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Original Research Articles

Comparative Efficacy of Oral Pharmaceuticals for the Treatment of Chronic Peripheral Neuropathic Pain: Meta-Analysis and Indirect Treatment Comparisons

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Abstract

Objective. Neuropathic pain is generally chronic and challenging to treat. Studies often ignore chronicity by reporting short-duration outcomes and fail to account for medication tolerability. We assessed efficacy of oral medications on chronic peripheral neuropathic pain.

Methods. Relevant published, English-language, randomized controlled trials administering oral medications for peripheral neuropathic pain were identified through MEDLINE (1966 to Dec 1, 2012), EMBASE (1980 to December 2012), the Cochrane Library Databases (through December 2012), and the Oxford Pain Relief Database (through 2012). Included studies reported end point pain or pain reduction from baseline on an 11-point scale (0–10); had active treatment ≥ 12 weeks; reported an intention-to-treat analysis, and had 5-point quality score ≥ 3. Abstracted information included patient characteristics, neuropathic pain condition, drug and dosage arms, adverse events rates causing dropout, and secondary measures (50% pain improvement, global improvement, and sleep interference). Primary outcome meta-analysis, stratified by drug and dosage, was followed by an indirect treatment comparison adjusting for study dropouts due to adverse events.

Results. Seventeen studies comprised of 5,975 subjects, totaling 38 active trial arms evaluating 7 drugs, and 17 drug-dosing combinations met inclusion criteria. Mean pain reduction over placebo ranked highest for duloxetine 120 mg (1.17 95% CI 0.77, 1.58) and pregabalin 600 mg (1.11 95% CI 0.77, 1.45). The Indirect treatment comparison showed largest effect size for duloxetine at 120 and 60 mg followed by pregabalin 600 mg.

Conclusions. Pregabalin and duloxetine had the largest beneficial effects for chronic peripheral neuropathic pain. In the absence of head-to-head trials, meta-analysis and indirect treatment comparisons inform best practice clinical decision-making.

Key Words. Neuropathy; Chronic Pain; Randomized Controlled Trial; Polyneuropathy, Pain Management

Introduction

Neuropathic pain is a common feature of neurological disorders and may represent disease entities distinct from their nervous system causes. Neuropathic pain carries implications for increased disability and morbidity beyond baseline neurological disease. Understanding of neuropathic pain has evolved over the past two decades, with the International Association for the Study of Pain (IASP) defining pain in 1994 as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" [1], with refinement as a proposed definition in 2008 as "pain arising from a lesion to the somatosensory nervous system." [2] Prevalence estimates of neuropathic range from 1% to 8% of the population at large [3–5]. Neuropathic pain can be further subdivided into central neuropathic pain, due to a lesion in the brain or spinal cord (such as multiple sclerosis or stroke), and peripheral neuropathic pain, secondary to damage to peripheral nerves (as in diabetic polyneuropathy). Unlike low back pain or headache that has a monophasic or relapsing-remitting pattern, the natural history of neuropathic pain depicts a condition that is generally chronic, defined by the IASP as persisting "beyond normal healing time, which is assumed to be 3 months." [6]

Greater awareness of neuropathic pain has prompted expansion of prescription oral treatments. In addition to analgesics with primary efficacy in pain disorders, non-analgesic medications, such as anticonvulsants and antidepressants, are increasingly used as first-line options for the management of neuropathic pain [7]. Many of these medications have a prolonged titration phase consisting of several weeks until patients achieve a dose associated with significant pain relief. Efficacy of some of these pharmaceuticals has been evaluated in both observational and randomized clinical trials. However, most published data are for relatively short interventions [8], generally 8 weeks or less [9], and implications for chronic pain may not be evident. In chronic pain conditions, trials shorter than 12 weeks have been shown to overestimate treatment effect [10]. Furthermore, head-to-head trials of oral pharmaceuticals for chronic neuropathic pain treatment are not available.

Due to the relatively large placebo effect in treatment of painful disorders, rigorous evaluation in blinded, randomized, and placebo-controlled trials is needed to establish true effect in ameliorating pain [11]. Tolerability must also be examined, as a large treatment effect is of little use if the patient discontinues the medication because of adverse events [12].

To reflect the chronic nature of neuropathic pain and the time required for effective dose titration, we are interested in 1) conducting a systematic review of the available literature for longer term studies that address the efficacy of oral prescription pharmaceuticals in managing chronic peripheral neuropathic pain disorders in a randomized, placebo-controlled setting; 2) determining effect sizes (ESs) in primary and secondary outcomes of these medications at each effective dosage using meta-analytic methods; and 3) comparing ESs between medication–dose combinations using indirect treatment comparisons (ITCs) and including study withdrawals due to adverse events to account for between-study heterogeneity.

Methods

Study Search Strategy

We undertook a meta-analysis of randomized placebo-controlled trials evaluating prescription oral pharmaceutical treatments for peripheral neuropathic pain. We used MEDLINE (1966 to December 1, 2012), EMBASE (1980 to December 2012), the Cochrane Library Databases (through December 2012), and the Oxford Pain Relief Database (through 2012) to identify studies with the search terms (randomized) AND (Clinical Trial) AND (neuropathic pain) AND ([treatment] OR [drug therapy]) limited to published English-language studies in adult humans.

Study Selection

Randomized, blinded clinical trials for peripheral neuropathic pain selected for inclusion compared a prescription oral pharmaceutical with placebo measured after 12 weeks or more of exposure to the active intervention, including titration and maintenance phases. Only fixed goal dosing studies were considered. Studies allowing continued use of baseline stable doses of analgesics (including opiates) were included. All included studies assessed continuous outcomes through an 11-point measure (0–10) using a visual analog scale, numeric pain rating scale, Likert scale, or Brief Pain Inventory. Study dropouts attributed to adverse effects of active intervention and placebo were available for all included studies. Only post-randomization intention-to-treat (ITT) analyses were considered. Articles reporting post hoc pooling of multiple studies were included provided that the pooled data were from ITT analysis and had not previously been reported. Studies where a primary outcome ES could not be ascertained or calculated from the data were excluded. Included studies scored $\geq$3 on a 5-point scale evaluating risk of internal bias by assessing blinding and randomization using the method described by Jadad et al. [13] by two independent raters.

