Mexican public healthcare system.

Materials and methods

Both a cost-effectiveness and a cost-utility analysis were performed[30]. The target population consists of adult diabetic patients with diagnosis of PDPN that is causing moderate-to-severe pain.

The following competing interventions were evaluated: Duloxetine (DUL) 60 mg once daily, pregabalin (PGB) 150 mg twice daily (300 mg/day) and gabapentin (GBP) 600 mg (two 300 mg capsules) three times daily (1800 mg/day), each administered orally. This analysis uses the 300 mg/day PGB dose that is believed to work well for most PDPN patients[19] and the lowest value of the clinically effective range dose of 1800–3600 mg/day for GBP[4]. The DUL 60 mg once daily is the recommended starting dose for this drug[20,26] and has been used as a base-case in previous cost-effectiveness studies[4,31–33]. Two different types of GBP were analyzed: a branded version (brand-GBP) and a generic one (gen-GBP); it was assumed there are no relevant differences in efficacy and safety among these two options.

Time horizon

Cost and outcomes were evaluated for a 12-week time-frame, which is consistent with the duration of the blinded phase of the randomized placebo-controlled clinical trials of DUL in PDPN[22–24]. Therefore, costs and benefits were not discounted as the analysis was conducted within a 1-year time horizon[34].

Model description

Since the time horizon is relatively short, a decision-tree can effectively represent the decision-making context. The structure of the decision-analytic model used in this analysis is shown in Figure 1. A quite similar framework has been previously used by other authors and is detailed elsewhere[33,35,36]. Briefly, the model consists of seven different pathways defined according to the magnitude of pain relief, the presence of adverse events (AE), and the possibility of withdrawal owing to intolerable AE or due to lack of efficacy. Treatment adherence depends on the daily frequency that the medication must be taken and estimates on adherence were used to calculate the expected costs of medications[27,28]. It was assumed that efficacy rates reported in clinical trials already reflect the effect of dosing frequency, and therefore they were not weighted by adherence. Poor pain relief and AE lead to additional costs and disutility. The model also assumes that all health states resulting from treatment are present for the entire horizon and that pain relief is related to a reduction in the symptoms, and not the duration, of pain[31,33].

Resource use and costs

According to the study perspective, only direct medical costs were analyzed. Following Drummond *et al.*[30] the analysis focuses on those items that may truly differ among the interventions, namely: (1) cost acquisition of the competitive drug's schemes; (2) additional costs derived from managing AE; and (3) additional costs due to poor pain relief. Patients achieving good pain relief are assumed to complete the 12-week treatment; some patients with poor pain relief may also remain in therapy for the whole period even if they had tolerable AE. Mean treatment duration for patients that stopped therapy due to intolerable AE or because of lack of efficacy were set at 7 and 28 days, respectively[4]. Cost of medication in each scheme was calculated as the product of three factors: the duration of therapy (expressed in days), the adherence rate, and the daily cost of that medication. Compared to patients achieving good pain relief without any AE, patients with good pain relief but tolerable AE were assumed to have one extra visit to a general practitioner during the study period. Patients with intolerable AE or poor pain relief were assumed to require one extra visit to a specialist per month (three visits in total)[33].

Health outcomes

Effectiveness was measured in terms of the extent of pain relief. As O'Connor *et al.*[33,36] did, 'good pain relief' was defined as: (1) patient-reported subjective pain relief of 'moderate' or better; or (2) 'much improved' or better on the Patient Global Impression of Change (PGIC) scale. For those studies that did not report the PGIC outcome data, the effectiveness was estimated by multiplying the proportion of patients achieving at least 50% pain score reduction by a factor of 1.193. This conversion ratio was proposed in the O'Connor *et al.*[33] study. The cost-utility analysis used the expected number of quality-adjusted life years (QALY) as an end-point.

Data sources

Adherence estimates were derived from a systematic review performed by Saini *et al.*[28]. These authors presented information of 20 published studies which explicitly analyzed treatment adherence related to the daily frequency

