

The Efficacy and Safety of Antidepressants in Inflammatory Arthritis: A Cochrane Systematic Review

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ABSTRACT. *Objectives.* To determine the efficacy and safety of antidepressants in pain management in patients with inflammatory arthritis (IA).

Methods. We searched the Cochrane Central Register of Controlled Trials, Medline, Embase, and PsychINFO for randomized controlled trials in adults with IA that compared any antidepressants (administered via any route) to another analgesic intervention or placebo. We also searched the 2008–2009 American College of Rheumatology and European League Against Rheumatism abstracts and performed a hand search of reference lists of relevant articles. Primary outcomes were patient-reported pain relief $\geq 30\%$ and withdrawals due to adverse events. Two authors independently assessed methodological quality and extracted data. A risk of bias assessment was performed using methods recommended by the Cochrane Collaboration.

Results. Eight trials (652 participants) in patients with rheumatoid arthritis (RA) and 1 trial in patients with ankylosing spondylitis (100 participants) were included in this review. The majority of studies were published in the late 1980s in patients with active disease receiving minimal disease-modifying antirheumatic drug therapy. All trials evaluated tricyclic antidepressants (TCA) and 2 studies included a selective serotonin uptake inhibitor. Seven of the 9 trials had high risk of bias, 2 were unclear, and metaanalysis was not performed due to trial heterogeneity. RA trials with short-term outcome (< 1 week) found no significant benefit of amitriptyline 25 mg in combination with dextropropoxyphene (DXP) 65 mg over placebo, and inferiority of amitriptyline + DXP versus DXP 130 mg [mean difference (MD) 10.0, 95% CI 0.4 to 19.6]. There was conflicting evidence regarding medium (1–6 wks) or longer-term (> 6 wks) benefits on pain. One trial in depressed patients with RA showed no significant difference between amitriptyline and paroxetine given for 8 weeks (65% vs 56% much or very much improved; RR 1.2, 95% CI 0.9 to 1.5). One trial found that amitriptyline was no better than placebo in reducing pain in patients with active AS over 2 weeks (MD -0.2 , 95% CI -1.2 to 0.8). From 5 trials, withdrawals due to adverse events were not significantly different from placebo. However, there were significantly more minor adverse events in patients receiving TCA compared with those receiving a placebo (RR 2.3, 95% CI 1.2 to 4.4). These included somnolence, dizziness, dry mouth, and nausea.

Conclusion. Based upon 9 trials of high or unclear risk of bias, it is not possible to draw firm conclusions about the efficacy of TCA as analgesics for patients with IA. The use of these agents may be associated with adverse events that are generally mild and do not lead to cessation of treatment. High-quality trials are needed in this area. (J Rheumatol Suppl. 2012 Sept;90: 21–7; doi:10.3899/jrheum.120338)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
ANTIDEPRESSANT

ANKYLOSING SPONDYLITIS
SYSTEMATIC REVIEW

Despite the positive effects of biological therapies on the outlook for patients with inflammatory arthritis (IA), many patients continue to experience musculoskeletal pain¹. Pain

that is untreated and pain despite treatment are well known to negatively affect sleep, overall well-being, mood, and functional status^{2,3}. With possible analgesic, sleep-promoting, and

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mood altering properties, antidepressants have been used to improve the symptoms and quality of life of patients with IA for over 50 years⁴. However, despite growing evidence of a benefit on pain in conditions such as fibromyalgia⁵, neuropathic pain⁶, and low back pain⁷, the evidence in IA remains less clear.

Classified by their structure and mechanism of action, antidepressants include the tricyclic antidepressants (TCA), monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRI), selective serotonin noradrenaline reuptake inhibitors, and norepinephrine reuptake inhibitors. Despite extraordinary advances in the understanding of pain pathways at the molecular level, the precise analgesic mechanisms of action of the antidepressants remain unclear. It is also debated whether any improvements in pain are independent of changes in mood. Evidence supporting this is that analgesia occurs more rapidly than any antidepressant effect, and at significantly lower doses^{8,9}.

