A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain

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Background: Cannabinergic medications have been postulated to demonstrate efficacy in the management of pain. The aim of this systematic review was to assess the analgesic efficacy and adverse effects of cannabinoids when used for the management of acute pain.

Methods: A systematic review was performed by searching the MEDLINE, EMBASE and CENTRAL databases, and the World Health Organization International Clinical Trials Registry Platform for human randomized controlled trials that assessed the analgesic efficacy of cannabinoids compared to placebo or active comparators. The reported outcomes for analgesic efficacy and adverse effects in included studies were qualitatively analysed.

Results: Seven studies, including 611 patients were included in the systematic review. In five studies, cannabinoids were found to provide equivalent analgesia to placebo, in one study the analgesia provided by cannabinoids was superior to placebo, and in one study cannabinoids provided analgesia that was inferior to that provided by placebo. No synergistic or additive analgesic effect was observed when cannabinoids were used in combination with opioids. In five of the seven studies, certain adverse effects were more frequent with cannabinoid treatment than with placebo or active comparator.

Conclusion: On the basis of the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.

Editorial Comment

The pharmacological arsenal for treatment of acute pain is ‘as old as the hills’, and there is a need for drugs with alternative mechanisms of action. Cannabinoids have been a candidate. This systematic review found no cannabinoid analgesic effect superior to placebo, also no analgesic effect of cannabinoids when combined with opioids.

Acute pain is defined as ‘pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship with injury or disease’.¹ Despite advances in medicine, the management of acute pain overall remains a challenge, with estimates of inadequately treated acute postoperative pain as high as 25%.² The mainstay of management of moderate to severe acute pain remains simple analgesia such as paracetamol, non-steroidal anti-inflammatory drugs and opioids in combination with adjunct agents and advanced analgesic techniques as required. Ongoing research is therefore required to improve our ability to manage acute pain and
aid patients’ recovery from surgery, trauma and other acutely painful states.

One novel group of agents that has been trialled for analgesic efficacy in acute pain are cannabinoids. Cannabinoids consist of a heterogeneous group of chemicals, both naturally occurring and synthetic, that act via CB1 and CB2 receptors. Despite the historical belief that they are effective in the management of pain, evidence from randomized controlled trials, along with other non-randomized clinical studies, pre-clinical and basic scientific studies, is conflicting regarding the efficacy of cannabinoid medications in treating acute pain. The analgesic efficacy of cannabinoids in managing acute pain has previously been considered in a systematic review by Campbell and colleagues in 2001 as a sub-group of a larger systematic review investigating the use of cannabinoids in the management of pain in general. However there were a number of limitations to the acute pain sub-group analysis in this systematic review; it included only a limited number of participants drawn from data from a single study, and it failed to include all of the available randomized controlled trials meeting its eligibility criteria that were available at the time. Furthermore, since 2001 additional studies have been published that have investigated the effectiveness of cannabinoids in the management of acute pain and these are yet to be synthesized in a systematic manner. This prompts reconsideration of this topic using systematic review methodology.

We conducted a systematic review of the use of cannabinoids to investigate their analgesic efficacy and observed adverse effects when used to manage acute pain. We hypothesized that cannabinoid medications would not demonstrate analgesic efficacy when used for the management of acute pain.

**Methods**

**Protocol and registration**

The systematic review was conducted in accordance with the PRISMA statement. A protocol for the review was prepared in accordance with the PRISMA-P statement and was prospectively registered with the PROSPERO database (CRD42015027200).

**Eligibility criteria**

Studies included in the systematic review were limited to human clinical randomized controlled trials of any cannabinoid medications that reported analgesic efficacy outcomes in acute pain when compared to placebo or active non-cannabinoid comparators. All studies were included regardless of route of administration, dosage or type of cannabinoid. No exclusion was made on the basis of article language, or on the age of subjects, gender or previous cannabinoid use of participants. Articles in a language other than English were translated prior to inclusion in the systematic review. Table 1 details the population, intervention, comparators and outcomes of interest for the systematic review.

**Search and study selection**

A search of the MEDLINE, EMBASE and CENTRAL databases was conducted using the search strategy “exp Cannabinoids/ or cannab* .mp.” AND (‘acute pain.mp. or exp Acute Pain/’ OR ‘postoperative pain.mp. or exp Pain, Postoperative/’ OR ‘exp Pain, Postoperative/ or postoperative pain.mp.’)” as a keyword search (MEDLINE and EMBASE), and a (title, abstract, keyword) search (CENTRAL). The search was conducted and subsequently updated inclusive to 20th August 2016. Initial title and abstract screening of search results was performed by both authors, and studies were excluded if they did not meet the eligibility criteria. If any uncertainty existed regarding the eligibility of studies after title and abstract screening, then studies were included in the final assessment.

