Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis

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BACKGROUND: There is a lack of consensus on the role of selective cannabinoids for the treatment of neuropathic pain (NP). Guidelines from national and international pain societies have provided contradictory recommendations. The primary objective of this systematic review and meta-analysis (SR-MA) was to determine the analgesic efficacy and safety of selective cannabinoids compared to conventional management or placebo for chronic NP.

METHODS: We reviewed randomized controlled trials that compared selective cannabinoids (dronabinol, nababine, nabiximols) with conventional treatments (eg, pharmacotherapy, physical therapy, or a combination of these) or placebo in patients with chronic NP because patients with NP may be on any of these therapies or none if all standard treatments have failed to provide analgesia and if these treatments have been associated with adverse effects. MEDLINE, EMBASE, and other major databases up to March 11, 2016, were searched. Data on scores of numerical rating scale for NP and its subtypes, central and peripheral, were meta-analyzed. The certainty of evidence was classified using the Grade of Recommendations Assessment, Development, and Evaluation approach.

RESULTS: Eleven randomized controlled trials including 1219 patients (614 in selective cannabinoid and 605 in comparator groups) were included in this SR-MA. There was variability in the studies in quality of reporting, etiology of NP, type and dose of selective cannabinoids. Patients who received selective cannabinoids reported a significant, but clinically small, reduction in mean numerical rating scale pain scores (0–10 scale) compared with comparator groups (−0.65 points; 95% confidence interval, −1.06 to −0.23 points; P = .002, I² = 60%; Grade of Recommendations Assessment, Development, and Evaluation: weak recommendation and moderate-quality evidence). Use of selective cannabinoids was also associated with improvements in quality of life and sleep with no major adverse effects.

CONCLUSIONS: Selective cannabinoids provide a small analgesic benefit in patients with chronic NP. There was a high degree of heterogeneity among publications included in this SR-MA. Well-designed, large, randomized studies are required to better evaluate specific dosage, duration of intervention, and the effect of this intervention on physical and psychologic function. (Anesth Analg 2017;XXX:00–00)

Neuropathic pain (NP) is common with a prevalence of 7% to 8% of the population.1 Challenges in management of NP include a high failure rate with available pharmacotherapy.2 It is acknowledged that, on average, for every 3 patients who receive treatments for NP, only one has analgesic benefit.3 In the last decade, the use of cannabis and selective cannabinoids (synthetic cannabinoids containing only tetrahydrocannabinol [THC] and cannabis-based medicinal extracts containing a combination of THC and cannabidiol [CBD]) has gained popularity for the treatment of NP.4 Cannabinoid receptors (CB1 and CB2) have been linked to processes in pain modulation. There is a lack of consensus regarding the role of selective cannabinoids in treating NP that is refractory to recommended first and second-line medications (anticonvulsants, antidepressants, opioids). In its most recent published guidelines, the Canadian Pain Society advocates for the use of selective cannabinoids as the third-line option for NP whereas the Special Interest Group on NP of the International Association for the Study of Pain has provided a weak recommendation against the use of these medications for NP.5,6 This dichotomy of opinion originates from conflicting results of randomized controlled trials (RCTs) involving the

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use of small study populations, different types of selective cannabinoids, varying periods of follow-up, a range of dosages, and inclusion of chronic pain syndromes with unclear neuropathic characteristics. There have also been recent attempts to synthesize available evidence on analgesic and adverse-effect profile of selective cannabinoids in patients with NP.\textsuperscript{10,11} However, the methodologies and conclusions of these reviews are hampered by inclusion of trials that enrolled participants with heterogeneous phenotypes (neuropathic and non-NP), variability in assessment of domains of pain, and absence of meta-analysis resulting in lack of information on effect size and its confidence limits.

A systematic review and meta-analysis (SR-MA) of this topic, by synthesizing the available evidence, would help arrive at conclusions regarding the benefits and risks of selective cannabinoids as well as dose-response effects. The primary objective of this SR-MA was to determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic NP after at least 2 weeks following commencement of treatment. Clinical recommendations based on the guidelines from the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group based on the result of this SR-MA have also been provided.