Data Extraction

One reviewer examined titles and abstracts for inclusion in full-text review. Following full-text review, studies were assessed for quality by two independent raters (described above), then included study details were abstracted to a spreadsheet. Abstracted information included demographics (mean age and gender), type of peripheral neuropathic pain condition, drug and total daily dosage (adjusted for creatinine clearance, as applicable) administered in active trial arms, mean duration of neuropathic pain (or neuropathy, when reported), whether steady-state analgesics (including opiates) were allowed, duration of titration and maintenance of the active treatment, primary and secondary outcome measures, and dropout rates due to adverse events.

Meta-Analysis of Drug–Dosage Combinations

Meta-analyses within drug–dosages were used to calculate medication–dose outcome ESs and standard errors. The primary outcome was the mean difference (MD) between placebo and active intervention for one of two end points: 1) reduction (change) in baseline pain at 12 or greater weeks or 2) pain at 12 or greater weeks (unadjusted or adjusted via analysis of covariance [ANCOVA] for baseline). As these measures were all conducted on continuous or ordinal 11-point scales with the same units, standardization was unnecessary. To facilitate ES calculation, reported standard errors were converted to standard deviations [14]. The use of reduction in baseline pain was preferred, but when standard deviations for this measure were not reported or not calculable from the published study, the measured pain score at end point was used, with the assumption that within-study randomization would create equivalent groups in terms of baseline pain, or ANCOVA adjustment (when applied) was sufficient to control for baseline pain. Furthermore, the two MD end points are statistically identical [15], and were ultimately combined for determination of overall ES.

We also performed a meta-analysis of each secondary outcome (sleep interference score, $\geq$ 50% reduction in pain, and global improvement measure). The sleep interference score is a continuous measure on a 0–10 scale reported in most studies as a change from baseline, but in some as an ANCOVA-adjusted final score. Calculations for MD over placebo were the same as for pain. For the 50% or greater placebo response and global improvement in pain measures, we used a dichotomous outcome for the proportion of responders over placebo. Global improvement in pain measures was based on an ordinal scale, which was reported in studies as the proportion of subjects rating in the top two categories as "much improved" or "very much improved" for the Global Assessment of Therapeutic Effect, Patient Global Impression of Change, or Clinical Global Impression of Change. We reported the ESs for the $\geq$50% response and global improvement metrics as a number needed to treat (NNT) for each medication/dosage.

Lastly, a meta-analysis of the proportion of dropouts due to adverse effects in each study arm was calculated to give an ES representing the mean risk difference of withdrawal from adverse events over placebo. This was reported as a number needed to harm (NNH).

For studies with multiple treatment arms of differing doses vs placebo, the presence of a common comparator (placebo) creates a unit-of-analysis error with correlated data [16]. We offer an analysis to overcome this issue without loss of data, one in which we split the placebo group equally among comparisons within study (only partially solving the unit-of-analysis error). Attempting to combine treatment arms was not possible for a number of these studies, as they reported only the MD in baseline to end point change in comparison to placebo (with standard deviations) rather than the distribution parameters for the treatment arms independent of placebo comparator.

All studies were weighted within each medication–dose meta-analysis based on the generic inverse-variance method [17]. A random-effects model was developed, built on the assumption that between-study variance results from factors other than measured treatment differences [18]. The random-effects model assumes a normal distribution of between-study variance, which is aided by the generally large (>100) size of the included trials.

Assessment of Heterogeneity

Quantifiable heterogeneity between studies evaluating same medication dosages was evaluated with the I^2 statistic. I^2 was developed by Higgins et al. [19] to account for the percent of total variation across studies attributable to heterogeneity beyond random chance. Values of 0% indicate no heterogeneity, while 25%, 50%, and 75% may be described as low, moderate, or high [19]. The I^2 builds upon the Q statistic, a sum of the weighted difference between summary effect across studies and within-study effects, modified by the number of trials measured [20].

Assessment of Publication Bias

Publication bias was determined by means of Begg [21] and Egger's [22] tests, assessing study pain reduction MD vs study pain reduction standard error or precision. Begg's test uses effect estimates and variances to perform an adjusted rank correlation test, depicted graphically by a funnel plot. Asymmetry in the funnel plot suggests that statistically insignificant smaller studies may not have been published. Egger's test creates a regression line of study standardized ES vs precision and comparing the linear intercept with zero. Both were applied to the primary end point only.

Evaluation of Role of Study Characteristics

The effect of several study characteristics on the primary outcome and adverse event rate resulting in study dropout (MD over placebo) was analyzed. We examined the role of demographics (age and gender), neuropathic pain condition, sample size, and inclusion of subjects on steady-state analgesics (opiates allowed) for each placebo vs drug–dosage comparison. Using meta-regression, we modeled the change to the ES of the primary outcome and adverse event rate (MD over placebo) for each drug–dose as an interaction between the study characteristic (defined as a binary covariate) and the drug–dose. Drug–doses where all the active trial arms either had or did not have the study characteristic had collinear interactions where the effect of the study characteristic could not be ascertained.

The effects of gender (50% or greater female subjects), age (60 or over), neuropathic pain condition (diabetic painful neuropathy or other), sample size (>150 subjects), and allowed analgesics on the primary outcome and

adverse event dropout rate were not ascertainable for over half the dosage/medication combinations due to collinearity. For those where an interaction could be determined, none of the interactions reached significance.

ITC with Meta-Regression

Without evidence directly comparing the effects of agents in randomized controlled trials (RCTs), ITCs can be employed to compare the pharmaceuticals indirectly [23]. ITCs are an extension of traditional meta-analysis which enables rank ordering of individual treatments. The success of the ITC method relies on the presence of a common comparator as the basis for creation of a network [24]. In the RTCs for oral pharmaceuticals in peripheral neuropathic pain, placebo is the comparator of interest (Figure 1).

The random-effects model is the basis of the ITC of MDs for primary outcomes between pairwise drug/dosage combinations. We utilized a meta-regression approach that relies on residual maximum likelihood to estimate the additive (between-study) variance [18] and subsequent linear combinations of subgroup MDs (here represented as categorical variable coefficients) and standard errors. We further accounted for heterogeneity between studies by including a covariate in the meta-regression that represented the risk difference over placebo of study discontinuation due to adverse events.

All statistical analyses were conducted using Stata 11.0 (StataCorp, College Park, TX, USA).

