Family Practice, 2017, Vol. 34, No. 2, 138–146
doi:10.1093/fampra/cmw134
Advance Access publication 30 January 2017

OXFORD

Review

Amitriptyline for musculoskeletal complaints: a systematic review

Jacoline J van den Driest[a,*], Sita M A Bierma-Zeinstra[a,b], Patrick J E Bindels[a] and Dieuwke Schiphof[a]

[a]Department of General Practice, Erasmus MC, University Medical Center, Rotterdam, The Netherlands and [b]Department of Orthopedics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

*Correspondence to Jacoline J van den Driest, Department of General Practice, Erasmus MC, Wytemaweg 80, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: j.vandendriest@erasmusmc.nl

Abstract

Background. The role of amitriptyline in musculoskeletal pain is not as clearly defined as in classical neuropathic pain conditions.
Objective. To assess the efficacy and effectiveness of amitriptyline in the treatment of pain in musculoskeletal complaints.
Methods. An extensive search (including Medline, Embase and Web of Science) was made up to April 2016 for randomised controlled trials on amitriptyline in musculoskeletal complaints compared to placebo, usual care, or other analgesic use. Included studies were assessed for risk of bias. Outcomes of interest were pain reduction and function improvement.
Results. Of the 2066 articles identified, seven were finally included. These studies were performed in patients with low back pain (4), rheumatoid arthritis (2), and patients with arm pain from repetitive use (1). No meta-analysis was performed due to clinical heterogeneity of the studies. Two studies with low risk of bias found positive results. One study found that 50 mg/day of amitriptyline [Visual Analogue Scale (VAS) –3.9 points] resulted in a significantly greater reduction in pain than treatment with pregabalin 600 mg/day (VAS –2.9 points) and improved function (improvement on the Oswestry Disability Index >20%: 65% versus 49.5%). Amitriptyline improved function in arm pain compared to placebo (Upper Extremity Function Scale: –3.9 versus 0.8). A similar amount of side-effects occurred in the amitriptyline and the comparison groups.
Conclusion. Few studies have evaluated the use of amitriptyline in musculoskeletal complaints. Although amitriptyline may be effective in musculoskeletal complaints, more studies are required to establish for whom amitriptyline works better than other analgesics.

Key words: Amitriptyline, analgesics, chronic pain, low back pain, musculoskeletal pain, review.

Introduction

Chronic musculoskeletal disorders are a common problem among patients visiting a general practitioner (GP). A Dutch database of GP records showed that ≥50% of the patients visited their GP with a new musculoskeletal complaint during a 10-year period (1). In the UK, one in seven of the consultations with a GP concerned musculoskeletal complaints (2). More importantly, these disorders are the major cause of chronic pain. A European study on the prevalence of chronic pain showed that almost 50% of the patients had back complaints and ≥40% of the patients had joint pain (3).

The use of standard analgesics is adequate for most patients with musculoskeletal complaints, but sufficient pain relief is not always obtained. Especially patients with chronic pain may benefit from

additional neuropathic pain medication. Although musculoskeletal complaints do not belong to the classic neuropathic syndromes, centrally-acting agents like antidepressants and anticonvulsants ($\alpha_2\delta$-ligands) can be helpful because of the pathophysiological changes in pain processing in the central nervous system (CNS; central sensitization) described in patients with chronic pain (4). Central sensitization can occur due to prolonged peripheral nociceptive input, which can lead to hyperexcitability of pain circuits in the CNS. A neuropathic pain component is present in 20–35% of the patients with low back pain (5,6) and in 28–45% of patients with osteoarthritis (7–9).

In Finland, antidepressants accounted for 1.9% of the prescriptions for musculoskeletal complaints and for 3% in the USA (10,11). The NICE guidelines for treatment of neuropathic pain in adults in a non-specialist setting, recommend duloxetine, amitriptyline, gabapentin and pregabalin as first choices (12), while the Dutch GP guidelines recommend amitriptyline as a first-line neuropathic agent (13). The target points of these analgesics in the CNS differ for antidepressants and anticonvulsants (14). We chose to focus on antidepressants; moreover, as the use of duloxetine in musculoskeletal pain is reviewed elsewhere (15,16), we focused on amitriptyline.

The role of amitriptyline in musculoskeletal disorders is not as well defined as in classic neuropathic pain syndromes. Therefore, the aim of this review is to assess the efficacy and effectiveness of amitriptyline in the treatment of pain in musculoskeletal complaints.

