Systematic Review

Drug Therapy for the Treatment of Chronic Nonspecific Low Back Pain: Systematic Review and Meta-analysis

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Background: Low back pain (LBP) is one of the most common health problems in adults. The impact of LBP on the individual can cause loss of health status in the form of symptoms and loss of function related to pain in the back; limitation of daily, leisure, and/or strenuous activities, and disability. LBP also poses an economic burden to society, mainly in terms of one of the most common reasons for seeking medical care (direct treatment costs), and accounts for the large number of work days lost (indirect costs). To reduce the impact of LBP on adults, drug therapy is the most frequently recommended intervention. Over the last decade, a substantial number of randomized clinical trials of drug therapy for LBP have been published.

Objective: To determine the effectiveness of drug therapy for the treatment of chronic nonspecific low back pain (CNLBP).

Study Design: Systematic review and meta-analysis

Methods: A systematic review and meta-analysis of randomized controlled trials was conducted. Five databases (Medline, CINAHL, Science Direct, CAJ Full-text Database, and Cochrane databases) were searched for articles published from 2002 to 2012. The eligibility criteria were randomized trials and double-blind controlled trials of oral or injection drug therapy for CNLBP in subjects who were aged at least 18 years old, published in English or Chinese. Two independent reviewers extracted the data.

Results: A total of 25 drug therapy trials were included. cyclo-oxygenase-2 (COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and opioids were commonly used. Only 5 trials studied the efficacy of adjuvant analgesics of antiepileptics (n = 1) and antidepressants (n = 4) for CNLBP. The standardized mean difference (SMD) for COX-2 NSAIDs in pain relief was -12.03 (95% confidence interval [CI]: -15.00 to -9.06). The SMD for tramadol in pain relief was -1.72 (95% CI: -3.45 to 0.01). As the 95% CI crossed 0, this effect size was not considered statistically significant. The SMD for the overall effects of opioids in pain relief was -5.18 (95% CI: -8.30 to -2.05). The SMD for the partial opioid agonist drug in pain relief was -7.46 (95% CI: -11.87 to -3.04).

Limitations: The follow-up periods of these included trials in the meta-analysis ranged from 4 to 24 weeks. The difference of follow-up periods influenced how study outcomes were recorded. These included trials also had significant differences in patient selections. Some trials may actually include CNLBP patients with neuropathic pain, as not having focal neurological findings or signs does not mean that the pain is not neuropathic. Consequently, different pain conditions may influence patients who responded to the same drug and then influence pooled estimates of treatment effect size.

Conclusion: This review endorses the use of COX-2 NSAIDs as the first-line drugs for CNLBP. Tramadol shows no statistically significant effect on pain relief, but has small effect sizes in improving functioning. Among included opioid therapy studies, the overall effects of opioids and the partial opioids agonist drug had statistically significant treatment effects in pain relief for CNLBP patients.

Key words: NSAIDs, opioids, antidepressants, drug therapy, low back pain, systematic review, meta-analysis, randomized clinical trials

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Low back pain (LBP) is one of most common health problems in adults. It is defined as pain localized between the costal margins and the inferior gluteal folds, with or without leg pain (1,2). LBP is a complex, heterogeneous medical condition that includes a wide variety of symptoms (3). Clinical practice guidelines typically categorize patients with LBP into 3 groups: LBP associated with a specific underlying disease (1 – 2% of cases); neuropathic LBP (about 5%), which is back pain associated with a neurological condition; and nonspecific LBP (more than 90%) (4). But one study reviewed 5 large-scale studies and reported the prevalence of neuropathic pain among chronic LBP patients was much higher, the prevalence rate ranged from 16% to 55% and the average prevalence rate was 40.8% (5).

The World Health Organization (WHO) International Classification of Functioning, Disability and Health provides the definition of nonspecific back pain as having no known underlying pathology, and no apparent tissue damage relevant to the problem (6). LBP that persists for more than 3 months is classified as chronic LBP (7). Reports of the prevalence of LBP varied in different studies. One recent systematic review reported that a one-year prevalence of LBP in adults ranges from 18.6% to 57.4% (8). Another study reported that over a year the occurrence of LBP of any duration is about 50% in the general population (9). Another report indicated that chronic LBP is a highly prevalent problem, and an estimated 70% to 85% of the people in North America will have an LBP episode at some point in their lives (10).

The consequences of LBP influence the individual patients and the society as a whole. The impact of LBP on the individual can cause loss of health status in the form of symptoms and loss of function related to pain in the back; limitation of daily, leisure, and/or strenuous activities; and disability (2). LBP is one of the leading causes of absence from work (2,4). LBP also poses an economic burden to society, mainly in terms of one of the most common reasons for seeking medical care (direct treatment costs), and accounts for the large number of work days lost (indirect costs) (2,11). A review of cost evaluation studies reported that in the US direct costs associated with LBP account for at least US$ 12 billion per year and indirect costs up to US$ 28 billion per year (12). In the UK, the direct health care costs for back pain are estimated at £1.6 billion (13). While LBP diagnosis and treatment have improved, chronic disability arising from nonspecific LBP appears to be increasing (14). Health care expenditures associated with back pain problems have also been increasing (15).

To reduce the impact of chronic nonspecific low back pain (CNLBP) on adults, drug therapy is the most frequently recommended intervention (16). As CNLBP is characterized by pain, muscle tension, or stiffness, drug therapies can control pain, may reduce muscle tension, and improve function (2). A challenge in choosing medications for LBP is negotiating the tradeoff between the efficacy and side effects of each class of drug (17). Over the last decade, a substantial number of randomized clinical trials (RCTs) have been published.

This review aims to summarize current evidence of clinical trials on the effectiveness and safety of drug interventions for CNLBP, so as to guide patients, physicians, and policy makers to seek the best drug therapy for CNLBP.

Methods

Data Sources and Study Selection

Five electronic databases in English (Medline, the Cochrane library, CINAHL, Science Direct, and CAJ Full-text Database) were searched from 2002 to 2012. Schnitzer et al (18) had conducted a similar review from 1980 to 2002, but much as changed in the recent decade, so an update was needed. Studies published in English or in Chinese were considered. Search terms were back / lumb* / low back / low-back / lower back; and pain / ache; and interven* / treat* / therap* / manage*. RCTs having at least one control group were considered for inclusion. Waiting list controls, usual care, and any other active control was accepted as appropriate controls. Studies evaluating medications by oral or injection therapies for chronic LBP were included in this review. The process of study selection consisted of the following 3 steps: (1) One author ran the predefined specific search strategy on each of the chosen databases (JWYC). All the search results were stored in an Excel file. (2) Two researchers independently screened the titles and abstracts of the studies (CKK, MHT); (3) All potential relevant studies meeting the predefined inclusion criteria were selected for inclusion in the review. Disagreements were resolved by a third review author (JWYC).

Types of Patients

Studies involving patients who were aged at least 18 years old, irrespective of gender, with CNLBP were included. CNLBP was defined as pain for more than 12

weeks; occurring specifically in the lower back, with/without radiation to the leg. Subjects with pain caused by specific pathological entities such as infection, inflammatory disorders, systemic diseases, or metastatic diseases were excluded. LBP associated with pregnancy, sciatica, cancer, or mechanical injuries were also excluded.

Outcome Measures

The categories of effectiveness were pain intensity, patient global assessment of pain, and specific functional status related to LBP. Pain intensity was the primary outcome measured using a validated scale (e.g., numerical rating scale [NRS], Visual Analogue Scale [VAS], and McGill Pain Questionnaire). The secondary outcome measures were patient global assessment of pain, specific functional status related to LBP, general health status, patient satisfaction with drug therapies; and quality of life measured using a validated scale (e.g. SF-36 or 12). The presence and frequency of adverse effects (e.g., abdominal pain, gastrointestinal, central nervous system related side effects) and withdrawals due to adverse events were reviewed to assess the safety of drug therapies.

Data Extraction and Assessment of Risk of Bias

Data was extracted by 2 authors (ZYC, JWYC) and checked by the third author (TKSW). Disagreements concerning data extraction were resolved by the third author (TKSW). The methodological quality of all the included studies was assessed by 2 authors independently (ZYC, JWYC). The risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias including the following domains: selection bias (e.g. random sequence generation); performance bias (e.g. blinding of participants and personnel, concealing group allocation); detection bias (e.g. blinding of outcome measures); attrition bias (e.g. drop-out rate described and acceptable); reporting bias (e.g. selective outcome reporting); other bias (e.g. baseline differences between control and intervention group). This review assessed each domain of risk-of-bias based on the recommendation of Higgins and Green (19).

Data Synthesis

The data were analyzed using the Cochrane Collaboration's Review Manager (RevMan 5.1) (20). For continuous variables (e.g. pain intensity, pain reduction), mean difference (MD) was calculated when outcomes were measured using the same scale, and the standardized mean difference (SMD) was used when different scales were used among different trails, with corresponding 95% confidence intervals (CI) (21). Dichotomous variables were calculated by relative risk (RR) with 95% CI (20). Pooling of data using meta-analysis was performed for intervention, outcome measures, and timing of outcome measures. If data of standard deviations (SDs) were missing for statistical pooling of effect size calculation, missing SDs were replaced by calculating the trail data using standard error of the mean or 95% CI (18). If variance data were not reported, missing SDs were replaced from other relevant studies, e.g. other systematic reviews concerning the same treatment (19).

Clinical heterogeneity was determined by discussion among the review authors and clinically heterogeneous trials were not combined statistically. Statistical heterogeneity was calculated by using the Chi-square and I^2 statistics, and determined whether to use the random-effects model or fixed-effects model for meta-analysis (21). A Chi-square of *P*-value greater than 0.1 and an I^2 value of less than 50% were considered to indicate statistical homogeneity (19). The random-effects model was used to combine clinically homogeneous but statistically heterogeneous clinical trials, whereas clinically and statistically homogeneous trials were combined using the fixed-effects model (19). A qualitative analysis was performed if relevant data enabling statistical pooling were lacking.

Results

Description of Included Trials

A flow diagram of the literature search process is given in Fig. 1. A total of 25 trials were included in this review.

Each included trial was evaluated in terms of its risk of bias (Table 1). Twenty trials had low risk of bias and 5 studies had high risk of bias. Major sources of risk of bias include inadequate description and application of intention-to-treat analysis (n = 15); unsatisfactory compliance rates (n = 11); not avoiding co-interventions and/or co-interventions not similar (n = 10); and unacceptable dropout rates (n = 8). A summary of meta-analysis results is presented in Table 2.

Effectiveness and Safety of Drug Therapy

Non-opioids: NSAIDs

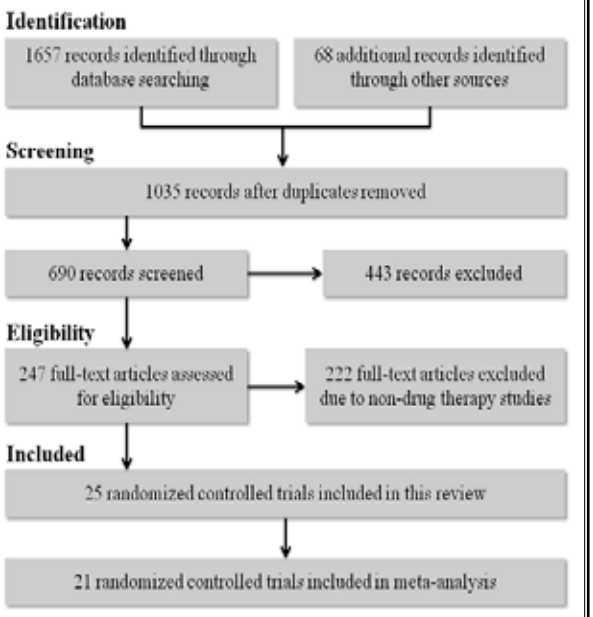

Fig. 1. *PRISMA flow diagram of included trials.*

1.1 Cyclo-oxygenase-2 (COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs) versus placebo

Five studies (22-26) compared the effects of COX-2 NSAIDs with placebo for CNLBP. Four of them reported sufficient data on pain reduction, on proportion of patients experiencing side effects, and on patients experiencing global improvement to enable statistical pooling. Fig. 2 shows the change in pain intensity from baseline by VAS. The Chi-square value for homogeneity of the weighted mean difference (WMD) was 1.38 (P = 0.71), indicating statistical homogeneity among these 4 studies. Using the fixed-effect model, the WMD of pain intensity was -12.03 (95% CI: -24.05 to -7.27), indicating a statistically significant effect in favor of COX-2 NSAIDs (Fig. 2).