METHODS
This SR-MA was conducted according to the recommendations of the Cochrane Collaboration\textsuperscript{12} and it is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. This SR-MA was registered with PROSPERO (an international prospective register of systematic reviews; #CRD42016036310).

Search Strategy and Study Selection
We conducted comprehensive, serial searches of the literature through March 11, 2016. The following databases were searched: EMBASE, 1947 onward; MEDLINE, 1946 onward; MEDLINE In-Process and Other Non-Indexed Citations (all using the OvidSP Platform); and Cochrane Database of Systematic Reviews. PROSPERO and Cochrane Central Register of Controlled Trials were included to identify reviews or trials that may have been published but missed during the initial search on MEDLINE and EMBASE. We also searched Google Scholar (first 200 search results were reviewed) to complement search results from the aforementioned databases with the objective of accessing all content relevant to the topic. Proceedings of the major annual meetings of anesthesiology and pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched. We also searched for RCTs in the meta-register of Controlled Trials (www.clinicaltrials.gov). We restricted our search to trials involving human subjects and manuscripts published in English language. Finally, experts with clinical and research experience on the role of selective cannabinoids for NP were also consulted. For EMBASE and MEDLINE, both controlled vocabulary terms (EMBASE-Emtree; MEDLINE-MeSH) and text word searching were conducted for each of the following search segments: cannabinoid (dronabinol, nabilone, nabiximols, THC, CBD, THC-CBD, THC/CBD); pain (hyperalgesia, allodynia, dysesthesia, paresthesia); nerve dysfunction (neuropathic, neuropathy, neuropathies); RCT (random allocation, placebo). We applied a highly sensitive search strategy to identify studies. Details of our search strategy are provided in Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/B747. We complemented our search by reviewing the bibliographies of every selected article to look for possible additional articles that had not been retrieved by our electronic search. Two authors (H.M. and A.B.) independently evaluated titles, abstracts, and full texts according to the inclusion criteria. All instances of discordance were discussed between the investigators to reach a consensus.

Criteria for Considering Trials for This Review
Trials. Type: We considered only RCTs for this review that compared the effect of selective cannabinoids (dronabinol, nabilone, and nabiximols) containing synthetic THC or a combination of extracted THC and CBD versus placebo or standard treatment.

Follow-up Period: Trials with a follow-up period of at least 2 weeks following initiation of treatment were included.

Diagnosis of NP: Trials that reported on diagnosis of central and/or peripheral NP based on etiology (eg, multiple sclerosis and diabetes mellitus), clinical presentation, validated questionnaires for NP, and/or investigations including quantitative sensory testing (QST) were included.

We prespecified eligibility criteria using the population, intervention, comparator, and outcomes as follows.

Participants: Only trials on human subjects above 18 years of age that had NP for at least 3 months were included in this SR-MA. Intensity of pain had to be moderate or severe (4 or higher on a 0–10 numerical rating score [NRS] or ≥40/100 for Visual Analog Scale [VAS] for pain). Participants enrolled in these studies may have been on other types of analgesics but pain level and doses needed to be stable prior to study enrollment.

Interventions and Comparators: Intervention was defined as administration of any of the 3 prescription selective cannabinoids (dronabinol, nabilone, and nabiximols) for at least 2 weeks in addition to the baseline pain regimen. The intended maximum daily dose of the selective cannabinoid in the trial methodology and the daily mean dose used were extracted. The comparators were placebo or standard management [pharmacotherapy [antidepressants, anticonvulsants, anti-inflammatories, opioids], physical therapy, or a combination of these] for the treatment of NP because patients with NP may be on any of these therapies, or none, if all standard treatments have failed to provide analgesia and/or if these treatments have been associated with adverse effects. Among open-label extended trials following an experimental RCT study period, only the RCT study period results were extracted and used for this review. We excluded reviews on cannabis and other selective nonprescription cannabinoids due to the lack of information on chemical composition and dose administered to participants.
Outcomes: The primary outcome was intensity of pain recorded after a minimum of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Intensity scores reported on a VAS (0—no pain to 10—worst possible pain) were transformed to a 0 to 10 NRS scale. So as to be inclusive given the paucity of well-designed trials, we chose to include trials that assessed the primary outcome at a wide range of time intervals because the duration of analgesic effect of selective cannabinoids depends on the interventional regimen (usually slow titration in the first few days following initiation of therapy). The following were considered as secondary outcomes if measured on validated scales: presence or absence of analgesia defined as reduction in pain scores (NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids (eg, dizziness, somnolence, muscle spasms, worsening pain, dry mouth).

