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The Effectiveness and Cost-effectiveness of Pregabalin in the Treatment of Diabetic Peripheral Neuropathy: A Systematic Review and Economic Model

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Abstract: The Diabetic Peripheral Neuropathy (DPN) is the most common complication in diabetic patients which is accompanied with substantial economic burden regarding the productivity loss and medical therapy. In this study, we analyzed the cost efficacy of pregabalin for treatment of diabetic neuropathic pain in Iran. To evaluate the efficacy of pregabalin, we conducted a systematic review of published articles by searching on PubMed, Scopus and Google scholar. The keywords were: "pregabalin", "neuropathic pain", "diabetic peripheral neuropathy". The "mean pain score" and also "percentage of patients with more than 50% pain reduction" were the outcome of interest for evaluation of efficacy of drug in peripheral neuropathic pain. For calculation of cost, only direct medical costs were evaluated. The Incremental Cost Effectiveness Ratio (ICER) was compared with one and three times of Gross Domestic Product (GDP) per capita as threshold to evaluate if the treatment is "highly cost effective", "cost effective" and "not cost effective". Out of 8476 evaluated papers, finally five articles were included in the study which met our inclusion criteria. All of these reports were Randomized Controlled Trial (RCT) of the comparison of pregabalin with placebo. Considering the efficacy extracted from the reports, pregabalin 75 and 150 mg day^{-1} did not have any significant efficacy in comparison with placebo. In pregabalin 300 mg day^{-1}, the ICER range for generic and brand pregabalin were 6-200 and 63-2059, respectively. Accordingly, for generic and brand pregabalin (600 mg day^{-1}), they were 11-755 and 78-5333 US Dollars (USD) per one more score reduction in mean pain score compared with placebo that could be seen as highly cost effective treatment. Our analysis indicated that pregabalin (300 mg day^{-1} or 600 mg day^{-1}) is highly cost effective treatments in both generic and brand forms. Considering the same efficacy of generic and brand pregabalin, it seems more rational to include generic pregabalin in positive list of reimbursement, although both of them are cost effective.

Key words: Cost-effectiveness, efficacy, pregabalin, diabetes, neuropathy, systematic review, economic model

INTRODUCTION

Neuropathic pain as the definition of International Association for the Study of Pain (IASP) is the pain associated with a lesion, trauma or dysfunction of somatosensory nervous system (central or peripheral) (International Association for the Study of Pain, 2012). There is no doubt that rate of diabetes in people is increasing and the new data indicate that industrialization and environmental pollution expand the problem (Mostafalou and Abdollahi, 2012). Diabetic Peripheral Neuropathy (DPN) is one of the diabetes complications that occur in up to 50% of diabetic patients (Thomas, 1991) and is accompanied with substantial economic burden regarding the productivity loss, medical therapy and pain (Gore *et al*., 2006) and also impairment in patients' quality of life (Benbow *et al*., 1998). The prevalence of pain is indicated to be 10-20% in diabetic patients and 40-50% in part of them with diabetic neuropathy (Veves *et al*., 2008).

Some medical treatments including antidepressants (Max *et al*., 1992), opioids (Gimbel *et al*., 2003), tramadol (Sindrup *et al*., 1999) and gabapentin (Backonja *et al*., 1998) are conventionally used to manage this disease. Pregabalin was approved in 2005 by Food and Drug Administration (FDA) of USA for treatment of both

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neuropathic pains related to diabetic peripheral neuropathy and post-herpetic neuralgia.

One of crucial objectives and principles in Iran national drug policy has always been to provide situation of equal access of patients to essential drugs (Abdollahiasl *et al*., 2011; Nikfar *et al*., 2005; Cheraghali *et al*., 2004). To implement this idea, the government should manage affordability of medicines and balance utilization of medicines (Nikfar *et al*., 2011).

Gabapentin has been the widely used treatment for DPN in Iran but recently Pregablin has become available in the market in both domestic generic and imported brand (Lyrica). The price of pregabalin is considerably more than other available medicines for DPN and is not currently covered by any insurance. Economic evaluation of medicines is a tool to assess NDP's criteria such as accessibility and equity (Nikfar *et al*., 2005; Nikfar, 2012).