Similarly, using the fixed-effect model, the WMD of changes in functional status of disability by Roland-Morris Disability Questionnaire (RMDQ) was -2.37 (95% CI: -3.33 to -1.40), indicating a statistically significant effect in favor of COX-2 NSAIDs in comparison to placebo (Fig. 3).

For the proportion of side effects reported among these 4 studies, Graph 3 shows COX-2 NSAIDs had higher proportion of side effects in comparison to placebo. The pooled Risk Ratio (RR) for side effects was 1.23 (95% CI: 1.07 to 1.41), indicating statistically significantly fewer side effects in the placebo group (Fig. 4).

1.2 COX-2 NSAIDs versus traditional NSAIDs

Two studies (27,28) compared the effects of COX-2 NSAIDs with traditional NSAIDs. Graph 4 shows change in pain intensity from baseline. The Chi-square value for homogeneity of the SMD was 4.16 (P = 0.04), indicating statistical heterogeneity among these 2 studies. Using the random-effect model, the SMD of pain intensity by VAS and NRS was 0.34 (95% CI: -0.12 to 0.80), indicating no statistically significant differences between traditional NSAIDs and COX-2 NSAIDs (Fig. 5).

For change of patients experiencing global improvement, the Chi-square value for homogeneity of the SMD was 0.35 (P = 0.56), indicating statistical homogeneity among these 2 studies. Using the fixed-effect model, the SMD was -0.06 (95% CI: -0.23 to 0.11), indicating no statistically significant differences between COX-2 NSAIDs and traditional NSAIDs (Fig. 6).

For the proportion of adverse events reported among these 2 studies, Graph 6 shows traditional NSAIDs had a higher proportion of side effects compared to COX-2 NSAIDs. The pooled RR for side effects was 0.91 (95% CI: 0.72 to 1.13), indicating statistically fewer side effects in the COX-2 NSAIDs (Fig. 7).

1.3 NSAIDs versus other drugs

Two studies (29,30) compared NSAIDs with tranezumab, and tramadol respectively in terms of pain reduction and side effects. Fig. 8 shows that the Chi-square value for homogeneity of the pooled RR for pain reduction was 0.31 (P = 0.58), indicating homogeneity among the studies. Using the fixed-effect model, the pooled RR was 0.80 (95% CI: 0.72 to 0.89), indicating statistically significantly less pain reduction in the NSAIDs group.

Fig. 9 shows the comparison of proportion of side effects between NSAIDs and other drugs. The Chi-square value for homogeneity of the pooled RR for pain reduction was 0.72 (P = 0.40), indicating homogeneity among the studies. Using the fixed-effect model, the pooled RR was 0.46 (95% CI: 0.35 to 0.60), indicating a slightly higher proportion of side effects in the NSAIDs group (Fig. 9).

Mild opioids: Tramadol versus placebo

Three studies (31-33) comparing tramadol with placebo for CNLBP reported sufficient data on pain intensity, side effects, and the proportion of patients

Table 1. *Assessment of risk-of-bias of included trials.*

Trials	Randomization adequate	Allocation concealed	Patient blinded	Care provider blinded	Outcome assessor blinded	Dropout rate described and acceptable	Intention-to-treat analysis	No suggestion of selective outcome reporting	Groups similar at baseline	Co-interventions avoided or similar	Compliance acceptable	Timing outcome assessment similar	Total score (12) ('+' as 1; '–'/or '?' as 0)
Birbara et al, 2003 (22)	+	+	+	+	+	–	–	+	+	–	–	+	8
Buynak et al, 2010 (34)	+	+	+	+	+	–	+	+	+	–	–	+	9
Chang et al, 2008 (48)	?	+	+	?	+	+	–	+	+	+	?	+	8
Chang et al, 2008 (49)	?	?	+	?	+	+	–	+	+	?	?	+	6
Chrubasik et al, 2003 (27)	+	?	+	+	?	+	+	+	+	–	?	+	8
Coats et al, 2004 (23)	+	?	+	?	+	–	–	+	+	?	+	+	7
Gordon et al, 2010 (38)	+	?	+	+	–	+	+	+	–	–	–	+	7
Gordon et al, 2010 (39)	+	+	+	+	–	–	+	+	+	–	–	+	8
Hale et al, 2007 (35)	?	?	–	+	+	+	–	+	–	+	–	+	6
Katz et al, 2003 (24)	+	+	+	+	+	+	+	+	+	?	?	+	10
Katz et al, 2005 (41)	+	?	+	+	+	+	–	?	–	–	?	+	6
Katz et al, 2007 (36)	+	+	+	+	+	–	–	+	+	?	–	+	8
Katz et al, 2011 (29)	+	?	+	+	?	+	–	+	+	–	+	+	8
Muehlbacher et al, 2006 (40)	+	+	+	+	?	+	–	+	–	+	?	+	8
O'Donnell et al, 2009 (30)	+	+	+	+	?	+	+	+	+	+	?	+	10
Pallay et al, 2004 (25)	+	+	–	+	+	+	+	+	?	?	+	+	9
Peloso et al, 2004 (31)	?	?	+	+	+	?	+	+	+	?	–	+	7
Ruoff et al, 2003 (32)	+	?	+	+	+	?	–	+	+	?	–	+	7
Skljarevski et al, 2009 (42)	+	+	+	+	?	–	–	+	?	+	?	+	7
Skljarevski et al, 2010 (43)	+	?	+	+	?	+	–	+	+	–	–	+	7
Skljarevski et al, 2010 (44)	+	?	+	+	?	+	–	+	+	–	–	+	7
Sprott et al, 2006 (26)	?	?	+	–	–	+	–	+	+	?	?	+	5
Vorsanger et al, 2008 (33)	?	?	+	?	+	–	+	?	+	+	?	+	6
Webster et al, 2006 (37)	+	?	+	+	+	–	+	+	+	–	–	+	8
Zerbini et al, 2005 (28)	–	?	+	+	+	+	–	+	+	+	+	+	9

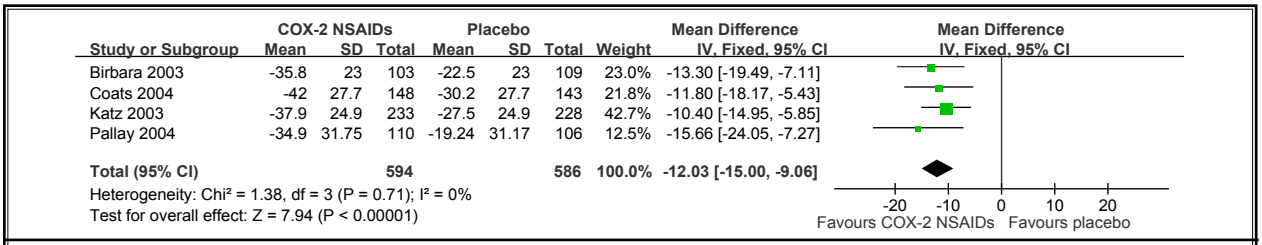

Fig. 2. *Change in pain intensity from baseline (outcome measure: VAS, 0 – 100; Follow-up: 4 – 12 weeks).*

Table 2. *Summary of meta-analysis results.*

Comparisons	Outcomes	No. of studies	No. of subjects	Statistical method	Effective size
Non-opioids:					
COX-2 NSAIDs versus placebo	Pain intensity, global improvement, side effects	4	1180	WMD (IV, Fixed, 95% CI) Risk Ratio (M-H, Fixed, 95% CI)	-12.03(-15.00, -9.06); -2.37 (-3.33, -1.40) 1.23 (1.07, 1.41)
COX-2 NSAIDs versus traditional NSAIDs	Pain intensity, global improvement, side effects	2	528	SMD (IV, Random, 95% CI) SMD (IV, Fixed, 95% CI) Risk Ratio (M-H, Fixed, 95% CI)	0.34 (-0.12, 0.80) -0.06 (-0.23, 0.11) 0.91 (0.72, 1.13)
NSAIDs versus other drugs	Pain intensity, side effects	2	972	Risk Ratio (M-H, Fixed, 95% CI)	0.80 (0.72, 0.89) 0.46 (0.35, 0.60)
Mild opioids:					
Tramadol versus placebo	Pain intensity, global improvement, side effects	3	613	SMD (IV, Random, 95% CI) SMD (IV, Fixed, 95% CI) Risk Ratio (M-H, Random, 95% CI)	-1.72 (-3.45, 0.01) -0.24 (-0.37, -0.11) 1.74 (1.20, 2.52)
Opioids:					
Opioids versus placebo	Pain intensity, functional status, side effects	4	1302	SMD (IV, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Fixed, 95% CI)	-5.18 (-8.30, -2.05) 1.59 (1.23, 2.05) 1.72 (0.81, 3.65)
Antidepressants	Pain intensity, global improvement, side effects	4	924	WMD (IV, Random, 95% CI) SMD (IV, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	-0.64 (-0.79, -0.49) 0.77 (-4.43, 5.98) 1.37 (0.99, 1.90)

WMD, weighted mean difference; SMD, standardized mean difference

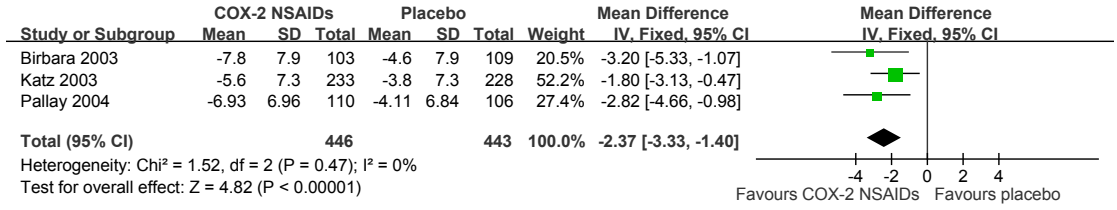

Fig. 3. *Change of patients experiencing global improvement from baseline (outcome measure: RMDQ, 0 – 24 point scale; Follow-up: 4 – 12 weeks).*

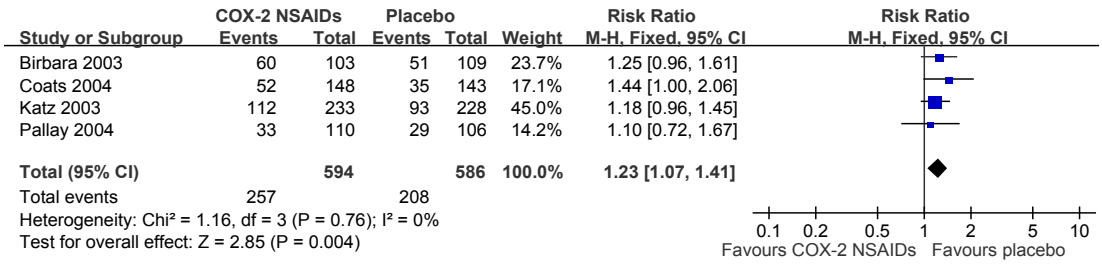

Fig. 4. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 4 – 12 weeks).*

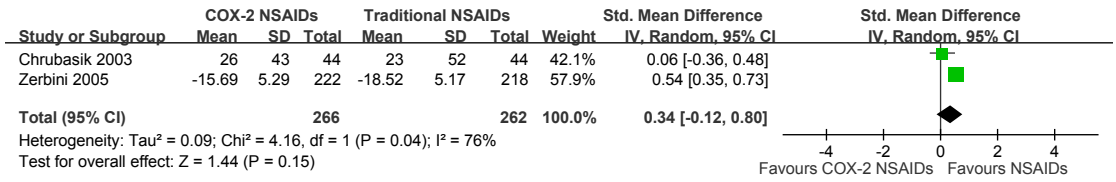

Fig. 5. *Change in pain intensity from baseline on different scales (outcome measure: VAS, 0 – 100, and NRS, 0 – 10; Follow-up: 4 – 6 weeks).*

