Antidepressant Drugs for Prevention of Acute and Chronic Postsurgical Pain

Early Evidence and Recommended Future Directions

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ABSTRACT

Background: This review evaluates trials of antidepressants for acute and chronic postsurgical pain.

Methods: Trials were systematically identified using predefined inclusion and exclusion criteria. Extracted data included the following: pain at rest and with movement, adverse effects, and other outcomes.

Results: Fifteen studies (985 participants) of early postoperative pain evaluated amitriptyline (three trials), bicifadine (two trials), desipramine (three trials), duloxetine (one trial), fluoxetine (one trial), fluradoline (one trial), tryptophan (four trials), and venlafaxine (one trial). Three studies (565 participants) of chronic postoperative pain prevention evaluated duloxetine (one trial), escitalopram (one trial), and venlafaxine (one trial). Heterogeneity because of differences in drug, dosing regimen, outcomes, and/or surgical procedure precluded any meta-analyses. Superiority to placebo was reported in 8 of 15 trials for early pain reduction and 1 of 3 trials for chronic pain reduction. The majority of positive trials did not report sufficient data to estimate treatment effect sizes. Many studies had inadequate size, safety evaluation/reporting, procedure specificity, and movement-evoked pain assessment.

Conclusions: There is currently insufficient evidence to support the clinical use of antidepressants—beyond controlled investigations—for treatment of acute, or prevention of chronic, postoperative pain. Multiple positive trials suggest the therapeutic potential of antidepressants, which need to be replicated. Other nontrial evidence suggests potential safety concerns of perioperative antidepressant use. Future studies are needed to better define the risk–benefit ratio of antidepressants in postoperative pain management. Higher-quality trials should optimize dosing, timing and duration of antidepressant treatment, trial size, patient selection, safety evaluation and reporting, procedure specificity, and assessment of movement-evoked pain relevant to postoperative functional recovery. (ANESTHESIOLOGY 2014; 121:591-608)

WITH well more than 40 million surgeries annually in North America alone, postoperative pain causes considerable morbidity and substantially impacts healthcare utilization.[1] Postoperative pain is mediated at multiple neural sites and *via* multiple mechanisms.[2] Thus, different analgesics can only partially reduce postoperative pain. A multimodal analgesic approach is commonly used[3,4]; however, currently using agents such as opioids,[5] local anesthetics,[6] nonsteroidal antiinflammatory drugs,[7] acetaminophen,[8,9] ketamine,[10] and gabapentin/pregabalin[11–13] have various limitations. Many other agents have been evaluated for efficacy, but evidence has not warranted their routine use. Thus, a continued search for safer, more effective agents for postoperative pain is needed.

What We Already Know about This Topic

- Antidepressants show efficacy in the treatment of chronic pain, but their safety and efficacy for analgesia in the perioperative period have not been critically reviewed

What This Article Tells Us That Is New

- In a systematic review of 15 studies including approximately 1,000 patients, heterogeneity in drug, dose, timing, and outcome measure as well as general low quality precludes definitive conclusions although a majority of studies reported positive outcomes
- There is insufficient evidence to support the routine use of antidepressants for analgesia in the perioperative period

Antidepressants are commonly used for various chronic pain conditions[14,15] and are classified according to chemical

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structure and/or mechanism of action. The most common classes of antidepressants included the following: (1) tricyclic antidepressants, (2) selective serotonin reuptake inhibitors, and (3) serotonin and norepinephrine reuptake inhibitors.[16] Tryptophan, with previously demonstrated antidepressant efficacy,[17] has also been evaluated for postoperative analgesia. Fluradoline has been classified as an antidepressant based on its tricyclic chemical structure and has also been studied in postoperative pain.[18] In addition to serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants antagonize peripheral sodium channels and spinal N-methyl-D-aspartate receptors.[15] These mechanisms serve to suppress central sensitization which is important in the pathophysiology of acute postoperative pain.[19–21]

Recent studies on antidepressants for postoperative pain have generated, possibly premature, enthusiasm for this potentially new indication. There is a great need for improved treatment options in the management of postoperative pain,[22] and antidepressants could potentially be a valuable addition here. However, safety problems including increased perioperative bleeding,[23–25] serotonin syndrome,[26] and other known adverse drug interactions necessitate a rigorous assessment. Thus, this review evaluates efficacy and safety of antidepressants from trials in acute postoperative pain. Prevention of chronic pain after surgery is an emerging goal with fundamental distinctions from acute postoperative pain.[27–29] However, given that studies evaluating the treatment of acute, and prevention of chronic, postoperative pain are conducted in similar perioperative settings, we will also review trials in postoperative chronic pain prevention.

Materials and Methods

This systematic review was conducted according to guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions.

Participants, Study Design, and Interventions

Given the absence of any previously published reviews of antidepressants for postoperative pain, we conducted a very broad literature search for studies with the following inclusion criteria:

Placebo-controlled, double-blind, randomized trials (≥10 patients per treatment arm)
Systemic perioperative administration of an antidepressant agent
Adults (>18 yr)
Study patients experiencing pain after any surgical procedure
Methods included a measure of pain

Outcomes of Interest for This Review

Primary Outcomes. Validated measures of pain intensity—at rest or with movement—or pain relief assessed during the postoperative period. Trials assessing early (<2 weeks postoperatively) and persistent (≥3 months postoperatively) pain

were included, but analysis of early and persistent pain outcomes was to be conducted separately, wherever appropriate. **Secondary Outcomes.** Treatment-emergent adverse effects, opioid-related side effects, and other outcomes including mood, sleep, and physical function assessed during the postoperative period.

Trial Assessment for the Measurement of Pain at Rest *versus* Movement-evoked Pain. Given the importance of reducing movement-evoked pain for postoperative functional recovery, each trial was evaluated for assessment of pain at rest *versus* movement-evoked pain.[30]

Search Methods for Identification of Studies

Electronic Searches. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and Web of Science (cited reference search from identified studies) were searched from the time of inception of each database until December 4, 2013. The specific search strategy used can be found in appendix 1.

Searching Other Resources. The reference lists of studies that met inclusion criteria, as well as other relevant articles, were searched to identify further trials.

Data Collection and Analysis

All the review authors made substantive contributions to the development, analysis, and interpretation of this review as well as drafting and approval of the final submission. Two authors (K.W. and I.G.) independently conducted the literature search, identified trials for inclusion, reviewed study quality and risk of bias, and performed data extraction. Between these two authors, no disagreements arose regarding inclusion or exclusion of trials from the review. However, there were some disagreements in ratings of trial quality and risk of bias (most frequently related to study descriptions of randomization and blinding methods) and all of which were resolved by discussion and thus obviating the need for a third adjudicator. All other authors reviewed the results of these judgments and commented as necessary, but no further disagreements arose from this.

Data Extraction and Management. The following data were extracted from each study, if available: (1) patient characteristics; (2) study drug, including dose, route, and timing of administration; (3) patient-reported pain intensity at baseline (physician-, nurse-, or care-giver–reported pain was not included in the analysis); (4) patient-reported pain relief expressed at least hourly over 4 to 6 h by using validated pain scales (pain intensity and pain relief in the form of visual analogue scale or categorical scales, or both); (5) patient global assessment of efficacy, using a standard categorical scale; (6) time to use and number of participants requiring rescue medication; (7) number of participants with one or more adverse events; (8) number of participants with a serious adverse event; and (9) number of withdrawals (all cause and adverse event related).

Assessment of Risk of Bias and Clinical Trial Quality. Risk of bias assessment was conducted on each study according

to the Cochrane Risk of Bias Tool.[31] Quality of each trial was assessed using the Oxford Quality Scoring System.[32] The scoring system was used as follows: One point each was scored if the study was randomized and double blind. One point each was scored if procedures for randomization and blinding were reported and appropriate. One point each was *deducted* if procedures for randomization and blinding were not appropriate. One point was scored if reasons for patient withdrawals and dropouts were described. Given that only randomized and double-blind studies were included, the lowest possible score is 2 and the highest is 5 for any included study.

