Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain

Hélène Cawston · Alison Davie · Marie-Ange Paget · Vladimir Skljarevski · Michael Happich

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Abstract

Introduction The objective of this study was to obtain parameter estimates for the efficacy of duloxetine versus alternative oral therapies for the treatment of chronic low back pain.

Materials and Methods Electronic databases were searched to identify randomised, double-blind placebo-controlled trials. Studies reporting pain intensity, with parallel-group design of oral treatments with length of treatment of more than 8 weeks were included. A Bayesian approach to indirect comparisons was applied, using standardised mean difference as a measure of relative treatment effect.

Results Fifteen studies were identified comparing duloxetine with the following oral drug classes: non-scheduled opioids, cyclooxygenase-2 inhibitors, scheduled opioids, selective serotonin reuptake inhibitors, and ‘other’ (i.e. glucosamine). The primary analysis found scheduled opioids to be more effective than duloxetine for the fixed effects model. However, the estimate of the treatment difference reflected a less than small magnitude of effect (standardised mean difference <0.2), and there was no difference for the random

effects model. No differences were found in sensitivity analyses involving the subset of patients not receiving concomitant non-steroidal anti-inflammatory medication.

Conclusion The available evidence shows that there does not seem to be any difference in efficacy between duloxetine and other oral pharmacological therapies, providing a valuable alternative for this disabling condition.

Keywords Duloxetine · Chronic low back pain · Meta-analysis · Indirect comparison

Introduction

Chronic low back pain (CLBP) is a disabling condition, defined as any pain in the low back that persists for at least 12 weeks [26, 27]. CLBP is one of the most common musculoskeletal disorders in developed countries, representing a large economic burden due to its deleterious effect on adults of working age [11]. Estimates for the prevalence of CLBP range from 1.0 to 58.1 % (mean 18.1 %; median 15.0 %) [18].

CLBP is often progressive and characterised as a symptom unrelated to a specific diagnosis, making cause difficult to determine [12]. Due to its refractory nature, prognosis and response to therapy are poor, and the appropriate choice of treatment is less certain [6], and aimed at symptom relief. Management strategies include the use of systemic or local pharmacological therapies [1]: non-scheduled opioids, non-steroidal anti-inflammatory drugs (NSAIDs), scheduled opioid analgesics, anticonvulsants, and antidepressants.

Duloxetine is a serotonin–norepinephrine reuptake inhibitor that acts by modulating the descending pain inhibitory pathways, under the hypothesis that this mode of action should work across all chronic pain states independent of the underlying pathology. In placebo-controlled

H. Cawston
OptumInsight, Nanterre, France

A. Davie (✉)
OptumInsight, 3rd Floor, Beaufort House, Cricket Field Road,
Uxbridge, Middlesex UB8 1QG, UK
e-mail: alison.davie@optum.com

M.-A. Paget
Eli Lilly and Company, Paris, France

V. Skljarevski
Eli Lilly and Company Research Laboratories, Indianapolis,
USA

M. Happich
Eli Lilly and Company, Frankfurt, Germany

phase III trials, excluding patients with limited medical radiography (LMR) and spinal stenosis duloxetine-treated patients with axial CLBP experienced reductions in pain and improvements in their physical functioning [28–30]. Two of these studies allowed concomitant NSAID use [28, 30]. However, duloxetine has not been compared in a head-to-head fashion with an active therapy for the treatment of CLBP.

The aim of this meta-analysis was to evaluate how the efficacy of available oral pharmacological therapies compared to duloxetine, by statistically pooling available data from randomised controlled trials (RCTs). As there were no head-to-head trials, an indirect comparison was chosen using placebo as the common comparator.

Materials and methods

Systematic literature review

A systematic review of the published literature, using PubMed, EMBASE, Cochrane and Centre for Reviews and Dissemination (CRD) databases, was conducted with the

objective of identifying all potentially relevant evidence relating to the efficacy and safety of pharmacological therapies for the treatment of CLBP (Table 1). A first review identified articles published between 1966 and 2008. An update to this review during January 2011 identified papers published from 2008 onwards. Internal study reports of all duloxetine trials were provided by the study sponsor, Eli Lilly and Company.