Results

Search Results

Initial search criteria identified 584 English-language published studies, with titles and abstracts screened for relevance. Seventy-three full-text articles were assessed. Further exclusions were largely due to duration of study or lack of calculable ES for the primary outcome. Final review of full-text articles revealed 17 eligible studies that met the inclusion criteria [25–41]. Figure 2 provides the details of the search. Five studies [25–28,30] had only placebo and single drug–dosage treatment arms (excluding flexible dosing schedules), while 12 articles [28,29,31–41] featured studies with multiple dosage treatment arms compared with a placebo arm. One article reported the results of three previously unpublished studies [33]. One study [29] arm was excluded due to very low dosing (duloxetine 20 mg) relative to clinical evidence-based practice [42], and another study arm was excluded because of a flexible dosing schedule where actual daily dose could not be ascertained [28]. Each included study rated 3 or greater for quality with Jadad's 5-point scale of quality assessment for RCTs. All included studies excluded patients on non-analgesic medications used to treat neuropathic pain (e.g., anticonvulsants) at the time of randomization, but

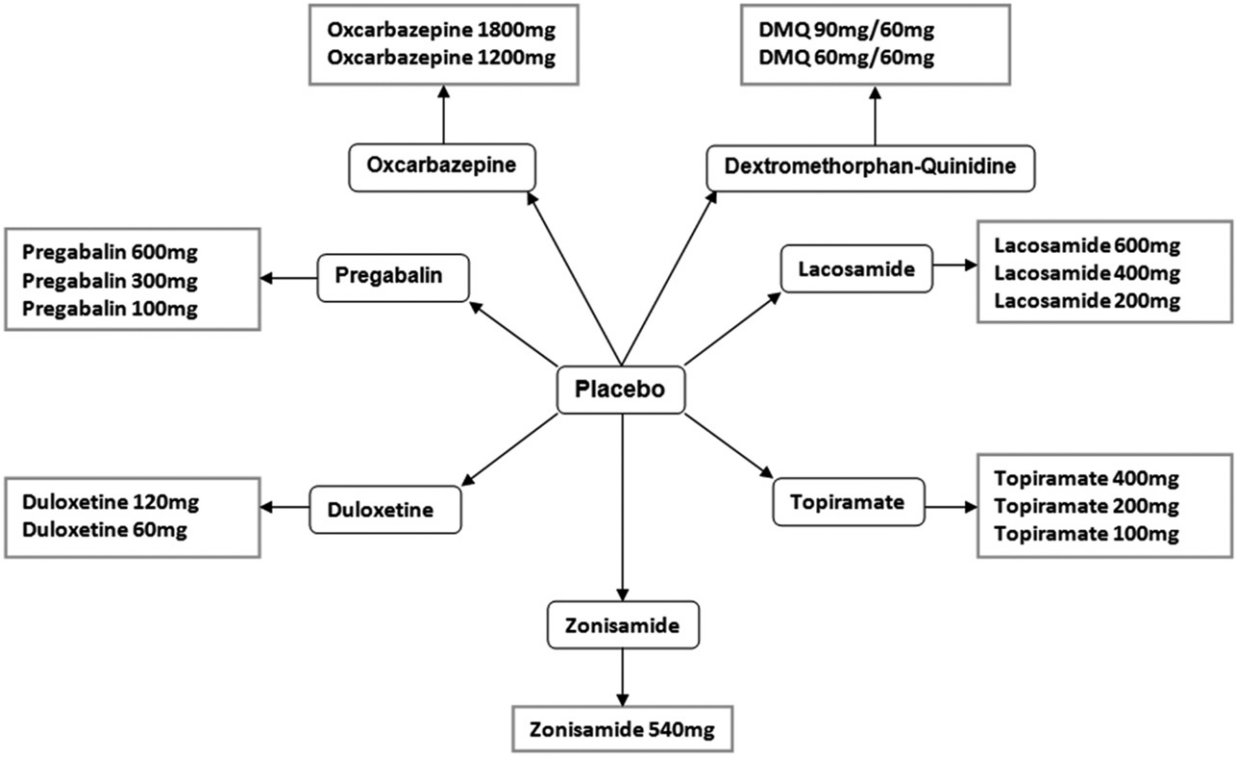

Figure 1 Indirect comparison network.

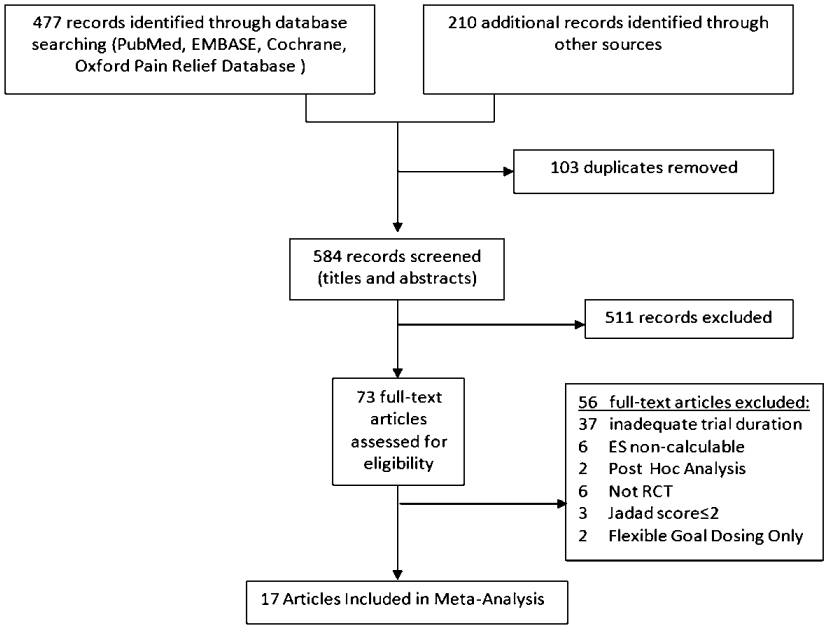

Figure 2 Search strategy: Flow-chart with studies meeting inclusion/exclusion criteria in sequence.

two studies allowed subjects to continue taking analgesics including opiates for breakthrough pain [26,35]. Most studies allowed use of acetaminophen as an acute pain treatment. All included studies had measured continuous pain outcomes in ITT analysis at 12 or greater weeks of exposure (post-randomization dropout data imputed as last observation carried forward) to the intervention vs placebo reported as primary end points (see Table 1).

Thirty-eight comparisons of drug–dosages vs placebo were evaluated. The total number of subjects (placebo and active intervention) evaluated was N = 5,975 (mean N = 157, range N = 23–317). The mean time of active intervention was 15.6 weeks (range 12–22 weeks), consisting of a dose-titration phase in 21 comparisons to placebo with a mean of 4 weeks (0–10 weeks), and a dose-maintenance phase averaging 11.6 weeks (range 4–16 weeks). Seven drugs and 17 drug-dosing combinations were evaluated. One drug (zonisamide) had only a single trial arm vs placebo [26] while another drug (pregabalin) had 10 dosing-placebo comparisons.