Methods

Eligibility criteria

Included in this study were randomised controlled trials (RCTs) on the use of amitriptyline for musculoskeletal disorders. Studies had to compare any dosage of amitriptyline to placebo, usual care, or standard analgesic use. We defined usual care as physiotherapy, education, other nonsurgical interventions, or 'wait and see'. Analgesics allowed as comparator were paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opiates, and other neuropathic pain medication. Moreover, corticosteroid injections were permitted as comparison. No restrictions on the duration of therapy were applied. Articles published in English, German, French, Spanish, Italian, Scandinavian or Dutch were eligible.

Outcomes of interest were pain reduction and improvement of function

Studies on fibromyalgia were excluded as these were recently evaluated in a Cochrane review (July 2015) (17). Also excluded were RCTs evaluating the use of amitriptyline in classic neuropathic pain (e.g. diabetic polyneuropathy, HIV-associated neuropathy, post-herpetic neuralgia and phantom pain).

Search strategy

An extensive search (including Medline, Embase, Web of Science and Cochrane) up to April 2016 was made with the help of a medical librarian. The main keywords were amitriptyline and musculoskeletal complaints (see Supplementary Data Table S1 for all search terms used). In addition, references of the included articles were screened, and to find unpublished studies the Clinical Trials Search Portal (which includes ClinicalTrials.gov and the EU Clinical Trials Register amongst others) was searched.

Study selection

Two independent reviewers (JD, DS) screened the title and abstract for potentially eligible articles. Then, full articles were retrieved and assessed for eligibility. Any disagreements were resolved during a consensus meeting. If no consensus was reached, a third reviewer (SBZ) made the final decision.

Methodological quality assessment

Two independent reviewers assessed the methodological quality of the selected articles. Any disagreements were discussed in a consensus meeting. The methodological quality of the selected articles was assessed using a checklist based on the Cochrane Collaboration's tool for assessing risk of bias (18). The following items related to the risk of bias were scored: (i) selection bias (random sequence generation and allocation concealment), (ii) performance bias (blinding participants and care providers), (iii) detection bias (blinding outcome assessors), (iv) attrition bias (drop-out rates, number of participants analysed in the group of allocation), (v) reporting bias (selective reporting) and (vi) other bias (comparability of study groups at baseline, co-interventions and compliance to treatment).

Each item on the checklist was rated as 'Yes' (indicating low risk of bias), 'No' (Indicating high risk of bias) or 'Unclear' (indicating unclear, or unknown risk of bias). We defined studies with a low risk of bias on the items 'allocation concealment' and 'participants analysed in the group of allocation', as being studies with a low risk of bias. These two items can affect our outcomes of interest (reducing pain and improvement of function) the most (19). Blinding of outcome assessors is less important, since in most studies two active treatments are compared.

Data extraction

Data extraction was performed by two reviewers using a standardised form. Disagreements were resolved during a consensus meeting. For each article we extracted data using the PICO approach.

- 'Participants': complaint, duration of the complaint, mean age of the patients, clinical setting and baseline pain intensity.
- 'Interventions': dosage of amitriptyline, duration of the treatment.
- 'Comparison': to placebo, usual care or analgesic use.
- 'Outcomes': pain reduction, improvement of function adverse events and loss to follow-up (when mentioned).

Results

Study selection

The initial search yielded 3816 articles; after removing duplicates, 2066 articles remained. No potentially eligible studies were identified by searching for unpublished literature. After screening the title and abstract, the full-texts of 24 articles were assessed for eligibility. Finally, seven articles were included in this review (Figure 1).

Study characteristics

The characteristics of the included studies (all RCTs) are presented in Table 1. Four studies evaluated amitriptyline in low back pain; three in chronic low back pain (CLBP) (20–22) and one in acute low back pain (ALBP) (23). One study examined amitriptyline in persistent arm pain due to repetitive use (24). Another two

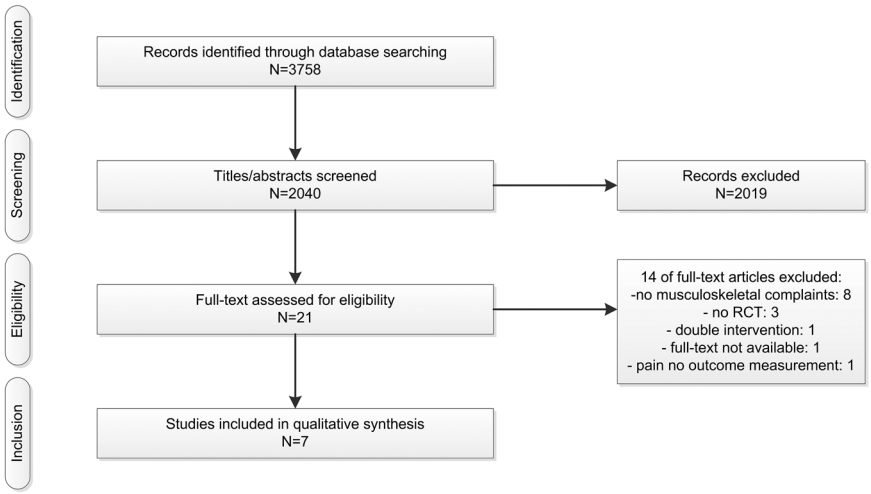

Figure 1. Flowchart inclusion.