Final assessment of studies was performed by both authors and consisted of an evaluation of the complete manuscript of a study with reference to the eligibility criteria. After eligible studies were

| Table 1 | The population, intervention, comparator and outcomes (PICO) of interest. |
|---------|--------------------------------------------------------------------------|
| Population | Human participants in clinical studies experiencing acute pain. Participants were included regardless of age, gender or previous cannabinoid use. |
| Intervention | The use of cannabinoid medication. |
| Comparator | Placebo or active non-cannabinoid comparator. |
| Outcomes | Analgesic efficacy and adverse effects. |
identified and included, reference lists from included studies were manually searched to identify any articles not found in the initial search strategy.

We also attempted to identify any publication citing the included studies to identify any further eligible articles. This was performed by searching the website of the article publisher (if available) and the Google Scholar database. The World Health Organization International Clinical Trials Registry Platform was searched to identify trials that were completed but not reported with the intention to include these studies if they met eligibility criteria.

Data extraction

Data extracted included the pharmacological agents and dose administered, groups and group sizes, the surgical procedures or other clinical contexts in which studies were performed, the timing of administration of study medication, and the analgesic efficacy outcomes and adverse effects reported in the studies. All data was extracted independently by both authors using a customized, pre-piloted data extraction tool. The primary outcome was the qualitative analysis of the analgesic efficacy of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative analysis of the reported adverse effects. Data from included studies was only considered to have reported a significant difference between cannabinoid and comparator groups when it reported a differences with a $P$ value of $< 0.05$ for study outcomes.

Risk of bias assessment and strength of the body of evidence

The risk of bias in included studies was assessed using the Cochrane Collaboration’s tool for assessing risk of bias, where each paper was assigned a rating of ‘unclear’, ‘low’ or ‘high’ for the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. The strength of the body of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology as applied to systematic reviews.

Results

Study selection and assessment

Details and results of the study assessment process are shown in Fig. 1. The database search

![Fig. 1. Flow diagram for study selection and exclusion.](image-url)
identified 310 unique potentially relevant studies. An additional four studies were identified from the reference lists or citing articles of included studies. No studies were identified from the search of the World Health Organization International Clinical Trials Registry Platform. 292 of these studies were excluded by title and abstract screening as they were either not randomized controlled trials \( (n = 273) \), were not performed in the setting of acute pain \( (n = 8) \), did not investigate cannabinoid medications \( (n = 4) \) or they were non-clinical experimental studies only \( (n = 7) \). Full text copies of 22 articles were reviewed, of which 15 were excluded from the qualitative analysis because they were either not randomized controlled trials \( (n = 7) \), were not performed in the setting of acute pain \( (n = 2) \), duplicated conference abstract of an included study \( (n = 1) \), it was a non-clinical experimental study \( (n = 1) \), abstract of a conference presentation and the authors could not be contacted \( (n = 1) \), a translated version of a study already included in the review \( (n = 1) \), or there was inadequate data presented in the study and the authors could not be contacted \( (n = 2) \).

Study characteristics

The remaining seven studies included in the systematic review were published between 1981 and 2013, and included a total of 611 patients. Details of the studies including treatment groups, group size, procedure(s), and timing of doses of medications are shown in Table 2.

Risk of bias and strength of evidence

Results of the assessment of risk of bias are shown in Table 3. In three studies, the majority of the domains were assessed as being at a low risk of bias,\(^{12-14}\) and in the remaining four studies,\(^{5,15-17}\) most or all domains were assessed as being at an unclear risk of bias. In total, 27 of the 42 domain assessments were assessed as unclear using the Cochrane Collaboration’s tool for assessing risk of bias. In two studies\(^{5,17}\) an unclear risk of bias was found in all domains. The most common reason for making an assessment of an unclear risk of bias across the included studies was due to inadequate description of study methodology that would enable a different result being given, or from incomplete reporting of results. No assessments of a high risk of bias were made in any of the included studies. The strength of evidence was assessed as moderate quality using the GRADE methodology.