Risk of Bias Assessment for Individual Trials
Two review authors (H.M. and A.B.) independently assessed the risk of bias for each included study using the Cochrane Collaboration’s instrument for assessing the risk of bias. Any disagreement was resolved through discussion or, if necessary, arbitration by a third reviewer (D.E.M.). The risk of bias instrument assesses the following domains: generation of the allocation sequence, allocation concealment, blinding of investigators and participant, blinding of Outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias that have less empirical evidence of bias but together may be considered important (unequal distribution of prognostic factors, industry funding, industry authorship, trial stopped early). Each item was classified as low, unclear, or high risk of bias. A decision to classify “overall bias” as low, unclear, or high was made by the reviewers using the following method:

- High: any trial with a high risk of bias listed on 3 or more domains.
- Unclear: any trial with a high risk of bias listed on more than 1 but less than 3 domains.
- Low: any trial with a high risk of bias on none or 1 domain and with no significant methodologic concerns that may have affected the study results.

We also intended to use a funnel plot (for assessment of its asymmetry to assess publication biases [citation bias, selective outcome reporting]) and Begg’s and Egger’s tests if a sufficient number of studies (10 or more) were available to apply these tests.

Data Collection
The reference data, populations, and outcomes were extracted from the articles into prespecified tables using a standardized data extraction form. The data-collection form was pilot-tested before its use. We extracted information on studies’ general characteristics (including design, number of arms, and primary outcomes), participants (characteristics of the populations, sample size, duration, and intensity of pain), and experimental intervention (type of selective cannabinoid, doses, and administration regimes). Dichotomous outcomes were extracted as the presence or absence of neuropathic scale and QST for the diagnosis of NP. For continuous data (pain NRS scores), we extracted means and standard deviations (SDs) from tables or graphs provided in the publications. If not reported, the SDs were obtained from confidence intervals (CIs) or P values that related to the difference between means in the 2 groups. Median values and interquartile ranges were converted to mean and SD (if data appeared to be normally distributed) using accepted techniques. We also contacted authors of studies included in our SR-MA when we needed more information about their analysis or reported results.

Data Synthesis and Analysis
We expected heterogeneity because of diverse populations with NP and doses of selective cannabinoids administered, and therefore, we used DerSimonian and Laird random effects meta-analysis models. Heterogeneity was assessed with the Q test, and Higgins I² statistic was used to quantify it (I² >50% indicates substantial heterogeneity). The estimated mean effect of each study of these outcomes was calculated with the respective 95% CI, and the pooled effect was then assessed. A P value of < .05 was considered significant for the analysis of the primary outcome (difference between pain scores). Bonferroni adjustment for multiple testing was not performed as per recommendations in the Cochrane Handbook. The Mantel-Haenszel method was used for calculating the pooled relative risk (risk ratio) with corresponding 95% CI. Investigation of sources of heterogeneity was based on analysis of prespecified subgroups for the primary outcome including type of selective cannabinoid (THC-CBD versus THC) and quality of trials (high versus unclear or low risk of bias). We performed random-effects meta-regression of the standardize mean difference (effect size) using both a restricted maximal likelihood approach, which assumes a normal distribution, and the DerSimonian and Laird method, which assumes a non-normal distribution, for between-study variance.

A sample size calculation was performed to estimate the number of patients required to detect a difference of 1.5, 1, or 0.5 points (on the 0–10 NRS for pain) between the selective cannabinoid and comparator groups with a SD of 2.0. Sample sizes of 40, 86, and 338 subjects per group, respectively, were required to obtain results with a probability of type I error of 5% and type II error of 10%. It should be recognized that the power is likely to be substantially lower for the subgroup analysis because of lesser number of observations. All statistical analyses were performed with the Review Manager (RevMan version 5.2.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and SAS version 9.3 (The SAS Institute, Cary, NC).