studies assessed the use of amitriptyline in rheumatoid arthritis (RA) (25,26). Only one study on CLBP reported whether a neuropathic pain component was present; of the 200 patients, 95 had backache with radiculopathy (22).

Amitriptyline was compared with different interventions. CLBP studies compared amitriptyline with buproprione (20), fluoxetine (21) or pregabalin (22). For ALBP, amitriptyline was compared with paracetamol (23). In persistent arm pain (24) and one study on RA (26), amitriptyline was compared with placebo. The second study on RA evaluated the use of amitriptyline in comparison to placebo, desipramine and trazodone; this study had a cross-over design in which patients received all four interventions (25). Dosage of amitriptyline ranged from 25 mg/day for persistent arm pain to a maximum of 150 mg/day for ALBP and CLBP. All studies were conducted in secondary and tertiary care centres. In the study on repetitive arm pain, patients were also recruited through advertisements (24).

In all studies, primary outcome was the reduction of pain. In five studies pain was measured with a 10-point Visual Analogue Scale (VAS) or a 0–10 Numeric Rating Scale (NRS) (21–25). The trial on RA [comparing amitriptyline with multiple interventions (cross-over design)] also evaluated pain on a 0–5 intensity scale in addition to the VAS (25). The study on RA (with a placebo as comparator) measured pain on a 5-point scale (26). The study on CLBP (comparing amitriptyline with bupropione) did not report which method was used to evaluate pain (20).

The secondary outcome, improvement of function, was reported in two studies (22,24). The study on persistent arm pain evaluated arm function using the Upper Extremity Function Scale (UEFS); the total score ranges from 8–80, with higher scores indicating greater disability (27). The study on CLBP (comparing amitriptyline with pregabalin) reported on function using the Oswestry Disability Index (ODI); this score ranges from 0–100% with a higher percentage indicating more impairment (28). Follow-up ranged from 5–32 weeks.

Table 2 shows the risk of bias for each study. Two studies had a low risk of bias (22,24), and 5 studies did not report on the allocation of treatment or intention-to-treat analysis (20,21,23,25,26).

In the present study, the reviewers agreed on 78% of the items scored (Cohen's kappa 0.75).

Effectiveness: improvement of pain

One study with low risk of bias found a significant improvement of pain in the amitriptyline group between baseline and follow-up, and between the treatment groups, in favour of amitriptyline (Table 3) (22). In this study on CLBP, 50 mg/day of amitriptyline reduced pain by 3.9 points (VAS 0–10), while 600 mg/day of pregabalin reduced pain by 2.9 points (VAS 0–10). Two studies, one on CLBP (20) and one on ALBP (23), found a significant improvement of pain with amitriptyline between baseline and follow-up; however, these studies found no difference between amitriptyline and bupriopione or paracetamol, respectively. In CLBP, treatment with 150 mg/day amitriptyline resulted in a pain score ≤2 in 50% of the patients, while at study start only 25% had a pain score ≤5 (20). In ALBP, 5 weeks of treatment with 150 mg/day of amitriptyline reduced pain by 4.83 points (VAS) (23).

The trial with the crossover design examining the effect of amitriptyline in comparison to different treatments, found that amitriptyline led to a significantly greater reduction in pain compared with baseline, placebo, trazodone or desipramine (on a 0–5 pain scale); however, no significant differences were found in pain reduction between the treatments when using the VAS (25).

Effectiveness: improvement of function

Two studies, both with a low risk of bias, reported on improvement of function (22,24). Both studies found a significant increase at the end of treatment, but they compared amitriptyline with a different treatment (Table 3). Amitriptyline let to a significant improvement in arm function in patients with persistent arm pain compared with placebo, i.e. the Upper Extremity Function Scale (UEFS (8–80) (27) improved by 3.9 points compared to 0.8 points in the placebo group (24).

In CLBP, 65% of the patients in the amitriptyline group showed an improvement in the Oswestry Disability Index (ODI (by ≥20%; 10 points) compared to 49.5% of the patients in the pregabalin group (P = 0.03) (22). In absolute improvement of function no significant difference was found between the two different treatments.