Primary Outcomes: MD in Pain Reduction vs Placebo

The MD for pain reduction from baseline evaluating mean effect of pharmaceuticals vs placebo ranged from 0 to 1.17 (Table 2). This calculation may be interpreted as a mean reduction in pain over placebo effect for 12 or greater weeks of active treatment. High-dose duloxetine (120 mg) and pregabalin (600 mg) had the largest effects on pain reduction on a continuous scale with the least variance. Heterogeneity was moderate to high for lower doses of pregabalin and topiramate (I^2 between 50% and 80%).

Secondary Outcomes

Meta-analysis of secondary outcomes was generally consistent with analysis of primary outcomes. The medication–dosage combinations with the greatest ESs in pain reduction also had the greatest improvement in sleep interference scores and the largest proportion of responders at 50% pain improvement and global improvement metrics (Table 3A–C).

Sleep Interference

Sleep interference scores were available for 18 drug–dose/placebo comparisons, with 5 articles not reporting sleep interference scores [26,27,29,33,37]. The MD of reduction in sleep interference ranged from 0.3 to 1.1. High-dose pregabalin had the greatest reduction in sleep interference, with a MD over placebo for 600 mg dosing of 1.1 (95% CI 0.7–1.6). Heterogeneity measures were moderate or less for all drug-dosing combinations.

50% Pain Improvement

Response rates at 50% improvement in pain could be determined for 23 of 38 drug–dosage/placebo comparisons. Three studies did not report this measure [33,37,39]. The NNT for a single 50% improvement in pain ranged from 3.7 to 21.3. The most beneficial ESs were for dextromethorphan–quinidine (DMQ) combination 90 mg/60 mg daily dosing at NNT of 3.7 (95% CI 2.4–8.2), pregabalin at 600 mg daily dosing with an NNT of 4.1 (95% CI 3.2–5.9), and zonisamide with an NNT of 3.7 (95% CI 2.4, 7.8). Heterogeneity was moderate or less ($I^2 \leq 40\%$) for any subgroup.

Table 1 Study characteristics of peripheral neuropathic pain, randomized controlled trials, ITT, ≥12 weeks of treatment

Article		Study Design								Subject Characteristics			Reported Secondary Outcomes		
Author (Reference)	Year	Condition	Drug	Active Dose(s) (mg)	Baseline Analgesics‡	Quality Score§	Active Duration (weeks)	ITT n (Active)	ITT n† (Placebo)	Mean Age (years)	% Female	Neuropathy/ Pain Duration (years)	50% Pain Relief	Global Response	Sleep Interference
Arezzo [25]	2008	DPN	Pregabalin	600	Excluded	5	13	82	85	58	38%	4.4	Yes	Yes	Yes
Atli [26]	2005	DPN	Zonisamide	540	Allowed	4.5	12	11	12	59	60%	NR	Yes	No	No
Beydoun [39]	2006	DPN	Oxcarbazepine	1,800	Excluded	4.5	16	88	45	60	46%	2.9	No	Yes	No
				1,200				87	44	61	47%	2.9	No	Yes	No
Dogra [27]	2005	DPN	Oxcarbazepine	1,800	Excluded	4.5	20	69	77	60	42%	2.6	Yes	Yes	No
Freynhagen [28]	2005	PHN + DPN	Pregabalin	600	Excluded	3.5	12	132	32	63	47%	3.2	Yes	Yes	Yes
				<600				141	33	62	45%	3.2	Yes	Yes	Yes
Goldstein [29]	2005	DPN	Duloxetine	60	Excluded	5	12	114	58	60	37%	4.0	Yes	Yes	No
				120				113	57	60	43%	4.0	Yes	Yes	No
Raskin [30]	2004	DPN	Topiramate	400	Excluded	4.5	12	208	109	59	52%	3.2	Yes	Yes	Yes
Raskin [31]	2005	DPN	Duloxetine	60	Excluded	4.5		113	56	59	46%	4.0	Yes	Yes	Yes
				120			13	114	57	59	50%	4.0	Yes	Yes	Yes
Satoh [41]	2011	DPN	Pregabalin	600	Excluded	3	14	45	68	62	29	4.5	Yes	No	Yes
				300				134	67	61	24	4.3	Yes	No	Yes
Shaibani [32]	2009	DPN	Lacosamide	400	Excluded	5	18	120	22	60	42%	3.0	Yes	Yes	Yes
				600				131	21	59	41%	3.0	Yes	Yes	Yes
				200				138	21	60	40%	3.0	Yes	Yes	No
Shaibani [40]	2012	DPN	DMQ	90/60	Excluded	4	13	131	45	61	38%	4.0	Yes	No	Yes
			DMQ	60/60			13	125	45	60	32%	3.6	Yes	No	Yes
*Thienel [33]a	2004	DPN	Topiramate	200	Excluded	5	22	130	45	58	41%	4.4	No	No	No
				100				128	45	58	44%	4.4	No	No	No
				400				130	46	58	42%	4.4	No	No	No
*Thienel [33]b	2004	DPN	Topiramate	400	Excluded	5	22	129	60	58	42%	4.4	No	No	No
				200				116	59	58	41%	4.4	No	No	No
*Thienel [33]c	2004	DPN	Topiramate	100	Excluded	5	18	122	63	58	43%	4.4	No	No	No
				200				123	63	58	41%	4.4	No	No	No
Tolle [34]	2007	DPN	Pregabalin	600	Excluded	3	12	101	32	60	41%	NR	Yes	Yes	Yes
				150				98	32	59	46%	NR	Yes	Yes	Yes
				300				99	32	58	47%	NR	Yes	Yes	Yes
Van Seventer [35]	2006	PHN	Pregabalin	600	Allowed	3	13	88	31	71	58%	3.6	Yes	Yes	Yes
				300				98	31	71	48%	3.6	Yes	Yes	Yes
				150				87	31	71	58%	3.6	Yes	Yes	Yes
Wernicke [36]	2006	DPN	Duloxetine	60	Excluded	5	13	110	53	61	35%	3.5	Yes	Yes	Yes
				120				111	53	61	42%	3.5	Yes	Yes	Yes
Wymer [37]	2009	DPN	Lacosamide	600	Excluded	5	18	92	30	57	45%	3.3	No	Yes	No
				400				91	30	59	43%	3.3	No	Yes	No
				200				92	30	59	48%	3.3	No	Yes	No
Ziegler [38]	2010	DPN	Lacosamide	400	Excluded	4	18	149	37	58	49%	3.0	Yes	Yes	Yes
				600				132	37	57	48%	3.0	Yes	Yes	Yes

* Published 3 studies, 10 arms (including placebo).
† Recalculated in multiarmed trials against single arm placebo.
‡ Other than acetaminophen.
§ Average score from two independent raters evaluating Jadad et al.'s [24] quality score.
DPN = diabetic peripheral neuropathy; HIV = human immunovirus; PHN = post-herpetic neuralgia; NR = not reported; ITT = intention-to-treat.