All aspects of the systematic literature review process (i.e. screening, data extraction and quality assessment) were undertaken by two independent reviewers for the purposes of verification, inclusive of dual entry into Microsoft *Excel*®. Any discrepancies and/or conflicts were arbitrated by a third reviewer. Titles, abstracts and keywords for all potentially relevant publications were screened based on pre-defined inclusion/exclusion criteria in accordance with the PICOS method. Those potentially eligible for inclusion in the meta-analysis were of English language, randomised, double-blind placebo-controlled trials among adults aged over 18 years, with a diagnosis of CLBP defined as having experienced pain for at least 3 months before entering the study. Studies were excluded

Table 1 Detailed search strategies (by database)

Topic	Search terms	Detailed strategy
Pubmed		
Disease area	Low back pain	“Low back pain”[MeSH Terms] OR (“low”[All Fields] AND “back”[All Fields] AND “pain”[All Fields]) OR “low back pain”[All Fields]
Treatment	Drug therapy	“Drug therapy”[Subheading] OR (“drug”[All Fields] AND “therapy”[All Fields]) OR “drug therapy”[All Fields] OR “drug therapy”[MeSH Terms] OR (“drug”[All Fields] AND “therapy”[All Fields])
Publication type	Clinical trials	“Clinical trial”[Publication Type] OR “clinical trials as topic”[MeSH Terms] OR “clinical trials”[All Fields]
Embase		
Disease area and treatment	Low back pain Drug therapy	Low back pain/dt [Drug Therapy]
Publication type	Clinical trials	Clinical trial/or randomised controlled trial.mp. or controlled clinical trial/or multicenter study/or observational study/or phase 1 clinical trial/or phase 2 clinical trial/or phase 3 clinical trial/or phase 4 clinical trial/
The Cochrane Library (CENTRAL and Cochrane Library Database of Systematic Reviews)^a		
Disease area	Low back pain	“Low back pain”[MeSH Terms] OR (“Low”[All Fields] AND “back”[All Fields] AND “pain”[All Fields]) OR “low back pain”[All Fields]
Treatment	Drug therapy	“Drug therapy”[Mesh] OR (“Drug”[All Fields] AND “therapy”[All Fields]) OR “drug therapy”[All Fields] OR “drug therapy”[MeSH Terms] OR (“drug”[All Fields] AND “therapy”[All Fields])
Publication type	Clinical trials	“Clinical trial”[Publication Type] OR “Clinical trials as topic”[MeSH Terms] OR “Clinical trials”[All Fields]
CRD (DARE and HTA)^a		
Disease area	Low back pain	(“Low back pain” OR “chronic low back pain”)

^a No date limits applied

CENTRAL Cochrane Register of Controlled Trials, *CRD* Centre for Reviews and Dissemination databases, *DARE* Database of Abstracts of Reviews of Effectiveness, *HTA* Health Technology Assessment

Fig. 1 Flow diagram of systematic literature review to identify eligible studies

if one or more patients were aged 18 years or less, if the focus of the study was acute exacerbations of low back pain or patients had experienced pain for less than

3 months, if only one treatment arm was allocated to a drug therapy, or were not English language. Following full-text review and final study selection, summary data from all

Fig. 2 Network of studies selected for the meta-analysis

included publications were extracted into a structured Excel workbook corresponding to distinct study outcomes of interest, including study design synopsis, comparator therapies, dosing regimen, titration schedule, duration of treatment, baseline characteristics (i.e. pain severity, age and sex), and efficacy outcomes [pain intensity measured on the visual analogue scale (VAS), numeric rating scale (NRS) or bodily pain index (BPI)]. The quality of each study was assessed using methodological checklist recommended by Cochrane for the critical appraisal of RCTs [33]. The checklist rates the quality of the methodology using a dichotomous scale, across seven different aspects of study design and reporting, such as the appropriateness and adequacy of reporting, randomisation and blinding methods, whether the type of analysis conducted was from an intention-to-treat principle, and if any imbalances were accounted for. The assessment also contains a concluding critique as to the extent to which study design and baseline characteristics influenced study outcomes.

A feasibility assessment was conducted to assess the level of heterogeneity between studies on the basis of patient characteristics, study characteristics and study outcomes available for generating pooled efficacy estimates, using a narrative approach. Overall, the number of interventions investigated across the clinical trials was high and the form of treatment administration differed across studies, thereby leading to various placebos being used. Time horizons also varied markedly across studies. The final list of studies eligible for the meta-analysis was

validated on the basis of clinical relevance, based on expert opinion. These studies evaluated oral treatments through parallel-group design, with a length of treatment between 8 and 12 weeks, and reported a pain intensity measure.

Evaluation

To address the issue of heterogeneity between pain intensity scales, standardised mean difference (SMD) in change from baseline relative to placebo was used as a summary statistic, as recommended by the 2011 Cochrane Handbook [16], whereby a negative value demonstrates a better outcome than the comparator. To avoid bias in the effect size, SMD was defined as Hedges adjusted $g(g^*)$ [15].

When the change from baseline in each treatment group was not provided, the SMD was approximated as the mean difference of final values divided by the estimated standard deviation of change from baseline [16].