Analgesic efficacy results

The analgesic efficacy outcomes reported in the included studies are summarized in Table 4. In five studies,\(^{5,12,13,15,16}\) the analgesic efficacy of cannabinoids was found to be equivalent to that provided by placebo. In one study, the use of a cannabinoid (nabilone) was associated with significantly worse pain scores compared to other groups.\(^{14}\) In only one study,\(^ {17}\) the analgesic efficacy of a cannabinoid agent (levonantradol), found to be superior to that of placebo.

Adverse effects results

The adverse effects outcomes reported in the included studies are summarized in Table 4.

Discussion

The results of this systematic review of seven studies have failed to demonstrate an overall benefit of the use of cannabinoids in the management of acute pain. Of the seven randomized controlled trials included in this systematic review, five demonstrated equivalent analgesia of cannabinoids to that of placebo, one demonstrated analgesia of cannabinoids that was inferior to that of placebo, and only one suggested that analgesia was superior to that of placebo. The conclusions of this systematic review therefore strengthen the evidence against the use of cannabinoids in the management of acute pain.

A previous systematic review\(^ 4\) that assessed the efficacy of cannabinoids in the management of acute pain based its results solely on the study by Jain and colleagues,\(^ {17}\) the lone study included in our review that reported favourable data for the use of cannabinoids. The study by Jain et al.\(^ {17}\) demonstrated a small but statistically significant effect of levonantradol in the management of acute pain. Why the study by Jain et al.\(^ {17}\) reported results that favoured...
analgesic efficacy of levonantradol over placebo is unclear. This study provided only a limited explanation of its methodology which made assessment for risk of bias difficult. Despite the results by Jain et al.17 in favour of levonantradol, the previous systematic review by Campbell et al.4 concluded that levonantradol provided pain relief only equivalent to that of codeine, and therefore cannabinoids were unlikely to be useful in the management of moderate to severe postoperative pain. Our results extend the finding in this previous systematic review and suggest no role for the use of cannabinoids in the management of acute pain.

The study by Ostenfeld et al.16 also demonstrated no overall benefit to the use of cannabinoids. However one outcome in that study, the ‘global evaluation of medication’ at 24 h post-third molar tooth extraction, demonstrated a significantly greater median evaluation score for cannabinoid compared to placebo. When this outcomes was assessed at the 10 h

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Table 2 Details of included studies.

| Reference | Procedure(s) | Treatment group | No. of Patients | Timing of dose |
|-----------|--------------|-----------------|-----------------|----------------|
| Beaulieu (2006)14 | Orthopaedic, gynaecology, urology, plastic or general surgery | Nabilone 1 mg PO | 11 | 1 h prior to induction of anaesthesia, then every 8 h for the first 24 h postoperatively |
| Buggy et al. (2003)12 | Elective abdominal hysterectomy | ∆-9-THC 5 mg PO | 20 | On second postoperative day when patient requested analgesia |
| Guillaud et al. (1983)5 | Renal surgery involving lumbar incision | Levonantradol 1 mg IM | 25 | Once patient fully awake in recovery room |
| Jain et al. (1981)17 | Moderate to severe acute postoperative, fracture or trauma pain | Levonantradol 1.5 mg IM | 10 | Not stated |
| Kalliomäki et al. (2013)15 | Removal of impacted lower third molar tooth | AZD1940 800 µg PO | 61 | 1.5 h prior to surgery commencing |
| Ostenfeld et al. (2011)16 | Third molar tooth extraction | GW842166 100 mg PO + Placebo‡ | 34 | Initial dose administered preoperatively within 1 h of surgery. Second dose administered postoperatively 4 h after initial dose |
| Seeling et al. (2006)13 | Radical retropubic prostatectomy with regional lymphadenectomy | Dronabinol 5 mg PO | 50‡ | Eight doses in total, commencing the evening prior to the day of surgery, and then 07:00 h, 14:00 h and 22:00 h on the day of surgery, and then 06:00 h, 14:00 h and 22:00 h daily thereafter until eight doses administered. |

IM, intramuscular; PO, per oral; THC, tetrahydrocannabinol. *The study by Jain et al. was performed in two segments comparing the 1.5 mg and 2 mg doses of levonantradol with placebo, and the 2.5 mg and 3 mg doses of levonantradol with placebo. The placebo group of each study segment consisted of eight patients, however, the results in the published article combined the two segments and included a single placebo group consisting of 16 patients. †Route of administration of placebo and ibuprofen not explicitly stated in paper. ‡Five patients withdrew from the study after randomization. In three patients the decision was made intraoperatively to not proceed with prostatectomy, and two patients remained intubated and was transferred to the intensive care unit postoperatively. Three of these five patients were randomized to the placebo group and the remaining two were randomized to the dronabinol group. An additional five patients were randomized to account for the withdrawal of these patients.
post-operative timepoint it did not demonstrate a significant difference compared to placebo. Furthermore, no statistically significant differences were detected in other analgesic outcomes in this study such as the weighted mean visual analogue scale scores, verbal rating scale scores, or time to administration of rescue analgesia. Ostenfeld and colleagues concluded that the global evaluation was not a reliable indicator of analgesia as it may be influenced by other factors, and that the significance of their findings at 24 h should be interpreted with caution as it was not consistent with other measures of pain assessment recorded in this study.