Antidepressants are known to cross the blood-brain barrier and exert central mechanisms of action that involve both spinal and supraspinal mechanisms¹⁰. They are also known to target serotonin and noradrenaline, which are key mediators of neural transmission. Other modes of action have been reported including a possible effect on opioid receptors¹¹, blocking adenosine uptake¹⁰, ion channels¹², and as antagonists of N-methyl-D-aspartic acid receptors¹³. Interestingly, there are also data suggesting that distinct peripheral analgesic mechanisms may be relevant in patients with IA^{14,15,16,17}. However, their role as analgesics in patients with IA also remains controversial.

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Pain Management by Pharmacotherapy in Inflammatory Arthritis¹⁸. The objective of this report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations: What is the effectiveness, safety, and role of antidepressants (muscle relaxants and neuromodulators) in inflammatory arthritis, and how should they be administered (i.e., interval, safety, and route)?”

This article is a modified version of a Cochrane Review that is specifically focused on rheumatoid arthritis¹⁹.

METHODS

We conducted a systematic literature review in several steps in accordance with the methods recommended by the Cochrane Collaboration²⁰.

Rephrasing the research question. The clinical question posed by the expert clinicians was rephrased to enable epidemiological enquiry using the PICO (Patient, Intervention, Comparator, Outcome) method²¹. Patients were defined as adults with rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis (AS), or spondyloarthritis. The intervention was defined as treatment with any formulation or dose of an antidepressant as either monotherapy or in combination. Comparators included placebo or any other pharmacological (excluding DMARD) or nonpharmacological analgesic modalities. The primary outcomes of interest were pain and withdrawals due to adverse events (AE), including mortality. The literature search was limited

to randomized controlled trials (RCT), including trials where treatment was allocated via a quasi-random method.

Systematic literature search. A literature search for articles published between January 1950 and May 2010 was performed in Medline, Embase, and the Cochrane Central Register of Controlled Trials. The search strategy was developed in collaboration with an experienced librarian; for details see the online Appendix available from www.3epain.com. In addition, a search was conducted of abstracts from the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) scientific meetings in 2008 and 2009. Review articles were also retrieved for identifying additional references via hand search.

Selection of articles. The titles and abstracts of all studies identified by the search strategy were screened, and all potentially eligible studies were reviewed in full text by 2 authors (BR and SW). Studies were excluded if they contained a mixed population where the data of those with IA could not be extracted separately, or if they were written in languages that could not be translated by one of the members of the 3e Initiative multinational panel. Drugs that had been withdrawn from the market due to safety concerns were excluded from the review. Any disagreement in study selection was resolved by consensus or by discussion with a third reviewer (RB).

Data extraction and quality appraisal. Raw data were extracted from the included studies by 2 authors (SW and BR), using predetermined forms. Differences in data extraction were resolved by referring to the original articles and establishing a consensus. A third reviewer (RB) was consulted to help resolve differences as necessary. Two authors (SW, BR) independently assessed risk of bias for all included studies for the following items: random sequence generation, allocation concealment, blinding of participants, care provider and outcome assessor for each outcome measure, incomplete outcome data, and other biases in accordance with the methods recommended by the Cochrane Collaboration²⁰. To determine the risk of bias of a study, each criterion was rated as Yes (low risk of bias), No (high risk of bias), or Unclear (either lack of information or uncertainty over the potential for bias).

Data analysis. For continuous data, results were analyzed as mean differences (MD) between the intervention and comparator group with 95% confidence intervals. However, when different scales were used to measure the same conceptual outcome (e.g., pain), standardized mean differences (SMD) were calculated. For dichotomous data, a relative risk (RR) with corresponding 95% confidence intervals was calculated. In cases where individuals were missing from the reported results, we assumed the missing values to have a poor outcome. Prior to metaanalysis, we assessed studies for clinical homogeneity and where studies were sufficiently homogeneous that it was clinically meaningful for them to be pooled, a metaanalysis was performed using a random-effects model. Statistical heterogeneity was assessed using the I² statistic²². In addition to the absolute and relative magnitude of effect, for dichotomous outcomes, the number needed to treat (NNT) to benefit or the number needed to treat to harm (NNTH) were calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (for details see: <http://www.nntonline.net/visualrx/>). Analysis was performed using Review Manager 5.

