Antidepressant Drugs for Prevention of Acute and Chronic Postsurgical Pain

Early Evidence and Recommended Future Directions


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)

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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. Tryptophan, with previously demonstrated antidepressant efficacy, 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. In addition to serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants antagonize peripheral sodium channels and spinal N-methyl-D-aspartate receptors. These mechanisms serve to suppress central sensitization which is important in the pathophysiology of acute postoperative pain.

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, and antidepressants could potentially be a valuable addition here. However, safety problems including increased perioperative bleeding, serotonin syndrome, 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. 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.

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. Quality of each trial was assessed using the Oxford Quality Scoring System. 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) 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). 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), bicifadine (2 trials), desipramine (3 trials), duloxetine (1 trial), fluoxetine (1 trial), and other analgesic interventions.
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 amitriptyline48 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

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

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

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

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

* Levine 198643 RCT included evaluation of both amitriptyline and desipramine. † No primary outcome declared for these trials; ‡ 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; 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 extraction43 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...
of postoperative opioid analgesia—may require several days of pretreatment before the surgical procedure.

**Serotonin Selective Reuptake Inhibitors.**

**Fluoxetine (One Study).** Gordon et al.\(^4\) 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.

**Venlafaxine (Two Studies).** Wang et al.\(^9\) evaluated the efficacy of venlafaxine 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 bicalutamide, or 650 mg aspirin. Both bicalutamide (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 bicalutamide 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 bicalutamide, or 60 mg of codeine in the immediate recovery period. No significant bicalutamide–placebo differences were reported for pain outcomes.

**Duloxetine (One Study).** A recent study in 50 patients after total knee arthroplasty by Ho et al.\(^4\) examined the analgesic effect of 60 mg of duloxetine administered preoperatively as

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

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>First Author, yr</th>
<th>Pain Measure</th>
<th>Time/Duration of Follow-up</th>
<th>Treatment vs. Placebo SES†</th>
<th>Treatment vs. Active Comparator Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Ho, 2010(^4)</td>
<td>Pain intensity (0–10 NRS)</td>
<td>3 and 6 months after surgery</td>
<td>No significant differences noted throughout the duration of follow-up</td>
<td>N/A</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Chocron, 2013(^36)</td>
<td>SF-36* (bodily pain domain)</td>
<td>1, 3, and 6 months after surgery</td>
<td>No significant differences noted throughout the duration of follow-up</td>
<td>N/A</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Amr, 2010(^34)</td>
<td>Pain intensity (100 mm VAS) with movement</td>
<td>6 months postoperatively</td>
<td>Venlafaxine superior to placebo for dynamic pain at 6 months; SES = 0.16</td>
<td>Venlafaxine superior to gabapentin for pain with movement at 6 months</td>
</tr>
</tbody>
</table>


**Table 5. Risk of Bias of Included Antidepressant Trials**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of Patients and Personnel</th>
<th>Blinding of Outcome Assessment</th>
<th>Incomplete Outcome Data</th>
<th>Selective Reporting</th>
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<tbody>
<tr>
<td>Amr, 2010(^34)</td>
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<tr>
<td>Ceccherelli, 1991(^35)</td>
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<td>Chocron, 2013(^36)</td>
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<td>Ekblom, 1991(^17)</td>
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<td>Frankin, 1988(^38)</td>
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<td>Gordon, 1993(^39)</td>
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<tr>
<td>Gordon, 1994(^40)</td>
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<tr>
<td>Ho, 2010(^41)</td>
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<tr>
<td>Kerrick, 1993(^42)</td>
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<tr>
<td>Levine, 1986(^43)</td>
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<tr>
<td>Max, 1992(^44)</td>
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<tr>
<td>McQuay, 1987(^45)</td>
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<tr>
<td>Porter, 1981(^46)</td>
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<td>Shpeen, 1984(^47)</td>
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<tr>
<td>Vahedi, 2010(^48)</td>
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<tr>
<td>Wang, 1981(^49)</td>
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</tbody>
</table>

○ = low risk of bias; ○○ = unclear risk of bias; ○○○ = high risk of bias.
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), escitalopram (one trial), and venlafaxine (one trial). 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.

**Tryptophan (Four Studies).** Ceccherelli et al. 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. 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. and Franklin et al. failed to demonstrate any significant tryptophan-placebo differences.

**Description of Studies and Treatment Effects—Chronic Postoperative Pain**

**Other Classified Antidepressant Agents.**

**Fluradoline (One Study).** McQuay et al. 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.

**Venlafaxine (One Study).** Amr and Yousef 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 again daily for the first 10 postoperative days. 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.