Measures of Treatment Effect. The primary comparison of interest for this review was between study drug and placebo. Studies would be combined for meta-analysis if they evaluated the same study drug at roughly similar doses and durations of treatment (*e.g.*, a study evaluating a single preoperative drug dose would not be compared with another study evaluating several weeks of treatment with the same drug) and used common outcome measures and time points. RevMan 5.1 (RevMan 2011)[33] was to be used to analyze study data for binary outcomes. Sensitivity analyses would be used to evaluate the robustness of a particular result by repeating primary analyses without any studies considered to be outliers with respect to study quality, drug dose and duration, or pain measurement scales.

Subgroup Analyses and Assessment of Clinical Heterogeneity. Two authors (K.W. and I.G.) independently evaluated differences in participants, interventions, outcomes, study settings, and methodology. Where substantial subjective differences were judged to be present by both reviewers, clinical or methodological heterogeneity was considered to exist. If multiple studies were considered to be adequately homogenous with respect to these features, they would be further evaluated for the presence or absence of statistical heterogeneity.

Subgroup analyses would be performed to compare trial outcomes across different:

1. Surgical procedures
2. Timing of the intervention
3. Duration of intervention

Conditions for Meta-analysis. Meta-analysis was to be conducted if the following conditions were met: identification of at least two relevant studies with a low risk of bias and absence of substantial heterogeneity.

Results

Figure 1 describes the flow of this systematic review, which included 16 trials in total (appendix 2).[34–49] Table 1 (acute pain) and table 2 (chronic pain) describe the main features of included trials. Table 3 (acute pain) and table 4 (chronic pain) describe the main results of pain outcomes from included trials.

Trial Quality, Risk of Bias, and Other Features of Included Studies

Table 5 describes the risk of bias of included studies and table 6 describes trial quality, assessment of rest *versus* dynamic pain, and assessment/reporting of adverse effects/events for the included studies.

Thirteen of the 16 included trials were of good to high quality, but 3 trials were missing important details regarding randomization and blinding methods. Although all studies assessed postoperative pain, only 3 of 16 studies acknowledged the distinction between pain at rest and during movement and these three trials assessed for pain during movement. Only 5 of 16 trials mentioned adverse effect assessment in their Methods section although 9 of 16 trials did provide some adverse effects reporting in their Results section.

Excluded Studies

Trials excluded from this review (17) and their reason(s) for exclusion are shown in appendix 3.

Description of Studies and Treatment Effects—Early Postoperative Pain

Inclusion criteria were met (appendix 2) by 15 heterogeneous studies (985 participants) of early postoperative pain involving different antidepressants including amitriptyline (3 trials),[39,42,48] bicifadine (2 trials),[46,49] desipramine (3 trials),[39,43,44] duloxetine (1 trial),[41] fluoxetine (1 trial),[40]
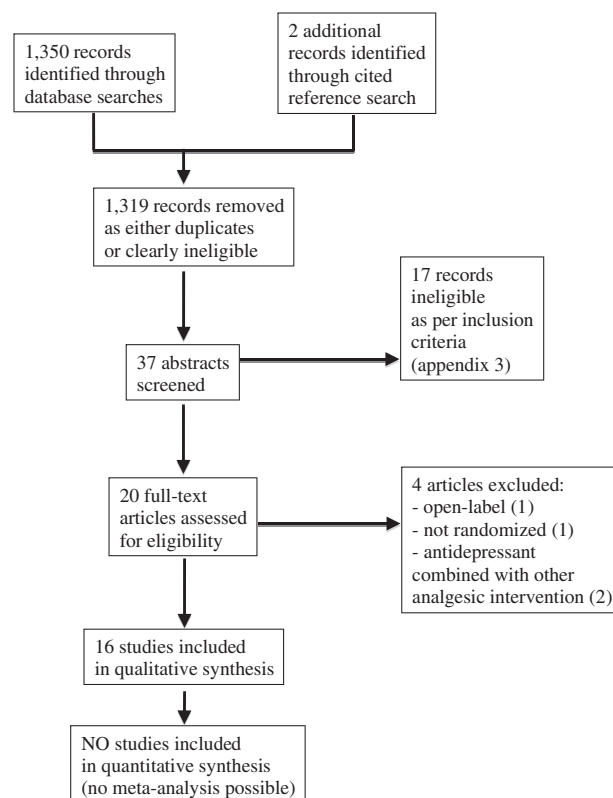

Fig. 1. Study flow diagram.

Table 1. Main Characteristics of Included Trials of Antidepressant for Early Postoperative Pain

Antidepressant	First Author, yr	Procedure	Trial Size	Dosing Regimen
Amitriptyline*	Levine, 1986*[43]	Third molar extraction	Placebo, 10; amitriptyline, 10; desipramine, 10	Multidose, PO amitriptyline 25 mg qHS days −7 to −5 preoperatively; 50 mg qHS days −4 to −3 preoperatively; 75 mg qHS days −2 to −1 preoperatively
Amitriptyline	Kerrick, 1993[42]	Hip or knee arthroplasty	Placebo, 14; amitriptyline, 14	Multidose, PO amitriptyline 50 mg qHS for 3 nights starting on the first night after surgery
Amitriptyline	Vahedi, 2010[48]	Lumbar laminectomy and discectomy	Placebo, 40; amitriptyline, 37	Single-dose, amitriptyline 25 mg PO 2 h before surgery
Bicifadine	Porter, 1981[46]	Elective lower limb surgery	Placebo, 21; codeine, 20; bicifadine 100 mg, 19; bicifadine 150 mg, 20	Single-dose, given upon arrival in PACU
Bicifadine	Wang, 1982[49]	Abdominal and orthopedic	Placebo, 25; aspirin, 25; bicifadine 75 mg, 25; bicifadine 150 mg, 25	Single-dose, given after surgery
Desipramine*	Levine, 1986*[43]	Third molar extraction	Placebo, 10; amitriptyline, 10; desipramine, 10	Multidose, PO desipramine 25 mg qHS days −7 to −5 preoperatively; 50 mg qHS days −4 to −3 preoperatively; 75 mg qHS days −2 to −1 preoperatively
Desipramine	Max, 1992[44]	Elective inpatient surgical procedures	Placebo, 31; desipramine, 31	Single-dose, PO desipramine 50 mg on the morning of postoperative day 1
Desipramine	Gordon, 1993[39]	Third molar extraction	Placebo, 15; desipramine, 45 (three different dosing regiments)	Multidose: (1) desipramine 50 mg qHS for 7 days before surgery; (2) desipramine 50 mg qHS for days −7 to −5 before surgery; (3) desipramine 50 mg qHS for days −3 to −1 before surgery
Duloxetine	Ho, 2010[41]	Knee replacement surgery	Placebo, 24; duloxetine, 23	Multidose, duloxetine 60 mg PO 2 h before surgery and on the morning of postoperative day 1
Fluoxetine	Gordon, 1994[40]	Third molar extraction	Placebo, 30; fluoxetine, 40	Multidose, fluoxetine 10 mg PO qHS for 7 days preoperatively
Fluradoline	McQuay, 1987[45]	Elective orthopedic surgery	Placebo, 30; aspirin, 30; fluradoline 150 mg, 30; fluradoline 300 mg, 30	Single-dose, given after surgery
Tryptophan	Shpeen, 1984[47]	Endodontic therapy	Placebo, 25; PO tryptophan, 25	Multidose, 0.5 g q6h starting before endodontic treatment for 24 h
Tryptophan	Franklin, 1990[38]	Hysterectomy or cholecystectomy	Placebo, 11; IV tryptophan, 15	Multidose, loading dose 10 mg/kg at start of surgery, then 10 mg kg^{-1} h^{-1} for 3 h
Tryptophan	Ceccherelli, 1991[35]	Cholecystectomy	Placebo, 15; IV tryptophan 7.5 mg/kg, 15; tryptophan 15 mg/kg, 15	Single-dose, given after surgery
Tryptophan	Ekblom, 1991[37]	Third molar extraction	Placebo, 20; PO tryptophan, 20	Multidose, 0.5 g q6h starting 3 days preoperatively through to 3 days postoperatively
Venlafaxine	Amr, 2010[34]	Breast cancer surgery	Placebo, 50; gabapentin, 50; venlafaxine, 50	Multidose, venlafaxine 37.5 mg PO (or gabapentin) qHS starting the night before surgery × 10 days

* Levine 1986[43] RCT included evaluation of both amitriptyline and desipramine.