The results of this systematic review differ from those obtained from systematic reviews that suggest a role of cannabinoids in pain management outside of the acute setting. These include evidence for the use of cannabinoids in managing chronic non-cancer pain and painful HIV-associated peripheral neuropathy. It is unclear why differences exist between acute pain and other types of pain, but it may be due to the neuroplastic changes that occur in chronic pain. Based on findings from experimental studies, it has been suggested that chronic pain results in changes in the endocannabinoid system including upregulation of cannabinoid receptors, changes in cannabinoid receptor function, altered formation or release of endocannabinoids, and synergistic interaction with other mediators of chronic pain. It is unknown if these changes also occur in acute pain, however, differences in the endocannabinoid system between acute and chronic pain would help to explain different analgesic responses to cannabinoid medications.

A small body of evidence has accumulated that points toward, a potential synergistic interaction between cannabinoids and opioids that results in improved pain relief. Studies included in this systematic review that assessed the analgesic efficacy of cannabinoids when combined with opioids, failed to demonstrate any additional analgesic benefit when used together. Similar research has suggested a synergistic interaction between cannabinoids and alpha agonists. Alpha agonists such as clonidine and dexmedetomidine are often used as co-analgesic agents in the management of acute pain and their combination with cannabinoids may yet prove to be an effective analgesic approach. However, clinical evidence to support their co-administration is lacking as no randomized controlled trials have yet combined cannabinoids with alpha agonists in the management of acute pain.

A role for the endocannabinoid system in nociception and acute pain is not entirely without basis, yet clinical evidence for this is limited. Azim and colleagues correlated concentrations of various endocannabinoid mediators measured in serum, cerebrospinal fluid and synovial fluid with pain level and opioid consumption following total knee arthroplasty in patients suffering from osteoarthritis. They found that levels of synovial and cerebrospinal fluid 2-arachidonoyl glycerol, an endogenous cannabinoid receptor agonist, were significantly correlated with postoperative pain.

