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Efficacy of pregabalin, gabapentin and duloxetine in neuropathic pain verified by the p*-curve analysis*

*Eficacia de pregabalina, gabapentina y duloxetina en el dolor neuropático verificado por el análisis de la curva-*p

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ABSTRACT

Introduction: There is a growing concern among clinicians and researchers that many results published in scientific journals are false positives.

Objective: To determine the value of evidence or integrity of the body of the published literature on the efficacy of pregabalin, gabapentin and duloxetine in the treatment of neuropathic pain.

Methods: A literature search was conducted selecting randomized clinical trials that evaluated the efficacy of pregabalin, gabapentin and duloxetine in neuropathic pain. The p-curve analysis of the studies with statistically significant results was applied to study their distribution.

Results: It was demonstrated that there was a significant asymmetry to the right in the p-curve of the three drugs (continuous test p <0.0001) confirming the value of evidence from the studies.

Conclusions: Clinicians, scientists and scientific publications should be aware of the growing problem with "p-hacking" and its harmful effects. All parties share the responsibility to maintain the scientific integrity of the published literature.

Key words: P-curve, duloxetine, pregabalin, gabapentin, neuropathic pain, treatment.

RESUMEN

Introducción: Existe una preocupación creciente entre los clínicos y los investigadores de que muchos resultados publicados en revistas científicas se tratan de falsos positivos.

Objetivo: Determinar el valor de evidencia o integridad del cuerpo de la literatura publicada sobre la eficacia de pregabalina, gabapentina y duloxetina en el tratamiento del dolor neuropático.

Métodos: Se realizó una búsqueda bibliográfica seleccionando ensayos clínicos aleatorizados que evaluaban la eficacia de pregabalina, gabapentina y duloxetina en dolor neuropático. Se aplicó el análisis de curva-*p* de los estudios con resultados estadísticamente significativos para estudiar su distribución.

Resultados: Se demostró que existía una asimetría significativa a la derecha en la curva-*p* de los tres fármacos (test continuo $p < 0{,}0001$) confirmando el valor de evidencia de los estudios.

Conclusiones: Los clínicos, los científicos y las publicaciones científicas deben ser conscientes del problema creciente con el "p-hacking" y sus efectos perjudiciales. Todas las partes comparten la responsabilidad en mantener la integridad científica de la literatura publicada.

Palabras clave: Curva-p, duloxetina, pregabalina, gabapentina, dolor neuropático, tratamiento.

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INTRODUCTION

Neuropathic pain is caused by an injury or disease affecting the somatosensory nervous system [1]. It involves a considerable impact on the quality of life of patients and an economic burden on society [2-4]. Neuropathic pain is considered a specific clinical entity with multiple etiologies [1].

Recent meta-analyses recommend with a strong level of evidence the use of gabapentin, pregabalin, duloxetine, venlafaxine and tricyclic antidepressants as front line therapy for the treatment of neuropathic pain [5]. Of the randomized and controlled clinical trials included in this meta-analysis, 7 out of 9 published studies were positive with duloxetine, 9 out of 14 with gabapentin, 4 out of 6 with gabapentin enacarbil and 18 out of 25 with pregabalin. Most of these studies have been performed in patients with painful diabetic neuropathy, postherpetic neuralgia and spinal injuries. However, in real or clinical practice studies the rate of clinical improvement is lower. This may be due to a diagnostic inaccuracy, a relative inefficacy of the drugs or insufficient knowledge on the effectiveness of these drugs.

It should be considered that there is a growing concern among clinicians and researchers that many results published in scientific journals are false positives, that is, type I errors, as in other areas [7] There is evidence that journals, especially those with the highest impact, publish disproportionately significant results [8].

There are two recognized types of publication biases: a) the "file-drawer" effect, which occurs when the researcher tends not to submit his/her findings when they are negative [9]; and b) the selective report or "*p*-hacking", which occurs when the authors manipulate, intentionally or not, the data through various statistical methods until statistically significant findings are obtained [10,11]. Among these incorrect techniques we can include intermediate analyzes in data collection, inclusion or not of outliers, modification of inclusion criteria, multiple comparisons and subgroup analyzes without statistical corrections. The publication of false positives is very detrimental to the advancement of medicine because it leads to the exploration and application of false theories that involve a waste of economic and human resources for researchers, for public administrators with changes in health policy and for patients. Therefore, quantification of selective reports is of vital importance [12].