IV = intravenous; PACU = postanesthetic care unit; PO = per os (by mouth); qHS = *quaque hora somni* (every bedtime); q6h = every 6 h; RCT = randomized controlled trial.

fluradoline (1 trial),[45] tryptophan (4 trials),[35,37,38,47] and venlafaxine (1 trial).[34] Tables 1 and 3 describe the 15 early postoperative pain studies included in the review. Taken together, the studies involving the four drugs that were evaluated with more than one randomized controlled trial (RCT)—amitriptyline, bicifadine, desipramine, and tryptophan—failed to meet our criteria for performing meta-analysis. Although superiority to placebo for pain outcomes was reported in 8 of the 15 included trials,[34,35,39,43,45,47–49] only 2 studies reported sufficient data to allow for estimation of standardized effect sizes which were 0.56 for amitriptyline[48] and 0.78 for fluradoline.[45]

No trends in trial outcome were observed across this heterogeneous group of trials to suggest an effect of dose,

Table 2. Main Characteristics of Included Trials of Antidepressant for Chronic Postoperative Pain

Antidepressant Agent	First Author, yr	Surgical Procedure	Trial Size	Dosing Regimen
Duloxetine	Ho, 2010[41]	Knee replacement surgery	Placebo, 24; duloxetine, 23	Duloxetine 60 mg PO 2 h before surgery and on the morning of postoperative day 1
Escitalopram	Chocron, 2013[36]	Coronary artery bypass grafting	Placebo, 183; escitalopram, 185	Escitalopram 10 mg PO daily from 2 to 3 weeks preoperatively to 6 months postoperatively
Venlafaxine	Amr, 2010[34]	Breast cancer surgery	Placebo, 50; gabapentin, 50; venlafaxine, 50	Venlafaxine 37.5 mg PO (or gabapentin) qHS starting the night before surgery × 10 days

PO = per os (by mouth); qHS = *quaque hora somni* (every bedtime).

Table 3. Main Results of Pain Outcomes from Included Trials of Antidepressant for Early Postoperative Pain

Antidepressant	First Author, yr	Pain Measure	Time/Duration of Follow-up	Treatment *vs.* Placebo SES‡	Treatment *vs.* Active Comparator Difference
Amitriptyline*	Levine, 1986[43]*†	10 cm VAS	Eight intervals from 10 to 150 min after postoperative morphine administration	No significant differences noted throughout the duration of follow-up	Desipramine superior in efficacy to amitriptyline
Amitriptyline	Kerrick, 1993[42]†	10 cm VAS	8 AM/3 PM on postoperative days 1, 2, and 3	Pain significantly *higher* with amitriptyline from 3 PM on day 1 to 8 AM on day 3	N/A
Amitriptyline	Vahedi, 2010[48]	10 cm VAS	6, 12, 18, and 24 h postoperatively	Pain significantly *lower* with amitriptyline at 24 h only; SES = 0.56	N/A
Bicifadine	Porter, 1981[46]†	Pain intensity (0–3); pain relief (0–4)	0.5, 1, 2, 3, and 4 h after study medication	No significant differences noted throughout the duration of follow-up	Codeine, but not bicifadine, was superior to placebo and NSD between codeine and bicifadine
Bicifadine	Wang, 1982[49]†	Pain intensity (0–3); pain relief (0–4)	0.5, 1, 2, 3, 4, 5, and 6 h after study medication	Pain intensity difference for bicifadine 150 mg and aspirin superior to placebo during the follow up period; *Insufficient data provided to estimate effect size*	Aspirin superior to 75 mg, but not 150 mg of bicifadine
Desipramine*	Levine, 1986[43]*	10 cm VAS	Eight intervals from 10 to 150 min after postoperative morphine administration	Desipramine superior to placebo from 30 to 150 min after surgery; *Insufficient data provided to estimate effect size*	Desipramine superior in efficacy to amitriptyline
Desipramine	Max, 1992[44]	Pain intensity (0–3); pain relief (100 mg VAS)	30, 60, 90, 120, 180, and 240 min after morphine administration	No significant differences noted throughout the duration of follow-up	N/A
Desipramine	Gordon, 1993[39]	Pain intensity (10 cm VAS)	Every 20 min after completion of surgery up to 6 h postoperatively	Desipramine superior to placebo from 60 to 120 min postoperatively when given from days −7 to −1 or days −7 to −5 before surgery, but not from days −3 to −1 before surgery; *Insufficient data provided to estimate effect size*	N/A

(Continued)

Table 3. (continued)

Antidepressant	First Author, yr	Pain Measure	Time/Duration of Follow-up	Treatment vs. Placebo SES‡	Treatment vs. Active Comparator Difference
Duloxetine	Ho, 2010[41]	Pain intensity (0–10 NRS)	0.5, 1, 2, 6, 12, 24, and 48 h after surgery	No significant differences noted throughout the duration of follow-up	N/A
Fluoxetine	Gordon, 1994[40]	Pain intensity (10 cm VAS)	Every 20 min after completion of surgery up to 6 h postoperatively	No significant differences noted throughout the duration of follow-up	N/A
Fluradoline	McQuay, 1987[45]	Pain intensity (0–3); pain relief (0–4)	0.5, 1, 1.5, 2, 3, 4, 5, and 6 h postoperatively	Fluradoline 300 mg superior to placebo for SPID and TOTPAR; SES = 0.78	Aspirin and fluradoline 300 mg, but not 150 mg, superior to placebo; NSD between aspirin and fluradoline 300 mg
Tryptophan	Shpeen, 1984[47]	Pain intensity (0–10 NRS)	1 and 7 days postoperatively	Tryptophan superior to placebo at 24 h; *Insufficient data provided to estimate effect size*	N/A
Tryptophan	Franklin, 1990[38]	Pain intensity (0–5 NRS)	Every 30 min from 30 to 180 min postoperatively	No significant differences noted throughout the duration of follow-up	N/A
Tryptophan	Ceccherelli, 1991[35]	Pain intensity (100 mm VAS)	30, 60, 120, 180, 240, 300, and 360 min after study drug infusion	Tryptophan at both doses superior to placebo for pain intensity reduction from 0 to 360 min after surgery; *Insufficient data provided to estimate effect size*	N/A
Tryptophan	Ekblom, 1991[37]	Pain intensity (10 cm VAS)	Every 12 h from 12 to 72 h postoperatively	No significant differences noted throughout the duration of follow-up	N/A
Venlafaxine	Amr, 2010[34]	Pain intensity (100 mm VAS) with movement	4, 12, and 24 h postoperatively; then every day from days 2 to 10 postoperatively; then 6 months	Venlafaxine superior to placebo for dynamic pain on postoperative days 8–10; *Insufficient data provided to estimate effect size*	Gabapentin superior to placebo on days 2–10 postoperatively; venlafaxine superior to placebo only on days 8–10; NSD between venlafaxine and gabapentin

* Levine 1986[43] RCT included evaluation of both amitriptyline and desipramine. † No primary outcome declared for these trials; ‡ Effect size estimated as ($Pain_{Tx} – Pain_{Placebo}$)/$Std\ Dev_P$ (Cohen J. A power primer. Psychol Bull 1992; 112: 155–9.[60]).
N/A = not applicable; NRS = numerical rating scale; NSD = no significant difference; RCT = randomized controlled trial; SES = standardized effect size; SPID = summed pain intensity difference; TOTPAR = total pain relief; VAS = visual analogue scale.

duration, or timing of treatment. Most studies failed to identify a primary outcome measure and reported treatment group differences not necessarily based on trial primary outcomes. Included studies are described below according to a pharmacological classification.

Tricyclic Antidepressants.
Amitriptyline (Three Studies). Following previous small negative trials in third molar extraction[43] and hip/knee arthroplasty,[42] Vahedi et al.[48] randomized 200 patients undergoing single-level lumbar discectomy and laminectomy to a single dose of either 25 mg amitriptyline or placebo, 2 h before surgery. Visual analogue scale for pain intensity, pain relief from baseline, and morphine consumption were measured during

24 h, and significantly lower pain intensity was reported in the amitriptyline group at 24 h only.[48] It should be noted that only one trial of amitriptyline for acute postoperative pain was positive but also that a very narrow range of doses and treatment durations were evaluated.