Quality of Evidence
The quality of evidence was assessed with GRADE methodology for the primary outcome. The quality of evidence was classified as high, moderate, low, or very low for each outcome based on the risk of bias, inconsistency, indirectness,
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Pain Diagnosis</th>
<th>Diagnosis of Neuropathic Pain</th>
<th>Type of Pain</th>
<th>Duration of Pain In Years (Range or SD)</th>
<th>Baseline Pain NRS (Range or SD)</th>
<th>Age in Years (Range), Gender (M/F)</th>
<th>Number of Subjects in Each Group (Can/Com)</th>
<th>Active Rx, Route</th>
<th>Comparator</th>
<th>Duration of Treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svendsen, 2004&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Multiple sclerosis</td>
<td>Clinical and QST</td>
<td>Central</td>
<td>4.5 (0.3–12)</td>
<td>5.5 (3.0–8.0)</td>
<td>50 (20–55); 10/14</td>
<td>24 (24/24)</td>
<td>Dronabinol po—daily dose 2.5–10 mg for 3 wk</td>
<td>Placebo</td>
<td>3 weeks</td>
<td>Crossover trial (treatments separated by a 3-wk washout period); pre-existing neuropathic pain medication not continued (except paracetamol)</td>
</tr>
<tr>
<td>Berman, 2004&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Neuropathic pain from brachial plexus root avulsion</td>
<td>Clinical</td>
<td>Central</td>
<td>5.0 (0.9–18.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.8 ± 1.4</td>
<td>46 (29–63); 46/2</td>
<td>48 (48/48)</td>
<td>THC-CBD&lt;sup&gt;b,c&lt;/sup&gt;: mean number of sprays/d in each group: 8</td>
<td>Placebo</td>
<td>2 wk</td>
<td>Crossover trial (three 2-wk treatments; no washout period between treatments; pre-existing neuropathic pain medication continued</td>
</tr>
<tr>
<td>Rog, 2005&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Multiple sclerosis</td>
<td>Clinical and NPS</td>
<td>Central</td>
<td>11.6 (1.6–36)</td>
<td>6.5 ± 1.6</td>
<td>49.2 (26.9–71.4); 14/52</td>
<td>66 (34/32)</td>
<td>THC-CBD&lt;sup&gt;c&lt;/sup&gt;: mean number of sprays/d: 9.6</td>
<td>Placebo</td>
<td>5 weeks</td>
<td>Pre-existing neuropathic pain medication continued</td>
</tr>
<tr>
<td>Numnikko, 2007&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Neuropathic pain of multiple etiologies</td>
<td>Clinical and NPS</td>
<td>Peripheral</td>
<td>6.4 ± 5.7 (Can) 6.2 ± 6.4 (Com)</td>
<td>7.3 ± 1.4 (Can); 7.2 ± 1.5 (Com)</td>
<td>52.4 ± 15.8 (Can); 54.3 ± 15.2 (Com); 51/74</td>
<td>125 (63/62)</td>
<td>THC-CBD&lt;sup&gt;c&lt;/sup&gt;: mean number of sprays/d: 10.9 ± 6.8</td>
<td>Placebo</td>
<td>5 wk</td>
<td>Pre-existing neuropathic pain medication continued</td>
</tr>
<tr>
<td>Frank, 2008&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Neuropathic pain of multiple etiologies</td>
<td>Clinical</td>
<td>Central (n = 30) and peripheral (n = 66)</td>