Table 2 Results of meta-analysis: primary outcome. Primary outcome is reduction in baseline pain score at end point over placebo (Pain Δ). Ranked in descending order of effect size

Drug and Dosage (mg)	Active Arms	N (Active)	Pain Δ	95% Confidence Interval	*P* value	I^2 (%)
Duloxetine 120	3	338	1.17	(0.77, 1.58)	<0.001	6
Pregabalin 600	5	448	1.11	(0.77, 1.45)	<0.001	6
Duloxetine 60	3	337	1.08	(0.70, 1.46)	<0.001	0
Zonisamide 540	1	11	1.08	(–0.33, 2.49)	0.13	NA*
Oxcarbazepine 1,800	2	157	0.85	(0.19, 1.51)	0.01	0
Pregabalin 150	2	185	0.66	(–0.13, 1.44)	0.1	68
DMQ 90/60	1	131	0.60	(0.41, 0.80)	<0.001	NA*
Lacosamide 400	3	360	0.56	(0.24, 0.89)	<0.001	0
Pregabalin 300	3	331	0.53	(0.11, 0.94)	0.01	36
Oxcarbazepine 1,200	1	87	0.50	(–0.27, 1.27)	0.2	NA*
Topiramate 400	3	467	0.45	(–0.05, 0.95)	0.08	0
Lacosamide 600	3	355	0.41	(0.14, 0.68)	<0.001	0
Lacosamide 200	2	230	0.36	(–0.05, 0.78)	0.09	0
DMQ 60 mg/60	1	125	0.20	(0.01, 0.39)	0.043	NA*
Topiramate 200	3	369	0.04	(–0.70, 0.79)	0.91	50
Topiramate 100	2	250	0.00	(–1.37, 1.36)	1	77

* NA = not applicable. I^2 as a measure of heterogeneity cannot be calculated from a single study.
DMQ = dextromethorphan–quinidine combination formula.

Global Improvement Measures

Response rates for better-than-minimal global improvement could not be assessed from reports of four studies [26,33,40,41]. The number needed for a single greater-than-minimal improvement was 4.5–11.4. NNTs for high-dose pregabalin and low and high doses of duloxetine were similar at 4.5–5.1. Heterogeneity was moderate or less ($I^2 < 40\%$) for any subgroup.

Adverse Events

All studies reported discontinuations in placebo and treatment arms secondary to adverse events. Oxcarbazepine 1,800 mg and zonisamide 540 mg had the smallest NNH to cause study dropout at 2.6 and 3.6, respectively. Drugs tested at the highest doses had smaller NNH (and therefore greater risk) than lower doses of the same drug (topiramate, pregabalin, and duloxetine) (Table 4).

Publication Bias

Evidence of publication bias by application of Begg and Egger's tests (Figures 3 and 4) produced mixed results. In Begg's test, a low probability result with a high z-score suggests bias, here the continuity corrected z-score was 1.47 ($P = 0.141$), not reaching significance. Egger's test had a bias coefficient of 1.04 (95% CI 0.13, 1.94), indicating that there is modest evidence of publication bias. Further, the slope of Egger's score, an estimate of the treatment effect corrected for bias, was significant at 0.29 (95% CI 0.05, 0.54). Together, this presents weak to modest evidence that asymmetry in the funnel plot may suggest non-publication of small studies that failed to reach statistical significance in differentiating primary outcome from placebo.

ITC with Meta-Regression

ITCs of drug-dosing effects were conducted on the primary outcome using meta-regression to account for adverse event rate resulting in study dropout. This is displayed as a forest plot in Figure 5 for those drug-daily dosing combinations for primary end points. Accounting for the MD in adverse event rates had the effect of increasing the relative ES of medications/dosing with lower Adverse Event Rate (AER) particularly duloxetine 60 mg. Duloxetine 120 mg was superior in rank ordering (not shown) and pairwise comparisons, followed by duloxetine at 60 mg and pregabalin at 600 mg, although the difference in adjusted primary outcome between duloxetine doses was only 0.02.

Discussion

In both the meta-analysis and indirect comparisons, total daily dosing of duloxetine at 120 mg showed modest advantages relative to other medications in the primary outcome at 12 or greater weeks. This indicates that the average effect is a reduction in baseline chronic neuropathic pain greater than that of other medications and lower doses of pregabalin, both before and after accounting for the tolerability of the medication. Duloxetine at 60 mg and pregabalin at 600 mg doses had slightly smaller effects, which were not significantly different from high-dose duloxetine.

Table 3 Meta-analysis: secondary outcomes. Ranked in efficacy from greatest to least

A. SIS Δ

Drug and Dosage (mg)	Active Arms	N (Active)	SIS Δ	95% Confidence Interval	*P* value	I^2 (%)
Pregabalin 600	5	448	1.1	(0.7, 1.6)	<0.001	46
Lacosamide 600	2	263	1	(0.3, 1.6)	0.003	0
Duloxetine 60	2	223	0.9	(0.5, 1.2)	<0.001	0
Pregabalin 300	3	331	0.9	(0.6, 1.2)	<0.001	0
Duloxetine 120	2	225	0.8	(0.3, 1.3)	0.003	0
Pregabalin 150	2	185	0.7	(0.1, 1.3)	0.016	27
Topiramate 400	1	208	0.7	(0.0, 1.4)	0.051	NA†
Lacosamide 400	2	269	0.5	(0.0, 0.9)	0.033	0
DMQ 90/60	1	131	0.5	(0.3, 0.7)	<0.001	NA†
DMQ 45/60	1	125	0.3	(0.1, 0.5)	0.01	NA†