The *p*-curve is the distribution of the statistically significant *p-value*s [9]. Analyzing its distribution, we can infer whether the findings of the different studies have a value of evidence or not. If the null hypothesis is true (there is no actual effect of the efficacy of the drug we want to study), in 5 % of the conducted studies we would obtain a *p-value* <0.05, in a 4 % a *p-value* of <0.04, in a 3 % a *p-value* of <0.03, and so on. The *p*-curve would be flat or horizontal. In contrast, if the frequency of the *p-value*s shows an asymmetry towards the right (that is, they are closer to 0.01 than to 0.05), this is an indication of evidence. Conversely, if most of the values are close to the threshold 0.05, we would be faced with a clear example of "*p*-hacking" or manipulation of results.

The main objective of the study is to analyze the efficacy of pregabalin, duloxetine and gabapentin in the treatment of neuropathic pain by applying the *p*-curve analysis.

MATERIAL AND METHODS

Search strategy

A systematic search was conducted on PubMed, https://www.ncbi.nlm.nih.gov/pubmed/, in October 2018 for terms related to "pregabalin", "duloxetine", "gabapentin" and "therapeutics". The "Randomized Controlled Studies" and "humans" filters were used. Inclusion criteria required the efficacy analysis of one of the target drugs (gabapentin, pregabalin, duloxetine) placebo-controlled in any known etiology of neuropathic pain. A single significant *p*-value was obtained for each of the studies, the first reported, to avoid correlations between the values of the same study (different doses, different scales studying the degree of pain, etc.). The search retrieved 237 studies, 156 of them were excluded because they did not meet the inclusion criteria (77 did not evaluate the efficacy of the drug or there was no placebo group, 46 did not have a therapeutic purpose as the main objective, 16 did not analyze a known etiology of neuropathic pain, 11 were meta-analyses and 6 were protocols or records prior to a clinical trial). A total of 31 papers of the remaining 81 studies were excluded because no significant findings were found, the *p-value* was not reported or it was described as p <0.05 with no greater accuracy (Figure 1).

Thus, this analysis of the *p*-curve comprised the findings of 50 studies investigating the efficacy of pregabalin, duloxetine or gabapentin in the different causes of neuropathic pain (Table I). Values below < 0.0001 were converted to 0.0001. All included studies were published in peer-reviewed journals.

Statistical analysis

The analysis of the *p*-curve was performed using the free software, http://p-curve.com, based on the theoretical and practical study of Simonsohn et al. [9]. This program allows entering the *p-value*s of the original studies, with which it develops two types of statistical analysis: binomial and continuous tests. The binomial tests compare the expected proportion of statistically significant findings that are below p < 0.025 (since all studies published in the medical literature use an alpha value of 0.05) when there is no actual effect assuming 33 % power. Power s defined as the probability of finding a positive finding when it is a true positive. In most clinical trials, a power of around 80 % is usually used, so that 33 % lead to a conservative curve that loosens the expected values. The continuous tests transform the *p*-values into a Z score, sum the Z scores, divide the result by the square root of the number of *p-value*s included in the analysis, in our study it corresponds to the number of studies, to obtain a mean Z score. This is known as the Stouffer's method. This mean Z score is compared with the null hypothesis (Z = 0).

With both techniques, binomial test and continuous test, we can determine an asymmetry test on the right to evaluate if the studies contain value of evidence, an