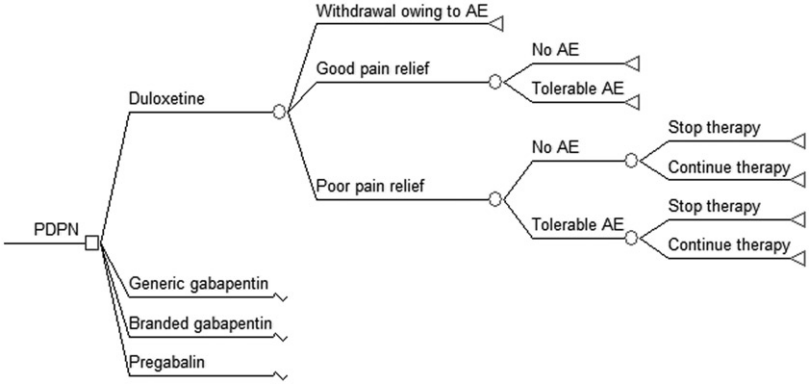

Figure 1. Structure of the model. PDPN: Painful diabetic peripheral neuropathy; AE: Adverse events. For simplicity, only branches for duloxetine are presented. All other strategies follow an identical pathway.

dosing needed. Of these, 15 studies quantified adherence as the proportion of correct number of doses taken (i.e., the proportion of total correct openings). Based on that definition, a once daily dosing scheme had a simple mean adherence of 93% (range 77–100%). Lower values were reported for twice daily (mean 87%, range 74–97%) and thrice daily (mean 80%, range 66–89%) dosing schemes.

Average wholesale prices for medications to governmental healthcare institutions in Mexico were obtained from local and official sources[37,38]. Unit costs of an outpatient consultation in a primary care facility and in a third-level center were obtained from a reference list at the Mexican Institute of Social Security (IMSS)[39]. All costs were calculated and are expressed in 2010 Mexican pesos (MXN; average exchange rate during 2010 year: 12.64 MXN per 1 US dollar)[40].

The PubMED/Medline electronic database was searched to identify potentially relevant articles in order to estimate the treatment effectiveness. The following Medical Subject Headings (MeSH) were used in the primary search: ((duloxetine *OR* pregabalin *OR* gabapentin) *AND* diabetic neuropathies). The search was filtered by type of article (limiting to clinical trials) and by language (limiting to English or Spanish publications). This search was supplemented by reviewing the bibliographies of key papers. Inclusion criteria were as follows: (1) randomized and placebo-controlled clinical trials; (2) prospective trial study design; (3) study population comprising adult patients with diabetic neuropathy; and (4) efficacy results reported as either PGIC or proportion of patients achieving at least 50% pain score reduction. Studies enrolling patients with diagnosis other than PDPN (post-herpetic neuralgia, for instance) were excluded. A total of 14 studies were finally selected to the analysis: three from DUL[22–24], seven from PGB[41–47] and four from GBP[48–51] (Figure 2). Study design comprised of cross-over and parallel group trials and period duration ranged from 5–12 weeks. Selected studies were comparable with respect to clinical and demographic characteristics of patients enrolled and the methods used to evaluate efficacy.

The approach followed to estimate the effectiveness of each competing strategy consisted of two steps: First, authors calculated the pooled proportion of patients achieving good pain relief in all the placebo arms in the whole 14 studies. The weighted probability of good pain relief for placebo was 29.2% and this figure can be seen as a reference placebo data or baseline risk (Table 1). Second, the risk ratio (RR) of achieving good pain relief in each treatment vs placebo was calculated by pooling the results from the individual trials involving the agent of interest (Table 2). A strict intention-to-treat analysis was employed. During the model, these placebo-controlled RR were applied in turn to the placebo reference probability of achieving good pain relief. It is important to mention that only three out of the seven PGB studies analyzed a 300 mg/day dosage[42,46,47]. Consequently, the placebo-controlled RR of achieving good pain relief with PGB was based on those three references alone. Since none of the GBP studies evaluated a fixed dose of 1800 mg/day the authors decided to include all the four references in the estimation of effectiveness. For DUL estimates, they took into account merely the 60 mg daily dose from the three studies found[22–24].

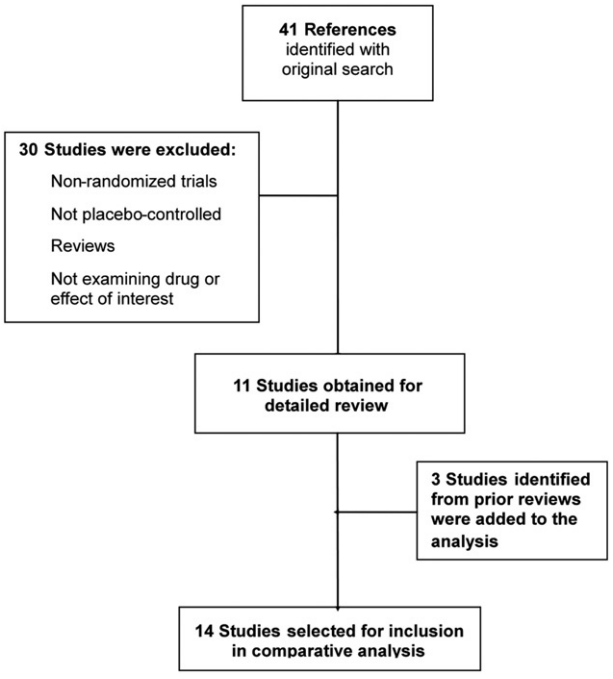

Figure 2. Flowchart outlining steps in search strategy.