Desipramine (Three Studies). Max et al.[44] reported no effect of single doses of desipramine on pain after a variety of different surgical procedures. In contrast to those results, Levine et al.[43] and Gordon et al.[39] demonstrated superior analgesia in patients receiving opioids after third molar extraction. However, in both of these trials, multiple repeated doses of desipramine were administered for 3 to 7 days before surgery. These are the earliest results to suggest that potential postoperative benefits of antidepressants—in this case, potentiation

Table 4. Main Results of Pain Outcomes from Included Trials of Antidepressant for Chronic Postoperative Pain

Antidepressant	First Author, yr	Pain Measure	Time/Duration of Follow-up	Treatment vs. Placebo SES†	Treatment vs. Active Comparator Difference
Duloxetine	Ho, 2010[41]	Pain intensity (0–10 NRS)	3 and 6 months after surgery	No significant differences noted throughout the duration of follow-up	N/A
Escitalopram	Chocron, 2013[36]	SF-36* (bodily pain domain)	1, 3, and 6 months after surgery	No significant differences noted throughout the duration of follow-up	N/A
Venlafaxine	Amr, 2010[34]	Pain intensity (100 mm VAS) with movement	6 months postoperatively	Venlafaxine superior to placebo for dynamic pain at 6 months; SES = 0.16	Venlafaxine superior to gabapentin for pain with movement at 6 months

* Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczeck A: Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures. Med Care 1995; 33(suppl 4):AS264–79. † Effect size estimated as (PainTx – PainPlacebo)/Std DevP (Cohen J: A power primer. Psychol Bull 1992; 112:155–9[60]).

N/A = not applicable; NRS = numerical rating scale; SES = standardized effect size; SF-36 = short-form (36) Health Survey; VAS = visual analogue scale.

Table 5. Risk of Bias of Included Antidepressant Trials

First Author	Sequence Generation	Allocation Concealment	Blinding of Patients and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Amr, 2010[34]	🟡	🟢	🟢	🟢	🟡	🟢
Ceccherelli, 1991[35]	🟡	🟡	🔴	🟡	🟢	🟡
Chocron, 2013[36]	🟢	🟢	🟢	🟢	🟢	🔴
Ekblom, 1991[37]	🟡	🟡	🟢	🟢	🟢	🟢
Franklin, 1988[38]	🟢	🟢	🟢	🟢	🟢	🟢
Gordon, 1993[39]	🟡	🟡	🟢	🟡	🟡	⚪
Gordon, 1994[40]	🟡	🟡	🟢	🟡	🟡	🟡
Ho, 2010[41]	🟢	🟢	🟢	🟢	🟢	🟢
Kerrick, 1993[42]	🟡	🟡	🟡	🟡	🟢	🔴
Levine, 1986[43]	🟡	🟡	🟡	🟡	🔴	🔴
Max, 1992[44]	🟢	🟢	🟢	🟢	🟢	🟢
McQuay, 1987[45]	🟡	🟡	🟡	🟡	🟡	🔴
Porter, 1981[46]	🟡	🟡	🟢	🟡	🟡	🟡
Shpeen, 1984[47]	🟢	🟢	🟢	🟢	🔴	🔴
Vahedi, 2010[48]	🟢	🟢	🟢	🟢	🟢	🟢
Wang, 1981[49]	🟡	🟡	🟢	🟡	🟡	🔴

🟢 = low risk of bias; 🟡 = unclear risk of bias; 🔴 = high risk of bias.

of postoperative opioid analgesia—may require several days of pretreatment before the surgical procedure.

Serotonin Selective Reuptake Inhibitors.

Fluoxetine (One Study). Gordon *et al.*[40] investigated the interaction of fluoxetine with morphine, or pentazocine, in 70 patients undergoing third molar extraction. Patients were randomized to receive either fluoxetine or placebo 7 days preoperatively and either IV morphine or pentazocine postoperatively. No significant fluoxetine–placebo differences in opioid analgesia were reported.

Serotonin Norepinephrine Reuptake Inhibitors (Nontricyclic)

Bicifadine (Two Studies). Wang *et al.*[49] evaluated the efficacy of bicifadine compared with aspirin and placebo. A total of

100 patients after abdominal or orthopedic surgery were randomized to receive oral placebo, 75 or 150 mg of bicifadine, or 650 mg aspirin. Both bicifadine (at 150 mg only) and aspirin were superior to placebo for pain intensity difference and pain relief. Porter *et al.* conducted a similar trial, comparing bicifadine with codeine and placebo in patients undergoing lower limb orthopedic surgery. A total of 80 patients were randomized to receive placebo, 150 or 200 mg of bicifadine, or 60 mg of codeine in the immediate recovery period. No significant bicifadine–placebo differences were reported for pain outcomes.

Duloxetine (One Study). A recent study in 50 patients after total knee arthroplasty by Ho *et al.*[41] examined the analgesic effect of 60 mg of duloxetine administered preoperatively as

Table 6. Trial Quality and Other Features of Included Antidepressant Trials

Antidepressant Agents	First Author, yr	Trial Quality	Assessment of Pain	Distinction between Rest and Dynamic Pain	Assessment of Dynamic Pain	Adverse Effects/Events Assessment and/or Analysis in Methods Section	Adverse Effects/Events Reported in Results Section
Amitriptyline*	Levine, 1986*[43]	3	+	–	–	–	–
Amitriptyline	Kerrick, 1993[42]	2	+	–	–	–	+
Amitriptyline	Vahedi, 2010[48]	5	+	–	–	–	–
Bicifadine	Porter, 1981[46]	4	+	–	–	–	+
Bicifadine	Wang, 1982[49]	3	+	–	–	+	+
Desipramine*	Levine, 1986*[43]	3	+	–	–	–	–
Desipramine	Max, 1992[44]	3	+	+	+	+	+
Desipramine	Gordon, 1993[39]	2	+	–	–	–	–
Duloxetine	Ho, 2010[41]	5	+	+	+	+	+
Escitalopram	Chocron, 2013[36]	5	+	–	–	+	+
Fluoxetine	Gordon, 1994[40]	2	+	–	–	–	–
Fluradoline	McQuay, 1987[45]	4	+	–	–	+	+
Tryptophan	Shpeen, 1984[47]	3	+	–	–	–	–
Tryptophan	Franklin, 1990[38]	3	+	–	–	–	–
Tryptophan	Ceccherelli, 1991[35]	3	+	–	–	+	+
Tryptophan	Ekblom, 1991[37]	3	+	–	–	–	–
Venlafaxine	Amr, 2010[34]	4	+	+	+	–	+

* Levine 1986[43] RCT included evaluation of both amitriptyline and desipramine.

RCT = randomized controlled trial; "+" = this feature was conducted in the trial; "–" = this feature was not conducted in the trial.

well as on postoperative day 1. Pain scores and opioid consumption were evaluated during a 48 h period, as well as a follow-up at 3 and 6 months postoperatively to evaluate the proportion of patients with persistent postoperative pain. Although no significant duloxetine–placebo differences were reported for early postoperative pain outcomes, morphine requirements were significantly lower in the duloxetine group.

Venlafaxine (One Study). Amr and Yousef[34] evaluated venlafaxine and gabapentin in 150 patients after partial or radical mastectomy. Patients received venlafaxine 37.5 mg, gabapentin 300 mg, or placebo beginning on the preoperative evening and on each day for the first 10 postoperative days. Pain at rest and active states (visual analogue scale) and consumption of analgesics were measured up to postoperative day 10 with a follow-up at 6 months. When compared with placebo, although no difference in pain at rest was observed in the venlafaxine group, pain with movement was reduced on the 7th to 10th postoperative days. In addition, the use of postoperative analgesics, codeine and paracetamol, on postoperative days 2 to 10 was reduced in the venlafaxine-treated patients.

Other Classified Antidepressant Agents.
Fluradoline (One Study). McQuay *et al.*[45] compared fluradoline to aspirin in 120 orthopedic patients with moderate to severe postoperative pain on postoperative day 1 and who were randomized to receive oral placebo, 150 mg fluradoline, 300 mg fluradoline, or 650 mg of aspirin. In this trial, both fluradoline and aspirin were superior for pain intensity and relief outcomes.