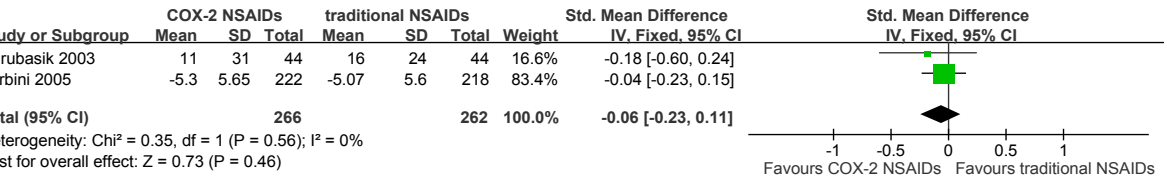

Fig. 6. *Change of patients experiencing global improvement (outcome measure: Health Assessment Questionnaire and RMDQ; Follow-up: 4 – 6 weeks).*

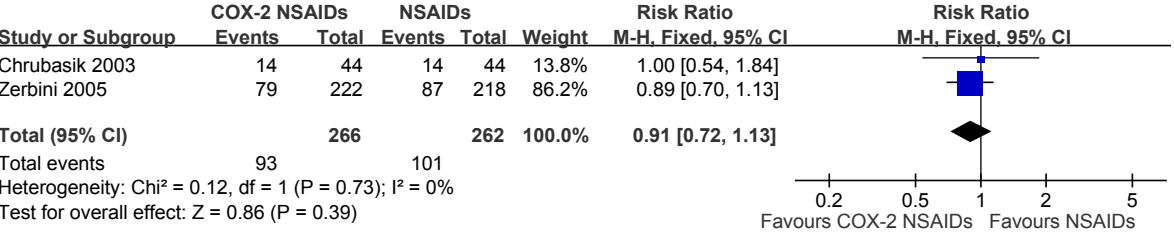

Fig. 7. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 4 – 6 weeks).*

Fig. 8. *Change in pain intensity from baseline (outcome measure: dichotomous, NRS, 0 – 10; Follow-up: 6 – 12 weeks).*

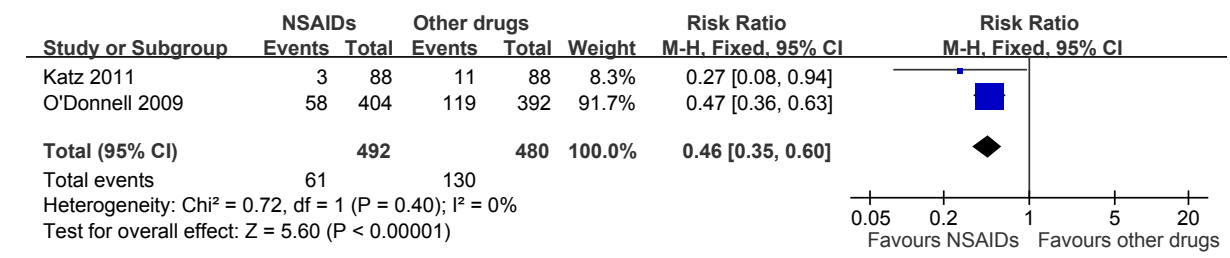

Fig. 9. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 6 – 12 weeks).*

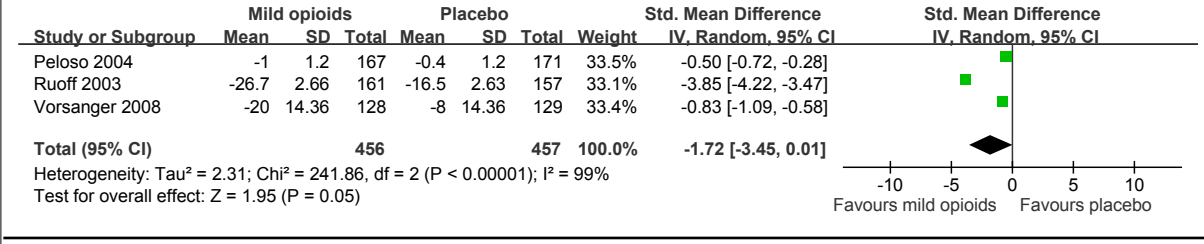

Fig. 10. *Change in pain intensity from baseline on different scales (outcome measure: VAS, 0 – 100, and NRS, 0 – 10; Follow-up: 12 weeks).*

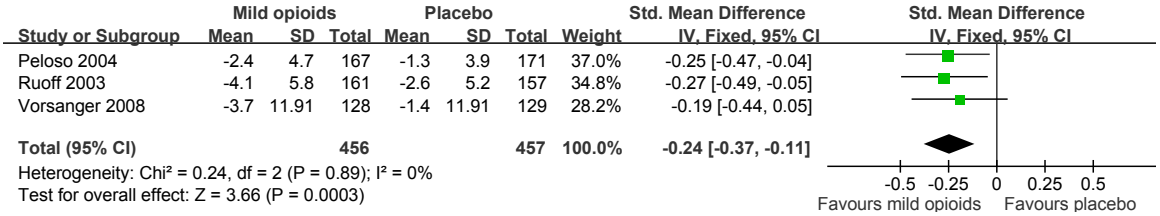

Fig. 11. *Change of patients experiencing global improvement (outcome measure: RMDQ, and Patients' Global Impressions of Improvement-Index, PGI-I; Follow-up: 12 weeks).*

experiencing global improvement to enable statistical pooling. Fig. 10 shows change in pain intensity from baseline. The Chi-square value for homogeneity of the SMD indicates statistical homogeneity among these 3 studies. Using the random-effect model, the SMD of pain intensity was -1.72 (95% CI: -3.45 to 0.01). As the 95% CI crossed 0, the effect of tramadol in pain relief should not be considered statistically significant (Fig. 10).

For the proportion of global improvement, the Chi-square value for homogeneity of the RR was 0.24 (P = 0.89), indicating homogeneity among the studies. Using the fixed-effect model, the WMD of changes in global improvement was -0.24 (95% CI: -0.37 to -0.11), indicating a slightly significant effect in favor of tramadol (Fig. 11).

For the proportion of side effects reported among these 3 studies, Fig. 12 shows that the tramadol group had a higher proportion of adverse events in comparison to the placebo group, the pooled RR for side effects was 1.74 (95% CI: 1.20 to 2.52) (Fig. 12).

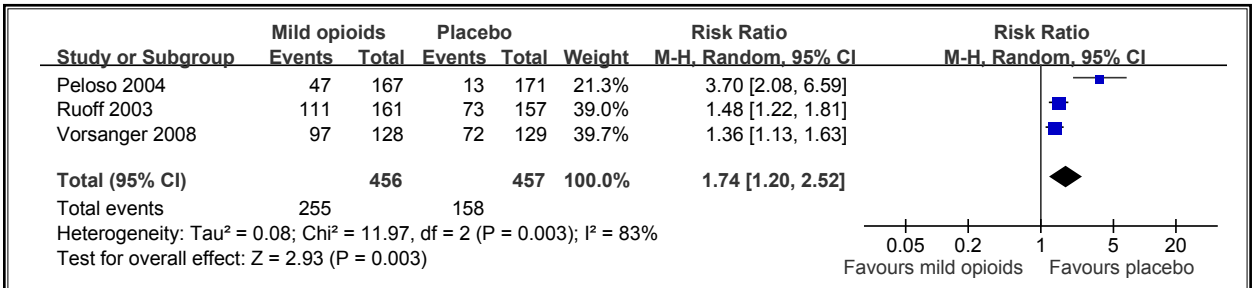

Fig. 12. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 12 weeks).*

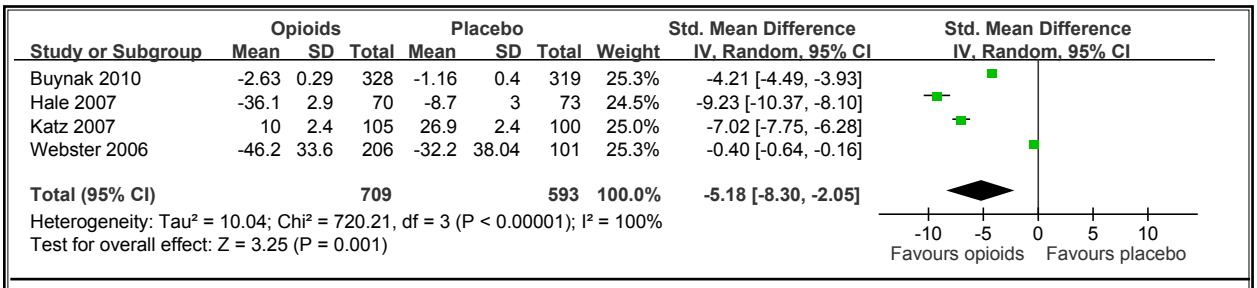

Fig. 13. *Change in pain intensity from baseline on different scales (outcome measure: VAS, 0 – 100, and NRS, 0 – 10; Follow-up: 12 weeks).*

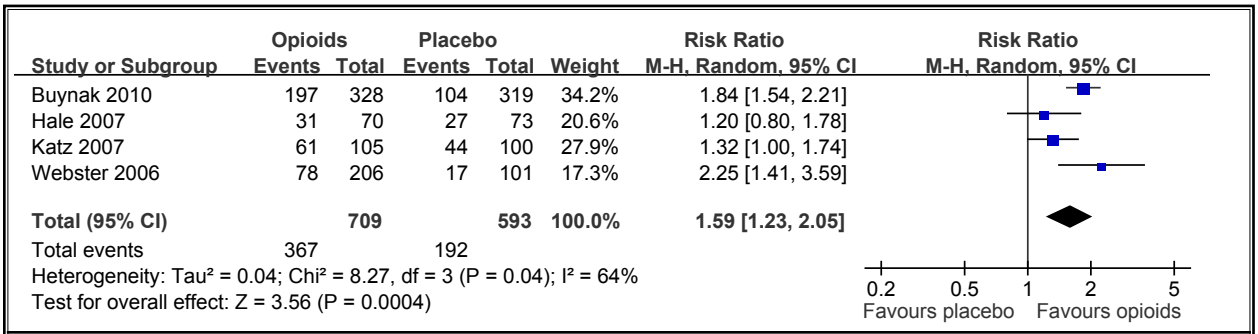

Fig. 14. *Proportion of patients experiencing global improvement (outcome measure: dichotomous, PGI-I, and satisfaction with medication from patients; Follow-up: 12 weeks).*

Opioids

3.1 Overall opioids versus placebo

Four studies (34-37) compared the effects of different opioids with placebo for CNLBP, and reported sufficient data on pain intensity to enable statistical pooling. Fig. 13 shows that the Chi-square value for homogeneity indicates statistical heterogeneity among these studies. Using the random-effect model, the SMD of pain intensity was -5.18 (95% CI: -8.30 to -2.05), indicating a statistically significant effect in favor of opioids (Fig. 13).

For the proportion of patients experiencing global improvement, the Chi-square value for homogeneity of the RR was 9.74 (P = 0.08), indicating the heterogeneity of the studies. Using the random-effect model, the pooled RR was 1.59 (95% CI: 1.23 to 2.05), indicating better global improvement of patients using opioids compared with placebo (Fig. 14).

Similarly, using the fixed-effect model for the proportion of side effects, the pooled RR was 1.72 (95% CI: 0.81 to 3.65), indicating statistically significantly fewer side effects in the placebo group (Fig. 15).