Table 1. Pooled analysis of achieving good pain relief in placebo arms.

Source	Patients enrolled in placebo arms		
	Patients	Response[a]	Response (%)
Goldstein *et al.*[22]	115	35	30.4
Raskin *et al.*[23]	116	32	27.6
Wernicke *et al.*[24]	108	33	30.6
Lesser *et al.*[46]	97	23	23.7
Rosenstock *et al.*[47]	70	12[b]	17.1
Tölle *et al.*[42]	96	35[b]	36.5
Richter *et al.*[45]	85	24	28.2
Freynhagen *et al.*[44]	65	20	30.8
US FDA[43]	81	29[b]	35.8
Arezzo *et al.*[41]	85	32	37.6
Backonja *et al.*[51]	81	25	30.9
Gorson *et al.*[49]	40	9	22.5
Simpson[50]	30	7	23.3
Backonja and Glanzman[48]	81	20	24.7
Pooled analysis	1150	336	29.2

[a]Good pain relief: patient-reported subjective pain relief of 'moderate' or better; or 'much improved' or better on the Patient Global Impression of Change (PGIC) scale.
[b]Estimated by using the conversion ratio derived by O'Connor *et al.*[33].

Table 2. Risk ratios of achieving good pain relief with active treatment.

Source	Number of patients		GPR		GPR (%)	
	DUL 60 mg	PBO	DUL 60 mg	PBO	DUL 60 mg	PBO
Goldstein *et al.*[22]	114	115	64	35	56.1	30.4
Raskin *et al.*[23]	116	116	57	32	49.1	27.6
Wernicke *et al.*[24]	114	108	65	33	57.0	30.6
Pooled analysis	344	339	186	100	54.1	29.5
	Risk ratio [CI 95%] DUL 60 mg vs PBO 1.83 [1.51–2.22]					
	PGB 300 mg	PBO	PGB 300 mg	PBO	PGB 300 mg	PBO
Lesser *et al.*[46]	81	97	44	23	54.3	23.7
Rosenstock *et al.*[47]	76	70	36[b]	12[b]	47.4	17.1
Tölle *et al.*[42]	99	96	39[b]	35[b]	39.4	36.5
Pooled analysis	256	263	119	70	46.5	26.6
	Risk ratio [CI 95%] PGB 300 mg vs PBO 1.75 [1.37–2.22]					
	GBP[a]	PBO	GBP[a]	PBO	GBP[a]	PBO
Backonja *et al.*[51]	84	81	47	25	56.0	30.9
Gorson *et al.*[49]	40	40	17	9	42.5	22.5
Simpson[50]	30	30	15	7	50.0	23.3
Backonja and Glanzman[48]	244	81	90	20	36.9	24.7
Pooled analysis	398	232	169	61	42.5	26.3
	Risk ratio [CI 95%] GAB vs PBO 1.61 [1.27–2.06]					

[a]Different doses; see text.
[b]Estimated by using the conversion ratio derived by O'Connor *et al.*[33]
GPR, Good pain relief, defined as patient-reported subjective pain relief of 'moderate' or better; or 'much improved' or better on the Patient Global Impression of Change (PGIC) scale; DUL, Duloxetine; PGB, Pregabalin; GBP, Gabapentin; PBO, Placebo; CI, Confidence interval.

A similar approach was followed to estimate the probabilities of any AE and withdrawal owing to intolerable AE. Data for reference placebo was obtained from the placebo arms in controlled clinical trials of PGB and GBP included in the NICE guideline[20]. Risk ratios for PGB and GBP were extracted from the same reference. Pooled analysis of the 60 mg branches in the DUL trials[22–24] were used to estimate RR for that drug.