Tryptophan (Four Studies). Ceccherelli *et al.*[35] evaluated intravenous tryptophan in 45 patients after cholecystectomy who were randomized to receive either placebo or 7.5 or 15 mg/kg IV tryptophan postoperatively. This trial reported significant pain reductions compared with placebo with tryptophan at either dose. Shpeen *et al.*[47] randomized 50 patients undergoing endodontic surgery to either 3 g of oral tryptophan or placebo 24 h before the procedure and also observed a significant analgesic effect of tryptophan. In contrast to these two positive trials, two other RCTs by Ekblom *et al.*[37] and Franklin *et al.*[38] failed to demonstrate any significant tryptophan–placebo differences.

Description of Studies and Treatment Effects—Chronic Postoperative Pain
Inclusion criteria were met (appendix 2) by three heterogeneous studies (565 participants) of *chronic* postoperative pain involving different antidepressants including duloxetine (one trial),[41] escitalopram (one trial),[36] and venlafaxine (one trial).[34] Tables 2 and 4 describe the three chronic postoperative pain studies included in the review. In the duloxetine trial, duloxetine 60 mg was given orally 2 h before surgery and again on the morning of postoperative day 1 and pain was measured at 3 and 6 months after surgery. In the venlafaxine trial, venlafaxine 37.5 mg (or gabapentin) were given orally at bedtime starting the night before surgery and again daily for the first 10 days after surgery and pain was measured 6 months after surgery. In the escitalopram trial, escitalopram 10 mg orally was given daily starting from 2 to 3 weeks before surgery and continued daily up to 6 months

after surgery. Clinical heterogeneity of trials with respect to drug, dosing regimen, outcome measure, and surgical procedure precluded any meta-analyses. In the venlafaxine mastectomy trial,[34] significantly lower pain was reported upon comparing venlafaxine to both placebo and gabapentin, and the standardized effect size for the venlafaxine–placebo comparison was estimated to be 0.16. In this trial,[34] 10 days of perioperative study drug administration resulted in a significantly lower 6-month incidence of burning (1 of 50) and stabbing (7 of 50) pain compared with 11 of 50 and 20 of 50 for placebo, respectively.

Adverse Effects

Only 9 of the 16 included trials reported on adverse effects (table 6). In the trial by Kerrick et al.,[42] 3 consecutive nighttime oral doses of amitriptyline 50 mg, starting on the first night after surgery was associated with a slightly higher (nonsignificant) level of sedation compared with placebo-treated patients. In both bicifadine RCTs by Porter et al.[46] and Wang et al.,[49] no significant placebo–bicifadine differences in adverse effects were reported; however, very few details were provided. In the postoperative trial by Max et al.,[44] measures of sedation and nausea were not significantly affected by desipramine, compared with placebo. Other reported side effects (dry mouth, itching, euphoria, and dizziness) were not statistically compared between desipramine and placebo. No significant adverse effects, compared with placebo, were reported in the single-dose duloxetine trial by Ho et al.,[41] or by the 10-day multidose venlafaxine trial.[34] In one of the tryptophan trials, Ceccherelli et al.[35] reported no significant differences in adverse effects compared with placebo. In the trial of fluradoline by McQuay et al.,[45] no significant increases in adverse effects were reported; however, significant increases in blood pressure were observed with the 300 mg dose. Finally, in a rather unique trial evaluating over 6 months of treatment with daily oral escitalopram,[36] starting 2 to 3 weeks before cardiac surgery and continuing to 6 months after surgery, reports of overall side effects were significantly more frequent with escitalopram (12.6%) compared with placebo (4.5%) and included diarrhea, constipation, nausea, shivering, somnolence, and tingling of extremities.

Characteristics of Ongoing Studies

A trial registry search for ongoing studies relevant to this review yielded one comparative trial of gabapentin and amitriptyline in the setting of lumbar laminectomy and discectomy (trial status—recruiting; ClinicalTrials.gov Identifier: NCT01014520) and another trial evaluating the efficacy of escitalopram after total knee arthroplasty (trial status—completed; ClinicalTrials.gov Identifier: NCT01430520).

Discussion

Summary of Main Results

This systematic review revealed 15 RCTs of eight different classified antidepressant drugs for the treatment of acute postoperative pain and 3 RCTs of three different antidepressants for the prevention of chronic postoperative pain. Because of inconsistent results, limitations in the numbers of RCTs for each antidepressant drug, poor procedure specificity, and other limitations in trial size and assessment of clinically relevant outcomes, there is no sufficient evidence to support the clinical use of antidepressants—beyond controlled investigations—for the treatment of acute, or prevention of chronic, postoperative pain. However, the existence of 8 of 15 positive RCTs of antidepressants in the setting of acute postoperative pain suggests the need to further conduct higher-quality, more definitive trials that either confirm or refute the efficacy and clinical utility of antidepressants for this indication.

Overall Quality, Completeness, and Applicability of Evidence

Overall, included trials were of good to high quality. Most common sources of bias included incomplete descriptions of trial methods with respect to randomization, blinding, and allocation concealment. With respect to potential bias associated with selective outcome reporting,[50] only five RCTs clearly defined, a priori, a primary outcome measure for the trial. Because small trial size (e.g., <50 patients per parallel treatment arm) may be another source of bias,[51] the observation that only 2 of the 16 RCTs included in this review had 50 or more patients per arm suggests that the vast majority of perioperative antidepressant studies should be considered as smaller proof-of-concept trials rather than more definitive confirmatory trials. Only three RCTs distinguished the difference between pain at rest and pain evoked by movement in their Methods sections. This is important for two reasons: (1) because movement-evoked pain is generally 95 to 226% more intense than pain at rest, failure to control the condition (i.e., at rest vs. during movement) during which pain is assessed during a clinical trial could result in highly variable pain intensity measures within and across trial patients. This increased variability could decrease assay sensitivity and lead to false-negative trial results. (2) If only pain at rest is evaluated in future trials, lack of evidence on the effect of the study medication on movement-evoked pain (which is more severe and may have more functional impact) will limit the clinical relevance of the trial. Given the various potential safety problems associated with perioperative antidepressant use, it is concerning that only six RCTs included a description of safety assessment in their Methods section and only nine RCTs reported any data on adverse effects in their Results section.[52,53] Given the various clinical factors that can differ substantially across surgical procedures, evaluation of postoperative pain treatments is best done in a procedure-specific manner.[54] Because six of the included RCTs were not exclusive to one specific surgical procedure, greater variability in results from those trials could have further increased variability and reduced assay sensitivity, thus increasing the likelihood of a false-negative

result. It should also be noted that except for desipramine in two RCTs of third molar extraction (which could not be combined for meta-analysis because of differences in dosing regimens), no single antidepressant drug was evaluated in more than one surgical procedure. The potential future utility of antidepressant drugs for postsurgical pain also requires the recognition of potential drug interactions with opioids[55] and other drugs commonly used in the perioperative period. Finally, we observed that 6 of the 15 acute pain treatment RCTs involved only a single dose of study medication suggesting evaluation of treatment during a rather narrow window in the postoperative period.

Review Limitations

The search strategy for this review was rather broad and comprehensive, and we also searched for other references using a cited reference search. However, we cannot rule out the possibility that other studies eluded our search. Furthermore, we are unable to locate studies that have never been published. Given previous observations that negative RCTs are less likely to be published, this raises the possibility of publication bias[51] and that there are more negative studies than those we identified. Given the heterogeneity of drugs, doses, and time of administration of the various studies included in this review, we elected not to produce a funnel plot to assess publication bias.