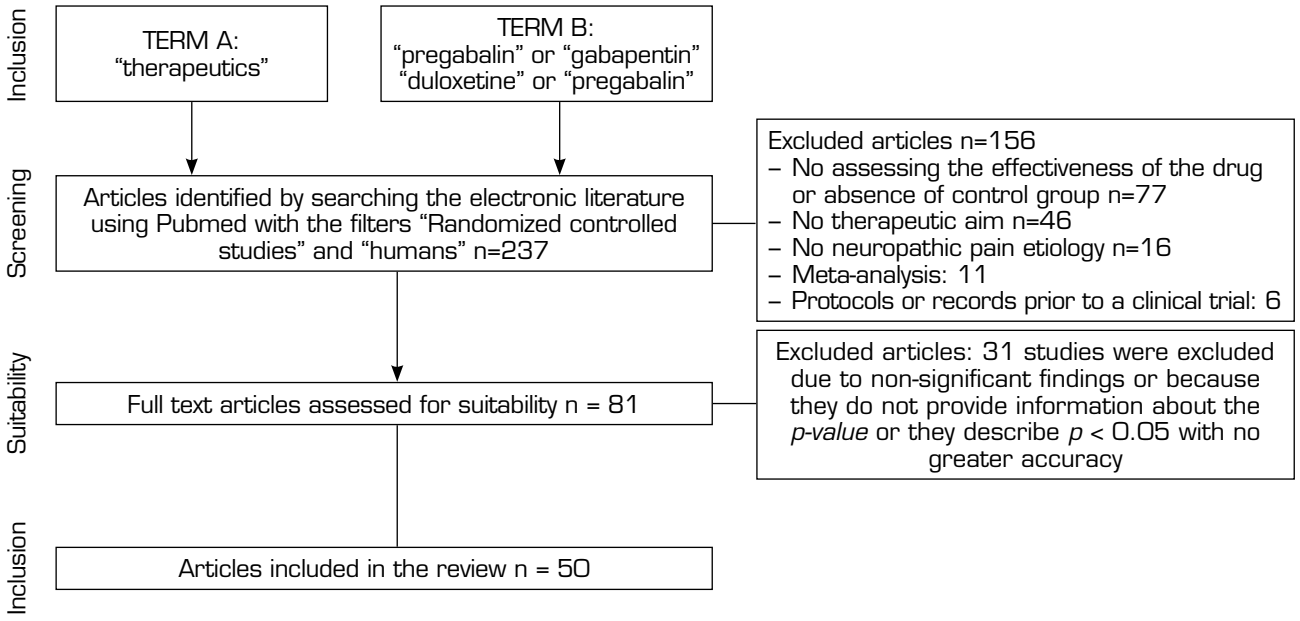

Fig. 1. Flow chart of included studies.

asymmetry test on the left to determine if the studies demonstrate an intense "*p*-hacking", and a test known as horizontality that determines whether the value of evidence found in the studies is inadequate. The *p*-curve analysis only uses significant *p-value*s below 0.05.

RESULTS

A total of 9, 18 and 24 out of the 50 studies reporting significant values corresponded to studies conducted with duloxetine, gabapentin and pregabalin, respectively **Table I** shows the data of the 50 studies included in the analysis, the studied drug and the analyzed *p* are shown. One of the studies evaluated the efficacy of gabapentin, pregabalin and placebo.

Duloxetine

A total of 89 % of the values reported a *p-value* equal or below 0.01, 0 % reported a *p-value* of approximately 0.02 or 0.03, 11 % of 0.04 and 0 % of 0.05 (Figure 2). The results indicate that the studies in the analysis contain evidence value indicated by a statistically significant right asymmetry of the *p-value*s with both the binomial test (p = 0.0195) and the continuous test (Z = -5.36, *p* <0.0001) as shown in Table II. In addition, the distribution did not show asymmetry on the left indicating that there was no "p-hacking". The horizontality test was not significant for the binomial test (p = 0.9517) nor for the continuous test (Z = 2.89, *p* = 0.9987). Therefore, the studies do not lack the value of evidence. Finally, the *post hoc* analysis of statistical power indicates that the average power of the tests included in the *p*-curve is 83 % with a confidence interval of 58-95 %.

Gabapentin

A total of 67 % of the values reported a *p-value* equal or below 0.01, 11 % corresponded to a *p-value* of approximately 0.02, 0 % to a *p-value* of 0.03, 17 % to a value of 0.04 and 6 % to a value of 0.05 (Figure 2). The results indicate that the studies in the analysis contain a value of evidence indicated by a statistically significant right asymmetry (binomial test, *p* = 0.0154; continuous test, Z = -5.36, *p* <0.0001 [Table II]). There was no evidence of "p-hacking." The horizontality test was not significant (binomial test, *p* = 0.8014; continuous test, Z = 1.05, *p* = 0.8526). Studies do not lack the value of evidence. The average power is 50 % with a confidence interval of 24-73 %.