Utilities associated with different pain states were derived from published literature. Doth *et al.*[11] performed a systematic review on the burden of neuropathic pain and reported that three full-text articles have assessed health utilities by pain severity in diabetic neuropathy[12–14]. Mean utility values were significantly lower in patients suffering severe pain (0.20–0.25) than in those experiencing mild pain (0.59–0.70)[11]. Simple average values for mild, moderate, and severe pain from data reported in the three original studies[12–14] were calculated. In a cross-sectional survey of 255 with PDPN performed in the US, more patients reported 'moderate' pain (45% of the sample) than 'severe' pain (26%)[12]. Since the target population in the present model is composed by patients with moderate-to-severe pain, a weighted average of the mean value of the moderate (0.48) and severe (0.22) pain states was estimated, yielding a baseline utility of 0.38, which was used for the outcome 'poor pain relief'. Following O'Connor *et al.*[33], it was assumed that outcome 'good pain relief' corresponds to improving from the baseline pain state to mild pain, with the associated utility of 0.64 (equal to the simple average of the mean values reported in the three studies)[12–14]. A disutility (loss of utility) of 5% was applied to patients experiencing tolerable AE; that figure for intolerable AE was 10%. This assumption has been made in prior cost-effectiveness studies[33,35]. When AE were present, the overall health-state utility was estimated by multiplying the pain state by the AE disutility factor adjustment (0.95 and 0.90 for tolerable and intolerable AE, respectively)[33].

Statistical analysis

Expected cost and effectiveness (utilities) were calculated for a hypothetical cohort of 4000 patients divided into four groups of 1000 patients each, assigned to any of the four competitive strategies. After the base-case results were completed, a sensitivity analysis was conducted to assess the potential impact of uncertainty in parameter values. The authors varied parameters through the range of published and plausible values (Table 3). When possible, ranges were derived from the 95% confidence intervals. Costs were allowed to vary by 10%. Disutility weights associated with AE were assumed to vary by 0.025 (tolerable AE) and by 0.05 (intolerable AE). One-way analysis was performed to all parameters and a tornado diagram was

Table 3. Model parameters values: base-case, ranges, and distributions.

Parameter	Base-case	Range	Distribution	Reference
Probability of good pain relief				
Baseline risk (placebo)	0.292	0.266–0.319	–	Table 1
Duloxetine (RR)	1.83	1.51–2.22	LogNormal	Table 2
Pregabalin (RR)	1.75	1.37–2.22	LogNormal	Table 2
Gabapentin (RR)	1.61	1.27–2.06	LogNormal	Table 2
Probability of any adverse events				
Baseline risk (placebo)	0.366	0.330–0.404	–	20
Duloxetine (RR)	1.45	1.29–1.63	LogNormal	22–24
Pregabalin (RR)	1.58	1.25–1.99	LogNormal	20
Gabapentin (RR)	1.80	1.50–2.17	LogNormal	20
Withdrawal owing to adverse events				
Baseline risk (placebo)	0.076	0.064–0.091	–	20
Duloxetine (RR)	2.14	1.23–3.73	LogNormal	22–24
Pregabalin (RR)	2.34	1.76–3.10	LogNormal	20
Gabapentin (RR)	1.53	1.17–2.00	LogNormal	20
Probability of treatment adherence				
Duloxetine	0.93	0.77–1.00	Beta	28
Pregabalin	0.87	0.74–0.97	Beta	28
Gabapentin	0.80	0.66–0.89	Beta	28
Probability of stopping drug because of poor pain relief	0.75	0.5–1.00	Uniform	33
Treatment stop timing (days)				
Intolerable adverse events	7	0–14	Uniform	4
Lack of efficacy	28	21–35	Uniform	4
Pain-state utility values				
Moderate-to-severe pain	0.64	0.59–0.70	Beta	11–14
Mild pain (good pain relief)	0.38	0.35–0.41	Beta	11–14
Disutility factor adjustment*				
Tolerable adverse events	0.95	±0.025	Uniform	33
Intolerable adverse events	0.90	±0.05	Uniform	33
Daily treatment cost (MXN)				
Duloxetine 60 mg/day	28.06	±10%	Gamma	38
Pregabalin 300 mg/day	49.00			38
Branded gabapentin 1800 mg/day	64.67			38
Generic gabapentin 1800 mg/day	16.26			37
Outpatient medical consultation cost				
General medicine office visit (MXN)	535	±10%	Gamma	39
Specialty medicine office visit (MXN)	1362			39

*Pain-state utility values were multiplied by the disutility factor adjustment to create the utility of the combined health state (presence of adverse events along with the extent of pain).

generated to summarize the results of the deterministic sensitivity analysis. Potential threshold values were also explored.