Rationale for Continued Evaluation and Future Research Directions

Recent preclinical studies provide some supportive evidence for the positive trials reported in this review and further reinforce the potential for analgesic efficacy of tricyclic antidepressants, serotonin, and norepinephrine reuptake inhibitors for postoperative pain.[56,57] Pharmacological mechanisms of these agents—in particular sodium-channel blockade and N-methyl-D-aspartate receptor antagonism[15,16]—likely have important antinociceptive effects in postoperative pain settings.[19–21] Because analgesic efficacy of antidepressant drugs becomes apparent after days to weeks of gradual dose titration in chronic pain settings, future postoperative analgesic trials may also require a similar duration of dose titration for days to weeks before surgery to demonstrate optimal results. Also, given the potential for adverse drug interactions with other concomitant drugs as well as increased risks of perioperative bleeding, future, more definitive trials should be safely conducted in carefully selected populations so as to avoid these problems. However, if results suggest more convincing evidence of analgesic efficacy, subsequent research will be needed to define appropriate indications and contraindications in surgical patients. Regarding future evaluation of antidepressants for the prevention of chronic postsurgical pain, recently developed methods[58,59] to identify patients at higher risk of this complication may facilitate this goal. Targeting the proposed intervention to patients at highest

risk of chronic postsurgical pain, and thus greatest need of prevention, would provide stronger justification for anticipated adverse effects and could also decrease the required patient numbers. Finally, given continued uncertainty about the postsurgical time period during which chronic pain develops,[27–29] consideration should be given to evaluating the preventive effects of antidepressant drugs—given for a longer duration of administration, that is, to continue for days, or even weeks, after postsurgical hospital discharge.

Conclusions

On the basis of currently available studies, there is insufficient evidence to support the clinical use of antidepressants for the treatment of acute postoperative pain. Several positive trial results suggest the potential for therapeutic benefits of antidepressants in certain postoperative clinical settings. Multiple positive trials suggest the therapeutic potential of antidepressants, which need to be replicated. Given current limitations in postoperative pain treatment and the need to more rigorously explore the efficacy of antidepressant drugs, future studies could more definitively characterize the value of antidepressants in postoperative pain management. Future, higher-quality RCTs should address the need for optimal dosing, timing and duration of antidepressant treatment, trial size, safety evaluation and reporting, procedure specificity, and assessment of movement-evoked pain relevant to postoperative functional recovery.

Competing Interests

Dr. Kalso has received consulting fees from Pfizer, Grunenthal, Janssen-Cilag, Orion-Pharmos, and Pharmaleads. Dr. Raja has received research support or consulting fees from Allergan, Alpharma, Schering-Plough, Medtronic, Pfizer, and QRx Pharma. Dr. Gilron has received support from Pfizer, Aventis Pharma, Novopharm, PharmaScience, Apotex, Merck-Frosst, Johnson & Johnson, Ortho-McNeill, and Janssen-Ortho and has received grants from the Canadian Institutes of Health Research (Ottawa, Ontario, Canada), Physicians' Services Incorporated Foundation, and Queen's University (Kingston, Ontario, Canada). The other authors declare no competing interests.

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Appendix 1. Search Strategy

EMBASE
1. Postoperative pain.mp. or exp postoperative pain/
2. Antidepressant.mp or exp antidepressant agent/
3. 1 and 2
4. limit 3 to human

MEDLINE
1. exp Pain, Postoperative/
2. exp monoamine oxidase inhibitors/or exp adrenergic uptake inhibitors/or exp serotonin uptake inhibitors/or exp serotonin agents/or exp serotonin receptor agonists/or exp antidepressive agents/or exp antidepressive agents, second-generation/or exp antidepressive agents, tricyclic/
3. 1 and 2
4. limit 3 to humans

CENTRAL
1. Antidepressive agents or monoamine oxidase inhibitors or serotonin uptake inhibitors or norepinephrine uptake inhibitors and pain, postoperative (limit to humans)

CINAHL
1. "Postoperative Pain"
2. "Antidepressive Agents" OR "Antidepressive Agents, Second Generation" OR "Antidepressive Agents, Tricyclic" OR "Serotonin Agents"
3. 1 and 2

Appendix 2. Included Studies

Amr 2010[34]

Amr YM, Yousef AA: Evaluation of efficacy of the perioperative administration of venlafaxine or gabapentin on acute and chronic postmastectomy pain. Clin J Pain 2010; 26:381–85.

Methods	DB, RCT, parallel group, multidose trial; VAS pain, analgesic consumption assessed up to POD10 and follow-up evaluation for residual pain at 6 months.
Participants	n = 150, females, mean age 44 ± 6.3 yr.
Interventions	Placebo, n = 50; venlafaxine, n = 50; gabapentin, n = 50.
Outcomes	VAS pain at rest and movement (from 4 h postoperatively to POD10); analgesic consumption; residual pain and analgesic requirement at 6 months; number of participants with adverse events; number of participants withdrawing because of adverse events.
Surgical procedure	Partial or radical mastectomy with axillary dissection.
Timing and dosage of antidepressant	Placebo, venlafaxine 37.5 mg, or gabapentin 300 mg given perioperatively, with first dose on the evening before surgery, up to POD10.
Treatment effect: comparison between drug and placebo	Venlafaxine superior to placebo for dynamic pain on PODs 8–10; *Insufficient data provided to estimate effect size.*
Concomitant nonstudy analgesic	Nurse-administered morphine IV for POD0–1; paracetamol and codeine POD2–10.

Ceccherelli 1991[35]

Ceccherelli F, Diani M, Altafini L, Varotto E, Stefecius A, Casale R, Costola A, Giron GP: Postoperative pain treated by intravenous L-tryptophan: A double-blind study *versus* placebo in cholecystectomized patients. Pain 1991; 47:163–72.

Methods	DB, RCT, three parallel groups, single-dose IV tryptophan given postoperatively. VAS pain, hemodynamics, and respiratory mechanics were monitored up to 6 h after study medication given.
Participants	n = 45, 34–61 yr, all females.
Interventions	Placebo, n = 15; tryptophan IV 7.5 mg/kg, n = 15; tryptophan IV 15 mg/kg, n = 15.
Outcomes	Mean VAS; number of participants with adverse events.
Surgical procedure	Uncomplicated cholecystectomy.
Timing and dosage of antidepressant	Patients with >55 mm on VAS pain in recovery room were randomized to receive either placebo or 7.5 or 15 mg/kg IV tryptophan.
Treatment effect: comparison between drug and placebo	Tryptophan at both doses superior to placebo for pain intensity reduction; *Insufficient data provided to estimate effect size.*
Concomitant nonstudy analgesic	None.

Chocron 2013[36]

Chocron S, Vandel P, Durst C, Laluc F, Kaili D, Chocron M, Etievent JP: Antidepressant therapy in patients undergoing coronary artery bypass grafting: The MOTIV-CABG trial. Ann Thorac Surg 2013; 95: 1609–18.

Methods	DB, parallel group, multidose RCT; SF-36 Health Survey completed at 6 and 12 months.
Participants	n = 368, mean age 67, 16% female.
Interventions	Group 1: escitalopram 10 mg PO daily starting 2–3 weeks preoperatively until 6 months postoperatively; group 2: matching placebo.
Outcomes	SF-36 Health Survey and Beck Depression Inventory at 6 and 12 months after surgery.
Surgical procedure	Coronary artery bypass grafting.
Timing and dosage of antidepressant	Escitalopram 10 mg PO daily starting 2–3 weeks preoperatively until 6 months postoperatively.
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	Not described.
Notes	Escitalopram was superior to placebo for the bodily pain domain of the SF-36.

Ekblom 1991[37]

Ekblom A, Hansson P, Thomsson M: L-Tryptophan supplementation does not affect postoperative pain intensity or consumption of analgesics. Pain 1991; 44:249–54.

Methods	DB, RCT, three parallel group, multidose; randomized participants to either control group (received no study medication), or to receive placebo or oral tryptophan. Baseline comparison of stress and tension measured before procedure. Pain scores, analgesic requirement, and adverse events were recorded by patients up to 72 h postoperatively.
Participants	n = 100; 18–56 yr healthy male and female.
Interventions	Control, n = 60; placebo, n = 20; tryptophan, n = 20.
Outcomes	Mean sum pain score; VAS stress and tension; mean total analgesics used postoperatively; number of patients reporting no pain postoperatively; number of patients requiring no analgesic postoperatively; number of patients with adverse events.
Surgical procedure	Impacted third molar dental extraction.
Timing and dosage of antidepressant	Tryptophan 500 mg PO four times a day starting 3 days preoperatively, continue to POD3 (total 7 days).
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	ASA (500 mg) + codeine (30 mg) or acetaminophen (500 mg) + codeine (30 mg).
Notes	Evaluation of patients by self-reporting at home after procedure.