### Table 3 Results of the assessment of risk of bias.

| Reference           | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|---------------------|---------------------------------------------|------------------------------------------|----------------------------------------------------------|-------------------------------------------------|-----------------------------------------|--------------------------------------|
| Beaulieu (2006)     | Low                                         | Low                                      | Low                                                      | Low                                             | Low                                     | Unclear                              |
| Buggy et al. (2003) | Low                                         | Low                                      | Low                                                      | Unclear                                         | Low                                     | Unclear                              |
| Guillaud et al. (1983) | Unclear                                    | Unclear                                  | Unclear                                                  | Unclear                                         | Unceal                                  | Low                                  |
| Jain et al. (1981)  | Unclear                                     | Unclear                                  | Unclear                                                  | Unclear                                         | Unclear                                 | Low                                  |
| Kalliomäki et al. (2013) | Unclear                                  | Unclear                                  | Unclear                                                  | Unclear                                         | Low                                     | Unclear                              |
| Ostenfeld et al. (2011) | Unclear                                    | Unclear                                  | Unclear                                                  | Unclear                                         | Low                                     | Low                                  |
| Seeling et al. (2006) | Low                                        | Low                                      | Unclear                                                  | Unclear                                         | Low                                     | Low                                  |
| Reference        | Analgesic Efficacy                                                                 | Outcome                                      | Result                                                                 |
|------------------|-----------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------|
| Beaulieu (2006)  | Quantity of morphine consumed via PCA                                              | Overall assessment of NVS pain scores at    | No statistically significant differences between groups at the          |
|                  |                                                                                   | rest (1/10)                                  | loading (recovery room) phase, or during the 1–8 h, 9–16 h or 17–24 h |
|                  |                                                                                   |                                               | timepoints. Total 24 h morphine                                       |
|                  |                                                                                   |                                               | consumption via PCA was 43.3 ± 8.2 mg in the placebo                    |
|                  |                                                                                   |                                               | group, 36.9 ± 5.9 mg in the ketoprofen group, 39.0 ± 6.8 mg             |
|                  |                                                                                   |                                               | in the nabilone 1 mg group, and 45.4 ± 8.1 mg in the nabilone 2 mg      |
|                  |                                                                                   |                                               | group (\(P = 0.84\)).                                                |
|                  |                                                                                   | Overall incidences of nausea and vomiting,  | quality of sleep, euphoria, sedation, pruritus and mood not            |
|                  |                                                                                   | vomiting, and mood not significantly different between groups, however, | sedation scores were significantly higher in the nabilone 2 mg group    |
|                  |                                                                                   | sedation scores were significantly higher    | compared to the ketoprofen group during the 17–24 h period (p value   |
|                  |                                                                                   | in the nabilone 2 mg group compared to       | not provided). No psychotic episodes recorded. No serious adverse       |
|                  |                                                                                   | the ketoprofen group during the 17–24 h      | events recorded.                                                      |
|                  |                                                                                   | period (p value not provided).                |                                                                         |
| Buggy et al. (2003) | Mean VAS pain scores at rest and movement (1/10)                                | No statistically significant differences      | Significantly more patients in the \(\delta\)-9-THC group reported     |
|                  |                                                                                   | existed between \(\delta\)-9-THC and        | increased awareness of surroundings compared to those in the placebo   |
|                  |                                                                                   | placebo mean VAS pain scores at rest or      | group (40% compared to 5%; \(P = 0.04\)). No other statistically       |
|                  |                                                                                   | movement at the 0 h, 2 h, 4 h or 6 h          | significant differences existed                                        |
|                  |                                                                                   | timepoints.                                 | between groups for adverse effects.                                    |
|                  |                                                                                   | SPID at rest was 8.8 (1.7) in the placebo    |                                                                         |
|                  |                                                                                   | group and 4.9 (1.2) in the \(\delta\)-9-THC  |                                                                         |
|                  |                                                                                   | group (95% CI of differences = −0.2 to 8.1)  |                                                                         |
|                  |                                                                                   | (p value not provided).                     |                                                                         |
|                  |                                                                                   | Time to rescue analgesia                     |                                                                         |
|                  |                                                                                   | No statistically significant differences       |                                                                         |
|                  |                                                                                   | between groups. The mean (SEM)               |                                                                         |
|                  |                                                                                   | was 217 (34) min in the placebo group and    |                                                                         |
|                  |                                                                                   | 163 (17) min in the \(\delta\)-9-THC         |                                                                         |
|                  |                                                                                   | group (p value not provided).                |                                                                         |
|                  |                                                                                   | % of patients receiving escape analgesia by 8 h |                                                                         |
|                  |                                                                                   | Pethidine group demonstrated significantly   |                                                                         |
|                  |                                                                                   | lower pain scores compared to                |                                                                         |
|                  |                                                                                   | levonantradol 1 mg, levonantradol 2 mg and   |                                                                         |
|                  |                                                                                   | placebo groups (\(P < 0.001\)) (timecourse  |                                                                         |
|                  |                                                                                   | of differences not specified).               |                                                                         |


Table 4 (Continued)