This study aimed to analyze the cost efficacy of pregabalin for treatment of diabetic neuropathic pain in Iran.

MATERIALS AND METHODS

Data sources

Efficacy: To evaluate the efficacy of pregabalin in the treatment of DPN, we conducted a systematic review on published studies in PubMed, Scopus and Google Scholar from 1965 up to first 2012 by a broad search strategy including keywords: "diabetic peripheral neuropathy", "diabetic neuropathic pain", "pregabalin", "pregabalin and neuropathy". The inclusion criteria consisted of published English language Randomized Controlled Trials (RCTs) about the efficacy of pregabalin in DPN and the exclusion criteria were animal studies, uncontrolled studies, observational studies, review articles and economic evaluation studies. Not being approved by institutional review or ethical committee and not getting the informed consent of patients before study was our exclusion criteria.

Cost: To evaluate cost of treatment by pregabalin in DPN, after consulting with experts, we only considered direct costs. Knowing that there are no special laboratory tests or other supplementary treatment strategy, we only considered the cost of pregabalin in our analysis. The medical cost for both brand and generic products which were available in the market was calculated based on the time period of each study considering the time period of double blind phase of trial with fixed dose of pregabalin and the primary phase of dose escalating were excluded from our analysis. For calculating the cost of generic and brand medicine, we considered the cheapest and the most expensive combination of available dosages forms in Iran. The exchange rate declared by Iran's central bank was used to exchange Iranian Rials (IRR) to US Dollars (USD).

Study selection: The search results were separately examined by two authors to eliminate duplicated and unrelated reports and the reports meeting exclusion criteria. Then the selected reports by each author were double-checked together to be included in the study or not. In the next step, the full texts of selected studies were reviewed to evaluate the inclusion and exclusion criteria in each of them and select the final studies.

Assessment of trial quality: Jadad score, which indicates the quality of the studies based on their description of randomization, blinding and dropouts (withdrawals) was used to assess the methodological quality of trials (Jadad, 1998). The quality scale ranges from 0 to 5 points with a report of score 2 or less when the quality is low and a report of score at least 3 for high quality. In this study the Jaded score less than 3 was considered as exclusion criteria.

Effects: The outcome of interest in our study was the differences in the mean pain score from the baseline at the end points of RCTs. This pain score was extracted from 11-points scale (0 = no pain, 10 = worse pain possible) which patients fill it based on the pain they have felt during the past 24 h. Also the percentage of cohorts with more than 30 and 50% of pain reduction from baseline at the endpoints of RCTs (which are considered as treatment responders) were included in our analysis as other outcomes of interest related to the pain control.

Incremental cost effectiveness ratio (ICER): The ICER was calculated and the parametric sensitivity analysis was performed for the efficacy confidence interval. The ICERs were compared with one and three times of Gross Domestic Product (GDP) per capita as the recommendation of World Health Organization (WHO) (WHO, 2012) to evaluate if the treatment of DPN with different doses are highly cost-effective (when the ICER is less than GDP per capita), cost-effective (when the ICER is between one to three times of GDP per capita) and not cost-effective (when the ICER is more than three times of GDP per capita), given that there is no accurate threshold calculated for Iran. The GDP per capita of Iran is 5608 USD based on 2010 statistics (IMF, 2012). It has to be mentioned that the Iranian pharmacoeconomists and health economists estimate the threshold for Iran to be near two times of GDP (10000 USD).