B. 50% Improvement Response (NNT)

Drug and Dosage (mg)	Active Arms	N (Active)	NNT	95% Confidence Interval	*P* value	I^2 (%)
Zonisamide 540	1	11	3.7	(2.4, 7.8)	<0.001	NA†
DMQ 90 mg/60	1	131	3.7	(2.4, 8.2)	<0.001	NA†
Pregabalin 600	5	448	4.1	(3.2, 5.9)	<0.001	0
Duloxetine 120	3	338	4.9	(3.2, 10.8)	<0.001	40
Duloxetine 60	3	337	5.1	(3.5, 9.0)	<0.001	0
Oxcarbazepine 1,800	1	69	6	(3.2, 38.5)	0.02	NA†
DMQ 45 mg/60	1	125	6.7	(3.3, NI)	0.05	NA†
Topiramate 400	1	208	6.9	(4.1, 22.2)	0.004	NA†
Pregabalin 150	2	185	7.6	(3.7, NI†)	0.067	38
Pregabalin 300	3	331	9.0	(5.0, 50)	0.017	19
Lacosamide 400	2	269	11.9	(4.7, NI†)	0.204	0
Lacosamide 600	2	263	21.3	(5.9, NI†)	0.452	8
Lacosamide 200	1	138	NI	(4.9, NI†)	1	NA†

C. Global Improvement (NNT)

Drug and Dosage (mg)	Active Arms	N (Active)	NNT	95% Confidence Interval	*P* value	I^2
Duloxetine 120	3	338	4.5	(3.39, 6.76)	<0.001	0
Duloxetine 60	3	337	4.6	(3.36, 7.52)	<0.001	19
Lacosamide 600	2	263	4.7	(2.75, 16.39)	0.006	28
Oxcarbazepine 1,800	2	157	5.1	(2.99, 16.13)	0.004	30
Pregabalin 600	4	403	5.1	(3.57, 9.01)	<0.001	0
Lacosamide 400	2	269	6.8	(3.69, 47.62)	0.022	0
Lacosamide 200	1	138	7.7	(3.29, NI‡)	0.144	NA†
Oxcarbazepine 1,200	1	87	7.9	(3.26, NI‡)	0.167	NA†
Topiramate 400	1	208	8.5	(4.57, 58.82)	0.022	NA†
Pregabalin 300	2	197	9.7	(4.44, NI‡)	0.098	0
Pregabalin 150	2	185	11.4	(4.76, NI‡)	0.156	0

No secondary outcomes were reported for topiramate at 100 and 200 mg dosages.
† NA = not applicable. I^2 as a measure of heterogeneity cannot be calculated from a single study.
‡ NI = not interpretable due to negative number reported in number needed to treat.
DMQ = dextromethorphan–quinidine combination formula; SIS Δ = Sleep Interference Score; NNT = number needed to treat.

Table 4 Meta-analysis: adverse event rate resulting in study dropout. Reported as NNH. Ranked in descending order of NNH (least harm to most harm)

Drug and Dosage (mg)	Active Arms	N (Active)	NNH	95% Confidence Interval	ES *P* value	I^2 (%)
Lacosamide 200	2	234	NI*	(11.6, NI*)	0.9	0
Pregabalin 150	2	186	47.6	(12.3, NI*)	0.49	0
Duloxetine 60	3	345	21.3	(10.4, NI)	0.06	28
Pregabalin 300	2	331	16.4	(9.1, 90.9)	0.02	0
Topiramate 100	2	250	12.5	(6.7, 90.9)	0.02	0
Lacosamide 400	3	366	10.4	(6.3, 29.4)	<0.001	0
DMQ 45 mg/60	1	125	10.4	(4.8, NI*)	0.10	NA†
Duloxetine 120	3	341	9	(6.3, 16.1)	<0.001	0
Pregabalin 600	5	448	7.6	(5.3, 13.3)	<0.001	25
DMQ 90/60	1	131	6.8	(3.7, 41.7)	0.02	NA†
Oxcarbazepine 1,200	1	87	6.2	(3.6, 21.7)	0.01	NA†
Topiramate 200	3	369	5.9	(4.3, 9.2)	<0.001	0
Topiramate 400	3	470	5.1	(4.0, 7.0)	<0.001	0
Lacosamide 600	3	363	4.1	(3.0, 6.5)	<0.001	24
Oxcarbazepine 1,800	2	157	3.6	(2.5, 6.9)	0.01	55
Zonisamide 540	1	12	2.6	(1.5, 8.3)	0	NA†

* NI = not interpretable due to negative number reported in number needed to harm.
† NA = not applicable. I^2 as a measure of heterogeneity cannot be calculated from a single study.
DMQ = dextromethorphan–quinidine combination formula; NNH = number needed to harm; ES = effect size.

Conversely, other medications considered had smaller, mixed, or negative results with regard to the average effect on pain amelioration. The DMQ combination medication had a relatively small effect in terms of mean pain improvement. Likewise, the newer anticonvulsant lacosamide had several large trials which showed mild to moderate efficacy, but significantly less effect in all formulations than high-dose pregabalin. Oxcarbazepine at 1,800 mg total dosing per day was responsible for a moderate but significant improvement in the primary outcome meta-analysis, which was adjusted downward due to the high withdrawal rate secondary to adverse events (NNH = 3.6). Topiramate had negative or mixed effects on neuropathic pain. The latter is somewhat surprising given that topiramate has shown efficacy in the treatment of other painful conditions, particularly migraine headache [43].

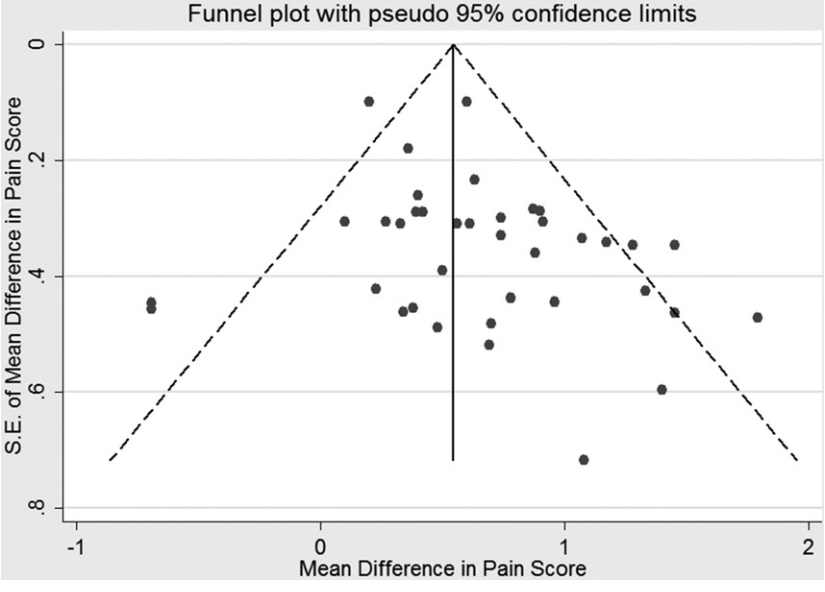

Figure 3 Funnel plot for assessment of publication bias. Begg's z-score (continuity corrected) = 1.47, *P* value = 0.14.