Meta-analysis

The meta-analysis was conducted according to a pre-specified analysis plan. The network included all labelled doses of oral treatments documented in the systematic literature review. Treatments were grouped according to their respective class [cyclooxygenase-2 (cox-2) inhibitors, scheduled opioids, non-scheduled opioids, selective serotonin reuptake inhibitors (SSRIs), and other (glucosamine)] due to the low number of studies available for the analysis.

Table 2 Population and study characteristics

Publication	Treatment class	Study treatments	Total length of follow-up	Washout period	Enriched enrolment	Treatment duration ^a (weeks)	Titration period	Mean age (years)	Gender (% F)	Concomitant analgesic use allowed	Categorisation by pain duration (months)	Baseline pain intensity
Dickens [7]	Antidepressant	Paroxetine 20 mg (<i>N</i> = 44) Placebo (<i>N</i> = 44)	Washout + 8 weeks	1 week	No	8	No	45.2	54	Yes	≥6	55.1 (SD = 22.8) 56.1 (SD = 23.8)
Skjarevski et al. [29] (HMEO study)	Antidepressant	Duloxetine 120 mg (<i>N</i> = 112) Duloxetine 60 mg (<i>N</i> = 116) Duloxetine 20 mg (<i>N</i> = 59) Placebo (<i>N</i> = 117)	Screening + 13 weeks	1 week screening with concomitant NSAID use allowed	No	13	Yes	53.9	57	Yes	≥6	6.06 (SD = 1.46) 6.12 (SD = 1.42) 6.23 (SD = 1.19)
Skjarevski et al. [28] (HMEN study)	Antidepressant	Duloxetine 60–120 mg (<i>N</i> = 115) Placebo (<i>N</i> = 121)	Screening + 13 weeks	1 week screening with concomitant NSAID use allowed	No	13	Yes	51.5	61	Yes	≥6	6.91 (SD = 1.24) 7.02 (SD = 1.21)
Skjarevski et al. [30] (HMGCS study)	Antidepressant	Duloxetine 60 mg (<i>N</i> = 198) Placebo (<i>N</i> = 203)	Screening + 12 weeks	1 week screening without concomitant analgesic use	No	12	No	54.1	61	No	≥6	5.84 (SD = 1.43) 5.75 (SD = 1.37)
Barbara et al. [2]	Cox-2 inhibitor	Etoricoxib 90 mg (<i>N</i> = 107) Etoricoxib 60 mg (<i>N</i> = 103) Placebo (<i>N</i> = 109)	Washout + 12 weeks	4–15 days	No	12	No	51.8	61	No	≥3	77.8 (SD = 13.6) 76.9 (SD = 12.7) 76.9 (SD = 12.8)
Pallay et al. [22]	Cox-2 inhibitor	Etoricoxib 90 mg (<i>N</i> = 106) Etoricoxib 60 mg (<i>N</i> = 109) Placebo (<i>N</i> = 110)	Washout + 12 weeks	4–15 days	No	12	No	52.8	63	No	≥3	76.7 (SD = 14.3) 76.6 (SD = 14.7) 75.2 (SD = 14.9)
Peloso et al. [23]	Non-scheduled opioid	Tramadol + paracetamol (<i>N</i> = 167) Placebo (<i>N</i> = 169)	Washout + 13 weeks	3 weeks max	No	13	10 days	57.5	63	No	≥3	67.9 (SD = 14.95) 67.6 (SD = 15.53)
Ruoff et al. [25]	Non-scheduled opioid	Tramadol + paracetamol (<i>N</i> = 161) Placebo (<i>N</i> = 157)	Washout + 13 weeks	3 weeks	No	13	10 days	53.8	63	No	≥3	71.1 (SD = 14.5) 68.8 (SD = 14.9)
Vorsanger et al. [34]	Non-scheduled opioid	Tramadol ER 300 mg (<i>N</i> = 127) Tramadol ER 200 mg (<i>N</i> = 129) Placebo (<i>N</i> = 126)	Washout + 15 weeks	2–7 days	3 weeks	12	No	47.8	50	NR	≥6	26.8 (SD = 23.7) 29.5 (SD = 26.0) 30.7 (SD = 25.9)