<td>6.4 ± 5.8 years 6.7 ± 1.4 years</td>
<td>50.1 y (range 23–84); 46/50</td>
<td>96 (96/96)</td>
<td>Nabilone po 2 mg daily</td>
<td>Dihydrocodeine 240 mg daily</td>
<td>Placebo</td>
<td>6 wk</td>
<td>Crossover trial; all adjuvant analgesics (except dihydrocodeine) allowed</td>
</tr>
<tr>
<td>Selvarajah, 2010&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Neuropathic pain-diabetic neuropathy</td>
<td>Clinical and NTSS-6</td>
<td>Peripheral</td>
<td>&gt;0.5 y</td>
<td>Can: 5.6 ± 2.7 years Com: 4.5 ± 2.2 years</td>
<td>Can: 58.2 ± 8.8 years Com: 54.4 ± 11.6 years; 19/11</td>
<td>30 (15/15)</td>
<td>THC-CBD&lt;sup&gt;c&lt;/sup&gt;: up to 4 sprays/d</td>
<td>Placebo</td>
<td>12 weeks</td>
<td>Treatment for 10 wk</td>
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<tr>
<th>First Author, Year</th>
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<th>Number of Subjects in Each Group (Can/Com)</th>
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<th>Comparator</th>
<th>Duration of Treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toth, 2012(^{10})</td>
<td>Neuropathic pain-diabetic neuropathy</td>
<td>Clinical and DN4</td>
<td>Peripheral</td>
<td>7.1 ± 7.3 y</td>
<td>5.8 ± 1.8</td>
<td>60.8 ± 15.3 y</td>
<td>61.6 ± 14.6 y; 14/12</td>
<td>26 (13/13)</td>
<td>Nabilone 1–4 mg/d</td>
<td>Placebo</td>
<td>5 weeks (following a 4-wk run-in phase to identify responders)</td>
</tr>
<tr>
<td>Langford, 2013(^{13})</td>
<td>Multiple sclerosis</td>
<td>Clinical</td>
<td>Central</td>
<td>5.5 ± 5.5 y</td>
<td>6.6 ± 1.4</td>
<td>49.0 ± 10.5 y</td>
<td>109/230</td>
<td>339 (167/172)</td>
<td>THC-CBD(^{1}): mean daily dose of THC/CBD spray was 8.8 ± 3.9 sprays</td>
<td>Placebo</td>
<td>14 wk</td>
</tr>
<tr>
<td>Serpell, 2014(^{18})</td>
<td>Neuropathic pain of multiple etiologies</td>
<td>Clinical</td>
<td>Peripheral</td>
<td>5.5 ± 5.9 y</td>
<td>≥4/10 NRS</td>
<td>57.3 ± 14.2; 96/150</td>
<td>246 (128/118)</td>
<td>THC-CBD(^{1}): mean daily dose of THC/CBD spray was 8.9 sprays</td>
<td>Placebo</td>
<td>15 wk</td>
<td></td>
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<tr>
<td>Lynch, 2014(^{14})</td>
<td>Neuropathic pain-chemotherapy-induced</td>
<td>Clinical</td>
<td>Central and peripheral</td>
<td>1.4 years (range not provided)</td>
<td>6.8 ± 1.2</td>
<td>56.0 ± 10.8; 3/15</td>
<td>18 (18/18)</td>
<td>THC-CBD(^{1}): mean daily dose of THC/CBD spray was 8 sprays</td>
<td>Placebo</td>
<td>4 wk</td>
<td></td>
</tr>
<tr>
<td>Turcotte, 2015(^{21})</td>
<td>Multiple sclerosis</td>
<td>Clinical and DN4</td>
<td>Central</td>
<td>4.5 y (2.3–5.8 y)</td>
<td>7.7 ± 1.4</td>
<td>45.5 ± 10.8; 2/13</td>
<td>15 (8/7)</td>
<td>Nabilone: 2 mg/d</td>
<td>Placebo</td>
<td>9 wk (initial 4 wk for titration)</td>
<td></td>
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</table>