RESULTS

Out of 8476 reports which included (653 were from PubMed and 3113 from Scopus and 4710 from Google

Scholar), 16 articles were included after reviewing titles and abstracts (Fig. 1). From these included reports, 2 articles were excluded because they were about neuropathic pains generally without distinction of DPN and post-herpetic neuralgia and other neuropathic diseases. Another article was excluded because it was about central neuropathic pain. Five articles were not about DPN and were excluded and 1 article was about the cognitive effects of pregabalin. Finally, 5 articles were included in the study (Richter *et al*., 2005; Tolle *et al*., 2008; Lesser *et al*., 2004; Rosenstock *et al*., 2004; Satoh *et al*., 2011). The Jadad score regarding each selected articles were calculated and summarized in Table 1. All of the selected articles were multicentre RCT evaluating the efficacy of pregabalin in comparison with placebo. The patients in these RCTs were men and women older than 18 years with diabetes type 1 or 2 who had scores≥40 mm on Visual Analogue Scale (VAS) of short-form McGill Pain Questionnaire (SF-MPQ) at baseline and average daily pain score≥4 on 11-points Numeric Rating Scale (NRS) during the baseline period. All the patients in these five studies had hemoglobin A_1C (HgA_1C) level≤11. The different doses of pregabalin were 75, 150, 300 and 600 mg day^{-1} which were compared with placebo in 4-13 weeks as period of time. There were no reports on direct comparing of pregabalin and other treatments of DPN. The characteristics of included studies are summarized in Table 2.

Because of diversity in reporting of pain control outcomes, the pooling of results for efficacy was not possible, thus we presented the extracted efficacy results regarding the treatment dose separately for each study.

Table 1: Jadad score to evaluate the quality of included studies

References	Randomization	Double blinded	Withdrawal and dropout	Total score
Tolle *et al*. (2008)	1	1	1	3
Richter *et al*. (2005)	2	2	1	5
Lesser *et al*. (2004)	2	2	1	5
Rosentack *et al*. (2003)	1	2	1	4
Satoh *et al*. (2011)	1	1	1	3

Table 2: Summarized characteristics of included studies

Study	Study duration (weeks)	Concurrent therapy	Dosage (mg day^{-1})	Patients		Age, year (Mean±SD)		
				Male	Female			
Tolle *et al*. (2008)	11	Benzodiazepines, Opioids, Tramadol, Memantine and local anesthetics	150, 300, 600 Twice daily	176	219	58.61±11.5		
Richter *et al*. (2005)	4	Prohibited	150, 600 t.d.s.	39	46	57.30±10.3		
Lesser *et al*. (2004)	4	SSRIs and Acetaminophen	75, 300, 600 t.d.s.	135	202	59.90±10.5		
Rosenstock *et al*. (2004)	8	Acetaminophen and SSRIs	300 t.d.s.	30	40	60.30±10.3		
Satoh *et al*. (2011)	12	Not reported	300, 600 twice daily	77	237	Placebo	Pre 300	Pre 600
						61.30±9.6	61.3±10.3	62.2±10.3

SSRI: Selective serotonin reuptake inhibitor, t.d.s.: Three times a day, pre: Pregabalin

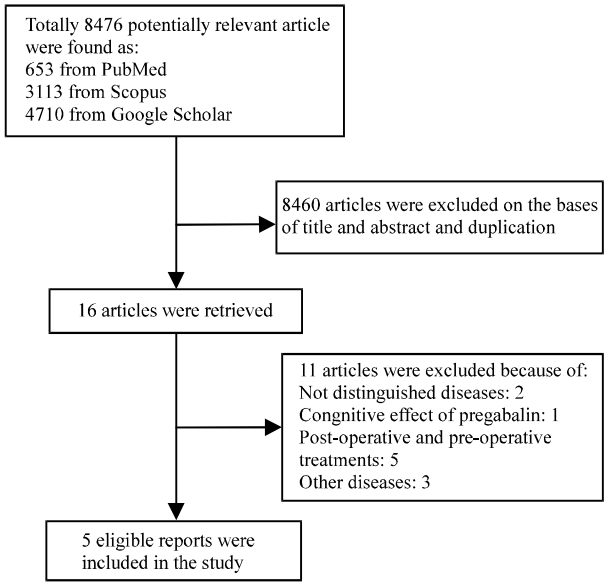

Fig. 1: Flow of process in the selection of studies regarding the efficacy of pregabalin in DPN

Table 3: Summarized results for the studies with difference in mean pain score as outcome