Table 2 continued

Publication	Treatment class	Study treatments	Total length of follow-up	Washout period	Enriched enrolment	Treatment duration ^a (weeks)	Titration period	Mean age (years)	Gender (% F)	Concomitant analgesic use allowed	Categorisation by pain duration (months)	Baseline pain intensity
Buyrak et al. [3]	Scheduled opioid	Tapentadol ER (<i>N</i> = 321) Oxycodone CR (<i>N</i> = 334) Placebo (<i>N</i> = 326)	Washout + 15 weeks	Yes	No	15	3 weeks	49.9	58	No	≥3	7.5 (SD = 1.33) 7.5 (SD = 1.21) 7.6 (SD = 1.33)
Hale et al. [14]	Scheduled opioid	Oxymorphone (<i>N</i> = 70) Placebo (<i>N</i> = 72)	12 weeks + EE	NR	Yes	12	Yes, during ER phase	47.1	45	No	≥3	23.9 (SD = 12.1) 22.2 (SD = 10.8)
Katz et al. [19]	Scheduled opioid	Oxymorphone ER (<i>N</i> = 105) Placebo (<i>N</i> = 100)	Open-label + 12 weeks	Opioid naïve	Yes	12	Yes, during ER phase	49.7	53	No	≥3	18.7 (SD = 11.32) 19.5 (SD = 11.09)
Hale et al. [13]	Scheduled opioid	Hydromorphone (<i>N</i> = 134) Placebo (<i>N</i> = 134)	Washout + EE + 12 weeks	2 weeks	2–4 weeks	12	Yes, during ER phase	48.6	50	No	≥6	3.2 (95 %CI = 3.1, 3.3) 3.1 (95 %CI = 3.0, 3.2)
Webster et al. [35]	Scheduled opioid	Oxycodone + naltrexone bid (<i>N</i> = 206) Oxycodone + naltrexone qid (<i>N</i> = 206) Oxycodone qid (<i>N</i> = 206) Placebo (<i>N</i> = 101)	Washout + 18 weeks	4–10 days	No	18	6 weeks	48.1	62	No	≥6	7.6 (SD = 1.33) 7.3 (SD = 1.36) 7.6 (SD = 1.36) 7.7 (SD = 1.44)
Wilkins et al. [36]	Other	Glucosamine (<i>N</i> = 125) Placebo (<i>N</i> = 125)	1 year	No glucosamine 1 year before	No	24	No	48.5	48	Yes	≥6	3.7 (SD = 2.6) 3.9 (SD = 2.4)

^a Excluding enriched enrolment phase

F Female

Table 3 Quality assessment scores for studies included in the meta-analysis

Studies	Treatment class	(1) Was randomisation carried out appropriately?	(2) Was the concealment of treatment allocation adequate?	(3) Were the groups similar at the outset of the study in terms of prognostic factors, for e.g., severity of disease?	(4) Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	(5) (a) Were there any unexpected imbalances in drop-outs between groups? ^a	(5) (b) If so, were they explained or adjusted for? ^a	(6) Is there evidence to suggest that the authors measured more outcomes than they reported?	(7) Did the analyses include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Overall score
Dickens [7]	Antidepressant	Yes	Yes	Yes	Yes	Unclear	NA	No	Yes	6
Skjjaevski et al. [29] (HMEO study)	Antidepressant	Yes	Yes	Yes	Yes	Yes	No	No	Yes	6
Skjjaevski et al. [28] (HMEN study)	Antidepressant	Yes	Yes	Yes	Yes	Yes	No	No	Yes	6
Skjjaevski et al. [30] (HMG study)	Antidepressant	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
Birbara [2]	Cox-2 inhibitor	Yes	Unclear	Yes	Yes	Unclear	NA	No	Yes	5
Pallay et al. [22]	Cox-2 inhibitor	Yes	Yes	Yes	Yes	No	NA	No	Yes	7
Peloso et al. [23]	Non-scheduled opioid	Yes	Unclear	Yes	Unclear	Yes	Unclear	No	Yes	4
Ruoff et al. [25]	Non-scheduled opioid	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	5
Vorsanger et al. [34]	Non-scheduled opioid	Yes	Yes	Unclear	Unclear	No	NA	No	Yes	4
Byynak et al. [3]	Scheduled opioid	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
Hale [14]	Scheduled opioid	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Yes	4
Katz [19]	Scheduled opioid	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	6
Hale [13]	Scheduled opioid	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	6

Table 3 continued

Studies	Treatment class	(1) Was randomisation carried out appropriately?	(2) Was the concealment of treatment allocation adequate?	(3) Were the groups similar at the outset of the study in terms of prognostic factors, for e.g., severity of disease?	(4) Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	5 (a) Were there any unexpected imbalances in drop-outs between groups? ^a	5 (b) If so, were they explained or adjusted for? ^a	(6) Is there evidence to suggest that the authors measured more outcomes than they reported?	(7) Did the analyses include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Overall score
Webster [35]	Scheduled opioid	Yes	Yes	Unclear	Yes	Yes	Yes	No	No	5
Wilkins [36]	Other	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	6

^a Note: Question five has two parts: a positive score for this question requires a 'no' for part a 'yes' for both parts

Due to the absence of head-to-head trials, duloxetine was compared to the other active treatments through indirect comparison using placebo as a common comparator. Fixed and random effects normal models provided estimates of the mean difference in treatment effect. To handle three-arm trials and the assumption of independence between pair-wise comparisons, hierarchical models were run in a Bayesian framework using Markov Chain Monte Carlo (MCMC) simulation in the WinBugs software [31].