Franklin 1988[38]

Franklin K, Abbott F, English M, Jeans M, Tasker R, Young S: Tryptophan–morphine interactions and postoperative pain. Pharmacology biochemistry and behaviour 1990; 35:157–63.

Methods	DB, RCT, two parallel groups, multiple dose (continuous perioperative infusion); pain assessments, morphine requirements, and blood levels of tryptophan were measured in recovery, up to 3 h postoperatively. Analgesic requirements were measured up to POD3.
Participants	n = 28, ASA 1 or 2.
Interventions	Placebo, n = 13 (2 dropped from analysis); tryptophan, n = 15.
Outcomes	Global pain score; sensory pain score; morphine requirement in recovery room; plasma tryptophan level; codeine or meperidine requirement from POD0–3.
Surgical procedure	Cholecystectomy or hysterectomy.
Timing and dosage of antidepressant	Tryptophan 10 mg/kg IV bolus intraoperatively, then 10 mg kg^{-1} h^{-1} up to 3 h postoperatively (less if patient's pain was controlled).
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	Morphine IV in recovery room; meperidine or codeine.

Gordon 1993[39]

Gordon NC, Heller PH, Gear RW, Levine JD: Temporal factors in the enhancement of morphine analgesia by desipramine. Pain 1993; 53:273–76.

Methods	DB, RCT, four parallel groups, multidose (number of doses randomized); 10-cm VAS pain assessed for 6 h after procedure; postoperatively all patients received 6 mg IV morphine as well.
Participants	60, male = 33, female = 27; mean age 23.6 ± 0.5 yr old.
Interventions	Placebo, n = 15; desipramine 50 mg 7 days preoperatively, n = 15; desipramine 50 mg days 7, 6, and 5 preoperatively, n = 15; desipramine 50 mg days 3, 2, and 1 preoperatively, n = 15.
Outcomes	Change in pain intensity from baseline after IV morphine.
Surgical procedure	Third molar dental extraction.
Timing and dosage of antidepressant	All patients received desipramine, placebo, or combination of both total 7 days preoperatively, according to randomization.
Treatment effect: comparison between drug and placebo	Desipramine superior to placebo only when given from days –7 to –1 or days –7 to –5 before surgery, but not from days –3 to –1 before surgery; *Insufficient* data provided to estimate effect size.
Concomitant nonstudy analgesic	6 mg IV morphine when pain ≥2.5 cm, no sooner than 80 min after local anesthetic injection.

Gordon 1994[40]

Gordon NC, Heller PH, Gear RW, Levine JD: Interactions between fluoxetine and opiate analgesia for postoperative dental pain. Pain 1994; 58:85–8.

Methods	DB (single blind for opiate administration), RCT, multidose, parallel groups; VAS pain measured q20min after surgery, up to 180 min after administration of opiate.
Participants	70, male = 29, female = 41, mean age 21.4 ± 0.6 yr.
Interventions	Placebo/morphine, n = 15; placebo/pentazocine, n = 15; fluoxetine/morphine, n = 20; placebo/pentazocine, n = 20.
Outcomes	Analgesic effect of opiate (change in pain intensity at each time point after opiate administration compared with before).
Surgical procedure	Third molar dental extraction.
Timing and dosage of antidepressant	Placebo or fluoxetine 10 mg for 7 days before procedure.
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	IV morphine 6 mg or pentazocine 45 mg IV when VAS pain >2.5 cm but no sooner than 80 min after local anesthetic injection.

Ho KY 2010[41]

Ho KY, Tay W, Yeo MC, Liu H, Yeo SJ, Chia SL, Lo NN: Duloxetine reduces morphine requirements after knee replacement surgery. BJA 2010; 105:371–76.

Methods	DB, RCT single oral dose, two parallel groups; outcomes: PCA morphine consumption (primary), NRS at 0.5, 1, 2, 6, 12, 24, and 48 h after surgery, chronic pain at 3 and 6 months.
Participants	ASA 1–3, 18–80 yr; N = 47 (analyzed; 50 randomized); male = 14; female = 33.
Interventions	Placebo, n = 24; duloxetine 60 mg, n = 23.
Outcomes	Morphine consumption in 48 h; 11-point NRS up to 48 h postsurgery; number of participants reporting any serious adverse events; number of participants withdrawing because of adverse events; presence of pain, NRS, and analgesic requirement at 3 and 6 months.
Surgical procedure	Total knee arthroplasty.
Timing and dosage of antidepressant	Duloxetine 60 mg 2 h preoperatively and morning of POD1
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	PCA IV morphine; acetaminophen 1 g q6h.

Kerrick 1993[42]

Kerrick JM, Fine PG, Lipman AG, Love G: Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: A placebo-controlled trial. Pain 1993; 52:325–30.

Methods	RCT, DB, parallel groups, multidose; pain, sedation, and sense of well-being were assessed twice-daily POD1, 2, and 3 as was the hourly opioid PCA consumption.
Participants	28, 18–79 yr (mean age: 61.8 yr); male = 17; female = 11.
Interventions	Placebo, n = 14; amitriptyline 50 mg, n = 14.
Outcomes	VAS, NVS; morphine consumption; global sense of well-being; sedation and sleep scale.
Surgical procedure	Elective total hip or knee arthroplasty.
Timing and dosage of antidepressant	Placebo or amitriptyline 50 mg POD0, 1, and 2.
Treatment effect: comparison between drug and placebo	Pain significantly higher with amitriptyline.
Concomitant nonstudy analgesic	Morphine IV PCA (meperidine if morphine sensitive).

Levine 1986[43]

Levine JD, Gordon NC, Smith R, McBryde R: Desipramine enhances opiate postoperative analgesia. Pain 1986; 27:45–49.

Methods	DB, RCT, parallel groups (randomized to placebo, amitriptyline or desipramine), multidose; standard dose IV morphine administered to all participants 3 h after surgery, and VAS pain measured just before morphine, up to 150 min.
Participants	30 patients.
Interventions	Placebo, n = 10; desipramine, n = 10; amitriptyline, n = 10.
Outcomes	VAS for pain; analgesic effect (average change in pain intensity pre- and postmorphine); relative duration of analgesic effect (comparison of pain at the end of study between groups).
Surgical procedure	Third molar dental extraction.
Timing and dosage of antidepressant	Amitriptyline or despiramine or placebo started 7 days before surgery, 25 mg for 3 days, then 50 mg for 2 days, and then 75 mg for 2 days.
Treatment effect: comparison between drug and placebo	No significant difference for amitriptyline *vs.* placebo. Desipramine significantly superior to placebo.
Concomitant nonstudy analgesic	6 mg morphine IV 3 h after local anesthetic was injected for molar extraction.

Max 1992[44]

Max MB, Zeigler D, Shoaf S, Craig E, Benjamin J, Li SH, Buzzanell C, Perez M, Ghosh B: Effects of a single oral dose of desipramine on postoperative morphine analgesia. J Pain Symptom Manage 1992; 7:454–62.

Methods	DB, RCT, 2×2 design (randomization to desipramine or placebo and high- or low-dose morphine), single-dose trial; pain score, pain relief, time to requiring remedication, nausea, and sedation evaluated over 4 h after study-dose morphine given (upon patient's request). Serum desipramine level was measured at 60 min after study-dose morphine given.
Participants	88 adults randomized, only 62 analyzed (no drop-out because of adverse effects); male = 29; female = 33.
Interventions	Placebo and 0.1 mg/kg morphine IV = 15; placebo and 0.033 mg/kg morphine IV = 16; desipramine 50 mg and 0.1 mg/kg morphine IV = 15; desipramine 50 mg and 0.033 mg/kg morphine IV = 16.
Outcomes	Pain relief (VAS and categorical); pain intensity from baseline; mean time from desipramine/placebo to study-dose morphine; number of participants requiring rescue analgesic after study-dose morphine; VAS sedation and nausea at time of study-dose morphine.
Surgical procedure	Orthopedics, hysterectomy/oopherectomy, breast reconstruction, or cholecystectomy. Some patients had intrathecal/epidural morphine for postoperative pain.
Timing and dosage of antidepressant	50 mg desipramine or placebo given at 6:00 POD1.
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	0.1 or 0.033 mg/kg IV morphine given when patients requests analgesic within 2–6 h after desipramine given. If rescue analgesic is required within after 30 min of study-dose morphine, 0.1 mg/kg morphine IV given.