Probabilistic sensitivity analysis was based on a second-order Monte Carlo simulation with 1000 repetitions. Parametric distributions were assigned to each parameter following the recommendations stated by Briggs *et al.*[52]. Therefore, the authors selected a beta distribution for binomial outcomes (probability of adherence) as well as for utility values related to pain severity, a gamma distribution for costs, and a logNormal distribution to fit risk ratios. The distributions for the probability of treatment adherence, the pain-states utilities and the costs were approximated with the mean (base-case value) and a standard deviation equal to 10% of the mean value. A uniform distribution was assigned to those parameters derived from a lower-quality evidence source. When it was necessary, calculation of confidence intervals and risk ratios was carried out in Stata version 9 (StataCorp LP, College Station, TX). All cost-effectiveness (utility) analyses were performed using TreeAge software (TreeAge Pro Suite 2009, TreeAge Software, Inc., Williamstown, MA).

Results

Base-case analysis

Table 4 shows the expected and incremental costs and benefits for the competing strategies. Generic gabapentin was the least costly alternative, with an average cost per patient of MXN 3 070 followed by DUL, PGB,

Table 4. Outcomes from the base-case analysis (per 1000 patients).

Model outcome	gen-GBP	DUL	PGB	Brand-GBP
Expected costs				
Treatment cost (MXN)	$3,069,735	$3,561,411	$4,571,247	$5,303,382
Expected benefits				
Patients with GPR	470	534	511	470
QALY	120.9	125.7	123.8	120.9
Incremental costs/benefits				
ΔTreatment cost (MXN)	Reference	$491,676	$1,501,512	$2,233,647
ΔPatients with GPR	Reference	64	41	0
ΔQALY	Reference	4.8	2.9	0
ΔCost effectiveness ratios				
Cost per additional patient with GPR (MXN)	Reference	$7647	$36,712	NC
Cost per additional QALY (MXN)	Reference	$102,433	$517,763	NC

GPR, Good pain relief, defined as patient-reported subjective pain relief of 'moderate' or better; or 'much improved' or better on the Patient Global Impression of Change (PGIC) scale; QALY, Quality adjusted life year; gen-GBP, Generic gabapentin 1800 mg/day; DUL, Duloxetine 60 mg/day; PGB, Pregabalin 300 mg/day; brand-GBP, Branded gabapentin 1800 mg/day; NC, Not calculable since incremental benefits are equal to zero.
Δdenotes 'increment'. Rounded data.

and brand-GBP. The most-effective treatment was DUL, with gains of 23 and 64 in the number of patients achieving GPR per each 1000 treated in comparison with PGB and the versions of GBP, respectively. As a consequence, DUL was also the treatment associated with the most number of QALY.

Branded gabapentin was dominated (i.e., it was more costly and at least equal of effective than comparators) by all the other three interventions. Both DUL and PGB were more effective and more costly than gen-GBP, warranting an incremental cost-effectiveness analysis (Table 4). Compared to gen-GBP, the cost per additional patient with good pain relief and the cost per additional QALY were much lower for DUL than with PGB. Indeed, DUL dominates (i.e., is more effective and less costly than) PGB. The cost per additional QALY gained when DUL is used instead of gen-GBP is MXN$ 102 433.

Sensitivity analysis

Figure 3 displays the tornado diagram for the net monetary benefit (NMB) using a willingness to pay (WTP) for an additional QALY equal to 3-times the gross domestic product (GDP) per capita in Mexico[53]. Instead of making a direct comparison between DUL and either PGB or any of the GBP formulations, the tornado plot shows the sensitivity analysis in terms of the effect of each variable on the NMB. This kind of analysis allows describing uncertainty when several competing alternatives are simultaneously evaluated. For simplicity, only the 10 parameters that influenced the most on the NMB are presented. Even though there are other variables that may generate more uncertainty in the magnitude of the NMB, the RR of achieving good pain relief with each of the active drugs relative to placebo were the only parameters with threshold values: 1.699 for DUL, 1.770 for gen-GBP, and 1.983 for PGB.

An incremental cost-effectiveness scatter plot of DUL vs gen-GBP is depicted in Figure 4. This is the most relevant comparison since in the base-case both brand-GBP and PGB were dominated by at least one of these two more preferred alternatives. As can be seen, most of the simulations are located on quadrant I, which means that DUL is more effective and more costly than its comparator. For a threshold value of 3-times the GDP per capita in Mexico (MXN$ 355 443) per QALY gained, DUL is a cost-effective intervention when compared to gen-GBP in ~64% of the simulations. In addition, DUL was dominant (both less costly and more effective than gen-GBP) in 7.3% of the simulations.

Figure 5 displays the acceptability curves. When the WTP for an additional QALY is set at the value of one GDP per capita, DUL and gen-GBP had practically the same chance of being cost-effective. For a most commonly used threshold of 3 GDP per capita, DUL had the highest probability of being cost-effective (61%), followed by gen-GBP (25%) and PGB (14%).