Pooled estimates of treatment difference in three-arm trials were used to calculate Cochrane Q tests, I^2 and τ^2 statistics to test and quantify between-study heterogeneity [17]. Forest plots were generated to visually assess the extent of heterogeneity. Sources of heterogeneity were explored through meta-regression analysis. Baseline pain score, score at screening, mean age, and sex (defined as the proportion of females in the study population), pain duration (dichotomous variable, ≥ 6 months of pain before baseline) and enriched enrolment design (i.e. exclusion of non-responders following exposure to study drug) were included in univariate meta-regressions. In studies with enriched enrolment design, it was hypothesised that baseline score could be higher than the true baseline severity of the population due to the exclusion of non-responders [32]. Therefore, score at screening, preceding the open-label treatment phase, was also tested.

A uniform prior distribution (Uniform [0, 2]) was applied to the between-study variance parameter in the base-case analysis. A uniform distribution (Uniform [0, 2]) for the prior between-study standard deviation and a gamma distribution (Gamma [0.01, 100]) for the prior precision were tested in sensitivity analysis. Additional analyses limited to trial arms corresponding to the most prevalent dosing regimens in the UK, as well as high-quality studies (with an overall rating of >6), were carried out.

Results

Literature search

Figure 1 displays the results of the literature search, screening, review and study selection. Sixty-two studies potentially eligible for inclusion in the meta-analysis were identified from 1,881 references screened; 15 were finally included, representing 5,374 patients. All trials compared active treatment to placebo (Fig. 2). Table 2 describes the population characteristics of the included studies.

Treatment study periods ranged from 8 weeks to 1 year. Of note, all scheduled and non-scheduled opioids, and cox-2 inhibitor trials were either of enriched enrolment or flare design. Flare design was defined as trials only inclusive of

Table 4 Detailed calculation of standardised mean difference

Study	Category	Total <i>N</i>	Adjusted SMDi ⁵	Unadjusted SMDi ¹	Var(SMDi)	Mdi	Si ²	Change from baseline comparator	SDi comparator	Change from baseline placebo	SDi Placebo
Dickens [7]*	Antidepressant	92	0.03	0.03	0.04	1.00	29.79	1.90**	26.67***	0.90**	32.38***
Eli Lilly and Company (HMEO CSR 2010) [9]	Duloxetine	332	-0.20	-0.20	0.01	-0.42	2.10	-2.24	2.09	-1.82	2.13
	Duloxetine 120 mg	222	-0.18	-0.19	0.02	-0.39	2.11	-2.21	2.09	-1.82	2.13
	Duloxetine 60 mg	223	-0.21	-0.21	0.01	-0.45	2.11	-2.27	2.10	-1.82	2.13
Eli Lilly and Company (HMEN CSR 2010) [10]	Duloxetine	227	-0.30	-0.30	0.02	-0.64	2.13	-2.12	2.11	-1.48	2.15
Eli Lilly and Company (HMGCSR 2010) [8]	Duloxetine	401	-0.26	-0.26	0.01	-0.55	2.12	-1.92	2.11	-1.37	2.14
Birbara et al. [2]	Cox-2 inhibitor	313	-0.28	-0.28	0.01	-7.89	27.67	-35.89	26.37	-28.00	30.00
	Etoricoxib 90 mg	212	-0.35	-0.35	0.02	-9.90	27.91	-37.90	25.62	-28.00	30.00
	Etoricoxib 60 mg	208	-0.20	-0.20	0.00	-5.80	28.64	-33.80	27.13	-28.00	30.00
Pallay et al. [22]	Cox-2 inhibitor	325	-0.34	-0.35	0.01	-10.07	29.15	-36.37	29.03	-26.30	29.37
	Etoricoxib 90 mg	216	-0.42	-0.43	0.02	-12.40	29.10	-38.70	28.83	-26.30	29.37
	Etoricoxib 60 mg	219	-0.27	-0.27	0.00	-7.80	29.30	-34.10	29.23	-26.30	29.37
Peloso et al. [23]*	Non-scheduled opioid	336	-0.64	-0.64	0.01	-15.80	24.55	-20.5**	24.48***	-4.70**	24.63***
Ruoff et al. [25]*	Non-scheduled opioid	318	-0.42	-0.42	0.01	-10.20	24.41	-26.70**	24.37***	-16.50**	24.46***
Vorsanger et al. [34]	Non-scheduled opioid	382	-0.20	-0.20	0.01	-5.69	28.83	6.51	28.63	12.20	29.24
	Tramadol 300 mg	253	-0.25	-0.25	0.02	-7.00	28.00	5.20	26.72	12.20	29.24
	Tramadol 200 mg	255	-0.15	-0.15	0.00	-4.40	29.83	7.80	30.39	12.20	29.24
Buynak et al. [3]	Scheduled opioid	981	-0.32	-0.32	0.00	-0.80	2.51	-2.90	2.59	-2.10	2.33
	Tapentadol ER	647	-0.32	-0.32	0.01	-0.80	2.50	-2.90	2.66	-2.10	2.33
	Oxycodone CR	660	-0.33	-0.33	0.02	-0.80	2.43	-2.90	2.52	-2.10	2.33
Hale et al. [14]	Scheduled opioid	142	-0.92	-0.92	0.03	-22.90	24.85	8.70	25.10	31.60	24.61
Hale et al. [13]	Scheduled opioid	268	-0.67	-0.68	0.02	-0.90	1.33	-0.10**	0.88***	0.80**	1.66***
Katz et al. [19]	Scheduled opioid	205	-0.69	-0.69	0.02	-16.90	24.34	10.00	24.29	26.90	24.40
Webster et al. [35]	Scheduled opioid	719	-0.29	-0.29	0.01	-0.77	2.63	-3.25	2.58	-2.48	2.93
	Oxycodone + naltrexone bid	307	-0.28	-0.28	0.01	-0.76	2.72	-3.24	2.62	-2.48	2.93
	Oxycodone + naltrexone qid	307	-0.20	-0.20	0.01	-0.53	2.69	-3.01	2.57	-2.48	2.93
	Oxycodone qid	307	-0.38	-0.38	0.03	-1.03	2.68	-3.51	2.55	-2.48	2.93
Wilkins et al. [36]*	Glucosamine	250	-0.02	-0.02	0.02	-0.20	9.74	-1.00**	9.44***	-1.00**	10.03***