Abbreviations: Can, cannabinoid; CBD, cannabidiol; Com, comparator; DN4, Douleur Neuropathique 4 questionnaire; NP, neuropathic pain; NRS, Numerical Rating Scale; NTSS-6, Neuropathy Total Symptom Score-6; QST, quantitative sensory testing; THC-CBD, δ-9-tetrahydrocannabinol (27 mg/mL) and cannabidiol (25 mg/mL).

\(^{1}\)Time since last surgical intervention.

\(^{2}\)Each 100 μL spray delivers 2.7 mg of THC and 2.5 mg of CBD.

\(^{3}\)Two active treatment groups (THC-CBD and THC) but data extracted only for THC-CBD group.

\(^{4}\)Maximum 24-h dose allowed was 48 sprays: 129.6 mg/120 mg of THC-CBD or 129.6 mg of THC.

\(^{5}\)Greater proportion of women randomized to the nabilone group than placebo.
imprecision, and publication bias. A summary table was constructed with the GRADEpro guideline development tool (http://www.guidelinedevelopment.org/; Evidence Prime Inc, Hamilton, ON, Canada).

RESULTS

Search Results

From the initial 1298 records identified through database searching, 980 records were screened but 959 of these were excluded because the publications were not RCTs or failed to report any of our primary or secondary outcomes. Twenty-one full-text articles were assessed for eligibility, and 10 were excluded because the study settings did not meet our inclusion criteria. Eleven RCTs consisting of 1219 patients (614 in selective cannabinoid and 605 in comparator groups) were included for the systematic review and data from 10 of these were subjected to meta-analysis (Table 1, Figure 1).

Trial, Participants, and Intervention Characteristics

Spectrum of Neuropathic Pain Syndromes. The median (range) sample size of the 11 RCTs was 48 (15–339) patients. All the trials evaluated patients with NP but there was variation in distribution of pain and its etiology. Five trials enrolled patients with central NP—the etiology was multiple sclerosis in 4 of these trials and avulsion injuries to the brachial plexus in the fifth trial. Four trials included patients with peripheral NP—the etiology was diabetes in 2 of these trials and patients with multiple etiologies for peripheral NP were included in 2 trials. Two trials enrolled patients with NP that was both central and peripheral—NP was secondary to chemotherapy in one of these trials and multiple etiologies in the other. Three trials included patient populations with multiple etiologies for NP (Table 1).

In the trials included in this SR-MA, the diagnosis of NP was based on clinical criteria (eg, presence of allodynia, hyperalgesia, numbness) in all trials but some of the included trials also used validated screening tools for NP. The screening tools used were Douleur Neuropathique 4 questionnaire, Neuropathic Pain Score, and Neuropathy Total Symptom Score. One trial also used QST to supplement clinical diagnostic criteria. Four other studies used QST as 1 of the outcomes but not as a selection criterion. The duration of NP ranged from 6 months to over 11 years and the intensity of pain was moderate-to-severe for patients in all the trials included in this review. The exclusion criteria were fairly similar in all the studies included in this review but 1 study excluded patients with NP who also had depression. Patients with severe concomitant illness, seizures, and history of substance abuse were excluded in all studies.

Selective cannabinoids were used as an adjunct (and not primary) analgesic for NP in all the studies included in this review. Five studies allowed for continuation of all previous analgesics prior to enrollment, but 1 study required all patients to stop taking dihydrocodeine 2 weeks prior to initiation of the trial (although all other analgesics were allowed), presumably because dihydrocodeine was the comparator medication in the trial. One study allowed use of all analgesics except for paracetamol (acetaminophen), 1 study did not allow use of any other analgesic.
Selective Cannabinoids and Comparators Used in the Trials

Three selective cannabinoids were assessed in the 11 included trials (1 trial was on dronabinol, 3 trials were on nabilone, 2,20,21,23 and 7 trials were on nabiximols13–18,22) and the duration of treatment ranged from 2 to 15 weeks (Table 1). Daily dose for dronabinol ranged from 2.5 to 10 mg,20 the daily dose for nabilone was between 1 and 4 mg,20,21,23 and the mean daily dose for nabiximols sprays was 8.3 sprays (ie, 22.4 mg of THC and 20.8 mg of CBD) with a range of 4 to 10.9 sprays. One trial had 2 active groups (THC and THC-CBD) and we extracted data for the THC-CBD group.22 All trials used placebos for comparison with the active treatment except 1 trial that allowed a daily dose of 240 mg of dihydrocodeine in the comparison group.23 Participants were allowed to continue medications for relieving NP in all the trials except 1 study.19

Risk of Bias Assessment of Included Studies

Overall risk of bias was assessed as low in 10 of 11 trials (Supplemental Digital Content 2, Table 2, http://links.lww.com/AA/B748).17 The trial deemed to have a high risk of bias did not adequately describe the procedure for generation of randomization, concealment of allocation, and blinding of participants.17 There was no difference in opinion between the 2 reviewers for assessment of risk of bias for all 11 trials. Quality of reporting24 was good in 8 trials,13–16,18,19,21,22 fair in 2 trials,20,23 and poor in 1 trial.17