RESULTS

Study characteristics. A total of 487 references were identified with the systematic search strategy. After title and abstract screening, 35 articles were retrieved for full-paper review. Eight trials (n = 652 participants) in patients with RA and one trial in patients with AS (100 participants) fulfilled the inclusion criteria. No further relevant studies were identified from searching the 2008-2009 ACR and EULAR abstracts or article references (Figure 1). For a detailed list of excluded references see the online Appendix available from: www.3epain.com.

Characteristics of included studies are summarized in

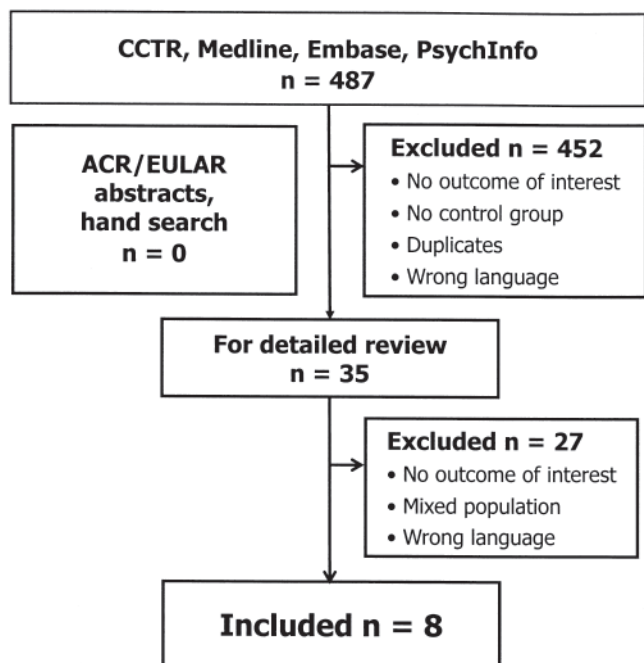


Figure 1. Literature search from which 35 articles were selected for detailed review. Eight articles met inclusion criteria.

Table 1. The majority of studies were published in the late 1980s, with the most recent publications being Ash, *et al*²³ and Bird and Broggin²⁴. Eight studies were performed in outpatients with RA who were taking various doses of non-steroidal antiinflammatory drugs (NSAID) and minimal or no disease-modifying antirheumatic drug (DMARD) therapy. All trials evaluated TCA, 7 trials were placebo controlled^{23,25,26,27,28,29,30}, and 2 studies included an SSRI as a comparator^{24,27}. There were 4 studies with 334 participants evaluating amitriptyline^{24,26,27,29}, 2 studies with 52 participants assessing dothiepin^{23,30}, and 1 small study each evaluating trimipramine (n = 20)²⁸ and imipramine (n = 36)²⁵. No trial was longer than 12 weeks in duration, with the shortest study being a single-dose trial with outcomes measured at 2 and 4 hours²⁹. The single trial with AS patients was an RCT that evaluated amitriptyline versus placebo³¹. All patients were attending a 2 week inpatient physiotherapy course.

Amitriptyline. The 4 studies assessing amitriptyline ranged from 2 hours to 3 months in duration. Three of these studies evaluated amitriptyline versus placebo^{26,27,29} and did not include patients with depression. These trials were heterogeneous, using different doses of amitriptyline, ranging from 25 to 150 mg, and reporting different outcome measures at varying points in time. The Grace 1985 trial²⁷ was a 12 week RCT of amitriptyline versus placebo in patients with active RA not taking corticosteroids or DMARD. The largest trial (n = 210) evaluated amitriptyline against paroxetine (SSRI) in white patients with RA and depression²⁴. In that trial, participants had a mean Ritchie Articular Index of 22 (0–78 scale), no

patient was taking DMARD therapy, and 36% were using corticosteroids.

Two trials were crossover studies that included several comparators. Frank, *et al*²⁶ assessed amitriptyline against desipramine, trazodone, and placebo in 8-week intervals, and Saarialho-Kere, *et al*²⁹ was a single-dose study that evaluated amitriptyline in combination with dextropropoxyphene versus dextropropoxyphene, indomethacin, and placebo. In both trials, baseline visual analog scale (VAS) scores for pain were about 40 to 50 (0 to 100 mm), and more than 50% of both groups of patients were also receiving corticosteroids or DMARD.