| Reference | Analgesic Efficacy | Overall Assessment | Adverse Effects |
|-----------|-------------------|-------------------|----------------|
|           | Outcome | Result                                                                 |               |
|           | VAS pain scores over first 6 h | Pethidine group demonstrated significantly lower pain scores compared to levonantradol 1 mg, levonantradol 2 mg and placebo groups ($P < 0.01$) (timecourse of differences not specified). |               |
|           | Global analgesic effect at 24 h post-dose | Pethidine provided significantly better analgesia compared to levonantradol 1 mg, levonantradol 2 mg and placebo groups ($P < 0.05$). There were no differences between the remaining groups. |               |
|           | Doses of supplementary analgesic administered | Number of patients requiring zero doses of supplementary analgesic medication was 4, 5, 8 and 1; one dose was 7, 9, 7 and 8; two doses was 11, 8, 6 and 5; and three doses was 3, 3, 4 and 10 in the levonantradol 1 mg, levonantradol 2 mg, pethidine and placebo groups respectively (statistical significance not reported). |               |
|           | Time to administration of supplementary analgesia | Patients in pethidine group waited significantly longer to request supplementary analgesia compared to other groups ($P < 0.05$). Patients in the pethidine group waited longer than 400 min to request the first dose, approximately 800 min to request the second dose, and approximately 1000 min to request the third dose of rescue analgesia. |               |
| Jain et al. (1981) | 6 h AUDC pain intensity score | AUDC pain intensity scores were 5.20 in the placebo group compared to 9.95 in the levonantradol 1.5 mg group, 9.84 in the levonantradol 2 mg group, 11.26 in the levonantradol 2.5 mg group and 9.10 in the levonantradol 3 mg group. Differences were statistically significant between the placebo and levonantradol 2 mg groups ($P < 0.01$), and the placebo and levonantradol 1.5 mg, 2.0 mg and 3.0 mg groups ($P < 0.05$). |               |
|           | 6 h AUDC pain relief score | AUDC pain relief scores were 9.87 in the placebo group compared to 16.48 in the levonantradol 1.5 mg group, 16.90 in the levonantradol 2 mg group, 19.10 in the levonantradol 2.5 mg group and 16.08 in the levonantradol 3 mg group. Differences were statistically significant between the placebo and levonantradol 2 mg and 2.5 mg groups ($P < 0.01$), and the placebo and levonantradol 1.5 mg and 3 mg groups ($P < 0.05$). |               |
|           | 6 h AUDC pain analogue score | AUDC pain analogue scores were 36.32 in the placebo group compared to 71.58 in the levonantradol 1.5 mg group, 70.33 in the levonantradol 2 mg group, 77.61 in the levonantradol 2.5 mg group and 61.18 in the levonantradol 3 mg group. Differences were statistically significant between the placebo and levonantradol 1.5 mg, 2 mg and 2.5 mg groups ($P < 0.01$), and the placebo and levonantradol 3 mg groups ($P < 0.05$). |               |
|           | 6 h global score | Global scores were 1.94 in the placebo group compared to 3.33 in the levonantradol 1.5 mg group, 3.30 in the levonantradol 2 mg group, 3.50 in the levonantradol 2.5 mg group and 3.00 in the levonantradol 3 mg group. Differences were statistically significant between the placebo and levonantradol 2 mg group with a history of depression experienced intense agitation and hallucinations necessitating parenteral administration of diazepam. One patient in the levonantradol 1 mg group experienced self-limiting episode of agitation of moderate severity. No significant difference in FVC and FEV1 results. |               |
|           |                   |                   | 2/16 patients in placebo group reported experiencing an adverse effect compared to 23/40 receiving levonantradol (statistical significance not reported). 3 patients receiving levonantradol reported hallucinations. No significant difference POMS scores (statistical significance not reported). No patients withdrew from the study due to adverse effects. |               |
### Table 4 (Continued)