**Antidepressants for Postoperative Pain**

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

<table>
<thead>
<tr>
<th>Antidepressant Agents</th>
<th>First Author, yr</th>
<th>Trial Quality</th>
<th>Assessment of Pain</th>
<th>Distinction between Rest and Dynamic Pain</th>
<th>Assessment of Dynamic Pain</th>
<th>Adverse Effects/Events Reported in Methods Section</th>
<th>Adverse Effects/Events Reported in Results Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline*</td>
<td>Levine, 198643</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Kerrick, 199342</td>
<td>2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Vahedi, 201048</td>
<td>5</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Bicifadine</td>
<td>Porter, 198146</td>
<td>4</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Bicifadine</td>
<td>Wang, 198249</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Desipramine*</td>
<td>Levine, 198643</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Max, 199244</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Gordon, 199339</td>
<td>2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Ho, 201041</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Chocron, 201346</td>
<td>5</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Gordon, 199440</td>
<td>2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Fluradoline</td>
<td>McQuay, 198745</td>
<td>4</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Shpeen, 198437</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Franklin, 199038</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Ceccherelli, 199136</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Ekblom, 199137</td>
<td>3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Amr, 201034</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

* 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.
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,\textsuperscript{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,\textsuperscript{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 \textit{et al.},\textsuperscript{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 \textit{et al.},\textsuperscript{46} and Wang \textit{et al.},\textsuperscript{49} no significant placebo–bicifadine differences in adverse effects were reported; however, very few details were provided. In the postoperative trial by Max \textit{et al.},\textsuperscript{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 \textit{et al.},\textsuperscript{41} or by the 10-day multidose venlafaxine trial.\textsuperscript{34} In one of the tryptophan trials, Ceccherelli \textit{et al.}\textsuperscript{35} reported no significant differences in adverse effects compared with placebo. In the trial of fluradoline by McQuay \textit{et al.},\textsuperscript{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,\textsuperscript{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,\textsuperscript{50} only five RCTs clearly defined, \textit{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 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 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. Pharmacological mechanisms of these agents—in particular sodium-channel blockade and N-methyl-D-aspartate receptor antagonism—likely have important antinociceptive effects in postoperative pain settings. 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 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, 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.

Acknowledgments
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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 Allegan, 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

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

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**

**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**

**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**

**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


| 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 analgesics | 6 mg IV morphine when pain ≥2.5 cm, no sooner than 80 min after local anesthetic injection. |

### Gordon 1994


| 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 analgesics | 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


| 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 at up to 48 h post-surgery; 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 analgesics | PCA IV morphine; acetaminophen 1 g q6h. |
**Kerrick 1993**


<table>
<thead>
<tr>
<th>Methods</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>28, 18–79 yr (mean age: 61.8 yr); male = 17; female = 11.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Placebo, n = 14; amitriptyline 50mg, n = 14.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>VAS, NVS; morphine consumption; global sense of well-being; sedation and sleep scale.</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Elective total hip or knee arthroplasty.</td>
</tr>
<tr>
<td>Timing and dosage of antidepressant</td>
<td>Placebo or amitriptyline 50mg POD0, 1, and 2.</td>
</tr>
<tr>
<td>Treatment effect: comparison between drug and placebo</td>
<td>Pain significantly higher with amitriptyline.</td>
</tr>
<tr>
<td>Concomitant nonstudy analgesic</td>
<td>Morphine IV PCA (meperidine if morphine sensitive).</td>
</tr>
</tbody>
</table>

**Levine 1986**


<table>
<thead>
<tr>
<th>Methods</th>
<th>DB, RCT, parallel groups (randomized to placebo, amitriptyline or desipramine), multidose; standard dose IV morphine administered to all participants 3h after surgery, and VAS pain measured just before morphine, up to 150 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>30 patients.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Placebo, n = 10; desipramine, n = 10; amitriptyline, n = 10.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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).</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Third molar dental extraction.</td>
</tr>
<tr>
<td>Timing and dosage of antidepressant</td>
<td>Amitriptyline or desipramine or placebo started 7 days before surgery, 25mg for 3 days, then 50mg for 2 days, and then 75mg for 2 days.</td>
</tr>
<tr>
<td>Treatment effect: comparison between drug and placebo</td>
<td>No significant difference for amitriptyline vs. placebo. Desipramine significantly superior to placebo.</td>
</tr>
<tr>
<td>Concomitant nonstudy analgesic</td>
<td>6mg morphine IV 3h after local anesthetic was injected for molar extraction.</td>
</tr>
</tbody>
</table>