Primary Outcome: Pain Scores

The primary outcome was intensity of pain after a minimum of 2 weeks following initiation of study treatments, expressed on an 11-point NRS. All studies included in this review except 1 reported this outcome.18 Serpell et al19 chose to report the proportion of patients achieving more than 30% reduction in intensity of NP as compared to baseline scores. Out of the 11 studies included in this review, 6 demonstrated analgesic superiority of selective cannabinoids compared to placebo based on change in NRS pain scores,13,16,19,20,21 or on proportion of patients achieving more than 30% reduction in intensity of pain as compared to baseline scores.18 Meta-analysis of data from the 10 trials that reported pain scores revealed a small reduction of pain scores with selective cannabinoids when compared to placebo or dihydrocodeine in patients with NP (mean difference −0.65 points; 95% CI, −1.06 to −0.23 points; P = .002, F = 60%) (Table 2, Figure 2).13–16,18,23

Comparison of Different Selective Cannabinoid Types

We examined results for the 3 types of selective cannabinoids evaluated in these trials. Only 1 trial evaluated analgesic potential of dronabinol in patients with central NP and it reported superiority of this selective cannabinoid over placebo.19 Three trials evaluated analgesic efficacy of nabilone in NP.20,21,23 Two of these trials (1 trial enrolled patients with central NP21 and the other trial enrolled patients with peripheral NP20) concluded that use of nabilone was associated with analgesic benefit in NP. The third trial on nabilone enrolled patients with mixed central and peripheral NP and it demonstrated analgesic inferiority of nabilone in comparison to dihydrocodeine.23 Meta-analysis of data from these 3 trials revealed no significant reduction of the 11-point pain NRS with nabilone when compared to placebo or dihydrocodeine in patients with NP (mean difference −1.22 points; 95% CI, −2.79 to 0.36 points; P = .13; F = 85%) (Figure 3A). Seven trials13–18,22 evaluated analgesic efficacy of nabiximols in NP and 613–17,22 of these reported pain scores. Two of these trials (one for central NP16 and the other for peripheral NP15) reported analgesic superiority of nabiximols over placebo. The other 5 trials did not show analgesic benefit with nabiximols (2 on central NP,13,22 2 on peripheral NP17,18 and 1 on mixed central and peripheral NP16). Meta-analysis of data from the 6 trials that reported pain scores revealed a significant but clinically small reduction of the 11-point pain NRS with nabiximols when compared to placebo in patients with NP (mean difference −0.50 points; 95% CI, −0.89 to −0.12 points; P = .010, F = 43%) (Figure 3B).

Efficacy of Selective Cannabinoids in Central and Peripheral Neuropathic Pain

We conducted meta-analyses to see whether the effect of selective cannabinoids differed depending on the location of NP—central, peripheral, and combined central-peripheral (Table 2). Two of 5 studies involving patients with central NP reported significantly lower pain scores in the selective cannabinoid group.16,21 Meta-analyses of the data from the 5 trials on central NP demonstrated significant analgesic benefit with selective cannabinoids (mean difference −0.73 points; 95% CI, −1.26 to −0.20 points; P = .007, F = 51%) (Figure 4A).13,14,16,19,21,22

Three of the 4 studies involving patients with peripheral NP reported significantly lower pain scores favoring selective cannabinoids.15,17,18,20 However, meta-analyses of the data from the 3 trials on peripheral NP that involved use of selective cannabinoids and reported pain scores did not demonstrate analgesic benefit (mean difference −0.72 points; 95% CI, −2.04 to 0.59 points; P = .28, F = 75%) (Figure 4B).15,17,20 Two studies of selective cannabinoids in patients with mixed central and peripheral NP did not demonstrate analgesic superiority of selective cannabinoids over the comparators—one of these trials involved the comparison of nabiximols against placebo14 and the other compared nabilone against dihydrocodeine.23

Secondary Outcomes

A variety of domains associated with pain were assessed by trials on selective cannabinoids included in this review (Table 2). Five of the 8 studies13,19,20,22,23 that assessed QoL demonstrated an improvement in this parameter with selective cannabinoids (questionnaires used to assess QoL included Short Form-36,14,17,19,23 European Quality of Life—5 Domains index score,17,18,20 and General Health...
## Table 2. Outcomes Reported in Included Studies on Selective Cannabinoids