| Reference        | Outcome                  | Result                                                                                   | Overall Assessment | Adverse Effects                  |
|------------------|--------------------------|------------------------------------------------------------------------------------------|--------------------|----------------------------------|
| Kalliomäki et al. (2013) | Mean postoperative pain AUC<sub>0-8h</sub> | 355 mm·h (90% CI = 316–394) in AZD1940 group, 356 mm·h (90% CI = 320–392) in placebo group, and 129 mm·h (90% CI = 97–161) in naproxen group. No statistically significant difference existed between the AZD1940 group and placebo (P = 0.48), however the differences between naproxen and placebo were statistically significant (P < 0.0001). | +/– | Postural dizziness, nausea, hypotension and headache more frequently reported in AZD1940 group compared to placebo and naproxen (statistical significance not reported). Patients receiving AZD1940 reported significantly higher VAMS scores compared to placebo for the ‘high’ subscale up to 7 h post-dose, and the ‘sedated’ subscale up to 9 h post-dose (p values not provided). No serious adverse events were recorded. |
|                  | Mean pain on jaw movement AUC<sub>0-8h</sub> | 342 mm·h (90% CI = 301–383) in AZD1940 group, 337 mm·h (90% CI = 300–374) in placebo group, and 135 mm·h (90% CI = 98–171) in naproxen group. No statistically significant difference existed between AZD1940 group and placebo (P = 0.06), however the differences between naproxen and placebo were statistically significant (P < 0.0001). | No statistically significant differences existed between AZD1940 and placebo (P = 0.06), however the time to first administration of rescue analgesia was statistically significantly sooner in the naproxen group compared to placebo (P < 0.0001). |
|                  | Proportion of patients requesting rescue analgesia | 61% for AZD1940, 73% for placebo and 23% for naproxen groups. Differences between naproxen and placebo were statistically significant (P < 0.0001). Differences between AZD1940 and placebo were not statistically significant (P = 0.08). | No statistically significant differences existed between AZD1940 and placebo (P = 0.06), however the time to first administration of rescue analgesia was statistically significantly sooner in the naproxen group compared to placebo (P < 0.0001). |
| Ostenfeld et al. (2011) | Weighted means LS VAS Score at 10 h post-surgery | 53.98 mm in the placebo group, 55.80 mm in the GW842166 100 mg group, 45.86 mm in the GW842166 800 mg group and 22.19 mm in the ibuprofen group. No statistically significant differences were observed between placebo and either the GW842166 100 mg group (point estimate 1.82 mm [95% CI = −0.42 to 13.07]) or the GW842166 800 mg group (point estimate −8.12 mm [90% CI = −20.87 to 4.62]). However, a clinically and statistically significant difference in VAS score was observed between placebo and ibuprofen (point estimate −31.79 mm [90% CI = −44.16 to −19.43]). | +/– | Adverse effects were similar across the four groups. No patients withdrew due to adverse effects. One non-fatal serious adverse event occurred each in the GW842166 800 mg group and ibuprofen group (submandibular abscess and adhesional intestinal obstruction respectively), but neither were judged to be related to the study medication. |
|                  | Weighted means LS VRS Score at 10 h post-surgery | 2.17 in the placebo group, 2.16 in the GW842166 100 mg group, 1.86 in the GW842166 800 mg group and 1.25 in the ibuprofen group. No statistically significant differences were observed between placebo and either the GW842166 100 mg group (point estimate −0.01 [95% CI = −0.34 to 0.32]) or the GW842166 800 mg group (point estimate −0.31 [95% CI = −0.68 to 0.07]). A significant difference was observed between placebo and ibuprofen groups (point estimate −0.92 to −1.28). | +/– | Adverse effects were similar across the four groups. No patients withdrew due to adverse effects. One non-fatal serious adverse event occurred each in the GW842166 800 mg group and ibuprofen group (submandibular abscess and adhesional intestinal obstruction respectively), but neither were judged to be related to the study medication. |
Table 4 (Continued)

| Reference | Analgesic Efficacy | Overall | Adverse Effects |
|-----------|-------------------|---------|----------------|
|           | Outcome Result | Assessment | |
| Global evaluation of medication | At the 10 h timepoint, no statistically significant differences existed in the median evaluation score between placebo and GW842166 100 mg group (median difference 0.0; \( P = 0.5487 \)) or GW842166 800 mg group (median difference 0.0, \( P = 0.2165 \)), however, ibuprofen had a significantly higher evaluation score compared to placebo (median difference 2.0; \( P < 0.0001 \)). At the 24 h timepoint, no statistically significant difference was observed between placebo and the GW842166 100 mg group (median difference 0.0; \( P = 0.0932 \)), however, the evaluation score for placebo was significantly lower than that of the GW842166 800 mg group (median difference 1.0; \( P = 0.0194 \)) and ibuprofen group (median difference 1.0; \( P < 0.0001 \)). |
| Time to first dose of rescue medication | Kaplan–Meier estimate of median time to rescue medication was 4.75 h for placebo, 4.74 h for GW842166 100 mg, 4.83 h for GW842166 800 mg and 11.47 h for ibuprofen. The likelihood of requiring rescue medication was significantly lower for ibuprofen (hazard ratio 0.77, \( P = 0.0054 \)), but not for GW842166 100 mg (hazard ratio 0.95, \( P = 0.8482 \)) or GW842166 800 mg (hazard ratio 0.95, \( P = 0.7023 \)). |
| Seeling et al. (2006) | NRS pain scores at rest | Median scores between 1 and 2.5 in all patients, interquartile range never exceeded 3. No significant difference between the groups (\( P > 0.1 \)). | +/- |
| | NRS pain scores at maximum cough | Median pain between 3.5 and 4.5. No significant difference between groups (\( P > 0.1 \)). |
| | Quantity of piritramide consumed via PCA | Median consumption 74 mg (IQR 44–90 mg) in the placebo group compared to 54 mg (IQR 46–99 mg) in the dronabinol group. No significant difference between groups (p value not provided). |

+, efficacy in favour of cannabinoid; --, efficacy in favour of placebo; +/-, efficacy favours neither cannabinoid or placebo; AUC, area under the curve; AUDC, area under the difference curve; CI, confidence interval; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; LS, least squares; NVS, numerical verbal scale; PCA, patient-controlled analgesia; POMS, profile of mood state; PONV, postoperative nausea and vomiting; SEM, standard error of the mean; SPI, **D_6**, summed pain intensity differences over 6 h; THC, tetrahydrocannabinol; VAMS, visual analogue mood scale; VAS, visual analogue scale; VRS, verbal rating scale.
scores and opioid consumption. A limitation of the study by Azim and colleagues is the potential confounding influence of participants’ osteoarthritis and its associated chronic pain state prior to surgery. It is therefore unclear whether these findings could be replicated in a patient population without antecedent chronic pain.