Side-effects

No serious side-effects were reported in any of the studies. Adverse events occurred in all treatment groups and the prevalence of

Table 1. Characteristics of the included studies (n = 7)

Study (year)	Complaint	Sample size (n)	Mean age: years (±SD)	Setting	Duration of disease	Dosage of AMT	Comparator	Duration of treatment (weeks)	Loss to follow-up
Farajirad (2013) (20)	CLBP	60	35.6 (9.5)	Outpatient neurosurgery clinic	NR	Initial 25 mg/day, added 25 mg/day every 3 days up to 150 mg/day within 2 weeks	Bupropione 150 mg/day in week 1, 300 mg/day in second week	8	NR
Schreiber (2001) (21)	LBP/ Whiplash	40	52.6	Pain clinic of a large tertiary center	AMT: 8 (4–18) months, FLX 8.5 (3–38) months	Start at 25 mg/day, increase every other day by 25 mg/day, max 75 mg/day	Fluoxetine: 20 mg/day	6	12.5% (3AMT/ 2 FLX)
Kalita (2014) (22)	CLBP	200	41.5 (11.1)	Department of Neurology	35 (4–360) months	Initial 12.5 mg (2 weeks), 25 mg (4 weeks), 50 mg (8 weeks)	Pregabalin: 150 mg/day for 2 weeks, 300 mg/day for 4 weeks, 600 mg/day after 6 weeks	14	15% (15 AMT /15 PGB)
Stein (1996)(23)	ALBP	45	36.4 (7.3)	Emergency patients	61.3 (SD 56.3) days	Start at 37.5 mg/day to 150 mg/day in 4 days	Paracetamol 2000 mg/day	5	13.3 % (3 AMT/3 PCM)
Goldman (2010) (24)	Persistent arm pain	118	37.5 (11.2)	Advertisement and referral	27% AMT and 36% PLA had complaints less than 1 year	25 mg	Placebo	6	10.2% (8 AMT/ 4 PLA)
Frank (1988) (25)	RA	73	58.1 (SD 9.2)	University hospital	NR	First 3 days 1.0 mg/kg/ day, afterwards 1.5 mg/ kg/day. Older than 60 years: 1/2 dosage	Placebo; Desipramine: first 3 days 1.0 mg/kg/ day, afterwards 1.5 mg/ kg/day; Trazodone: first 3 days 1.5 mg/ kg/day 3.0 mg/kg/day. Older than 60 years: 1/2 dosage	each intervention: 6 weeks, 1 week tapering and 1 week wash-out	36%
Grace (1985) (26)	RA	36	58.05	Urban rheumatic disease clinic, referred by their GP	NR	Start at 25 mg/day, second week 50 mg/day, third week 75 mg/week	Placebo	12	22.2 % (4 AMT/ 4 PLA)

ALBP acute low back pain, AMT amitriptyline, BUP bupropione, CI confidence interval, CLBP chronic low back pain, FLX fluoxetine, LBP low back pain, NR not reported, PCM paracetamol, PGB pregabalin, PLA placebo, RA rheumatoid arthritis.

Table 2. Methodological quality of the included studies ($n = 7$)

Study (year)	Sequence generation	Allocation of treatment	Blinding of patients and personnel	Blinding of outcome assessors	Drop-out	Participant analysed in group of allocation	Selective outcome reporting	Similar groups at baseline	Co-interventions	Industry involvement
Farajirad (2013)(20)	Low	Unclear	High	High	Unclear	Unclear	Unclear	Low	Low	Unclear
Schreiber (2001)(21)	Low	Unclear	High	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kalita (2014)(22)	Low	Low	High	High	Low	Low	Unclear	Low	Low	Low
Stein (1996)(23)	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Goldman (2010)(24)	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Frank (1988)(25)	Low	Unclear	Low	Low	High	High	Unclear	Low	High	Unclear
Grace (1985)(26)	Low	Unclear	Low	Unclear	High	Unclear	Unclear	Low	Low	Unclear

side-effects was relatively high. In 6 RCTs no significant difference was found between amitriptyline and the comparator. In the study on arm pain due to repetitive use, significantly more side-effects occurred in the amitriptyline group at the midpoint of the treatment period (after 3 weeks); however, this difference had disappeared by the end of the treatment period (after 6 weeks) (24). In the crossover trial on RA, patients reported significantly more side-effects during treatment with amitriptyline than with a placebo or trazodone. These side-effects did not lead to dose reductions (25). Frequently occurring side-effects during amitriptyline use were drowsiness, dry mouth and constipation (Table 4).