* Pain duration not reported, estimation using: $g = \left(\frac{\Delta_{\text{Treat}} - \Delta_{\text{Placebo}}}{s^*} \right)$, with s^* defined as $2s^* = \sqrt{\frac{(n_{\text{Treat}} - 1)s_{\text{Treat}}^2 + (n_{\text{Placebo}} - 1)s_{\text{Placebo}}^2}{n_{\text{Treat}} + n_{\text{Placebo}} - 2}}$, $3g^* = J(n_{\text{Treat}} + n_{\text{Placebo}} - 2) \left(\frac{\Delta_{\text{Treat}} - \Delta_{\text{Placebo}}}{s^*} \right) \approx \left(1 - \frac{3}{4(n_{\text{Treat}} + n_{\text{Placebo}}) - 5} \right) g$, with J defined as $J(a) = \frac{\Gamma(a/2)}{\sqrt{a/2} \Gamma((a-1)/2)}$

Estimation of treatment difference when change from baseline is not reported: $^{**}\Delta = \text{Mean}_{\text{Final endpoint}} - \text{Mean}_{\text{Baseline}}$; $^{***} s_{\Delta \text{Treat}} = \sqrt{s_{\text{Treat, Baseline}}^2 + s_{\text{Treat, Final}}^2 - 2 \cdot \text{Corr} * s_{\text{Treat, Baseline}} s_{\text{Treat, Final}}}$

With Corr defined as the correlation coefficient between baseline and final measurements. Corr was imputed as the mean correlation coefficient of studies reporting baseline, final measurements and change from baseline for all treatment groups

MDi mean difference, SDi comparator, SDi placebo standard deviation of change from baseline in comparator and placebo groups, Si standard deviation of changes from baseline in total population, SMDi standardised mean difference

Fig. 3 Forest plot, direct evidence against placebo with fixed and random Bayesian estimates, by drug class

Table 5 Results of the fixed and random effects of the indirect comparison

Intervention against duloxetine	SMD	SE (SMD)	95 % CrI
Fixed effects analysis			
Antidepressants	0.27	0.22	(−0.15, 0.69)
Cox-2 inhibitors	−0.02	0.07	(−0.15, 0.12)
Non-scheduled opioids	−0.01	0.07	(−0.14, 0.13)
Scheduled opioids	−0.15	0.07	(−0.29, −0.01)
Other	0.22	0.14	(−0.05, 0.49)
Random effects analysis			
Antidepressants	0.28	0.31	(−0.33, 0.89)
Cox-2 inhibitors	−0.05	0.18	(−0.40, 0.30)
Non-scheduled opioids	−0.13	0.17	(−0.47, 0.20)
Scheduled opioids	−0.24	0.15	(−0.55, 0.05)
Other	0.22	0.26	(−0.29, 0.74)
Between-study variance	0.04		

CrI credibility interval, SMD standardised mean difference, SE (SMD) standard error of standardised mean difference

those with increased pain following the washout period. Nine studies included titration periods and four included enriched enrolment periods (three of which compared scheduled opioids to placebo). Concomitant analgesic use was allowed in five studies. The results of the quality assessment showed that the majority of studies (60 %) achieved a rating of greater than 6 (Table 3). Three studies (20 %) rated 7 on 7; one of which was the duloxetine trial [30] comparing duloxetine 60 mg to placebo. The other two duloxetine trials [28, 29] were among those scoring 6 on 7.