Discussion

In this study, the cost and effectiveness of four different alternatives commonly used in the first-line setting to manage pain in adults with PDPN were evaluated. Under the perspective of the public healthcare institutions in Mexico, the present analysis showed that DUL provides good value for money. This investigation suggests that DUL is associated with a higher probability of achieving good pain relief when compared to either PGB or GBP. This is consistent with the recommendations on sequential management of PDPN stated by NICE,

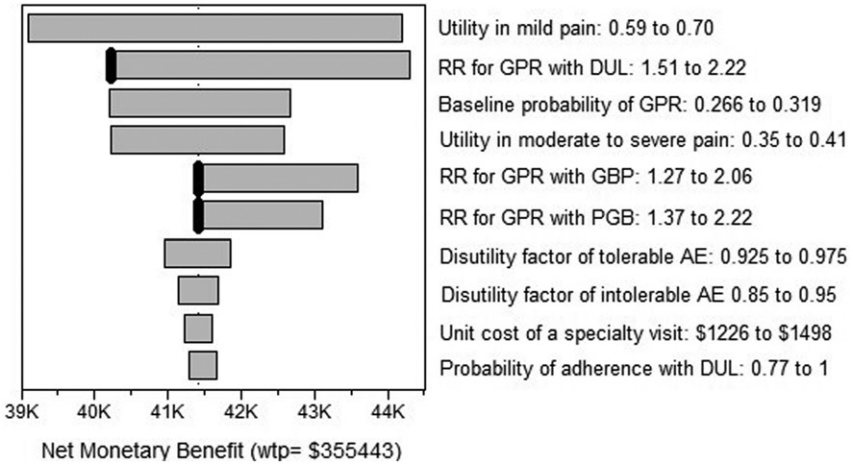

Figure 3. The tornado diagram: Painful diabetic peripheral neuropathy. The WTP for an additional QALY is set equal to 3 × GDP per capita in Mexico. RR: Risk ratio; GPR: Good pain relief; DUL: Duloxetine; GBP: Gabapentin; PGB: Pregabalin; AE: Adverse events; K denotes a thousand; WTP:Willingness to pay; GDP: Gross domestic product.

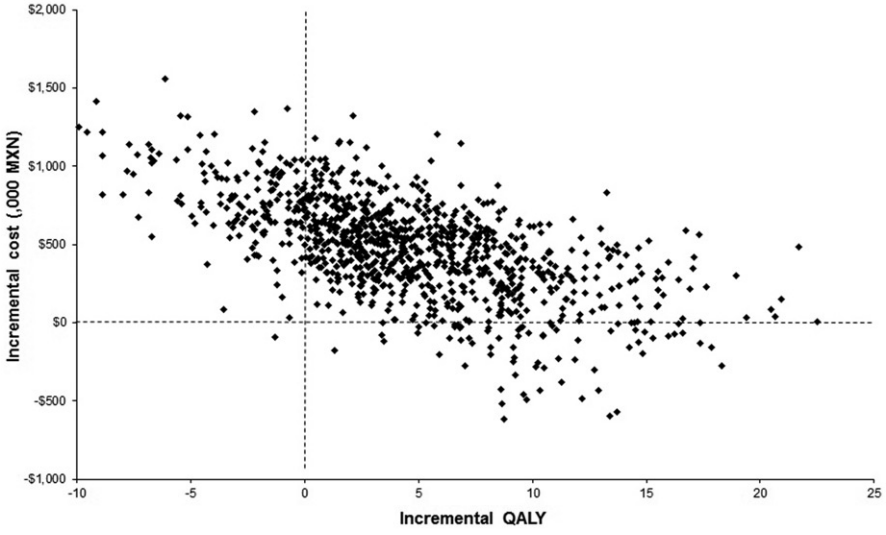

Figure 4. Incremental cost-effectiveness scatter plot (DUL vs. gen-GBP). MXN: Mexican pesos; DUL:Duloxetine; gen-GBP: Generic gabapentin; QALY: Quality adjusted life year. Data per 1000 patients.