Discussion

Summary

This systematic review assessed the effectiveness of amitriptyline in musculoskeletal complaints. We found four studies on amitriptyline in LBP, one on amitriptyline in persistent arm pain and two studies on RA.

Overall, one study on CLBP (22) with low risk of bias found a significant improvement of pain with amitriptyline compared with pregabalin. Two studies with low risk of bias found a significant improvement of function when comparing amitriptyline with pregabalin in CLBP, or placebo in persistent arm pain (22,24). In CLBP, the effect on function is regarded as clinically relevant since the minimal clinically important difference of the Oswestry Disability Index (ODI) ranges from 6–11 points (28–32). In absolute improvement of function no significant difference was found between amitriptyline and pregabalin, though the clinically relevant difference occurred significantly more often with treatment with amitriptyline compared with pregabalin. This clinically important difference is not as clearly defined for the Upper Extremity Function Scale (UEFS), but the improvement with amitriptyline compared to placebo is small. Overall, a similar amount of side-effects occurred in patients treated with amitriptyline and in patients treated with other analgesics; however, the prevalence of side-effects was relatively high in all studies. In chronic arm pain, patients reported more side-effects (especially drowsiness) after 3 weeks of treatment, which diminished by the end of the study period. This type of pattern is known for amitriptyline (33).

Strengths and limitations

Although we aimed to study the role of amitriptyline in musculoskeletal complaints in general, most of the included studies investigated the role of amitriptyline in LBP. Only one study investigated its use in chronic pain due to repetitive arm use, and two trials in RA. No studies were found for osteoarthritis, another condition in which central sensitization is reported (34,35). Much research on amitriptyline in musculoskeletal complaints has been performed in patients with fibromyalgia; however, we excluded these studies because a Cochrane review on this topic was recently published (17). This latter review reported that there is no unbiased evidence for the effect of amitriptyline in fibromyalgia, but there is also no good evidence for a lack of effect of amitriptyline in fibromyalgia (17).

In some of the patients with musculoskeletal pain, central sensitization is thought to be present (5–9) and it may be expected that these patients have a better response to a centrally acting agent such as amitriptyline (4). Only one of the included studies in our review investigated whether the presence of a neuropathic pain component

Table 3. Data on outcome of the included studies ($n = 7$)

Study (year)	Severity pain baseline AMT	Severity pain baseline comparator	Pain reduction AMT (CI)	Pain reduction comparator (CI)	Improvement of function
Farajirad (2013) (20)	<5: 25%, <7.5: 50%, <8: 75%	NR	<2: 50%[a]	NR	NR
Schreiber (2001) (21)	NR (*VAS 7.3*[f])	NR (*VAS 7.8*[f])	NR (*VAS –2.3*[f])	NR (*VAS –2.4*[f])	NR
Kalita (2014)(22)	VAS 6.7 (1.6)	VAS 6.7 (1.9)	VAS –3.9[a,d]	VAS –2.9[b]	ODI improvement >20%: AMT 65% and PGB 49.5%[e]
Stein (1996)(23)	VAS 7.48 (3.73)	VAS 7.94 (3.42)	VAS –4.83[a]	VAS –3.46[b]	NR
Goldman (2010) (24)	NRS 4.7 (1.8)	NRS 4.3 (1.8)	NRS –0.7 (1.5)	NRS –0.4 (1.8)	UEFS: AMT –3.9, PLA –0.8[e]
Frank (1988)(25)	VAS 4.3; PP 1.9		VAS –0.5; PP-0.5[c]	PLA: VAS –0.3; PP –0.1 TRA: –0.2; PP: 0 DES: VAS –0.3, PP –0.3	NR
Grace (1985)(26)	2.44[g]	2.45[g]	–0.94[g]	–1.07[g]	NR

AMT, amitriptyline; DES, desipramine; NR, not reported; NRS, Numeric Rating Scale for pain; ODI, Oswestry Disability Index; PLA, placebo; PP, Present Pain Intensity (0–5 scale); TRA, trazodone; UEFS, upper extremity function scale; VAS, Visual Analog Scale for pain.

[a]Significant difference between baseline AMT and follow-up AMT.

[b]Significant difference between baseline comparator and follow-up comparator.

[c]Significant difference between present pain baseline and placebo compared to amitriptyline.

[d]Significant difference between AMT and comparator follow-up.

[e]Significant difference.

[f]Estimation, only reported in figure.

[g]Pain intensity rating [0 (no pain) to 4 (severe pain)].

modulated the treatment response (22); the authors found no significant differences in the results.