Meta-analysis

Primary analysis: total population

Standardised mean differences for each study are reported in Table 4. Figure 3 illustrates the estimated SMDs of study treatments against placebo with their 95 % confidence intervals (CI), as well as the pooled Bayesian fixed and random effect estimates by drug class. With the exception of four studies [7, 29, 34, 36], all reported at least

a small magnitude of effect according to the American guideline definition of magnitude of effect [4] (SMD ranges small [0.2, 0.5], moderate [0.5, 0.8] and large [>0.8] magnitudes of effect). Overall SMDs were highest in studies assessing scheduled opioid treatment strategies, with the largest effect reported by Hale et al. [14] [SMD = −0.9 (Var = 0.03)]. Substantial heterogeneity was observed within the subgroups of studies comparing non-scheduled opioids to placebo ($I^2 = 75\%$) and scheduled opioids to placebo ($I^2 = 79\%$). The estimated heterogeneity was very low for all other drug classes.

The base-case meta-analysis results (Fig. 3) showed that in the fixed effects model, with the exception of SSRIs and glucosamine, all drug classes were more effective than placebo. The indirect comparison (Table 5) demonstrated that scheduled opioids were more effective than duloxetine, although the estimated SMD was less than small [$|SMD| < 0.2$; SMD = −0.15 (95 % credibility interval, CrI −0.29, −0.01)]. No difference was shown between duloxetine and non-scheduled opioids, cox-2 inhibitors, SSRIs, or glucosamine as their respective credibility intervals included zero. The random effects model provided a better fit (deviance information criterion, DIC = −17.9 versus 4.7 for the fixed effects model) and led to a similar interpretation to that of the fixed effects model. The estimated between-study variance was very low ($\tau^2 = 0.04$). There was no difference between duloxetine and all of the other drug classes.

Sources of heterogeneity were explored through meta-regression analysis. In a univariate analysis (Table 6), only pain duration was found to be associated with treatment effect. Studies in which patients had suffered pain for more than 6 months had lower treatment differences.

Sensitivity analysis: NSAID non-users, prior distributions, most prevalent dosing regimen and high-quality studies

Sensitivity analyses results for the random effects model are reported in Table 7. The first sensitivity analysis focussed on duloxetine monotherapy (i.e. excluding those with concomitant NSAID use) and was conducted using results from a pre-specified sub-group of patients from the duloxetine trials. Studies by Dickens [7] and Wilkens et al. [36]

Table 6 Univariate meta-regression: primary analysis

Variable name	Estimate	SD	95 % CrI
Baseline score	0.03	0.03	(−0.02, 0.09)
Score at screening	−0.01	0.08	(−0.16, 0.15)
Pain duration (required ≥ 6 months before baseline)	0.22	0.08	(0.06, 0.38)
Study mean age	−0.03	0.02	(−0.07, 0.01)
Study female percentage	0.76	1.04	(−1.24, 2.88)
Enriched enrolment (yes/no)	−0.06	0.13	(−0.33, 0.19)

CrI credibility interval, SD standard deviation

were excluded from this analysis as they allowed concomitant NSAID use. No drug class was found to be more effective than duloxetine. This was also true for the fixed effects model. In a second sensitivity analysis, the random effects model (including all studies) was robust to the prior distribution assigned to the between-study variance. Tramadol 300 mg [34], etoricoxib 90 mg [2, 22], duloxetine 120 mg and oxycodone + naltrexone qid were excluded from the sensitivity analysis focusing on the most prevalent dose. Another analysis excluded studies with overall quality ratings below 6. These lead to the same conclusions as the base-case analysis.

Discussion

The objective of this study was to conduct an indirect comparison of the efficacy of duloxetine relative to alternative oral pharmacological therapies in the treatment of CLBP, in the absence of direct evidence.

Fifteen studies evaluating oral treatments for CLBP were included in a meta-analysis. The overall quality of the included studies was high. The base-case fixed effects model showed a difference between scheduled opioids and duloxetine, although the estimated magnitude of effect was less than small ($|SMD| < 0.2$). However, no difference was found for the random effects model, which provided a better fit. Although sensitivity analyses showed slight variations in parameter estimates, the results led to the same conclusions as demonstrated in the base-case analyses. Meta-regression analyses did not provide any conclusive insight into observed variability; with the exception of pain duration, no covariate was found to be associated with treatment effect. The effect of pain duration was not explored further as it was not deemed clinically relevant as a dichotomous variable.