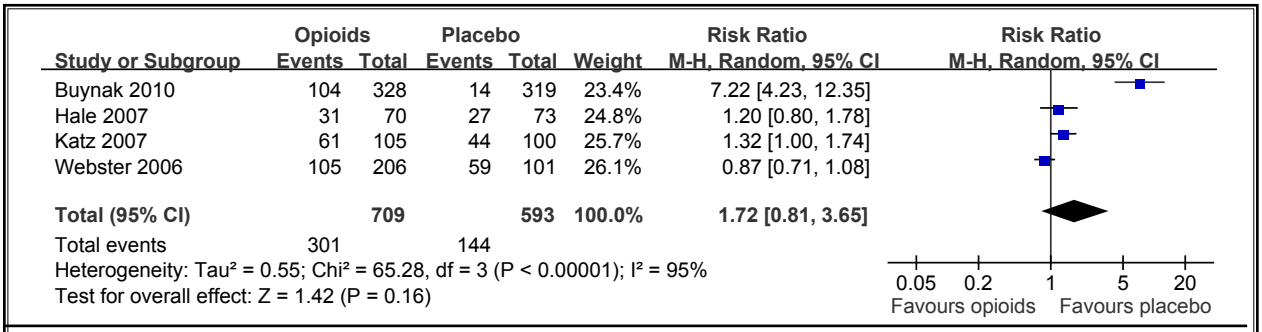

Fig. 15. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 12 weeks).*

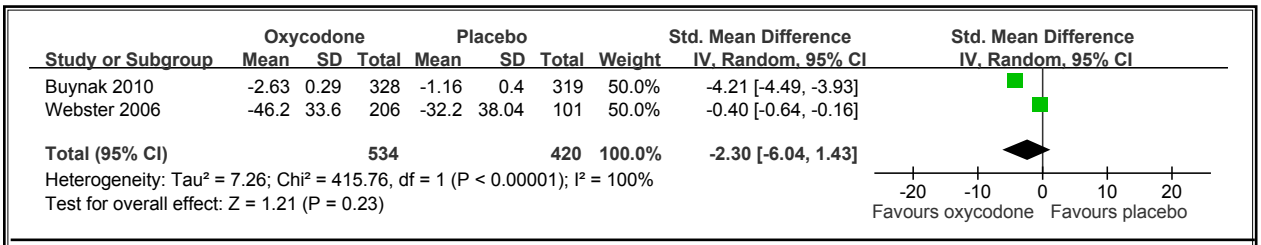

Fig. 16. *Change in pain intensity from baseline on different scales (outcome measure: VAS, 0 – 100, and NRS, 0 – 10; Follow-up: 12 weeks).*

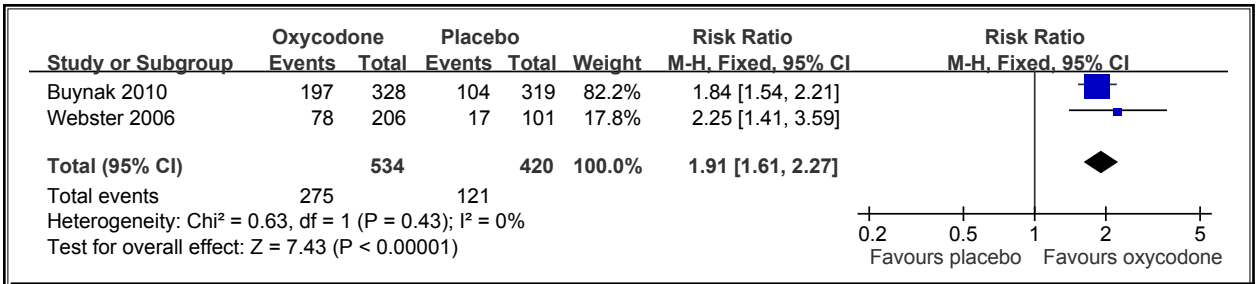

Fig. 17. *Proportion of patients experiencing global improvement (outcome measure: dichotomous, PGI-I, and satisfaction of medication from patients; Follow-up: 12 weeks).*

3.2 Individual opioids versus placebo

Two studies (34,36) compared the effects of oxycodone with placebo for CNLBP. Fig. 16 shows that the Chi-square value for homogeneity indicates statistical heterogeneity among these studies. Using the random-effect model, the SMD of pain intensity was -2.30 (95% CI: -6.04 to 1.43), indicating a non-statistically significant difference for oxycodone (Fig. 16).

For the proportion of patients experiencing global improvement, the Chi-square value for homogeneity of the RR was 0.63 (P = 0.43), indicating the homogeneity of the studies. Using the fixed-effect model, the pooled RR was 1.91 (95% CI: 1.61 to 2.27), indicating better global improvement of patients using oxycodone compared with placebo (Fig. 17).

For the proportion of side effects, the pooled RR was 2.48 (95% CI: 0.21 to 28.99), indicating statistically significant fewer adverse events in the placebo group (Fig. 18).

Similarly, 2 studies (37,38) compared the effects of oxymorphone with placebo for CNLBP. Fig. 19 shows that the Chi-square value indicates statistical heterogeneity among these studies. Using the random-effect model, the SMD of pain intensity was -22.14 (95% CI: -32.43 to -11.85), indicating a statistically significant effect in favor of oxymorphone (Fig. 19).

For the proportion of patients experiencing global improvement, the Chi-square value for homogeneity of the RR was 0.75 (P = 0.39), indicating the homogeneity

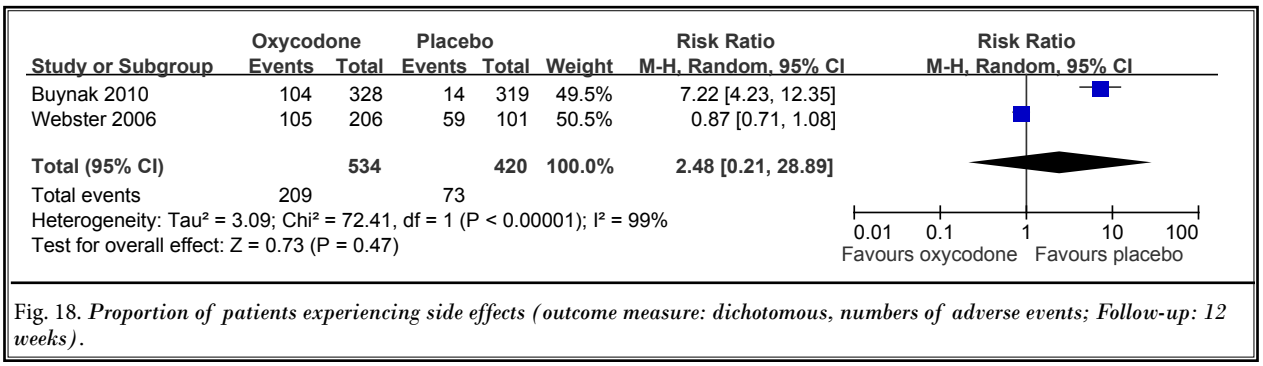

Fig. 18. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 12 weeks).*

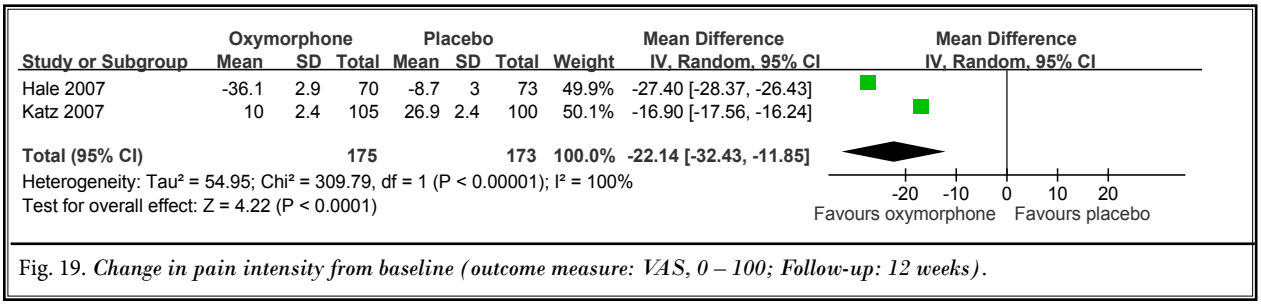

Fig. 19. *Change in pain intensity from baseline (outcome measure: VAS, 0 – 100; Follow-up: 12 weeks).*

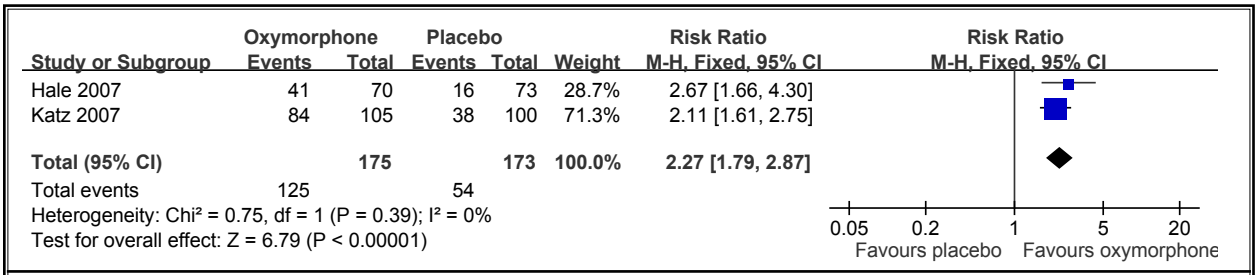

Fig. 20. *Proportion of patients experiencing global improvement (outcome measure: dichotomous, satisfaction of medication from patients; Follow-up: 12 weeks).*

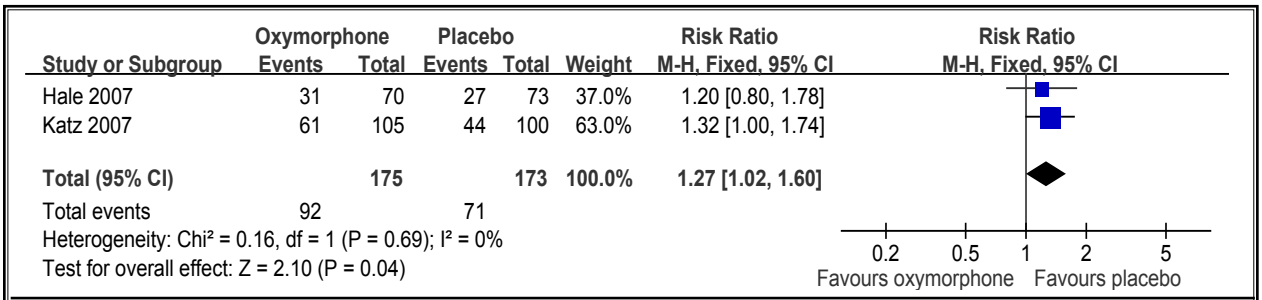

Fig. 21. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 12 weeks).*

of the studies. Using the fixed-effect model, the pooled RR was 2.27 (95% CI: 1.79 to 2.87), indicating the better global improvement of oxymorphone compared with placebo (Fig. 20).

For the proportion of side effects, the pooled RR was 1.27 (95% CI: 1.02 to 1.60), indicating statistically significantly fewer adverse events in the placebo group (Fig. 21).