Pregabalin dose of treatment (mg day^{-1})	Difference in mean pain score: ΔE	CI 95%: Lower limit	CI 95%: Upper limit	Cost of treatment (USD)	ICER (cost per one unit reduction in mean pain score): Generic	ICER: Brand	The consideration based on comparison of ICER with threshold: Generic	Brand
75	-0.150	-0.760*	0.460*	3-39	NA	NA	NA	NA
150	-0.440	-1.080*	0.199*	11-91	NA	NA	NA	NA
150	-0.330	-0.940*	0.280*	2-160	NA	NA	NA	NA
300	-1.260	-1.860	-0.650	11-116	9 (18-6)	92 (179-63)	HCE	HCE
300	-1.470	-2.190	-0.750	23-233	16 (30-10)	158 (311-106)	HCE	HCE
300	-0.630	-1.090	-0.170	34-350	54 (200-31)	555 (2059-321)	HCE	HCE
300	-0.180	-0.790*	0.430*	31-320	NA	NA	NA	NA
600	-1.264	-1.890	-0.639	54-377	43 (84- 28)	298 (590-199)	HCE	HCE
600	-1.450	-2.060	-0.850	23-160	16 (27-11)	110 (188-78)	HCE	HCE
600	-0.740	-1.390	-0.090	68-480	92 (755-49)	649 (5333-34)	HCE	HCE
600	-0.970	-1.580	-0.360	63-440	65 (174- 40)	453 (1221-278)	HCE	HCE

*Not significant results (95% CI), NA: Not applicable, USD: US Dollars, HCE: Highly cost-effective, Values in brackets are range

Table 4: Summarized results for the studies with percentage of patients with more than 50% pain reduction as outcome

Pregabalin dose of treatment (mg day^{-1})	Difference in number of patient with 50% pain reduction (from 100 patients): ΔE	Cost of treatment in 100 patients (USD)	ICER (cost per one more patient with 50% pain reduction): Generic	ICER: Brand	The consideration based on comparison of ICER with threshold: Generic	Brand
150	5	187-16015	37	3203	HCE	HCE
300	4	3140-32031	785	8008	HCE	CE
300	8	3425-34943	428	4368	HCE	HCE
600	16	6281-43964	393	2748	HCE	HCE
600	15	6851-47961	457	3197	HCE	HCE

CE: Cost-effective, HCE: Highly cost-effective, USD: US dollars

Two ICERs for each dose in the results refer to the generic and brand pregabalin in Iran market.

Pregabalin 75 and 150 mg day^{-1}: Our review showed that pregabalin 75 and 150 mg day^{-1} have no significant efficacy in term of reduction in mean pain score from baseline in comparison with placebo in treatment of DPN (Richter *et al*., 2005; Lesser *et al*., 2004), thus the ICER for none of them was calculated. Based on the available evidence, we can claim pregabalin in these doses are dominated in term of economic evaluation because pregabalin was not effective in these doses comparing to placebo. This indicates the cost (USD) needed to achieve one patient with more than 50% pain reduction and since both of them were less than GDP per capita, they could be considered as highly cost-effective treatment.

Pregabalin 300 mg day^{-1}: For pregabalin 300 mg day^{-1}, the results showed that based on three out of four studies (Lesser *et al*., 2004; Rosenstock *et al*., 2004; Satoh *et al*., 2011) evaluated this dose in different dosage forms (100 and 150 mg tablets) and regarding the calculated domestic costs, the ICER range for generic and brand pregabalin is 6-200 and 63-2059, respectively according to reported efficacies. This identifies the cost (USD) of pregabalin per one more score reduction in mean pain score in comparison to placebo that could be considered as highly cost effective treatment for DPN because they both are less than GDP per capita. It is notable that one out of four studies (Tolle *et al*., 2008) indicated no significant efficacy for pregabalin 300 mg day^{-1} (Table 3). There was also two studies (Satoh *et al*., 2011; Tolle *et al*., 2008) reported the outcome of interest as the percentage of patients with more than 50% pain reduction for pregabalin 300 mg day^{-1}. The ICERs of them with generic medicines were 428 and 785 and with brand medicines were 4368 and 8008 that indicate highly cost-effective in one of the studies and cost-effective in the other one for branded dosage forms of pregabalin 300 mg day^{-1}. Also in all cases, generic pregabalin 300 mg day^{-1} could be considered as highly cost-effective treatment in DPN (Table 4).