Limitations of the present study include the low number of studies available for inclusion in the analysis, considering the high number of comparators included within the network. The meta-analysis feasibility study concluded that strict inclusion criteria were necessary to obtain a subset of studies sufficiently homogeneous for pooling. One study was excluded as it was open-label, seven studies had cross-over designs and the 8-week minimum treatment duration cut-off inclusion criteria resulted in the exclusion of ten studies. The comparison of SSRIs to placebo was only based on one study. The low number of studies resulted in difficulties distinguishing spurious variability from heterogeneity due to study characteristics. Furthermore, it was not possible to assess the overall influence of study design on treatment effect, as three of the four studies with an enriched enrolment phase evaluated the effect of scheduled opioid use. The power to identify significant effects for

Table 7 Sensitivity analysis results for the random effects model

Intervention against duloxetine	SMD	SE (SMD)	95 % CrI
Sensitivity analysis: concomitant NSAID non-users			
Cox-2 inhibitors	−0.02	0.19	(−0.39, 0.35)
Non-scheduled opioids	−0.1	0.18	(−0.46, 0.25)
Scheduled opioids	−0.22	0.16	(−0.54, 0.10)
Between-study variance	0.04		
Sensitivity analysis on prior distributions			
Uniform distribution on between-study standard deviation			
Antidepressants	0.28	0.30	(−0.31, 0.86)
Cox-2 inhibitors	−0.04	0.16	(−0.38, 0.28)
Non-scheduled opioids	−0.13	0.16	(−0.45, 0.19)
Scheduled opioids	−0.24	0.14	(−0.53, 0.04)
Other: glucosamine	0.22	0.25	(−0.27, 0.72)
Between-study variance	0.032		
Gamma distribution on between-study precision			
Antidepressants	0.28	0.30	(−0.30, 0.86)
Cox-2 inhibitors	−0.04	0.16	(−0.36, 0.28)
Non-scheduled opioids	−0.13	0.16	(−0.44, 0.18)
Scheduled opioids	−0.24	0.14	(−0.52, 0.04)
Other: glucosamine	0.23	0.24	(−0.25, 0.71)
Between-study variance	0.031		
Sensitivity analysis: most prevalent dosing regimen			
Antidepressants	0.29	0.34	(−0.38, 0.97)
Cox-2 inhibitors	0.02	0.22	(−0.42, 0.46)
Non-scheduled opioids	−0.12	0.20	(−0.54, 0.27)
Scheduled opioids	−0.27	0.18	(−0.64, 0.09)
Other: glucosamine	0.24	0.30	(−0.36, 0.83)
Sensitivity analysis: study quality			
High-quality studies (Overall score ≥ 6)			
Antidepressants	0.28	0.32	(−0.35, 0.91)
Non-scheduled opioids	−0.07	0.23	(−0.54, 0.38)
Scheduled opioids	−0.27	0.18	(−0.64, 0.08)
Other: glucosamine	0.23	0.28	(−0.32, 0.77)
Between-study variance	0.044		

Uniform distribution: Uniform [0, 2]; Gamma distribution: Gamma [0.01,100]

CrI credibility interval, SE (SMD) standard error of standardised mean difference, SMD standardised mean difference

baseline study characteristics was low, due to the low number of studies available. For example, although baseline severity is thought to have a clinical impact, it was not found to be associated with treatment effect. Therefore, the analysis would benefit from further research as studies become available. It was also not possible to accurately investigate publication bias due to the low number of studies by treatment category.

Another limitation was the different outcome measures reported. The use of a standardised measure (i.e. SMD), which is more difficult to interpret than a clinical measure,

was deemed necessary to handle the different scales (VAS, BPI and NRS). Differences were also observed in the reporting of outcomes (e.g. change from baseline, difference between treatment arms, mean values at baseline and endpoint) which made the use of assumptions necessary to suitably derive SMDs. As in Machado et al. [20], the efficacy of treatments was only compared using pain intensity outcomes, which may not fully reflect the potential benefits of treatments in terms of function and quality of life.

To the best of our knowledge, following publications by Machado et al. [20] and Moore et al. [21] analysing direct evidence of analgesic effects of treatments for non-specific low back pain, this is the first attempt at an indirect comparison of the clinical evidence for the treatment of chronic lower back pain. Although Moore et al. [21] questioned the feasibility of an indirect comparison in CLBP, and while the number of eligible studies was small, we believe this study provides useful insight into the relative efficacy of treatments using pain intensity scales. Similar to diabetic peripheral neuropathic pain [24] and fibromyalgia [5], the available evidence shows that there does not seem to be any difference in efficacy between duloxetine and other oral pharmacological therapies for CLBP.

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