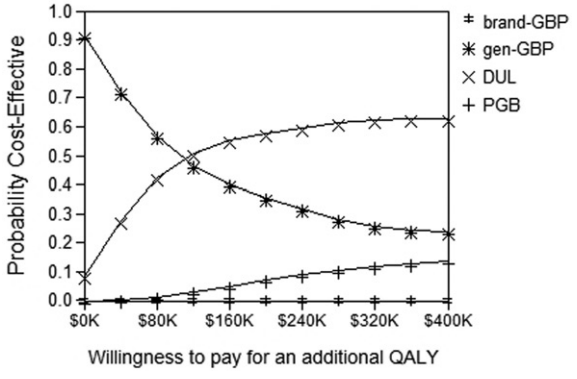

Figure 5. Acceptability curves. QALY: Quality adjusted life years; brand-GBP: Branded gabapentin; gen-GBP: Generic gabapentin; DUL: Duloxetine; PGB: Pregabalin; K denotes a thousand.

where DUL is described as the preferred option for first-line treatment[20]. Other authors have previously pointed out that DUL has better outcomes than PGB and GBP[4,33].

PGB was shown to be dominant over brand-GBP in the treatment of neuropathic pain associated with PDPN or post-herpetic neuralgia in Canada[54]. In the O'Connor *et al.*[33] study, DUL dominated both brand-GBP and PGB. Beard *et al.*[4] proposed that there is a strong case for the use of first-line DUL, prior to anticonvulsant therapy. The present analysis seems to confirm all these conclusions. In the base-case of this economic evaluation, DUL therapy yielded 23 and 64 additional patients with good pain relief (per 1000) compared to PGB and GBP,

respectively. These differences represent increments of 4.6% and 13.7% for DUL in each case. In addition, DUL was less costly, with savings reaching MXN$ 1 009 836 (22%) and MXN$ 1 741 971 (33%) per 1000 patients in comparison to PGB and brand-GBP, respectively. Compared with gen-GBP, DUL was projected to be more effective and more costly. For situations like that, decisions had to be made on the basis of the incremental cost effectiveness ratio[30]. There is a kind of consensus that interventions that cost less than the local GDP per capita to get an extra QALY are highly cost-effective and, traditionally, the threshold value for cost-effectiveness has been set at 3 local GDP per capita per QALY gained[55–57]. In the present study, the mean cost per additional QALY obtained with DUL in comparison to gen-GBP was MXN$ 102 433. This figure is slightly lower than the amount projected as the GDP per capita for 2010 year in Mexico (MXN 118 481)[53]. Therefore, DUL should be considered a highly cost-effective intervention to treat PDPN in adults in Mexico.

To the authors' knowledge, this is the second economic evaluation that included a generic formulation of GBP into the analysis and the first one that aimed to compare DUL vs gen-GBP in PDPN. Rodríguez *et al.*[55] found that PGB is more effective and more costly than gen-GBP in the treatment of PDPN or post-herpetic neuralgia in Spain. The authors reported an incremental cost per QALY gained of €20 535 and concluded that PGB is cost-effective, since this estimate is around the value of one GDP per capita in Spain. A different conclusion was drawn from the present study given that the mean cost per QALY gained with PGB in comparison to gen-GBP is 4.4-times the GDP per capita in Mexico. This could be a consequence of the differences in the GDP per capita between Mexico and Spain (Mexican value is less than a third of the Spanish)[55].

The results derived in the present model were quite sensitive to the estimates of the efficacy in the competitive treatments. Maintaining all other things constant, if the RR of achieving good pain relief with DUL drops to less than 1.669 or the correspondent RR with GBP is higher than 1.77, then gen-GBP would emerge as the preferred option. In the same way, if the RR of achieving good pain relief with PGB is higher than 1.983, this treatment would displace DUL as the more cost-effective therapy. Besides these three variables, the model was robust to changes in the parameters. Letting all the parameters vary at the same time during the probabilistic sensitivity analysis showed that DUL possess the highest probability (61%) of being classified as the more cost-effective intervention. Generic GBP and PGB would earn this honor in 25% and 14% of the cases, respectively.

When evaluating several competing alternatives it is desirable that evidence comes from clinical trials that included all the treatments of interest in the same study. Nevertheless, this is often not possible. In the absence of direct comparisons obtained from head-to-head clinical trials, an indirect comparison may be performed[58,59]. One of the most reliable and frequently applied methods of indirect comparison consists of using a common shared comparator[60–62]. Therefore, efficacy and safety data adjusted by placebo were used during the analysis. It appears that O'Connor *et al.*[33] did not perform any kind of indirect comparison but they used the pooled proportions of good pain relief for each treatment without adjusting by a common comparator. On the other hand, Beard *et al.*[4] used placebo-adjusted RR but they had limited information at that moment.

Another strength of the present study consists of using the most recent published evidence of the effect of medication dosing frequency on adherence[28]. Since the analysis was performed in an intention-to-treat basis, the authors believe that the proportion of patients achieving good pain relief in each treatment already reflect the differences in the frequency the medications have to been taken. Consequently, adherence rates were incorporated only for the calculation of the expected cost and not for the outcomes.