Dothiepin. Of the 2 trials evaluating dothiepin, one was a 12-week placebo-controlled trial²³ and one was a 7-week combination trial with ibuprofen (600 mg orally tds) versus placebo and ibuprofen (600 mg orally tds)³⁰. The Ash²³ trial included only patients with RA and depression, whereas the Sarzi Puttini trial³⁰ included patients with RA only. Both trials recruited patients with active disease and VAS score for pain > 50 mm. Patients were predominantly women (87%–100%) and additional medications including DMARD were not described in either study.

Trimipramine. One small 12-week trial evaluated trimipramine versus placebo in patients with RA and depression²⁸. These patients had active disease (mean erythrocyte sedimentation rate 61 mm/h) and were not receiving corticosteroids or other DMARD therapy.

Imipramine. One 10-week trial evaluated imipramine against placebo²⁵. This study was designed to assess the effect of imipramine on the titer of rheumatoid factor. Pain was a secondary outcome. No patient was taking corticosteroids or other DMARD and mean baseline pain scores were 2.7–2.8 (0–3 point scale).

Risk of bias assessment. Seven of the 9 trials had high risk of bias, and 2 did not provide enough information and were deemed “unclear.” The predominant methodological flaws of the included trials included failure to describe randomization, allocation concealment, and blinding of study personnel (Figure 2). There were also high dropout rates in many studies, and it was often unclear whether an intention-to-treat analysis was performed or how missing data were dealt with. The clinical trials often used poorly described methods to measure important clinical outcomes, including pain, with studies using the same scale often reporting results differently (e.g., mean scores after treatment, mean improvement from baseline, or number of patients “improved”). The included studies also did not record the concomitant use of other analgesic agents.

Primary outcomes. Efficacy. No study reported the primary outcome measure of patient-reported pain relief ≥ 30%.

Pain intensity (< 1 week). Two small heterogeneous trials evaluated short-term outcomes and hence metaanalysis was not performed^{29,30}. One small (n = 15) crossover study evalu-

Table 1. Characteristics of included studies.