Another limitation of the present review is the clinical heterogeneity of the included studies. Although all studies investigated the use of amitriptyline in musculoskeletal complaints, different conditions were evaluated. Moreover, amitriptyline was compared with a different treatment in each study, and the dosage of paracetamol was suboptimal at 2000 mg/day (23). Furthermore, dosages of amitriptyline ranged from 25–150 mg/day. Although, in the studies in which amitriptyline showed a significant improvement of pain and/or function compared with the comparator, the dosage of amitriptyline was 25 mg/day or 50 mg/day. These are the same dosages frequently prescribed in patients with fibromyalgia (17), a condition in which central sensitization is known to occur (14).

Another limitation of the included studies is the relatively short follow-up period. In chronic pain it is advised to evaluate the effect of an analgesic after 12 weeks of treatment. Only one of the included studies treated patients for ≥12 weeks (14 weeks) (22). A longer treatment period could lead to more robust findings compared with a shorter treatment period.

Moreover, the studies in this review were conducted in relatively young patients; i.e. the mean age was ≤40 years in three studies (20,23,24) and was 41.5 years in one study (22), while the incidence of musculoskeletal increases with age and these conditions are especially troublesome in patients aged ≥50 years (36,37). Also, pain processing changes with increasing age. In elderly people endogenous pain inhibition (conditioned pain modulation) functions poorly (e.g. the lack of descending analgesia). Furthermore, temporal summation of heat pain may be enhanced in older people (38,39). Both the lack of endogenous pain inhibition and enhanced temporal summation are known to occur in central sensitization (4,40). Therefore, amitriptyline might be more effective in older patients. On the other hand, side-effects may be more common in the elderly due to comorbidities, age-related physiological changes, and polypharmacy (41,42).

Comparison with the literature

Multiple systematic reviews have been published on the use of antidepressants in CLBP (43–47). However, none of the studies included in our review was included in these earlier reviews. These reviews evaluated tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); they found conflicting results on the use of antidepressants for CLBP, two reviews found no evidence for the use of antidepressants (43,46), while three found some evidence (44,45,47). Pooled analyses for TCAs showed also contradictory results: Staiger *et al*. found a significant decrease of pain with TCAs (47) while two other reviews (including a Cochrane review) found no decrease of pain (43,46). However, the conclusions of these reviews should be interpreted with caution due to the diversity of the included studies and different pooling methods used (48). Furthermore, different antidepressants with different affinities for receptors were used and these antidepressants may have different analgesic properties (48). More recent studies with larger samples sizes investigating the use of duloxetine for CLBP show a benefit of treatment with duloxetine, although most of these studies were sponsored by the pharmaceutical industry (49–51).

The use of antidepressants in RA was evaluated in a Cochrane review and concluded that no reliable statement could be made on the use of antidepressants in RA with the current level of evidence (52).

Our review found results similar to the previous reviews; due to the clinical heterogeneity of our included studies it was not possible to perform a meta-analysis; this makes it difficult to draw conclusions about the benefit of amitriptyline. Moreover, we did not include the study by Pheasant *et al*. (53), a study frequently included in other systematic reviews on CLBP, because it did not report on our primary outcome measurement.

Table 4. Observed side-effects in the included studies ($n = 7$)

Study (year)	Dosage of AMT	Comparator	Adverse events AMT (%)	Adverse events comparator (%)	Side-effect amitriptyline	Side-effects comparator
Farajirad (2013)(20)	150 mg/day	BUP 300 mg/day	AE 43%	30%	Dry mouth, somnolence and constipation. DC: 1 orthostatic hypotension, 1 nausea	Nausea and insomnia, DC: 0
Schreiber (2001)(21)	75 mg/day	FLX 20 mg/day	7.5% DC	5% DC	DC: 3; blurred vision, dry mouth, constipation and urinary retention	DC: 2; nausea, diarrhoea and headache
Kalita (2014)(22)	50 mg/day	PGB 600 mg/day	DC 10.7% and AE 17.5	12.4% DC and 21.6% AE	9.7% Drowsiness, 2.9% sedation, 1.9% unsteadiness, 1.9% vertigo	6.2% Vertigo, 4.1% sedation, 1% dry mouth, 1% skin rash, 1% restlessness
Stein (1996)(23)	150 mg/day	PCM 2000 mg/day	AE 10%	0%	DC: 1 orthostatic hypotension, 1 urinary retention	DC: 0
Goldman (2010)(24)	25 mg/day	PLA	AE 31%	22%	41% drowsiness, 2 DC	15% drowsiness
Frank (1988)(25)	1.5 mg/kg/day	PLA, DES 1.5 mg/kg/day, TRA 3.0 mg/kg/day	AE 40%, DC 2.7%	PLA: AE 20% DC 1,3%, DES AE 51% DC 4.1%, TRA AE 33% DC 5.5%	NR	NR
Grace (1985)(26)	75 mg/day	PLA	DC 22.2%	DC 22.2%	DC: 1 drowsiness, 1 'groggy' feeling. 5 patients reduced dosage AMT to 50 mg/day due to side-effects	DC: 3; nausea and dyspepsia