Pregabalin

A total of 83 % of the values reported a value equal or below 0.01, 8 % corresponded to a *p-value* of approximately 0.02, 0 % to a *p-value* of 0.03, 4 % to a value of 0.04 and 4 % to a value of 0.05 (Figure 2). The results indicate that the studies in the analysis contain a value of evidence indicated by a statistically significant right asymmetry (binomial test, *p* <0.0001; continuous test, Z = -7.68, *p* <0.0001 [Table II]). There was no evidence of "p-hacking." The horizontality test was not significant (binomial test, *p* = 0.9967; continuous test, Z = 3.8, *p* = 0.9999). Studies do not lack the value of evidence. The average power is 77 % with a confidence interval of 61-88 %.

DISCUSSION

The analysis of the *p*-curve performed in our study suggests that the results of the publications evaluat-

TABLE I

CLINICAL TRIALS INCLUDED IN THE *P*-CURVE ANALYSIS

Study	*Evaluation*	*Drug*	*Dose (mg)*	*Time (weeks)*	*No. Patients*	*Etiology*	*P*
Raskin, 2005	11-point Likert scale	Duloxetine	120 mg/placebo	52	110/47	Painful Diabetic Neuropathy	< 0.001
Wernicke, 2006	11-point Likert scale	Duloxetine	60/120/placebo	12	114/118/112	Painful Diabetic Neuropathy	< 0.001
Vollmer, 2014	11-point Likert scale	Duloxetine	60/placebo	6	118/121	Multiple sclerosis	0.001
Raskin, 2006	Average pain change	Duloxetine	60/120	28	334/115	Painful Diabetic Neuropathy	< 0.001
Kajdasz, 2007	Short Form 36	Duloxetine	60/120/placebo	12	344/341/339	Painful Diabetic Neuropathy	< 0.0001
Smith, 2013	Short Form 36	Duloxetine	60/placebo	6	115/116	Chemotherapy neuropathic pain	0.003
Schukro, 2016	Visual analog scale (VAS)	Duloxetine	120/placebo	10	21/21	Chronic low back pain with root pain	0.001
Gao, 2015	Average pain change	Duloxetine	60/placebo	12	203/202	Painful Diabetic Neuropathy	0.03
Zhang, 2013	Average pain change	Gabapentin	1200/2400/3600/ placebo	14	107/82/87/95	Postherpetic Neuralgia	0.013
Irving, 2009	Average pain change	Gabapentin	1800/600-0-1200/ placebo	4	52/52/52	Postherpetic Neuralgia	0.0089
Backonja, 2011	Average pain change	Gabapentin	1200/placebo	2	47/54	Postherpetic Neuralgia	0.0321
Ho, 2009	Average pain change	Gabapentin	900-4800/placebo	1	8/8	Idiopathic Small-Fiber Neuropathy	0.001
Brogly, 2008	Average pain change	Gabapentin	1600/placebo	4	29/30	Cervical plexopathy	0.04
Pandey, 2002	Visual analog scale (VAS)	Gabapentin	15mg/kg/día	54	18/18	Guillain Barre syndrome	< 0.001
Rowbotham, 1998	Visual analog scale (VAS)	Gabapentin	3600/placebo	8	113/116	Postherpetic Neuralgia	< 0.001
Serpell, 2002	Average pain change	Gabapentin	2800/placebo	8	153/152	Neuropathic pain	0.048
Bone, 2002	Visual analog scale (VAS)	Gabapentin	2400/placebo	6	19/19	Phantom limb pain	0.03
Rice, 2001	Average pain change	Gabapentin	1200/2400/placebo	7	115/108/111	Postherpetic Neuralgia	< 0.01
Naini, 2007	Visual analog scale (VAS)	Gabapentin	400/placebo	4	17/17	Uremic pruritus	< 0.001
Sang, 2013	Average pain change	Gabapentin	1800/placebo	11	221/231	Postherpetic Neuralgia	0.013

(Continue in the next page)