Study	Population	Intervention	Comparator(s)	Outcome(s)	Study Design
Ash 1999 ²³	48 women outpatients with RA and concurrent anxiety and/or depression; mean age 18-70 yrs, ESR 26-29 mm/h, pain VAS 57-60 mm, EMS mean 139-157 min	Dothiepin 75-150 mg	Placebo	Primary: 1. Mood, 2. Pain status, 2. Disease activity	RCT, double blind, 12 wks
Bird 2000 ²⁴	191 outpatients with RA (48 M, 140 F) and depression mean age 55 yrs (18-75); Steinbrocker functional status 1-3, majority mild-moderate depression. 34% taking corticosteroids.	Amitriptyline 75-150 mg + placebo	Paroxetine 20-40 mg + placebo	Primary: 1. Change in MADRS Secondary: 1. Disease activity, 2. Global pain, 3. HAQ, 4. Adverse events	Double dummy RCT, double blind, 8 wks
Fowler 1977 ²⁵	20 patients with RA (16 F, 4 M), mean age 52-55 yrs, ≥ 1 yr disease duration, RF titer > 1:64, all on NSAID, no prior corticosteroid or DMARD	Imipramine 20-75 mg	Placebo	Primary: 1. RF titer Secondary: 1. Pain score, 2. Disease activity, 3. Beck Depression Inventory scale	RCT, double blind, 6 wks
Frank 1988 ²⁶	47 consecutive outpatients (24 M, 23 F) with RA, mean age 58.1 yrs, mean ESR 25.3-26.1 mm/h, mean pain VAS 4.3 (0-10 cm), 25% taking prednisone, 73% DMARD	Amitriptyline 1-1.5 mg/kg	Desipramine 1-1.5 mg/kg/day vs trazodone 1.5-3 mg/kg/day vs placebo	Primary: 1. Pain, 2. Disease activity, 3. Mood	Crossover trial, double blind, 6 wks
Grace 1985 ²⁷	36 outpatients (7 M, 29 F) with RA, age 27-76 yrs, mean ESR 60 mm/h. All patients on "adequate dose of NSAID". No patient was taking corticosteroid or another DMARD.	Amitriptyline 25-75 mg	Placebo	Primary: 1. Daytime somnolence, 2. Insomnia Secondary: 1. Pain, 2. Sleep	RCT, double blind, 12 wks
Macfarlane 1986 ²⁸	36 patients (9 M, 27 F) with RF+ RA and depression; age range 28-76 yrs, ESR 61 mm/h. No patient was taking corticosteroid or another DMARD.	Trimipramine 25 mg-75 mg	Placebo	Primary: 1. Pain, 2. Disease activity Secondary: 1. Depression, 2. Adverse events	RCT, double blind, 12 wks
Saarialho-Kere 1988 ²⁹	16 patients with RA (14 F and 2 M), age range 21-67 yrs, mean disease duration 6.2 yrs, EMS 1.5h, RIA 19, mean pain 46 to 52 (0-100 mm). Gold (60%), penicillamine (20%), chloroquine (13%) or low dose prednisone (7%).	D-Propoxyphene 130 mg +/- amitriptyline 25 mg	Indomethacin 50 mg vs placebo	Primary 1. Psychomotor tests Secondary: 1. Pain VAS, 3. Disease activity, 4. Adverse events	Randomized crossover trial, double blind, single dose
Sarzi 1988 ³⁰	60 patients with active RA (8 M, 52 F) and depression mean age 49 yrs, disease duration 9 yrs; exclusion: HRS score 7-19 (range 0-52)	Dothiepin 75 mg + ibuprofen 1800 mg/day	Placebo + ibuprofen 1800 mg/day	Primary: 1. Pain, 2. Depression, 3. Disease activity	RCT, double blind, 7 wks
Koh 1997 ³¹	100 inpatients with AS (88 completers), Age 20-68 yrs, mean VAS 4.8 cm	10-30 mg amitriptyline	Placebo	Primary: 1. Pain 2. Fatigue, EMS 3. BASDAI, BASFI	RCT, double blind, 2 wks

RF, Rheumatoid Factor; ESR, erythrocyte sedimentation rate; RIA, Ritchie's articular index; NSAID, non steroidal antiinflammatory drug; DMARD, disease modifying anti rheumatic drug; VAS, visual analog scale; RCT, randomized controlled trial; MADRS, Montgomery Asberg Depression Rating Scale

	Ash 1999	Bird 2000	Fowler 1977	Frank 1988	Grace 1985	Koh 1997	MacFarlane 1986	Saarialho-Kere 1988	Sarzi 1988
Adequate sequence generation?	x	?	x	?	?	?	?	?	?
Allocation concealment?	?	?	?	?	?	✓	?	?	?
Blinding?	?	?	?	?	?	?	?	?	?
Incomplete outcome data addressed?	x	✓	✓	?	x	✓	x	✓	✓
Free of selective reporting?	✓	✓	✓	✓	✓	✓	✓	x	x
Compliance?	?	?	?	✓	?	✓	?	?	?
Cointerventions?	?	?	?	✓	?	?	?	✓	?
Were Baseline Characteristics similar?	x	✓	x	✓	✓	✓	✓	✓	✓
Intention to treat analysis performed?	✓	✓	?	?	?	x	?	?	x
Was there a high dropout rate?	x	✓	✓	x	✓	✓	x	✓	x
Summary Assessment of Bias	x	?	x	x	x	?	x	x	x
x: high risk of bias, ✓: low risk of bias, ?: unclear risk of bias									

Figure 2. Risk of bias summary: review of authors' judgments about each risk of bias item for each included study.

ated amitriptyline in combination with 65 mg dextropropoxyphene and reported inferior pain control at 4 h compared to 130 mg dextropropoxyphene alone using a 100-mm VAS (MD 10.00, 95% CI 0.43 to 19.57) and no significant benefit over placebo (insufficient data provided for analysis)²⁹. A second study compared dothiepin and ibuprofen versus ibuprofen alone and also reported no evidence of benefit³⁰.