In contrast to other studies, information derived from clinical trials that enrolled patients presenting a diagnosis other than PDPN was excluded, even if they were conformed by a mixed population. Thus, the results of the present analysis are only applicable to those patients suffering PDPN.

This study has several limitations. In first place, since none of the clinical trials of GBP investigated the 1800 mg/day dosing scheme, it was necessary to pool efficacy data derived from different doses. A weighted mean daily dose from the six arms included in the four clinical trials of GPB evaluated in the present analysis yields 1980 mg/day, which is close to the average dose of interest[48–51]. By the other way, the efficacy analysis focused on the typical daily dosage of PGB (300 mg), which can be achieved by giving either 100 mg thrice or 150 mg twice a day. In the National Formulary of Drugs in Mexico[63], pregabalin is available only in 75 and 150 mg. Hence, to accomplish the 300 mg/day dosage, the usual scheme consists of administering a 150 mg capsule twice a day. It is important to note that two out of the three studies of PGB evaluated 300 mg/day dosage had a thrice scheme[46,47], meanwhile the other had a twice a day scheme[42]. Freeman *et al.*[64] found in a systematic review that only the PGB 600 mg/day dosage showed efficacy when administered twice a day. The US Food and Drug Administration (FDA) approved the pregabalin dosage of 300 mg/day administered in three divided doses[33]. In Mexico, the recommended dosage for this anticonvulsant ranges from 150–600 mg/day, divided into two or three doses[26].

Pain relief was based on categorical scales such as PGIC, which was the most common instrument applied across the trials in which results were reported as proportions.

However, two out the 10 studies used to estimate efficacy (both of PGB[42,47]) did not provide enough information, and in those cases good pain relief rates were calculated indirectly by using a conversion ratio[33]. Therefore, results for PGB should be taken with some caution. Other questionnaires such as The Brief Pain Inventory (BPI) contains several 11-point numeric rating scales that ranges from 0 (no pain) to 10 (worst possible pain)[65]. Results from these numerical scales were reported only in an aggregated level (e.g., mean pain scores), with no patient-level data available. Therefore, these kinds of scales were not considered an option, given the need to count with efficacy measures reported as proportions to be included into the decision tree. Since there are a wide range of instruments to assess pain relief, as well as diverse type of variables (continuous, categorical, etc.) to be analyzed, it is possible that comparisons of efficacy among competing alternatives look different when distinct measures are used.

One can reasonably argue that a longer timeframe would better represent the chronic nature of PDPN, but, following O'Connor *et al.*[33], the authors decided to kept the time horizon of the model at 3 months to be in line with the duration of the clinical trials of DUL and to reflect the usual time to evaluate a first-line therapy for this condition. Adopting a short timeframe avoids the need to make assumptions about titration schemes, the composition of the sequential treatments and sustainability (duration) of the effects (i.e., duration of pain control). Studies that have explored these assumptions in longer timeframes agree that DUL is the more cost-effective option[31]. Beard *et al.*[4] suggest that giving DUL as a first or second-line (after a TCA) instead of using first a TCA and then an anticonvulsant result in a dominant scenario favorable to DUL sequences. Fox-Rushby *et al.*[20,31] analyzed a life-time horizon and also found that first-line DUL is the preferred alternative to treat PDPN.

There is scarce information regarding health-related quality-of-life issues in the Mexican population, so it is not infrequent to gather utility values from international published literature. It is noteworthy that pain-state utility values derived through different regions of the world are very consistent with each other[11].

Conclusion

The present study suggests that duloxetine, when administered as 60 mg once daily to the first-line treatment of PDPN in adults in Mexico, provide both additional benefits and overall reductions in health-related cost in comparison with PGB in doses of 300 mg/day and branded gabapentin in doses of 1800 mg/day. This economic evaluation also suggests that giving duloxetine 60 mg once daily rather than generic gabapentin is a highly cost-effective intervention to the first-line management of PDPN in adults in Mexico.

Transparency

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Declaration of financial/other relationship
Authors Jocelyn Ramírez-Gámez, Héctor Dueñas, and Rosa María Galindo-Suárez are or were employees of Eli Lilly y Compañía de México, S.A. de C.V. when this study was conducted. Author Fernando Carlos has received funds for health economics research from Eli Lilly y Compañía de México, S.A. de C.V. and Pfizer, S.A. de C.V. over the past 12 months. Author Elisa Ramos has no conflict of interest to report.

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