TABLE I (CONT.)
CLINICAL TRIALS INCLUDED IN THE *P*-CURVE ANALYSIS

Study	*Evaluation*	*Drug*	*Dose (mg)*	*Time (weeks)*	*No. Patients*	*Etiology*	*P*
Calkins, 2016	Average pain change	Gabapentin	1200/2400/3600/ placebo	10	102/87/107/	Postherpetic Neuralgia	0.07
Rauck, 2013	Average pain change	Gabapentin	1800/placebo	10	357/364	Postherpetic Neuralgia	0.0025
Jensen, 2012	Average pain change	Gabapentin	1800/placebo	10	279/270	Postherpetic Neuralgia	0.003
Caraceni, 2004	Average pain change	Gabapentin	600-1800/placebo	10	79/41	Neuropathic cancer pain	0.025
Yaksi, 2007	Average pain change	Gabapentin	2400/placebo	17	28/27	Lumbar spinal stenosis	0.006
Mishra, 2012	Visual analog scale (VAS)	AT, GBP,	50/2400/300/ placebo	19	30/30/30/30	Dolor neuropático por cáncer	< 0,001
Mishra, 2012	Visual analog scale (VAS)	AT, GBP, PG/ placebo	50/2400/300/ placebo	3	30/30/30/30	Neuropathic cancer pain	< 0.001
Cardenas, 2013	Average pain change	Pregabalin	150-600/placebo	17	108/112	Spinal cord injury	0.003
Liu, 2017	11-point Likert scale	Pregabalin	300/placebo	8	111/109	Postherpetic Neuralgia	0.0002
Huffman, 2017	Time to loss of efficiency greater than 30%	Pregabalin	660/placebo	13	208/205	Postherpetic Neuralgia	< 0.0001
Arezzo, 2008	11-point Likert scale	Pregabalin	600/placebo	12	82/85	Painful Diabetic Neuropathy	< 0.001
Satoh, 2011	Average pain change	Pregabalin	300/600/placebo	15	132/44/132	Painful Diabetic Neuropathy	0.0075
Dou, 2017	Decrease in morphine dose	Pregabalin	300/placebo	12	20/20	Neuropathic cancer pain	< 0.001
Moon, 2010	Decrease in morphine dose	Pregabalin	150-600/placebo	10	162/78	Multifactorial neuropathic pain	0.049
van Seventer, 2006	Average pain change	Pregabalin	150/300/600/ placebo	13	87/98/90/93	Postherpetic neuralgia	0.0077
Guan, 2011	Average pain change	Pregabalin	150-600/placebo	8	206/102	Postherpetic and diabetic neuralgia	0.005
Freynhagen, 2005	Average pain change	Pregabalin	150-600/placebo	12	141/65	Postherpetic and diabetic neuralgia	0.002
Buvanendran, 2010	Leeds neuropathic pain scale	Pregabalin	300/placebo	6	113/115	Knee arthroplasty with neuropathic pain	0.014

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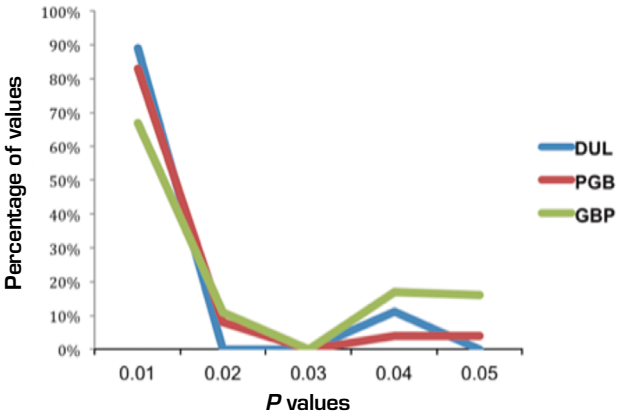
TABLE I (CONT.)
CLINICAL TRIALS INCLUDED IN THE *P*-CURVE ANALYSIS

Study	*Evaluation*	*Drug*	*Dose (mg)*	*Time (weeks)*	*No. Patients*	*Etiology*	*P*
Gilron, 2011	Average pain change	Pregabalin	300-600/placebo	9	80/78	Postherpetic neuralgia and painful diabetic pain	0.002
Stacety, 2008	Average pain change	Pregabalin	150-600/300/placebo	4	91/88/90	Postherpetic Neuralgia	< 0.0001
Tolle, 2008	Average pain change	Pregabalin	150/300/600/placebo	12	96/99/99/101	Painful Diabetic Neuropathy	0.036
Dworkin, 2003	Average pain change	Pregabalin	600/placebo	8	89/84	Postherpetic Neuralgia	0.0001
Siddall, 2006	Average pain change	Pregabalin	150-600/placebo	12	70/67	Spinal cord injury	< 0.001
Vranken, 2008	Visual analog scale (VAS)	Pregabalin	600/placebo	4	20/20	Central neuropathic pain	0.016
Gray, 2011	Numerical rating scale	Pregabalin	600/placebo	6	46/44	Burn	0.01
Van Seventer, 2010	Average pain change	Pregabalin	150-600/placebo	8	127/127	Post Traumatic Neuropathic Pain	0.01
Sabatowski, 2004	Average pain change	Pregabalin	150/300/placebo	8	81/76/81	Postherpetic Neuralgia	0.0060
Lesser, 2004	Average pain change	Pregabalin	75/300/600/placebo	5	77/81/82/97	Painful Diabetic Neuropathy	0.0001
Richter, 2005	Average pain change	Pregabalin	150/600/placebo	6	79/82/85	Painful Diabetic Neuropathy	0.0002
González-Duarte, 2016	Numerical rating scale	Pregabalin	300/placebo	9	27/27	Painful Diabetic Neuropathy	0.000