AE adverse event, AMT amitriptyline, BUP bupropione, DC discontinued, DES desipramine, FLX fluoxetine, NR Not Reported, PCM Paracetamol, PGB pregabalin, PLA placebo, TRA trazodone.

Conclusions

This systematic review assessed the use of amitriptyline in musculoskeletal complaints. While the rationale for prescribing amitriptyline in chronic musculoskeletal complaints is present in other conditions (34), we only found studies on LBP, persistent arm pain and RA. Despite the few studies, the heterogeneity and the short period of treatment, amitriptyline may improve pain and function in patients with musculoskeletal complaints. However, amitriptyline may not result in a significantly greater improvement of pain compared with other analgesics. More research is needed to establish whether and for which patients amitriptyline may be more effective than other analgesics.

Supplementary material

Supplementary data are available at *Family Practice* online.

Acknowledgements

The authors thank Wichor Bramer, biomedical information specialist at Erasmus MC, for conducting the database search.

Declaration

Funding: Netherlands Organisation for Health Research and Development (ZonMW) (80-83600-98-3141).
Ethical approval: none.
Conflict of interest: none.

References

1. Koffeman AR, Valkhoff VE, Jong GW *et al*. Ischaemic cardiovascular risk and prescription of non-steroidal anti-inflammatory drugs for musculoskeletal complaints. *Scand J Prim Health Care* 2014; 32(2): 90–8.
2. Jordan KP, Kadam UT, Hayward R *et al*. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010; 11: 144.
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10(4): 287–333.
4. Abrahams MJ. Neuropathic pain in soft tissue complaints. *Best Pract Res Clin Rheumatol* 2007; 21(2): 223–44.
5. Smart KM, Blake C, Staines A, Doody C. The Discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanisms-based classifications of musculoskeletal pain. *Clin J Pain* 2011; 27(8): 655–63.
6. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep* 2009; 13(3): 185–90.
7. Hochman JR, Davis AM, Elkayam J, Gagliese L, Hawker GA. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthritis Cartilage* 2013; 21(9): 1236–42.
8. Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis Cartilage* 2011; 19(6): 647–54.
9. Murphy SL, Lyden AK, Phillips K, Clauw DJ, Williams DA. Subgroups of older adults with osteoarthritis based upon differing comorbid symptom presentations and potential underlying pain mechanisms. *Arthritis Res Ther* 2011; 13(4): R135.
10. Mantyselka P, Ahonen R, Kumpusalo E, Takala J. Variability in prescribing for musculoskeletal pain in Finnish primary health care. *Pharm World Sci* 2001; 23(6): 232–6.
11. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain* 2004; 109(3): 514–9.
12. National Institute for Health and Care Excellence (2014). Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173).
13. Dutch General Practitioners Guideline (NHG-standaard): Pain (M106). 2015. https://www.nhg.org/standaarden/volledig/nhg-standaard-pijn#Begrippen (accessed on 27 June 2016).
14. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther* 2011; 13(2): 211.
15. Pergolizzi JV Jr, Raffa RB, Taylor R Jr *et al*. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract* 2013; 13(3): 239–52.
16. Wang ZY, Shi SY, Li SJ *et al*. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. *Pain Med* 2015; 16(7): 1373–85.
17. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for fibromyalgia in adults. *Cochrane Database Syst Rev* 2015; 7: CD011824.
18. Cochrane Collaboration. The Cochrane Collaboration's tool for assessing risk of bias. http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm (accessed on 22 June 2016).
19. Cochrane Collaboration. Summary assessments of risk of bias. Cochrane Collaboration; 2016 http://handbook.cochrane.org/ (accessed on 22 June 2016).
20. Farajirad S, Behdani F, Hebrani P, Farajirad M. Comparison between the effects of amitriptyline and bupropione on the quality of life and the reduction in the severity of pain in patients with chronic low-back pain. *Neurosurg Q* 2013; 23(4): 227–9.
21. Schreiber S, Vinokur S, Shavelzon V *et al*. A randomized trial of fluoxetine versus amitriptyline in musculo-skeletal pain. *Isr J Psychiatry Relat Sci* 2001; 38: 88–94.
22. Kalita J, Kohat AK, Misra UK, Bhoi SK. An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache. *J Neurol Sci* 2014; 342: 127–32.
23. Stein D, Peri T, Edelstein E, Elizur A, Floman Y. The efficacy of amitriptyline and acetaminophen in the management of acute low back pain. *Psychosomatics* 1996; 37: 63–70.
24. Goldman RH, Stason WB, Park SK *et al*. Low-dose amitriptyline for treatment of persistent arm pain due to repetitive use. *Pain* 2010; 149(1): 117–23.
25. Frank RG, Kashani JH, Parker JC *et al*. Antidepressant analgesia in rheumatoid arthritis. *J Rheumatol* 1988; 15(11): 1632–8.
26. Grace EM, Bellamy N, Kassam Y, Buchanan WW. Controlled, double-blind, randomized trial of amitriptyline in relieving articular pain and tenderness in patients with rheumatoid arthritis. *Curr Med Res Opin* 1985; 9(6): 426–9.
27. Pransky G, Feuerstein M, Himmelstein J, Katz JN, Vickers-Lahti M. Measuring functional outcomes in work-related upper extremity disorders. Development and validation of the Upper Extremity Function Scale. *J Occup Environ Med* 1997; 39(12): 1195–202.
28. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000; 25(22): 2940–52; discussion 52.
29. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Phys Ther* 2001; 81(2): 776–88.
30. Hagg O, Fritzell P, Nordwall A, Swedish Lumbar Spine Study G. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003; 12(1): 12–20.
31. Lauridsen HH, Hartvigsen J, Manniche C, Korsholm L, Grunnet-Nilsson N. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. *BMC Musculoskelet Disord* 2006; 7: 82.
32. Mannion AF, Junge A, Grob D, Dvorak J, Fairbank JC. Development of a German version of the Oswestry Disability Index. Part 2: sensitivity to change after spinal surgery. *Eur Spine J* 2006; 15(1): 66–73.