Pain intensity (1–6 weeks). Seven trials evaluated pain outcomes between 1 and 6 weeks' duration^{23,24,25,26,27,28,30}. There was considerable variability in the doses and types of antidepressants used in these trials, and outcomes were reported at different timepoints. Metaanalysis was not performed due to heterogeneity and high risk of bias in all of the studies.

Two studies reported no benefit of dothiepin at Week 2²³ and Week 3³⁰, respectively. Four studies with high or unclear risk of bias evaluated pain outcomes at 4 weeks^{23,24,27,28}, with 2 studies reporting a benefit over placebo^{23,28} and 2 studies reporting no benefit over placebo²⁷ or paroxetine²⁴. Two of these studies evaluated amitriptyline and reported no significant benefit over placebo²⁸ or the active comparator paroxetine²⁴.

Macfarlane, *et al*²⁸ evaluated trimipramine versus placebo in patients with RA and depression, and reported a modest but significant reduction in pain [MD (0–4 pain scale) –0.40, 95% CI –0.78 to –0.02; NNT 3.7, 95% CI 1.9 to 237.4), while Ash, *et al*²³ also reported a significant reduction in pain in depressed patients taking dothiepin versus placebo [MD (VAS 0–100 mm) –25.10, 95% CI –39.97 to –10.23; NNT 2.4, 95% CI 1.6 to 6.8].

Three studies with high risk of bias evaluated pain outcomes at 6 weeks^{23,25,26}. All evaluated different TCA. Ash, *et al*²³ reported a significant reduction in pain in patients taking

dothiepin compared to placebo on average of 30.9 points on 100-point scale (95% CI –56.59 to –5.21; NNT 3.1, 95% CI 1.8 to 26.4), Fowler, *et al*²⁵ did not provide enough data to enable extraction and reported no significant difference in patients taking imipramine. Frank, *et al*²⁶ reported no significant difference on a 10-cm VAS, but a significant difference on present pain intensity and worst pain in patients taking amitriptyline over placebo (insufficient data for extraction). This finding may have been due to chance and not to true differences. In this trial, trazodone and desipramine failed to show a benefit over placebo.

Pain intensity (> 6 weeks). Five studies evaluated pain outcomes of more than 6 weeks' duration^{23,24,27,28,30}. Only 3 of these studies provided data that could be extracted^{23,24,28}. With significant heterogeneity and high or unclear risk of bias, a metaanalysis was not performed.

Two studies^{23,28} suggested a benefit over placebo, and 2 studies reported no benefit over placebo^{27,30}. Specifically, Ash, *et al*²³ reported a benefit of dothiepin over placebo in depressed patients with RA at up to 12 weeks using a 100-mm VAS (MD –21.90, 95% CI –37.76 to –6.04; NNT 2.2, 95% CI 1.5 to 9.9), while Macfarlane, *et al*²⁸ reported a significant reduction in pain in patients with RA and depression receiving trimipramine at 8 weeks (MD –0.60, 95% CI –0.89 to –0.31) and 12 weeks (MD –0.80, 95% CI –1.21 to –0.39) using a 0–4 numeric rating scale. Bird and Brogini²⁴ reported that the paroxetine group contained a higher proportion of patients in the “very much improved” and “much improved” categories compared with the amitriptyline group (65% vs 56%, respectively) after 8 weeks; however, this was not statistically significant (RR 1.17, 95% CI 0.93 to 1.48).

Safety. Number of withdrawals due to adverse events. Withdrawals due to adverse events were analyzed across all included studies, with 6 trials reporting data^{24,25,26,27,28,30}. One study reported no withdrawals due to adverse events and so did not contribute to the metaanalysis²⁵. Overall there were 25 withdrawals in 230 patients receiving a TCA and 25 withdrawals in 225 patients receiving a comparator. Event rates in the trials ranged from 3.4% to 27.8%. When pooled there was no significant difference between those receiving a TCA agent versus a comparator (RR 0.98, 95% CI 0.59 to 1.64). When comparing only placebo-controlled trials²⁴ (study removed) the results were unchanged (RR 1.09, 95% CI 0.49 to 2.42).