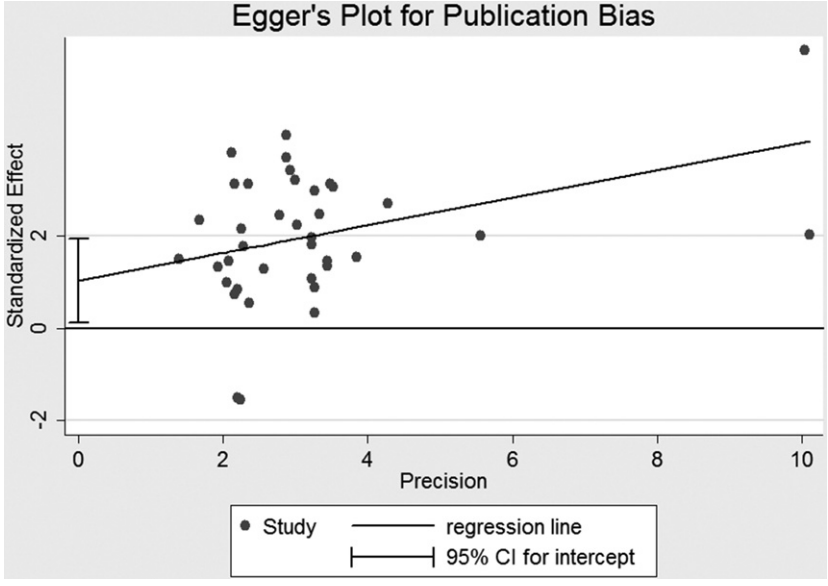

Figure 4 Egger's regression plot for publication bias. Slope = 0.3, bias intercept = 1.04 (P = 0.03).

This suggests that neuropathic pain may be fundamentally different from other types of pain, and medications that work for one variety of pain may not work for another.

Our meta-analysis of secondary outcomes generally confirmed the results of the primary outcome meta-analysis. For reduction in sleep interference, pregabalin at 600 mg dosing was superior, followed by high-dose lacosamide (600 mg) and duloxetine (60 mg), with DMQ combinations having the least, but still significant effect. The proportion of subjects with 50% improvement in pain showed greatest benefit for two medications (Zonisamide and DMQ) that did not perform as well in mean pain improvement. However, the IMMPACT recommendations for chronic pain trials [44] indicate that responder analysis may be a better reflection of the actual composition of a chronic pain trial, where the mean effect may be a very potent one for responders diluted by an insignificant or negative effect for subjects who do not respond. Meanwhile, both duloxetine-dosing formulations were consistent with the primary analysis as they had the largest proportion with improvement in global measures.

Heterogeneity between trial arms evaluating mean pain reduction for the same medication dosage was generally low. The moderate-to-high heterogeneity for 150 and 300 mg pregabalin is in part due to the inclusion of Tolle et al. [34], where a very high placebo response in one geographic region was sourced as a potential cause for failure of the lower dose pregabalin arms to separate from placebo. Still, within-dose heterogeneity was very high only for topiramate 100 mg dosing (I^2 = 77%).

Our work compares favorably with other recent attempts to compare neuropathic pain medications. Finnerup et al. [45] reported a meta-analysis that looked at the available evidence for all neuropathic pain treatments (oral, topical, subcutaneous) in all central and peripheral neuropathic pain conditions of any treatment length. Outcomes were dichotomized into an NNT for responders with 50% improvement in pain and adverse event rates resulting in dropout into an NNH, then ranked treatments (mostly) by drug class. In that analysis, the pregabalin/gabapentin and serotonin-norepinephrine reuptake inhibitor (SNRI) drug classes had similar ESs with NNTs of 4–8, with corresponding estimated NNHs of 13–20. Quilici et al. [46] published a meta-analysis and indirect comparisons of pregabalin and duloxetine in diabetic neuropathic pain for RCTs of any treatment duration. Both medications had significant reductions in 11-point (0–10) 24-hour pain score over placebo, duloxetine (1.1) and pregabalin (0.9), although the difference in effect between these was drugs were not significant in the ITCs. Pregabalin was found to be superior in global impression of change scores to duloxetine, while duloxetine had a significantly smaller risk of dizziness than pregabalin.

Our meta-analysis lends additional specificity to these published analyses. The smaller ES in pain reduction for pregabalin seen in Quilici et al. [46] was in part due to the heterogeneity seen from using different dose formulations among the six trials meta-analyzed. Likewise, the conflation of individual drugs into drug classes in Finnerup et al. [45] may lose some information to create an average effect of a drug class, for example, a "generic" SNRI effect on pain, diluting the effect of duloxetine among other less efficacious drugs. Although both of these works looked at adverse effects, neither attempted to account for their mean effect on pain amelioration.

We give a more focused evaluation for optimal drug choice for the clinician treating chronic neuropathic pain. Clinicians face an uphill battle in escalating medication doses to best effect while assessing side effects for a variety of pain that is often refractory and long lasting. In choosing trials of 12 weeks or greater duration, we assess