Pregabalin 600 mg day^{-1}: The ICER range for generic and brand pregabalin 600 mg day^{-1} (Richter *et al*., 2005; Lesser *et al*., 2004; Rosenstock *et al*., 2004; Satoh *et al*., 2011) was 11-755 and 78-5333 USD per one more score reduction in mean pain score in comparison to placebo that could be seen as highly cost-effective treatment as they were less than GDP per capita. There were also two studies (Satoh *et al*., 2011; Tolle *et al*., 2008) that reported the outcome of interest as the percentage of patients with more than 50% pain reduction for pregabalin 600 mg day^{-1}. The ICERs of them with generic medicines were 393 and 457 and with brand medicine, they were 2747 and 3197 indicating that

in all cases (generic and brand) this dose could be considered as highly cost-effective treatment in comparison to placebo.

The results about efficacy and cost of pregabalin which were extracted from the included studies are summarized in details in Table 3 and 4.

DISCUSSION

In general, based on the available evidences, pregabalin 75 is not cost-effective and may need further studies to be able to decide about that. About pregabalin 150 mg day^{-1}, regarding the differences in the result of different studies, it could not be strongly accepted as cost-effective treatment and would be dependent to the view of policy makers and further evidences in future. Regardless of one study reported no significant efficacy for pregabalin 300 mg day^{-1} and one study in which pregabalin 300 mg day^{-1} with brand medicine was "cost-effective", in other cases, pregabalin 300 and 600 mg day^{-1}, both with generic and brand forms are found as "highly cost-effective" treatment for DPN in the context of Iran.

This study was the first cost efficacy analysis for treatment of DPN with pregabalin and would be useful for policy makers to make appropriate decision with regard to available evidences.

It has to be noted that managing diseases like DPN which has been shown to reduce health related quality of life in the patients incur direct medical and non medical costs to patients (O'Connor, 2009). Therefore treatment of DPN could have positive impact on reduction of burden of disease from the perspective of society. In this study we did not consider direct non-medical and indirect costs regarding treatment with pregabalin in comparison to placebo but including these items can most probably intensify the present results in favor of pregabalin.

There is several published cost effectiveness analysis around the world which have evaluated pregabalin for DPN. In a Canadian setting, in a 12-week treatment study, pregabalin was compared with gabapentin and the results indicated that pregabalin causes additional 0.0047 Quality Adjusted Life Years (QALY) and less than 20 Canadian Dollars which means it is dominant cost effective (Tarride *et al*., 2006). In another study conducted in the Spain, pregabalin was found more cost effective treatment than generic gabapentin because the ICER was 20535 euro per QALY gained while pregabalin caused additional 0.1186 QALYs for 12 weeks (Rodriguez *et al*., 2007).

On the basis of present findings, the authors of this study suggest that pregabalin 300 and 600 mg day^{-1} in both generic and brand forms could be included in Iranian clinical practice guidelines for managing DPN. Although in most cases, pregabalin 300 and 600 mg day^{-1} are highly cost-effective medicines in both generic and brand forms but when the bioequivalent efficacy of brand and generic is considered, it seems more rational to add generic forms of them to the insurance reimbursement list. It should be considered that selecting appropriated dosage forms among different dosage forms of this medicine is very crucial. Given that pregabalin could be ordered once, twice and three times daily, the dosages forms of 100, 150, 200 and 300 mg day^{-1} could be included in positive list of insurances but this may make physicians to prescribe pregabalin by not cost-effective doses. Therefore, providing treatment guidelines and education programs is highly recommended.

Also evidences regarding the efficacy of pregabalin in direct comparison with alternative treatments of DPN are essential to make decision about choosing one of them as the most cost effective treatment for being covered by insurance companies.

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