**Max 1992**


<table>
<thead>
<tr>
<th>Methods</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>88 adults randomized, only 62 analyzed (no drop-out because of adverse effects); male = 29; female = 33.</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Orthopedics, hysterectomy/oophorectomy, breast reconstruction, or cholecystectomy. Some patients had intrathecal/epidural morphine for postoperative pain.</td>
</tr>
<tr>
<td>Timing and dosage of antidepressant</td>
<td>50mg desipramine or placebo given at 6:00 POD1.</td>
</tr>
<tr>
<td>Treatment effect: comparison between drug and placebo</td>
<td>No significant difference.</td>
</tr>
<tr>
<td>Concomitant nonstudy analgesic</td>
<td>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.</td>
</tr>
</tbody>
</table>
McQuay 1987\textsuperscript{45}


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 6h 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 6h study period, and pain intensity scores were given as the initial values and pain relief scores of zero.

Porter 1981\textsuperscript{46}


Methods
DB, RCT, parallel groups, single oral dose, noncrossover; pain intensity, pain relief, global impression, adverse effects evaluated over 4h.

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 1h of study medication, IM papaveretum given).

Shpeen 1984\textsuperscript{47}


Methods
DB, RCT, multidose, two parallel groups; study medication was given before procedure and continued for 24h 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 24h 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 q8h for 24h. Also received placebo or 1 g tryptophan just before treatment.

Treatment effect: comparison between drug and placebo
Tryptophan superior to placebo at 24h; Insufficient data provided to estimate effect size.

Concomitant nonstudy analgesic
Acetaminophen and codeine (30 mg).
Antidepressants for Postoperative Pain

**Vahedi 2010**


**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 = 48 (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/discectomy.

**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**


**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

<table>
<thead>
<tr>
<th>First Author, yr</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campagna, 1988</td>
<td>Not an English language RCT report.</td>
</tr>
<tr>
<td>Coquoz, 1993</td>
<td>Study of analgesic effect of fluvoxamine, meclobamide, and desipramine in non–postoperative pain setting.</td>
</tr>
<tr>
<td>Cuocolo, 1988</td>
<td>Not an antidepressant study.</td>
</tr>
<tr>
<td>Doenicke, 1993</td>
<td>Study of analgesic effect of ondansetron, which is not used clinically as an antidepressant.</td>
</tr>
<tr>
<td>Eisenach, 1997</td>
<td>Not a postoperative pain investigation.</td>
</tr>
<tr>
<td>Erjavec, 2000</td>
<td>Not a postoperative pain investigation.</td>
</tr>
<tr>
<td>Fanton, 2008</td>
<td>Study drug is a combination of amitriptyline, ketoprofen, and oxymetazolin.</td>
</tr>
<tr>
<td>Garrett, 2011</td>
<td>Study drug is a combination of amitriptyline, ketoprofen, and oxymetazolin.</td>
</tr>
<tr>
<td>Jui, 2010</td>
<td>Animal study.</td>
</tr>
<tr>
<td>Krimmer, 1986</td>
<td>Not an RCT.</td>
</tr>
<tr>
<td>Kudoh, 2002</td>
<td>Observational study.</td>
</tr>
<tr>
<td>Rottinger, 1990</td>
<td>Not an English language RCT report.</td>
</tr>
<tr>
<td>Saoud, 2013</td>
<td>Not randomized.</td>
</tr>
<tr>
<td>Soluti, 2000</td>
<td>Article and abstract not found.</td>
</tr>
<tr>
<td>Tiengo, 1987</td>
<td>Not a blinded study.</td>
</tr>
<tr>
<td>Wallace, 2002</td>
<td>Not a postoperative pain investigation.</td>
</tr>
<tr>
<td>Wordliczek, 2001</td>
<td>Animal study.</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.
References

51. Andrew Moore R, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, McQuay H: ACTITION Writing Group of the IASP Special Interest Group on Systematic Reviews in Pain Relief; Cochrane Pain, Palliative and Supportive Care Systematic Review Group Editors: "Evidence" in chronic pain—Establishing best practice in the reporting of systematic reviews. Pain 2010; 150:386–9
64. Doenicke A, Mayer M, Vogginger T: [Postoperative pain therapy. The efficacy of a serotonin antagonist (GR 36032F,ondansetron) and the prostaglandin synthesis inhibitor lysin acetylsalicylate (Aispol)]. Anaesthesist 1995; 42:800–6