McQuay 1987[45]

McQuay HJ, Carroll D, Poppleton P, Summerfield RJ, Moore RA: Fluradoline and aspirin for orthopedic postoperative pain. Clin Pharmacol Ther 1987; 41:531–36.

Methods	DB, RCT, single dose, parallel group; pain (VAS and VRS), mood (VAS), sedation, blood pressure, HR, RR measured before study medication on POD1, then again 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after, along with measurements of pain relief (VAS and categorical). A global rating was evaluated at the end of the study period.
Participants	120 randomized but only 32 received test medications; 18–70 yr, male and female.
Interventions	Placebo, n = 6; aspirin 650 mg, n = 12; fluradoline 300 mg, n = 7; fluradoline 150 mg, n = 7.
Outcomes	Four-word SPID; eight-word SPID; TOTPAR; peak pain relief; VAS SPID; VAS TOTPAR; global rating (observer and patient); median time to remedication; mood and sedation scores; number of participants with adverse events; number of participants withdrawing because of adverse events.
Surgical procedure	Elective orthopedic surgery (upper and lower limbs, spine, and rib).
Timing and dosage of antidepressant	Study medication given only to patients reporting moderate to severe pain on POD1.
Treatment effect: comparison between drug and placebo	Fluradoline 300 mg superior to placebo for SPID and TOTPAR; standardized effect size = 0.78.
Concomitant nonstudy analgesic	None. Routine analgesic given if required within 6-h study period, and pain intensity scores were given as the initial values and pain relief scores of zero.

Porter 1981[46]

Porter EJB, Rolfe M, McQuay HJ: Single dose comparison of bicifadine and placebo in postoperative pain. Curr Ther ResClin Exp 1981; 30:156–60.

Methods	DB, RCT, parallel groups, single oral dose, noncrossover; pain intensity, pain relieve, global impression, adverse effects evaluated over 4 h.
Participants	80, >18 yr male and female.
Interventions	Placebo, n = 21; codeine 60 mg, n = 20; bicifadine 100 mg, n = 19; bicifadine 150 mg, n = 20.
Outcomes	SPID; TOTPAR; 50% pain relief; global impression by observer and patient; number of participants with any adverse events and withdrawals because of side effects.
Surgical procedure	Elective lower limb orthopedic surgery.
Timing and dosage of antidepressant	Study medications were given in the recovery room immediately postoperatively.
Treatment effect: comparison between drug and placebo	No significant difference.
Concomitant nonstudy analgesic	None (if rescue analgesic required within 1 h of study medication, IM papaveretum given).

Shpeen 1984[47]

Shpeen SE, Morse DR, Furst ML: The effect of tryptophan on postoperative endodontic pain. Oral Surg 1984; 58:446–49.

Methods	DB, RCT, multidose, two parallel groups; study medication was given before procedure and continued for 24 h postoperatively. NVS pain was obtained at baseline, 24 h postoperatively, and 1 week postoperatively.
Participants	n = 50, age 18–59 yr; male = 17, female = 33.
Interventions	Placebo, n = 25; tryptophan, n = 25.
Outcomes	10-point NVS pain before, 24 h posttreatment, and 1 week posttreatment; analgesic requirement after 24 h posttreatment.
Surgical procedure	Nonsurgical endodontic treatment.
Timing and dosage of antidepressant	Randomized to receive either placebo or 3 g tryptophan postoperatively divided into 0.5 g q6h for 24 h. Also received placebo or 1 g tryptophan just before treatment.
Treatment effect: comparison between drug and placebo	Tryptophan superior to placebo at 24 h; *Insufficient data provided to estimate effect size*.
Concomitant nonstudy analgesic	Acetaminophen and codeine (30 mg).

Vahedi 2010[48]

Vahedi P, Salehpour F, Aghamohammadi D, Shimia M, Lotfinia I, Mohajernezhadfard Z, Vahedi Y: Single dose preemptive amitriptyline reduces postoperative neuropathic pain after lumbar laminectomy and discectomy. Neurosurg Quarterly 2010; 20:151–58.

Methods	DB, RCT single oral dose, two parallel groups, pain and morphine consumption measured 6, 12, 18, and 24 h postoperatively.
Participants	200, 18–60 yr, ASA 1–2 randomized; only 77 analyzed (male = 41; female = 36).
Interventions	Placebo, n = 40 (analyzed); amitriptyline, n = 37 (analyzed).
Outcomes	VAS; relief from baseline pain; morphine consumption; number of participants with any and serious adverse events; number of participants withdrawing because of adverse events.
Surgical procedure	Single level lumbar laminectomy/discetomy.
Timing and dosage of antidepressant	Amitriptyline 25 mg or placebo given 2 h preoperatively.
Treatment effect: comparison between drug and placebo	Pain significantly lower with amitriptyline at 24 h only; standardized effect size = 0.56.
Concomitant nonstudy analgesic	Morphine IV PCA.

Wang 1981[49]

Wang RI, Johnson RP, Lee JC, Waite EM: The oral analgesic efficacy of bicifadine hydrochloride in postoperative pain. J Clin Pharm 1982; 22:160–63.

Methods	RCT, DB single dose, four parallel treatment groups; pain intensity, pain relief, and global assessment were evaluated over 6 h after administration of study medication.
Participants	100, 18–61 yr with moderate to severe postoperative pain.
Interventions	Placebo, n = 25; aspirin 650 mg, n = 25; bicifadine 75 mg, n = 25; bicifadine 150 mg, n = 25.
Outcomes	Mean analgesic score; pain intensity difference; global impression; adverse events observed and reported; number of participants withdrawing because of adverse events.
Surgical procedure	Abdominal or orthopedic procedures.
Timing and dosage of antidepressant	Placebo, aspirin, high- or low-dose bicifadine given to postoperatively patients with moderate to severe pain who had not received analgesics 3 h before receiving study medication.
Treatment effect: comparison between drug and placebo	Bicifadine 150 mg and aspirin superior to placebo for pain relief; *Insufficient data provided to estimate effect size*.
Concomitant nonstudy analgesic	None (if requires analgesic after study medication, "conventional" analgesic given, and hourly pain relief scores recorded as zero).

ASA = aspirin (acetylsalicylic acid); DB = double blind; IM = intramuscular; IV = intravenous; HR = heart rate; NRS = numerical rating scale; NVS = numerical verbal pain rating scale; PCA = patient-controlled analgesia; PO = per os (by mouth); POD = postoperative day; q6h = every 6 h; q20min = every 20 min; RCT = randomized controlled trial; RR = respiratory rate; SF-36 = short-form (36) Health Survey; SPID = summed pain intensity difference; TOTPAR = total pain relief; VAS = visual analogue scale.

Appendix 3. Excluded Studies

First Author, yr	Reason for Exclusion
Campagna, 1988[61]	Not an English language RCT report.
Coquoz, 1993[62]	Study of analgesic effect of fluvoxamine, meclobamide, and desipramine in non–postoperative pain setting.
Cuocolo, 1988[63]	Not an antidepressant study.
Doenicke, 1993[64]	Study of analgesic effect of ondansetron, which is not used clinically as an antidepressant.
Eisenach, 1997[65]	Not a postoperative pain investigation.
Erjavec, 2000[66]	Not a postoperative pain investigation.
Fanton, 2008[67]	Study drug is a combination of amitriptyline, ketoprofen, and oxymetazolin.
Garrett, 2011[68]	Study drug is a combination of amitriptyline, ketoprofen, and oxymetazolin.
Juś, 2010[69]	Animal study.
Krimmer, 1986[70]	Not an RCT.
Kudoh, 2002[71]	Observational study.
Rottinger, 1990[72]	Not an English language RCT report.
Saoud, 2013[73]	Not randomized.
Soluti, 2000[74]	Article and abstract not found.
Tiengo, 1987[75]	Not a blinded study.
Wallace, 2002[76]	Not a postoperative pain investigation.
Wordliczek, 2001[77]	Animal study.

RCT = randomized controlled trial.

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