Outside of randomized controlled trials, there is only limited clinical evidence for the use cannabinoids in the management of acute pain. Holdcroft and colleagues performed a multicentre dose escalation study assessing the analgesic efficacy of an oral cannabis extract in postoperative patients with at least moderate pain following cessation of patient-controlled analgesia. The study found significant dose-related improvements in rescue analgesia requirements when the two highest doses were used. However the methodology of this study has been criticized due to a lack of blinding, the absence of a placebo group and short duration of follow-up. Furthermore, this study was terminated due to the occurrence of a serious vasovagal adverse event in a patient receiving the highest dose of cannabinoid. In contrast, Miller and colleagues reported the results of a retrospective matched-control study investigating the use of dronabinol as an adjunct analgesic agent in 32 burns patients with a history of recreational cannabis use and compared them to the results of 32 matched controls. The study found that patients receiving dronabinol used significantly greater amounts of analgesic and anxiolytic medications to achieve equivalent pain relief when compared to controls. Individual case reports have also been published that have suggested a potential benefit to using cannabinoid medications postoperatively in patients with poorly controlled pain, however, little can be drawn from these reports due to the anecdotal nature of this evidence.

Across the seven studies in this systematic review, cannabinoids were found to be well-tolerated, with most reported adverse effects only mild to moderate in severity. There did appear to be a tendency for some adverse effects to occur more frequently in the cannabinoid groups than in placebo. In five of the seven studies, cannabinoids demonstrated greater adverse effects compared to placebo for some types of adverse events or in particular time periods. However, analysing the adverse effect profile of cannabinoids was difficult due to differences between studies in reporting and defining adverse effects, and that some of the studies did not assess or report the statistical significance of differences between groups. In one study, it was reported that patients receiving placebo were more likely to report postoperative nausea and vomiting compared to dronabinol, but the statistical significance of this finding was not reported. Furthermore a recent randomized controlled trial assessing the efficacy of intravenous tetrahydrocannabinol in the prevention of postoperative nausea and vomiting recommended against its use due to an unacceptable side effect profile and limited efficacy. The profile of adverse effect of cannabinoids in the management of acute pain that we found are in keeping with the results of a previous systematic review of the adverse effects of medical cannabinoids which found that the short-term use of cannabinoids was associated with an increased risk of non-serious adverse effects when used in the treatment of a range of pain and non-pain indications.

Substantial heterogeneity existed between the studies included in this systematic review. Studies included in this systematic review examined the analgesic efficacy of different cannabinoid medications with different mechanisms of action and activity at the CB1 and CB2 receptors. Furthermore studies used different protocols, different comparator drugs, different clinical models of acute pain, different populations and different methods of assessing and reporting pain. Overall the results in the included studies were similar, but it is nevertheless possible that the heterogeneity between studies may have influenced the collective interpretation of their findings. A limitation of our review relates to the assessment of the risk of bias, specifically, that the risk of bias was unclear for a high proportion of the assessments. Commonly the reasons for this were inadequate description of study methodology or incomplete reporting of results. Had these details been available, then it is possible that a high risk of bias may have been found in some studies. If this were true, then our results would have to be interpreted with a higher degree of caution,
and the grading of the quality of evidence would be lower than that initially afforded by our review. Other limitations to this systematic review include the limited sample sizes, the small number, and the age of some of the studies. However excluding the smaller or older studies from consideration, the overall findings of this systematic review would not be altered, suggesting that the influence of these factors was not substantial. Similarly, the strongly negative findings from the included studies suggest that there would be only minimal impact from any publication bias arising from non-publication of negative studies. The findings of this systematic review nevertheless be enhanced by including future larger prospective randomized controlled trials.

The role of cannabinoid medications in the management of various medical conditions is subject to ongoing interest from healthcare practitioners, researchers and the general public alike. It is therefore important that the best available evidence for their use be synthesized in a systematic manner to provide clinicians, researchers and healthcare consumers with the most objective information to best support decision-making and inform future research. This systematic review has found that on the basis of the currently available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain.

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