33. Bryant SG, Fisher S, Kluge RM. Long-term versus short-term amitriptyline side effects as measured by a postmarketing surveillance system. *J Clin Psychopharmacol* 1987; 7(2): 78–82.
34. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Man Ther* 2010; 15(2): *135*–41.
35. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; 152 (suppl 3): S2–15.
36. Parsons S, Breen A, Foster NE *et al*. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. *Fam Pract* 2007; 24(4): 308–16.
37. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. *Pain* 2003; 102(1–2): 167–78.
38. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin J Pain* 2004; 20(4): 227–39.
39. Lautenbacher S. Experimental approaches in the study of pain in the elderly. *Pain Med* 2012; 13 (suppl 2): S44–50.
40. Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. *Nat Rev Rheumatol* 2013; 9(11): 654–64.
41. Cadieux RJ. Antidepressant drug interactions in the elderly. Understanding the P-450 system is half the battle in reducing risks. *Postgrad Med* 1999; 106(6): 231–2, 7–40, 45–9.
42. Coupland C, Dhiman P, Morriss R *et al*. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *Bmj* 2011; 343: d4551.
43. Kuijpers T, van Middelkoop M, Rubinstein SM *et al*. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J* 2011; 20(1): 40–50.
44. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. *Arch Intern Med* 2002; 162(1): 19–24.
45. 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(1): 72–95.
46. Urquhart DM, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev* 2008; 1: CD001703.
47. Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. *Spine (Phila Pa 1976)* 2003; 28(22): 2540–5.
48. Williamson OD, Sagman D, Bruins RH, Boulay LJ, Schacht A. Antidepressants in the treatment for chronic low back pain: questioning the validity of meta-analyses. *Pain Pract* 2014; 14(2): E33–41.
49. Schukro RP, Oehmke MJ, Geroldinger A *et al*. Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component: A Randomized, Double-blind, Placebo-controlled Crossover Trial. *Anesthesiology* 2016; 124(1): 150–8.
50. Skljarevski V, Ossanna M, Liu-Seifert H *et al*. A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *Eur J Neurol* 2009; 16(9): 1041–8.
51. Skljarevski V, Zhang S, Chappell AS *et al*. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. *Pain Med* 2010; 11(5): 648–57.
52. Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev* 2011; 11: CD008920.
53. Pheasant H, Bursk A, Goldfarb J *et al*. Amitriptyline and chronic low-back pain. A randomized double-blind crossover study. *Spine (Phila Pa 1976)* 1983; 8(5): 552–7.