DUL: duloxetine. PFG: pregabalin. GBP: gabapentin.

Fig. 2. Distribution of the values found in the studies with positive results that assessed the efficacy of duloxetine, pregabalin and gabapentin.

ing the therapeutic efficacy of duloxetine, gabapentin and pregabalin compared to placebo in different types of neuropathic pain demonstrate value of evidence as demonstrated by the right asymmetry for each of the examined drugs. The analysis showed no evidence of "p-hacking." Prior registration of clinical trials with the main aim of the study mitigates the possibility of "p-hacking." However, the non-publication of studies with negative results makes it difficult to extrapolate the true effect of a drug. In this specific case, it is estimated that the actual efficacy of these drugs could be overestimated by 10 %, taking into account the registered studies that have not been published. Three reviews of the Cochrane Database guarantee efficacy with low to moderate quality for neuropathic pain of duloxetine at doses between 60 and 120 mg/day with a good safety profile compared to other antidepressants or to pregabalin. In these reviews, pregabalin has demonstrated efficacy in most patients with chronic neuropathic pain, with a minority unanswered and with a smaller percentage who will not notice beneficial effects or who will not tolerate side effects. With gabapentin, up to 50 % reduction in pain was obtained that affected the quality of sleep, fatigue, depression and quality of life [5-8]. In this way, our results complement these findings confirming that the positive results are true positives, eliminating the doubt of the existence of false positive assumptions or the effects of manipulating the results from the pivotal studies. The study of the *p-curve* demonstrates the body of quality of the available literature.

When Ronald Fisher introduced the concept of *p-value* in the 1920s, his intention was not to be a definitive test to judge the evidence on the hypothesis that was to be studied, but a warning that a second look or a confirmatory study was required. Fisher pointed out that the smaller the value of p, the greater the probability that the null hypothesis would be false. However, over the years, obtaining a *p*-value of 0.05 has become the main objective of many scientific papers and current research medicine has a low rate of study replication [7].

It is necessary to underline that the analysis of the *p*-curve is different from a meta-analysis, but at the same time it is complementary. Both types of statistical analyzes try to clarify whether a medical effect or intervention is real. A meta-analysis estimates with more strength the actual size of the effect compared to pivotal studies. In contrast, an analysis of the *p*-curve evaluates the integrity of the findings rather than the magnitude of the effect. It would answer the question of whether positive results reflect publication biases or if they are the result of statistical data manipulation.

The main limitation of the present study is that most of the studies were aimed at populations with painful diabetic polyneuropathy and postherpetic neuralgia, while the other causes of neuropathic pain are not well represented [13-23]. For this reason, it is more difficult to extrapolate our data to the different etiologies of neuropathic pain, either central or peripheral.

CONCLUSIONS

Clinicians, scientists and scientific publications should be aware of the growing problem with "p-hacking" and its harmful effects. All stakeholders share responsibility for maintaining the scientific integrity of published literature.

CONFLICTS OF INTEREST

No conflicts of interest or funding sources are declared.

FUNDING

This study has not received funding sources.

TABLE II
BINOMIAL AND CONTINUOUS TEST FOR THE ASSESSMENT OF EVIDENCE

Number of p-values				
Drug	*0 to < 0.025*	*≥ 0.025 to 0.05*	*Binomial test*	*Continuous test*
Duloxetine	8	1	0.0195	< 0.0001
Gabapentin	13	5	0.0154	< 0.0001
Pregabalin	22	2	< 0.0001	< 0.0001

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