Total number of adverse events. Despite not leading to withdrawal there were significantly more adverse events in patients receiving TCA compared with those receiving placebo (RR 2.27, 95% CI 1.17 to 4.42). Overall, 50% of patients receiving a TCA reported side effects compared with 32% of patients in the placebo groups (NNT 5, 95% CI 3 to 22). There was no significant difference when comparing amitriptyline versus paroxetine (RR 1.20, 95% CI 0.96 to 1.50). Adverse event rates in the trials varied from 0% to 56%. The low event rate for individual drugs and doses prohibited any further subgroup analysis.

The most common side effects reported in patients receiving TCA were central nervous system 22% (somnolence, fatigue, headache, dizziness), anticholinergic symptoms 15% (dry mouth, constipation, palpitations), and gastrointestinal 12% (nausea, abdominal pain). Other reported adverse events included hypotension and tremor. There were no cases of serotonin syndrome and no other serious adverse events reported.

Paroxetine was better tolerated than amitriptyline in one trial, with an overall frequency of adverse experiences of 56% and 68% in the 2 groups, respectively²⁴. There was a lower frequency of anticholinergic adverse experiences (18% vs 44% taking amitriptyline), and somnolence was much lower in the paroxetine treatment group (25.0% vs 9.6% with paroxetine).

DISCUSSION

This is the first systematic review to assess the efficacy and safety of antidepressants for treating pain in patients solely with IA. The results of this review served as an evidence base for one of the 10 recommendations regarding pain management by pharmacotherapy, which were generated by a multinational panel of rheumatologists as part of the 3e Initiative. A detailed description of all final recommendations can be found elsewhere¹⁸.

Based upon 9 trials of high or unclear risk of bias, it is not possible to draw firm conclusions about the efficacy of TCA as analgesics for patients with IA. In the RA trials with short-term outcomes (< 1 week) there was no significant benefit of amitriptyline 25 mg in combination with dextropropoxyphene (DXP) 65 mg over placebo and inferiority of

amitriptyline + DXP versus DXP 130 mg. There was conflicting evidence regarding medium (1–6 weeks) and longer-term (> 6 weeks) benefits on pain. One trial in patients with RA with depression showed no significant difference between amitriptyline and paroxetine over 8 weeks. In AS there was no benefit of amitriptyline over placebo in reducing pain over 2 weeks.

The use of these agents may be associated with adverse events, which are generally mild and do not lead to cessation of treatment. From 5 trials, withdrawals due to adverse events were poorly reported and not significantly different from placebo. However, there were significantly more minor adverse events (somnolence, dizziness, dry mouth, nausea) in patients receiving TCA compared with placebo (RR 2.3, 95% CI 1.2 to 4.4), occurring in 1 in every 5 patients treated on average.

There are several limitations in the interpretation of the results of our review. There were relatively small numbers of placebo or head-to-head trials, short duration of followup, generally poor quality of adverse event assessment, and heterogeneity in study design and interventions. The study populations in the included trials of this review are not reflective of current-day patients with RA. In general they had poorly controlled disease and were receiving only NSAID, with occasional low-dose corticosteroid or DMARD only. The interpretation of a patient's pain response may also be confounded by associated changes in mood. The percentage of patients with and without depression, and the severity of their depression, varied among the trials. Both trials that showed a benefit of antidepressants for pain included patients with depression, raising the possibility that pain improvement occurred as a result of improvements in mood.

All these factors make comparisons across trials difficult and the conflicting results of the studies are likely to have resulted from these inconsistencies both within and between studies. It is also likely that the methodological failures in the majority of the included trials have contributed to their success or failure in demonstrating the benefits of efficacious treatments. There were no studies that evaluated drugs from antidepressant classes other than the TCA and SSRI, and no trials included newer antidepressant agents (e.g., venlafaxine, paroxetine, sertraline). No conclusions could be drawn regarding optimal dosages of individual agents.

In conclusion, based upon 9 trials of high or unclear risk of bias, it is not possible to draw firm conclusions about the efficacy of TCA as analgesics for patients with IA. The use of these agents may be associated with adverse events, which are generally mild and do not lead to cessation of treatment. Further high-quality trials are required in this area.

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