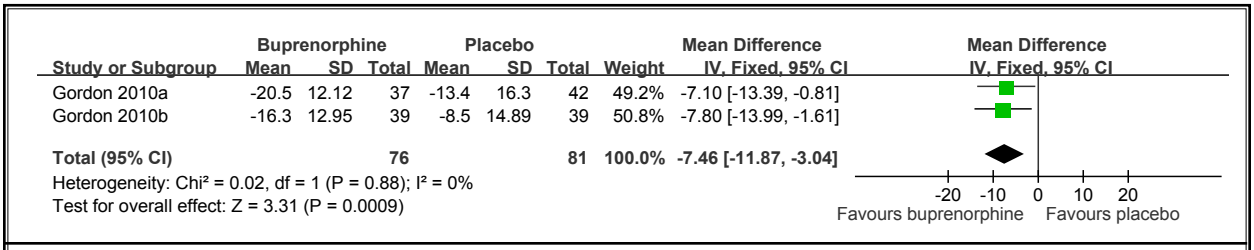

Fig. 22. *Change in pain intensity from baseline (outcome measure: VAS, 0 – 100; Follow-up: 8 – 24 weeks).*

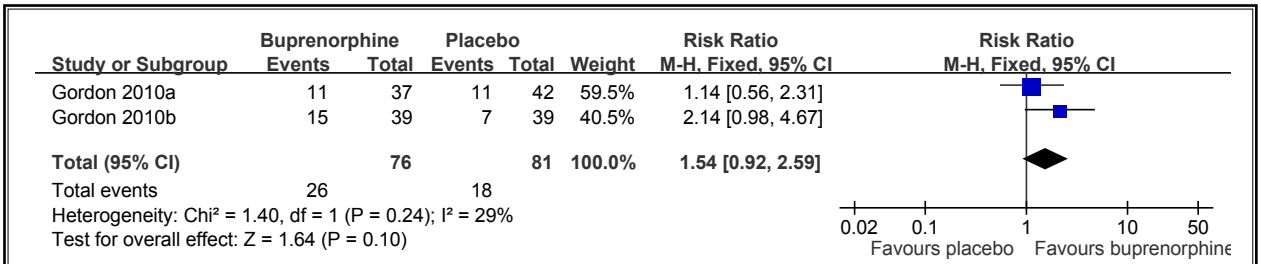

Fig. 23. *Proportion of patients experiencing global improvement (outcome measure: dichotomous, Pain Disability Index; Follow-up: 8 – 24 weeks).*

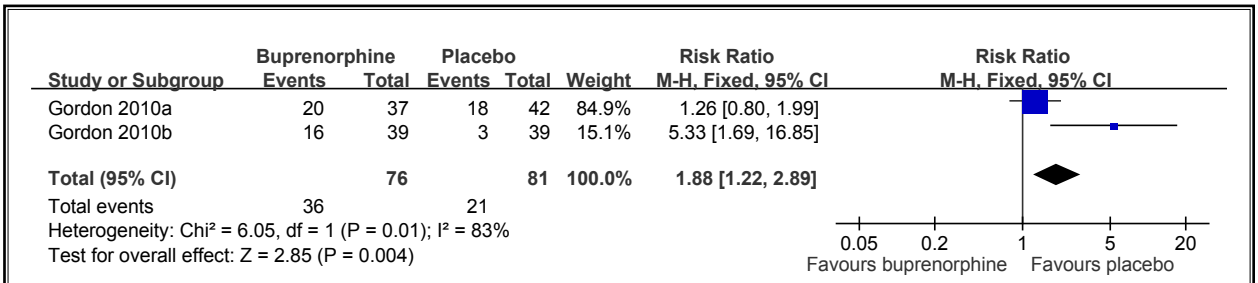

Fig. 24. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 8 – 24 weeks).*

Partial opioid agonist drug versus placebo

Two studies (38,39) compared the effects of buprenorphine with placebo, Fig. 22 shows the Chi-square value indicates statistical homogeneity among these studies. Using the fixed-effect model, the WMD of pain intensity was -7.46 (95% CI: -11.87 to -3.04), indicating a statistically significant effect in favor of buprenorphine (Fig. 22).

Similarly, using the fixed-effect model for the proportion of patients experiencing global improvement, the pooled RR was 1.54 (95% CI: 0.92 to 2.59), indicating the better global improvement of buprenorphine compared with placebo (Fig. 23).

For the proportion of side effects, the pooled RR was 1.88 (95% CI: 1.22 to 2.89), indicating statistically significantly fewer side effects in the placebo group (Fig. 24).

Adjuvant analgesics: Antiepileptics / antidepressants versus placebo

As just one study (40) included for data on the effect of antiepileptics, pain reduction and quality of life scores were better in the antiepileptics group in comparison to the placebo group, and both outcomes had statistically significant differences (all *P* values < 0.05), but the proportion of side effects in the placebo group was fewer.

Four studies (41-44) compared the effects of antidepressants with placebo for CNLBP. Three of them reported sufficient data on pain intensity to enable sta-

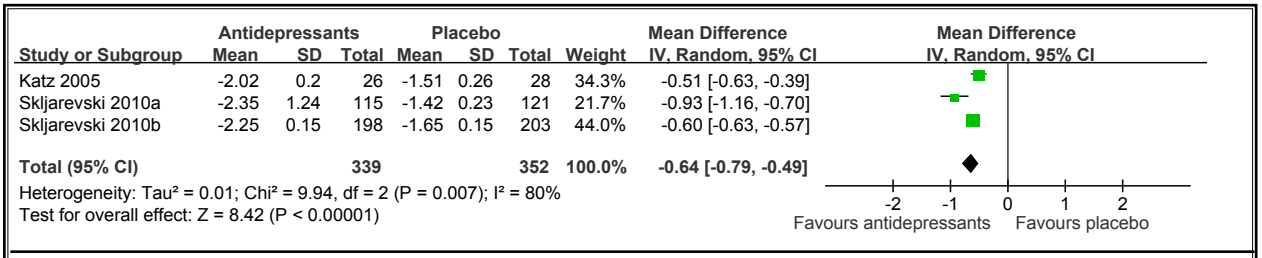

Fig. 25. *Change in pain intensity from baseline (outcome measure: NRS, 0 – 10; Follow-up: 7 – 13 weeks).*

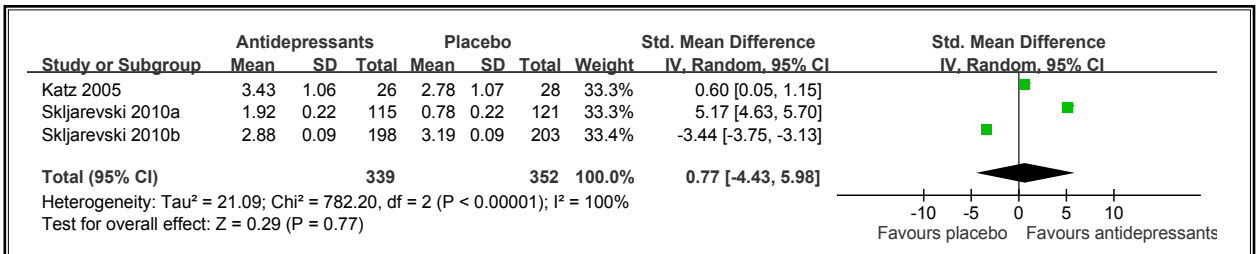

Fig. 26. *Change of patients experiencing global improvement (outcome measures: Satisfaction with Pain Relief Scale and PGI-I; Follow-up: 7 – 13 weeks).*

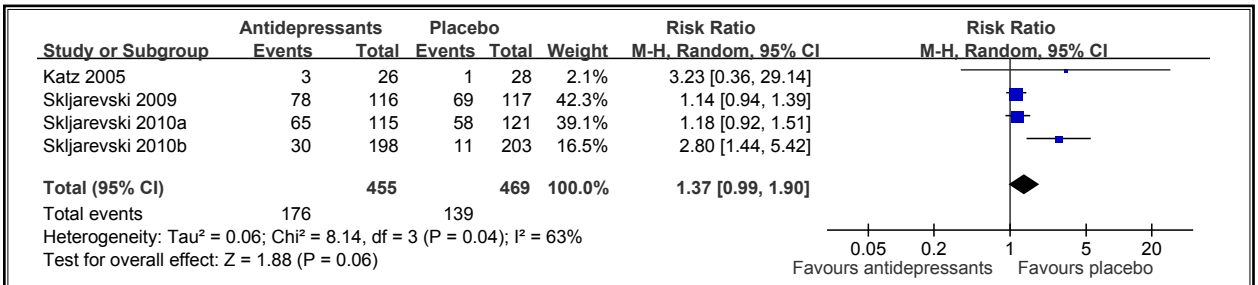

Fig. 27. *Proportion of patients experiencing side effects (outcome measure: dichotomous, numbers of adverse events; Follow-up: 7 – 13 weeks).*

tistical pooling. The Chi-square value for homogeneity of the WMD was 9.94 (P = 0.007), indicating statistical heterogeneity among these studies. Using the random-effect model, the WMD of pain intensity was -0.64 (95% CI: -0.79 to -0.49), indicating a significant effect in favor of antidepressants (Fig. 25).

Similarly, using the random-effect model for the change of global improvement, the WMD was 0.77 (95% CI: -4.43 to 5.98), indicating a non-statistically significant difference for antidepressants (Fig. 26).

For the proportion of antidepressant side effects, the Chi-square value for homogeneity of the RR was 8.14 (P = 0.04), indicating heterogeneity among the studies. Using the random-effect model, the pooled RR for side effects was 1.37 (95% CI: 0.99 to 1.90), indicating statistically fewer side effects in the placebo group (Fig. 27).

Discussion

Among the included trials published in the last decade, COX-2 NSAIDs, tramadol, and opioids were commonly used for the treatment of CNLBP. Drug therapy was mainly delivered orally. For the drug class of NSAIDs, there were no statistically significant differences between traditional NSAIDs and COX-2 NSAIDs. But traditional NSAIDs caused more side effects. In a Cochrane review of NSAIDs for low back pain, Roelofs et al (45) also reported that there were not many differences for pain relief between 2 types of NSAIDs, and

they reported that COX-2 NSAIDs were associated with fewer side effects.

Four trials examined the effectiveness and safety of tramadol, 3 of them compared its effects with placebo. Non-statistically significant differences were found for tramadol in pain relief (SMD = -1.72, 95% CI: -3.45 to 0.01), but the functional improvement was slightly in favor of tramadol (SMD = -0.24, 95% CI: -0.37 to -0.11). The proportion of side effects was also statistically significant in favor of tramadol (RR = 1.74, 95% CI: 1.20 to 2.52). Due to this trade-off between efficacy and side effects, the recommendations for the use of tramadol for CNLBP should be regarded with caution. In addition, these trials used 2 types of tramadol; that is, one used tramadol, while 2 used a tramadol-acetaminophen combination. Schnitzer et al (18) reported that safety results of tramadol seem to be better than tramadol-acetaminophen (paracetamol), as 35% of the tramadol-acetaminophen patients withdrew from the trials due to side effects versus 4% of tramadol patients who had discontinued treatment in a 4-week follow-up study. Thus, even within the same drug class, treatment effects of tramadol vary due to different types.

In terms of opioids for the treatment of CNLBP, 6 studies involved involving 1,459 patients indicate that opioids were more effective in pain relief and functional improvement than placebo (34-39). The SMD was -3.60 (95% CI: -5.74 to -1.47) for pain relief, and the pooled RR for functional improvement was 1.58 (95% CI: 1.27 to 1.97). Studies were pooled respectively for examining the effect of oxycodone, oxymorphone, and buprenorphine. Oxymorphone had statistically significant effects of pain relief, the SMD was -8.08 (95% CI: -10.25 to -5.91). Oxymorphone shows fewer side effects (pooled RR: 1.27, 95% CI: 1.02 to 1.60), compared with oxycodone (pooled RR: 2.48, 95% CI: 0.21 to 28.89) and buprenorphine (pooled RR: 1.88, 95% CI: 1.22 to 2.89). One Cochrane review found that opioids were statistically significant for relieving pain but not improving functional status (SMD: -0.06, 95% CI: -0.88 to 0.76) (46). In this review, the proportion of global functional improvement by pooled RR was 1.58 (95% CI: 1.27 to 1.97). The differences may be attributed to study co-interventions. As these included opioids trials permitted study patients to take NSAIDs or acetaminophen as needed for relief of symptoms other than pain. Thus, other drugs rather than opioids may have played a role in functioning improvement. Also, some of these opioid trials used the "flare study design." In flare studies, subjects were randomized into treatment group or placebo group, followed by a wash-out period, during which only subjects who were already responding well to opioids were included.