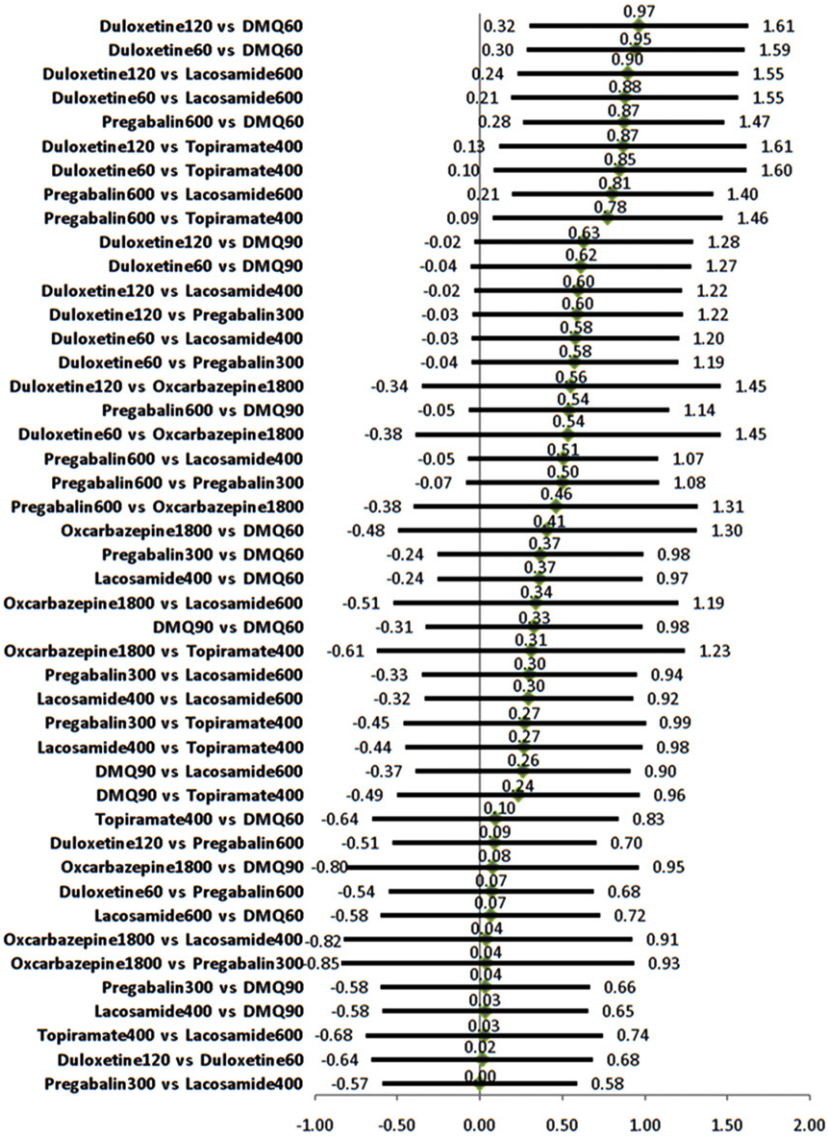

Figure 5 Adjusted indirect treatment comparisons–primary outcome–mean difference in pain reduction at end point (over placebo) with confidence intervals. Adjusted via meta-regression for adverse event rate resulting in dropouts (over placebo). Point estimates are the arithmetic differences between the two interventions.

the durability of the effect in pain reduction, and longer term side effects resulting in discontinuation than prior analyses.

By stratifying our meta-analysis by daily drug dose, we show that both efficacy and adverse events causing dropout are dose dependent. Rather than basing the decision on a general "class effect" and attempting to titrate to an average dose, the practicing clinician can rank the efficacy of the goal dosage of a particular pharmaceutical relative to other medication–dosage combinations. The ITCs give an additional level of information in pairwise comparisons of drugs of different dosages, while accounting for relative discontinuation rates. Thus, from our review, the clinician can determine that duloxetine at 120 mg daily has the greatest evidence for efficacy for neuropathic pain relief in the chronic setting, that the effect remains even after accounting for adverse events, and that lower doses are slightly less efficacious, with the difference being largely negligible after adjustment.

The limitations to this approach arise both from the clinical question that we are attempting to answer, and the data from available studies. As only studies involving two chronic peripheral neuropathic pain conditions (diabetic peripheral neuropathy and post-herpetic neuralgia [PHN]) met the criteria for inclusion, the results for this meta-analysis may not be generalizable to other neuropathic pain conditions. However, these conditions are among the most common and the least ambiguous neuropathic pain entities that lend themselves both to recruitment for clinical trials and differentiation from less specific conditions

such as lumbosacral radiculopathy, which may be difficult to distinguish from mechanical low back pain.

The criterion of trial duration was a further limiting factor. Medications that are studied for 12 or more weeks often have long titration phases and pain relief is gradual. Analysis of shorter duration trials in chronic pain [10] has indicated that these tend to overestimate treatment effects that may not be evident in longer studies. No analgesics (such as controlled-release narcotics) met study inclusion criteria, as their effects on pain amelioration are generally evident at far shorter end points, reducing the perceived need for a lengthy clinical trial to establish effect. Likewise, gabapentin and tricyclic antidepressant (TCA) medications, common treatment for neuropathic pain, have not been evaluated in rigorous, blinded, randomized, placebo-controlled trials with 12-week or greater end points. We speculate that the incentive to fund RCTs of gabapentin or TCAs vs placebo for 3 months is minimal, as these are available in generic form, and gabapentin is the first medication that U.S. Food and Drug Administration (FDA) approved for PHN, therefore enjoying considerable popularity among prescribers. The two medications that most favored our analysis, duloxetine and pregabalin, have FDA indications for neuropathic pain conditions and have the largest number of 12+ week trials, and may reflect the motivation of the manufacturers to show primary efficacy in these conditions and to distinguish themselves from gabapentin and TCAs. The modest evidence of publication bias seen in the funnel plot and Egger's plot may reflect the desire of manufacturers to not publish insignificant results from smaller trials. Additionally, the purpose of this analysis is not to discourage pain practitioners from using lower cost alternatives to the admittedly newer and more expensive treatments reviewed here, but to provide the highest quality evidence for chronic pain treatment using the most rigorous methodology available. Lastly, we did not evaluate trials for topical or injectable medications such as capsaicin or botulinum toxin [47,48].

In attempting to get the highest quality data, we have left out observational studies and nonrandomized treatments, as well as post hoc, as-treated analyses. Although we did not specifically exclude multiple or combination drug trials, none met inclusion requirements. For the pain patient, having an intervention of any kind exerts a powerful effect, which is reflected in the placebo arms of the randomized trials chosen for inclusion. While excluded nonrandomized treatments may provide additional information, it is unclear how they address placebo effect and as-treated analyses often ignore dropouts to produce possibly biased results [11].

Despite these issues, our analysis gives useful information on relative efficacy of medications at varying doses, which is currently lacking in the literature. Without head-to-head trials, meta-analysis and ITCs provide the best possible guidance for clinicians, making decisions on how to treat a difficult chronic condition where medication noncompliance is a substantial barrier to effective pain management.

Conclusions

Our findings indicate that among medications evaluated for chronic neuropathic pain reduction, total daily dosages of duloxetine at 120 and 60 mg and pregabalin at 600 mg are particularly efficacious even accounting for side-effect-related dropouts. Major differences in effect between these medications were not found. Absent direct treatment comparisons, meta-analysis, and ITCs are the best tools for evaluating the available neuropathic pain treatment literature. Future trials addressing chronic treatment of neuropathic pain with analgesics and common generic medications as well as head-to-head trials between frequently used medications are needed.

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