Among the 25 included trials, only one study compared the effects of antiepileptics with placebo (40). A qualitative analysis supports the efficacy of antiepileptics in terms of pain reduction and improvement of quality of life. For antidepressants, pooled analysis indicated its limited effects for the treatment of CNLBP. The WMD for pain relief was -0.64 (95% CI: -0.79 to -0.49). A Cochrane review of antidepressants for both acute and chronic LBP patients by Urquhart et al (47) included 6 trials and reported no statistically significant differences in pain relief. But antidepressants did cause side effects. This review found that the pooled RR of the proportion of side effects was 1.37 (95% CI: 0.99 to 1.99).

Limitations

Although methodological heterogeneity has been kept to a minimum by including only RCT studies, 2 trials (48,49) did not include a placebo group so that they were excluded for statistical pooling. Of the 23 trials included in this review, some, especially the opioid treatment studies, experienced dropout rates greater than 50% in the treatment group. Although the reasons for dropouts were clearly documented and intention-to-treat analysis was performed, substantial dropout rates may compromise the interpretation of the study outcomes. The follow-up periods of these included trials in meta-analysis ranged from 4 to 12 weeks. The difference of follow-up periods influences how study outcomes were recorded. These included trials also had significant differences in patient selections. Some trials may actually include CNLBP patients with neuropathic pain, as not having focal neurological findings does not mean that the pain is not neuropathic. Consequently, different pain conditions may influence patients who responded to the same drug and then influence pooled estimates of treatment effect size.

Conclusion

Findings from this review endorse the use of NSAIDs as the first-line drugs for CNLBP. COX-2 NSAIDs have been used more frequently than traditional NSAIDs, as COX-2 NSAIDs incur fewer side effects, according to statistical pooling analysis. The mild opioid tramadol shows no statistically significant effect of pain relief, but has small effect sizes in improving function. Among included opioid therapy studies, the overall effects of opioids and the partial opioids agonist drug show sta-

tistically significant effects of pain relief. Another angle that should be evaluated is the cost effectiveness of each line of drug therapy. This review found that opioids gave statistically significant pain relief for CNLBP. This finding should encourage more research to better understand the effects of opioids in general, and the relative value of different opioids, especially in relation to other medications and/or other types of co-interventions. As CNLBP is a prevalent condition with significant socioeconomic implications, future quality trial studies should include meaningful socioeconomic outcomes such as work status and return-to-work for evaluation.

Appendix 1

Characteristics of included trials on oral drug therapy.

Trials	Participants characteristics	Interventions (TG-treatment group; PG-placebo group)	Follow-up	Outcome measures
Non-opoids - NSAIDS				
Birbara 2003	319 patients were randomized, 212 completers. TG1 (n=103); TG2 (n=107); PG (n=109)	**COX-2 NSAIDs vs Placebo** TG1: etoricoxib 60mg/day TG2: etoricoxib 90mg/day PG: placebo, daily	12 weeks	VAS (100mm): mean difference (95% CI) at week-12 compared with baseline: TG1 vs PG=-10.45 (-16.77 to -4.14); TG2 vs PG =-7.5 (-13.71 to -1.28) RMDQ (0-24 points scale): TG1 vs PG=-2.42 (-3.87 to -0.98); TG2 vs PG =-2.06 (-3.46 to -0.65) LBP bothersomeness scale (4-point Likert, 0-not at all, 4=extremely): TG1 vs PG=-0.38 (-0.62 to -0.14); TG2 vs PG =-0.33 (-0.57 to -0.09) AE: TG1-60 /103patients; TG2- 56/107 patients; PG-51 /109patients
Chang 2008a	47 patients were randomized, 42 completers. TG: (n=24); PG: (n=23)	**Sachet-form NSAIDs vs Tablet-form NSAIDs** TG1:piroxicam-beta-cyclodextrin Sachets, 20mg/day TG2: piroxicam tablets, 20 mg/day	4 weeks	VAS (100mm): net changes at week-4 of TG1: 3.07 (1.56); TG2: 1.80 (1.41) ODI (0-24 points scale): net changes at week-4 of TG1: 18.05 (14.73); TG2:8.90 (9.51) AE:TG1-4/24 patients; TG2-7/23 patients
Chang 2008b	42 patients were randomized, 42 completers TG: (n=23); PG: (n=19)	**Sachet-form NSAIDs vs Tablet-form NSAIDs** TG1: Piroxicam-beta-cyclodextrin Sachets, 20mg/day TG2: piroxicam tablets, 20 mg/day	4 weeks	VAS (100mm): net changes at week-4 of TG1: 3.07 (1.56); TG2: 1.75 (1.48) ODI (0-24 points scale): net changes at week-4 of TG1: 18.05 (14.73); TG2:8.78 (10.02)
Chrubasik 2003	88 patients were randomized, 79 completers TG1 (n=44); TG2 (n=44)	**COX-2 NSAIDs vs NSAIDs** TG1: rofecoxib 12.5 mg/day; TG2: doloteffin 2400 mg/day	6 weeks	Arhus LBP Index: mean percentage decrease from baseline, TG1 vs TG2 = 26 (43) vs 23 (52) AE: TG-14/44 patients (1withdrew); TG2-14/44 patients (6 withdrew)
Coats 2004	293 patients were randomized, 249 completers TG: (n=148); PG: (n=145)	**COX-2 NSAIDs vs Placedo** TG: valdecoxib-40 mg/day; PG: placebo tablets, daily	4 weeks	VAS (100mm): at week-1, TG vs PG=29.2 vs 41.9 ($P < 0.001$); at week-4, TG vs PG=17.7 vs 31.1 ($P <0.001$) AE: TG-52/148 patients ; PG-35/145 patients
Katz 2003	690 patients were randomized, 580 completers TG1: (n=233); TG2: (n=229); PG: (n=228)	**COX-2 NSAIDs vs Placebo** TG1: rofecoxib 25 mg/day; TG2: rofecoxib 50 mg/day; PG: placebo, daily	4 weeks	VAS (100mm): mean difference (95% CI) at week-4 compared with baseline: TG1 vs. PG=-13.5 (-18.1 to -8.9); TG2 vs. PG =-13.8 (-18.5 to -9.2) RMDQ (0-24 points scale): TG1 vs. PG=-2.2 (-3.2 to -1.3); TG2 vs. PG =-2.3 (-3.3 to -1.3) LBP bothersomeness scale (4-point Likert, 0-not at all, 4=extremely): TG1 vs. PG=-0.5 (-0.6 to -0.3); TG2 vs. PG =-0.5 (-0.7 to -0.3) AE: TG1-112/233 patients; TG2- 106/229 patients; PG-93 /228 patients
Pallay 2004	325 patients were randomized, 231 completers TG1: (n=110); TG2: (n=109); PG: (n=106)	**COX-2 NSAIDs vs placebo** TGI: etoricoxib 60mg/day; TG2: etoricoxib 90mg/day; PG: placebo, daily	12 weeks	VAS (100mm): mean changes compared with baseline of TG1: -34.39; TG2: -32.28; PG: -19.24 RMDQ (0-24 points scale): mean changes compared with baseline TG1: -6.93; TG2: -6.49; PG: -4.11 PGI-I (4-point Likert scale: 'very well' to 'very poor'): TG (65-70%) vs PG (35-40%) AE:TG1-33/110 patients; TG2-32/109 patients; PG-29/106 patients
Sprott 2006	19 patients were randomized, 19 completers TG: (n=10); PG: (n=9)	**COX-2 NSAIDs vs Placebo** TG: ibuprofen-argininc 400mg/day PG: placebo, daily	<1 week	VAS (100mm): no significant mean changes between TG and PG

Appendix 1 (cont.)

Characteristics of included trials on oral drug therapy.

Trials	Participants characteristics	Interventions (TG-treatment group; PG-placebo group)	Follow-up	Outcome measures
Katz 2011	217 patients were randomized, 148 completers TG1: (n=88); TG2: (n=88); PG: (n=41)	**NSAIDs vs other types of drug vs placebo** TG1: naproxen 500mg, tid, plus intravenous placebo TG2: intravenous Tanezumab plus oral placebo PG: intravenous placebo plus oral placebo	12 weeks	aLBP I(0-10 NRS): mean changes compared with baseline, TG1vs TG2 vs PG= -2.35 vs -3.2 vs -2.1 RMDQ (0-24 points scale): mean changes compared with baseline, TG1vs TG2 vs PG= -4.2 vs -6.5 vs -3.6 PGI-I (4-point Likert scale: 'very well' to 'very poor'): TG1vs TG2 vs PG= 0.65 vs. 0.78 vs. 0.71 AE:TG1-3/88 patients; TG2-11/88 patients; PG-1/41 patients
Zerbini 2005	440 patients were randomized, 401 completers TG1: (n=222); TG2: (n=218)	**COX-2 NSAIDs vs traditional NSAIDs** TG1: etoricoxib 60 mg/day TG2: diclofenac 50mg, three times/day	4 weeks	VAS (100mm): mean changes at week-4 compared with baseline: TG1 vs TG2=-15.69 (5.29) vs -18.52 (5.17) RMDQ (0-24 points scale): TG1 vs TG2=-5.30 vs -5.07 LBP bothersomeness scale (4-point Likert, 0-not at all, 4=extremely): TG1 vs TG2=-1.25 vs -1.23 PGI-I (4-point Likert scale: 'very well' to 'very poor'): TG1 vs TG2=1.76 vs 1.64 AE:TG-179/222 patients; TG2-87/218 patients
Mild Opioids - Tramadol				
Peloso 2004	338 patients were randomized, 147 completers TG: (n=167); PG: (n=171)	**Mild opioid plus acetaminophen vs placebo** TG: tramadol 37.5mg/APAP 325mg/day for 91 days PG: placebo daily	12 weeks	VAS (100mm): mean difference (95% CI) at week-12 compared with baseline: TG vs. PG=-20.5 vs-4.7 Pain relief score: TG vs PG=1.8 vs 0.7 RMDQ (0-24 points scale): TG vs. PG=-2.4 vs -1.3 AE:TG-47/167 patients; PG-13/171 patients
Ruoff 2003	318 patients were randomized, 165 completers TG: (n=161); PG: (n=157)	**Mild opioid plus acetaminophen vs placebo** TG: tramadol 37.5mg/APAP 325mg/day for 91 days PG: placebo daily	12 weeks	VAS (100mm): mean changes compared with baseline of TG: -26.7; PG: -16.5 RMDQ (0-24 points scale): mean changes compared with baseline TG: -4.1 (5.8); PG: -2.6 (5.2) AE:TG-111/161 patients; PG-73/157 patients
O'Donnell 2009	796 patients were randomized, 614completers TG1: (n=392); TG2: (n=404)	**Mild opioids vs COX2 NSAIDs** TG1: tramadol HCI 50 mg qid TG2: celecoxib 200mg bid	6 weeks	NRS (11-point Likert Scale): with at least 30% improvement, TG1 vs TG2=63.2% vs 49.9% AE: TG1-119/392 patients ; TG2- 58/404 patients;
Vorsanger 2008	386 patients were randomized , 241completers TG1: (n=128); TG2: (n=129); PG: (n=129)	**Mild opioids vs placebo** TG1: tramadol ER 100mg/day for 3 days, then increase as 300mg/day; TG2: tramadol ER 100mg/day for 3 days, then increase as 200mg/day PG: placebo, daily	12 weeks	VAS (100mm): mean difference (95% CI) at week-12 compared with baseline: TG1 vs TG2 vs PG=-20.0 vs -17.2 vs -8.0 RMDQ (0-24-point scale): TG1 vs TG2 vs PG=-3.7 vs -3.2 vs -1.4 PGI-I (0-4-point scale): TG1 vs TG2 vs PG = 0.8 vs 0.5 vs 0.4 AE:TG1-97/128 patients; TG2-79/129patients; PG-72/129 patients
Opioids				
Buynak 2010	965 patients were randomized, 451completers TG1: (n=328); TG2: (n=318); PG: (n=319).	**Opioids vs placebo** TG1: oxycodone CR 10mg, bid for 3 days, then increase as 20mg, bid/day TG2: tapentadol ER 50mg, bid for 3 days, then increase as 100mg, bid; PG: placebo, daily	3 weeks treatment, and 12 weeks follow up	BPI (0-10-point scale): mean changes of pain intensity compared with baseline: TG1 vs TG2 vs PG= -2.63 (0.29) vs -2.28 (0.06) vs -1.16 (0.4) PGI-I (0-4-point scale): TG1 vs TG2 vs PG = 60.0% vs 55.5% vs 32.7% AE:TG1-104/328 patients; TG2-53/318patients; PG-14/319 patients
Gordon 2010a	79 patients were randomized , 59 completers TG: (n=37); PG: (n=42)	**Opioids vs placebo** TG: buprenorphine transdermal system (BTSD) in 5μg/h, 10μg/h, or 20μg/h for 4 weeks; PG: placebo	4 weeks treatment, and 4 weeks cross-over	VAS (100mm): mean difference compared with baseline: TG vs PG=-20.5 vs -13.4 PDI (0-5 points scale): TG vs PG=-0.4 vs -0.3 AE:TG -20/37patients; PG-18/42 patients
Gordon 2010b	78 patients were randomized, 49 completers TG: (n=39); PG: (n=39)	**Opioids vs placebo** TG: buprenorphine-BTSD in 20 or 40μg/h, weekly; PG: placebo	24 weeks	VAS (100mm): mean difference compared with baseline: TG vs PG=-16.3 vs -8.5 PDI (0-5 points scale): TG vs PG=-0.6 vs -0.4 AE:TG -16/39patients; PG-3/39 patients

Appendix 1 (cont.)

Characteristics of included trials on oral drug therapy.

Trials	Participants characteristics	Interventions (TG-treatment group; PG-placebo group)	Follow-up	Outcome measures
Hale 2007	143 patients were randomized, 67 completers TG: (n=70); PG: (n=73)	**Opioids vs placebo** TG: oxymorphone ER 10mg, tid; PG: placebo	12 weeks	VAS (100mm): mean difference compared with baseline: TG vs PG=-36.1 (2.9) vs -8.7 (3.0) Satisfaction with medication from patients: TG vs PG= 58% vs 22% AE:TG -31/70patients; PG-27/73 patients
Katz 2007	205 patients were randomized, 118 completers TG: (n=105); PG: (n=100)	**Opioids vs placebo** TG: oxymorphone ER 5-10mg, every 12h; PG: placebo	12 weeks	VAS (100mm): mean difference compared with baseline: TG vs PG=10.9 (24.53) vs 26.0 (27.88) Satisfaction with medication from patients: TG vs PG= 80% vs 38% AE:TG -61/105patients; PG-44/100 patients
Webster 2006	719 patients were randomized, 328 completers TG1: (n=206); TG2: (n=206); TG3: (n=206); PG: (n=101)	**Opioids vs placebo** TG1: oxycodone, qid; TG2: oxytrex, qid; TG3: oxytrex, bid; PG: placebo	12 weeks	VAS (100mm): mean difference compared with baseline: TG1 vs TG2 vs TG3 vs PG=-46.2 (33.60) vs -41.2 (35.15) vs -42.6 (34.46) vs -32.2 (38.04) AE:TG1 -105/206 patients; TG2 -119/206 patients; TG3 -108/206 patients; PG-59/101 patients

Trials	Participants characteristics	Interventions (TG-treatment group; PG-placebo group)	Follow-up	Outcome measures
Adjuvant Analgesics - Antiepileptics - Antidepressants				
Muehlbacher 2006	96 patients were randomized, 89 completers TG: (n=48); PG: (n=48)	Antiepileptics vs Placebo TG:Topiramate, titrated to 300 mg/d PG: placebo, daily	10 weeks	Pain Rating Index (mean change from baseline on 0-100 scale): TG vs PG=-12.9 vs. -1.5 SF-36, physical functioning score: TG vs PG=8.7 vs. -0.4; bodily pain score: TG vs PG=4.1 vs. 0.9; other subscale scores: differences in change compared with baseline, favoring topiramate and $p<0.05$ AE: TG-20/48 patients; PG: 10/48 patients
Katz 2005	54 patients were randomized, 40 completers. TG: (n=26); PG: (n=28)	Antidepressant vs placebo TG: bupropion SR 150 mg/day, for 3 days, 150mg tid, for 6 weeks, 150 mg/day for one more week PG: placebo	7 weeks	Pain Intensity Rating: (0-10-point scale): TG vs PG=-2.02 (0.20) vs -1.51 (0.26) Pain relief: TG-2.00 (0.89) vs 2.60 (1.03); PG- 2.00 (0.89) vs2.33 (1.13) Satisfaction with pain relief: TG=3.43 (1.06) vs PG=2.78 (1.07) AE:TG-3/26 patients; PG-1/28 patients
Skljarevski 2009	404 patients were randomized, 267 completers. TG1: (n=59); TG2: (n=116); TG3: (n=112); PG: (n=117)	Antidepressant vs placebo TG1/2/3: duloxetine 20/60/120 mg/day PG: placebo, daily	13 weeks	BPI (0-10-point scale): TG vs PG= -2.4 vs -1.8 RMDQ (0-24 points scale): TG vs PG=-2.5vs-1.3 PGI-I (0-4-point scale, 0=not at all, 4=extremely): TG vs. PG=2.64vs.2.9 AE: TG1-38/59 patients; TG2-78/116 patients; ; TG3-78/116 patients; PG-69/117 patients
Skljarevski 2010a	236 patients were randomized, 182 completers. LBP for greater than 6 months. TG: (n=115); PG: (n=121)	Antidepressant vs placebo TG: duloxetine 60/120 mg/day PG: placebo, daily	13 weeks	BPI (11-point NRS): TG vs. PG=-2.35 (1.24) vs -1.42 (0.23) RMDQ (0-24 points scale): TG vs. PG=-3.60 vs -1.93 PGI-I (4-point Likert, 0-not at all, 4=extremely): TG vs. PG=2.59 vs. 3.16 AE: TG-65/115 patients (4serious AE); PG-58/121 patients
Skljarevski 2010b	401 patients were randomized, 303 completers. LBP for greater than 6 months. TG: (n=198); PG: (n=203)	Antidepressant vs placebo TG: duloxetine 60 mg/day PG: placebo, daily	12 weeks	BPI (11-point NRS): TG vs. PG=-2.25 (0.15) vs -1.65 (0.15) RMDQ (0-24 points scale): TG vs. PG=-2.69 (0.31) vs -2.22 (0.32) PGI-I (0-4 point scale): TG vs. PG=2.88 (0.09) vs. 3.19 (0.09) AE: TG-30/198 patients (4serious AE); PG-11/203 patients

aLBP I: average low back pain intensity; BPI: Brief Pain Inventory; NRS: Numerical Rating Scale; NSAIDs: Non-steroidal anti-inflammatory drugs; ODI: Oswestry Disability Index; PDI: Pain Disability Index; PGI-I: Patients' Global Impressions of Improvement-Index; RMDQ: Roland-Morris Disability Questionnaire; VAS: Visual Analogue Scale

Appendix 2

Characteristics of included trials on oral drug therapy.

Trials	Participants characteristics	Interventions	Follow-up	Outcome measures
Chiu 2011	60 patients were randomized, 58 completers TG (n=33); PG (n=27)	Local site injection: TG: received methylcobal containing parenteral methylcobalamin PG: received normal saline	2 months of post-treatment	VAS: at baseline: TG=56.0 (18.6) vs PG=54.8 (16.1) ($P > .05$) At 2-month: TG=38.6 (22.3) vs PG=51.5 (19.4) ($P > .05$) ODI: at baseline: TG=64.0 (18.3) vs PG=60.5 (15.4) ($P > .05$) At 2-month: TG=47.0 (22.3) vs PG=55.3 (20.5) ($P > .05$) AE: 13/33 patients; 11/27 patients
Manchikanti 2007	60 patients were randomized, 60 completers TG1 (n=15); TG2 (n=15); TG3 (n=15); TG4 (n=15)	Facet joint site injection: TG1: lumbar facet joint nerve blocks with bupivacaine; TG2: lumbar facet joint nerve blocks with of bupivacaine and Sarapin; TG3: lumbar facet joint nerve blocks with of bupivacaine, and steroids; TG4: lumbar facet joint nerve blocks with of bupivacaine, Sarapin, and steroids	3, 6, and 12 months of post-treatment	NRS pain: at baseline: 8.1 (1.4) vs 8.3 (0.9) vs 8.1 (0.8) vs 8.5 (1.2); at 3 months: 3.9 (1.2) vs 3.7 (0.8) vs 3.7 (1.1) vs 4.0 (0.9); at 6 months: 3.6 (1.1) vs 3.5 (0.8) vs 3.3 (0.6) vs 3.7 (0.6); at 12 months: 3.9 (1.2) vs 3.7 (0.9) vs 3.8 (0.9) vs 3.5 (0.6) ODI functioning: at baseline: 23.0 (7.4) vs. 27.9 (4.2) vs. 24.2 (6.8) vs. 23.9 (5.6); at 3 months: 12.1 (5.5) vs. 12.5 (3.9) vs. 14.3 (3.6) vs. 13.7 (4.4); at 6 months: 11.5 (5.4) vs. 13.5 (3.7) vs. 14.3 (4.7) vs. 12.0 (4.7); at 12 months: 11.3 (5.1) vs 13.0 (4.2) vs 13.9 (4.2) vs 12.2 (4.9) No adverse events reported over a year of follow-up
Manchikanti 2008	120 patients were randomized, 111 completers TG1 (n=60); TG2 (n=60)	Facet joint site injection: TG1: lumbar facet joint nerve blocks with local anaesthetic of bupivacaine; TG2: with a mixture of bupivacaine and betamethasone	3, 6, and 12 months of post-treatment	No significant differences in treatment effects of two treatment: NRS pain: at baseline: 8.2 (0.8) vs 7.9 (1.0) ; at 3 months: 3.8 (1.3) vs 3.5 (1.1); at 6 months: 3.6 (1.5) vs 3.3 (0.8); at 12 months: 3.7 (1.7) vs 3.5 (1.1) ODI functioning: at baseline: 26.6 (4.6) vs 25.9 (5.0) ; at 3 months: 12.7 (4.7) vs 13.5 (5.6); at 6 months: 12.7 (4.7) vs 12.2 (5.0); at 12 months: 12.3 (4.8) vs 12.0 (5.4) No adverse events reported over a year of follow-u*P*
Manchikanti 2010	120 patients were randomized, 107 completers TG1 (n=60); TG2 (n=60)	Facet joint site injection: TG1: lumbar facet joint nerve blocks with local anaesthetic of bupivacaine; TG2: with a mixture of bupivacaine and betamethasone	3, 6, 12,18, and 24 months of post-treatment	NRS: at 18 months: 3.5 (1.5) vs 3.3 (1.0); and at 24 months: 3.5 (1.5) vs 3.2 (0.9) ODI: at 18 months: 12.1 (5.0) vs 11.2 (4.9); at 24 months: 12.0 (4.9) vs 11.0 (4.8) No adverse events reported over two years of follow-up

Pach 2011	150 patients were randomized, 136 completers
	TG (n=54);
	PG (n=48);
	No treatment (n=51)
		Local site injection:
		TG: injection of verum (Disci/Rhus toxicodendron compositum)
		PG: injection of placebo (isotonic saline)
		No treatment
		All groups' co-interventions with orally rescue pain medication of acetaminophen or NSAIDS
			8, and 26 weeks of post-treatment	VAS: at baseline: TG=58.9 (14.3) vs PG=62.5 (13.9) vs no treatment=59.0 (14.1);
				at 8-week (97.5% CI): TG= 37.0 (25.3-48.8) vs PG=41.8 (30.1-53.6) ($P = 0.350$);
				TG=37.0 (25.3-48.8) vs no treatment=53.0 (41.8-64.2) ($P = 0.001$);
				at 26-week: TG= 36.6 (25.4-47.8) vs PG=35.5 (24.2-46.9) ($P = 0.837$); TG=36.6 (25.4-47.8) vs no treatment=45.0 (34.1-55.9) ($P = 0.085$);
				PDI: at baseline: TG=27.1 (10.7) vs PG=29.0 (13.8) vs no treatment=27.7 (10.7);
				at 8-week: TG= 22.7 (19.3-26.2) vs PG=21.4 (17.7-25.1) ($P = 0.598$); TG=22.7 (19.3-26.2) vs no treatment=25.9 (22.5-29.3) ($P = 0.200$);
				at 26-week: TG= 18.1 (14.0-22.3) vs PG=21.4 (17.2-25.6) ($P = 0.173$); TG=18.1 (14.0-22.3) vs no treatment=22.7 (18.7-26.7) ($P = 0.046$);
				SF-36 of physical component score: at baseline: TG=36.2 (6.3) vs PG=31.6 (8.9) vs no treatment=35.1 (7.7);
				at 8-week: TG= 37.1 (34.9-39.2) vs PG=39.8 (37.5-42.1) ($P = 0.089$); TG=37.1 (34.9-39.2) vs no treatment=35.4 (33.3-37.5) ($P = 0.278$);
				at 26-week: TG= 38.20(35.0-41.5) vs PG=40.9 (37.5-44.2) ($P = 0.163$); TG=38.20(35.0-41.5) vs.no treatment=36.5 (33.3-39.7) ($P = 0.326$);
				SF-36 of Mental component score: at baseline: TG=48.8 (12.3) vs PG=50.5 (11.5) vs no treatment=49.2 (11.0);
				at 8-week: TG= 48.5(46.0-50.9) vs PG=47.5 (44.9-50.1) ($P = 0.609$); TG=48.5(46.0-50.9) vs no treatment=50.9 (48.4-53.3) ($P = 0.174$);
				at 26-week: TG= 51.2(48.9-53.3) vs PG=48.9 (46.4-51.4) ($P = 0.185$); TG=51.2(48.9-53.3) vs no treatment=51.5 (49.1-53.9) ($P = 0.861$)
				AE: 37/54 patients in the TG; 34/48 patients in the PG

Appendix 2

Characteristics of included trials on oral drug therapy.

Trials	Participants characteristics	Interventions	Follow-up	Outcome measures
Yelland 2004	110 patients were randomized, 88 completers TG: (n=54) PG: (n=56)	Local site injection: TG: lumbopelvic ligaments with glucose (20%), 10 to 30 ml, no. of times=7; PG: lumbopelvic ligaments with saline, 10 to 30 ml, no. of times=7 Both groups' co-interventions: daily flexion-extension exercise	6, 12, and 24 months of post-treatment	VAS: at baseline: 51.9 (19.3) vs 55.0 (20.7); at 6 months: 31.4 (26.6) vs 34.0 (27.5); at 12 months: 33.1 (24.5) vs 36.6 (27.9); and at 24 months: 32.8 (25.8) vs 37.1 (24.6) RMDQ: at baseline: 13.7 (4.9) vs 14.3 (4.6); at 6 months: 7.9 (7.5) vs 9.3 (5.7); at 12 months: 8.0 (7.1) vs 9.8 (6.5); at 24 months: 8.6 (7.5) vs 9.4 (7.3)

TG: Treatment Group; PG: Placebo Group
NRS: Numerical Rating Scale; NSAIDs: Non-steroidal anti-inflammatory drugs; ODI: Oswestry Disability Index;
PDI: Pain Disability Index; RMDQ: Roland-Morris Disability Questionnaire; VAS: Visual Analogue Scale

References

1. Chou R. Pharmacological management of low back pain. *Drugs* 2010; 70:387-402.
2. Krismer M, van Tulder M; The Low Back Pain Group of the Bone and Joint Health Strategies for Europe Project. Low back pain (non-specific). *Best Prac Res Clin Rheumatol* 2007; 21:77-91.
3. Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW Real-world practice patterns, health-care utilization, and costs in patients with low back pain: The long road to guideline-concordant care. *Spine* 2011; 11:622-632.
4. Rozenberg S, Foltz V, Fautrel B. Treatment strategy for chronic low back pain. *Joint Bone Spine* 2012; 79:555-559.
5. Wilkinson IM, Cohen SP. Epidural steroid injections. *Curr Pain Headache Rep* 2012; 16:50-59.
6. WHO International Classification of Functioning, Disability and Health. www.who.int/classifications/icf/en/ accessed on December 23, 2012.
7. Chou R, Qaseem A, Snow V, Casey D, Cross Jr JT, Shekelle P, Owens D; Clinical Efficacy Assessment Subcommittee of the American College of Physicians and the American College of Physicians/American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478-491.
8. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, Woolf A, Vos T, Buchbinder R. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 24:181-191.
9. Rossignol M, Rozenberg S, Leclerc A. Epidemiology of low back pain: What's new? *Joint Bone Spine* 2009; 76:608-613.
10. White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: Synthesis of the evidence. *Spine* 2011; 36:S131-S143.
11. Licciardone JC. The epidemiology and medical management of lowback pain during ambulatory medical visits in the United States. *Osteopath Med Primary Care* 2008; 2:11. www.om-pc.com/content/2/1/11.
12. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008; 8:8-20.
13. Hughes CM, Quinn F, Baxter GD. Complementary and alternative medicine: Perception and use by physiotherapists in the management of low back pain, *Complement Ther Med* 2011; 19:149-154.
14. Murphy AY, van Teijlingen ER, Gobbi MO. Inconsistent grading of evidence across countries: A review of low back pain guidelines. *J Manipulative Physiol Ther* 2006; 29:576-581.
15. Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, Sullivan SD. Expenditures and health status among adults with back and neck problems. *JAMA* 2008; 299:656-664.
16. Vogt MT, Kwoh CK, Cope DK, Osiai TA, Culyba M, Starz TW. Analgesic usage for low back pain: Impact on health care costs and service use. *Spine* 2005; 30:1075-1081.
17. Chou R, Huffman LH. Medications for acute and chronic low back pain: A review of the evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2007; 147:504-514.
18. Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Symptom Manage* 2004; 28:72-95.
19. Higgns JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions.* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
20. Review Manager (RevMan) [Computer Program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
21. Littell, JH, Corcoran J, Pillai V. *Systematic Reviews and Meta-analysis.* Oxford University Press, USA, 2008.
22. Birbara CA, Puopolo AD, Munoz DR, Sheldon EA, Mangione A, Bohidar NR, Geba GP; Etoricoxib Protocol 042 Study Group. Treatment of chronic low back pain with etoricoxib, a new cyclo-oxygenase-2 selective inhibitor: Improvement in pain and disability – a randomized, placebo-controlled, 3-month trial. *J Pain* 2003; 4:307-315.
23. Coats TL, Borenstein DG, Nangia NK, Brown MT. Effects of valdecoxib in the treatment of chronic low back pain: Results of a randomized, placebo-controlled trial. *Clin Ther* 2004; 26:1249-1260.
24. Katz N, Ju WD, Krupa DA, Sperling RS, Bozalis Rodgers D, Gertz BJ. Efficacy and safety of rofecoxib in patients with chronic low back pain: Results from two 4-week, randomized, placebo-controlled, parallel-group, double-blind tri-

als. *Spine* 2003; 28:851-8; discussion 859.

25. Pallay RM, Seger W, Adler JL, Ettlinger RE, Quaidoo EA, Lipetz R. Etoricoxib reduced pain and disability and improved quality of life in patients with chronic low back pain: A 3 month, randomized, controlled trial. *Scand J Rheumatol* 2004; 33:257-266.
26. Sprott H, Gay RE, Michel BA, Gay S. Influence of ibuprofen-arginine on serum levels of nitric oxide metabolites in patients with chronic low back pain—a single-blind, placebo controlled pilot trial (ISRCTN18723747). *J Rheumatol* 2006; 33:2515-2518.
27. Chrubasik S, Model A, Black A, Pollak S. A randomized double-blind pilot study comparing doloteffin and vioxx in the treatment of low back pain. *Rheumatol* 2003; 42:141-148.
28. Zerbini C, Ozturk ZE, Grifka J, Maini M, Nilganuwong S, Morales R. Efficacy of etoricoxib 60 mg/day and diclofenac 150 mg/day in reduction of pain and disability in patients with chronic low back pain: Results of a 4-week, multinational, randomized, double-blind study. *Curr Med Res Opin* 2005; 21:2037-2049.
29. Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, Brown MT. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain* 2011; 152:2248-58.
30. O'Donnell JB, Ekman EF, Spalding WM, Bhadra P, McCabe D, Berger MF. The effectiveness of a weak opioid medication versus a cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug in treating flare-up of chronic low-back pain: Results from two randomized, double-blind, 6-week studies. *J Int Med Res* 2009; 37:1789-1802.
31. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N; Protocol TRP-CAN-1SG. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (ultracet) in treatment of chronic low back pain: A multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol* 2004; 31:2454-2463.
32. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M; Protocol CAPSS-112SG. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: A multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 2003; 25:1123-1141.
33. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *J Opioid Manag* 2008; 4:87-97.
34. Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, Lange C, Etropolski M. Efficiency and safety of tapentadol extended release for the management of chronic low back pain: Results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother* 2010; 11:1787-1804.
35. Hale ME, Ahdieh H, Ma T, Rauck R; Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *J Pain* 2007; 8:175-184.
36. Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin* 2007; 23:117-128.
37. Webster LR, Butera PG, Moran LV, Wu,N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain* 2006; 7:937-946.
38. Gordon A, Rashiq S, Moulin DE, Clark AJ, Beaulieu AD, Eisenhoffer J. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain Res Manag* 2010; 15:169-178.
39. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W. Buprenorphine transdermal system in adults with chronic low back pain: A randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther* 2010; 32:844-860. .
40. Muehlbacher M, Nickel MK, Kettler C, Tritt K, Lahmann C, Leiberich PK. Topiramate in treatment of patients with chronic low back pain: A randomized, double-blind, placebo-controlled study. *Clin J Pain* 2006; 22:526-531.
41. Katz J, Pennella-Vaughan J, Hetzel RD, Kanazi GE, Dworkin RH. A randomized, placebo-controlled trial of bupropion sustained release in chronic low back pain. *J Pain* 2005; 6:656-661.
42. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol* 2009; 16:1041-1048. .
43. Skljarevski V, Desaiah D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ. Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine* 2010; 35:E578-85.
44. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T. Duloxetine versus placebo in patients with chronic low back pain: A 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010; 11:1282-1290.
45. Roelofs PDDM, Deyo RA, Koes BW, Scholten RJPM, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2011; 2. Available at: http://thecochranelibrary.com.
46. Deshpande A, Furlan AD, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low-back pain. *Cochrane Database Syst Rev* 2010; 5.
http://thecochranelibrary.com.
47. Urquhart DM, Hoving JL, Assendelft WJJ, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev* 2010; 10. http://thecochranelibrary.com.
48. Chang S, Chen L, Chang C, Chu H, Hsieh M, Tsai K. Efficacy and safety of piroxicam beta-cyclodextrin sachets for treating chronic low back pain: A randomized, parallel, active-controlled trial. *J Med Sci* 2008; 28:111-119.
49. Chang ST, Chen LC, Chang CC, Chu HY, Tsai KC. Effects of piroxicam-beta-cyclodextrin sachets on abnormal postural sway in patients with chronic low back pain. *J Clin Pharmacol* 2008; 33:495-506.