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Primary Outcome</th>
<th>Secondary Outcome(s)</th>
<th>Adverse Events</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svendsen, 2004</td>
<td>Median pain intensity score in the last (third) week of treatment</td>
<td>Improvements in Dronabinol group (versus placebo) in: • Median radiating pain intensity and pain relief score • QoL (SF-36: bodily pain and mental health domains) • QST</td>
<td>More patients had AE (dizziness, headache, tiredness, myalgia) during active treatment, especially in the first week of treatment; 17% of patients in dronabinol group could not tolerate 10 mg od</td>
<td>Diagnosis of central pain established by history, examination, QST</td>
</tr>
<tr>
<td>Berman, 2004</td>
<td>Mean pain intensity score in the last (second) week of treatment</td>
<td>Improvements in THC-CBD group (versus placebo) in: • Sleep quality • SF-MPQ PRI and VAS • PDI: similar in 3 groups • GHQ-12 score</td>
<td>Common adverse effects in active groups: dizziness, somnolence, dysgeusia, nausea, euphoria</td>
<td>3 withdrawals during the study: Placebo: 1—N&amp;V during placebo administration; 1—anxiety and paranoia, experienced while taking placebo THC-CBD: 1—feeling faint</td>
</tr>
<tr>
<td>Rog, 2005</td>
<td>Mean pain intensity score in the last (fifth) wk of treatment</td>
<td>Improvements in THC-CBD group (versus placebo) in: • NPS score • PGIC</td>
<td>More patients on THC-CBD than placebo reported dizziness, dry mouth, and somnolence; cognitive side effects were limited to long-term memory storage</td>
<td>Withdrawals due to AE: THC-CBD: 11 (19%) patients Placebo: 2 (3%) patients</td>
</tr>
<tr>
<td>Nurmikko, 2007</td>
<td>Mean pain intensity score in the last (fifth) wk of treatment: THC-CBD: 5.8 ± 1.4 Placebo: 6.7 ± 1.5</td>
<td>Improvements in THC-CBD group (versus placebo) in: • NPS composite score • Sleep quality • QST (dynamic and punctate allodynia) • Physical function (PDI) • PGIC</td>
<td>Sedative and gastrointestinal side effects were reported more commonly by patients on THC-CBD</td>
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<tr>
<td>Frank, 2008</td>
<td>Mean VAS over the last 2 (fifth and sixth) wk of treatment Nabilone: 6 ± 2.4 Dihydrocodeine: 5.9 ± 2.4</td>
<td>Improvements in nabilone group (versus placebo) in: • QoL (nabilone superior to dihydrocodeine for physical function but dihydrocodeine superior for bodily pain domain) No difference between groups in: • Mental functioning • Sleep quality • Psychometric function</td>
<td>More N&amp;V with nabilone and more tiredness and nightmares with dihydrocodeine</td>
<td>33 patients failed to complete the trial and the cohort studied had a variety of neuropathic pain syndromes</td>
</tr>
<tr>
<td>Selvarajah, 2010</td>
<td>Mean total pain scores in the last (12th) wk of treatment: Can: 4 ± 2.9 Com: 2.5 ± 2.9</td>
<td>No difference between groups in: • MPQ • QoL (SF-36, EQ-5D)</td>
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<tr>
<td>Toth, 2012</td>
<td>Mean daily pain score in the last (5th) wk of treatment Can: 3.5 ± 1.3 Com: 5.4 ± 1.7</td>
<td>Improvements in nabilone group (versus placebo) in: • Anxiety (HADS-A) • Sleep quality (MOSSSPI) • QoL (EQ-5D) • PGIC and PTSS</td>
<td>Mild-to-moderate: dizziness and drowsiness most common</td>
<td>Potential unmasking occurred in 6 patients</td>
</tr>
<tr>
<td>Langford, 2013</td>
<td>Patients with &gt;30% reduction in pain NRS compared to baseline: Can: 50% Com: 45%</td>
<td>No difference between groups in: • Sleep quality • QoL (BPI-SF) • PGIC</td>
<td>Mild-to-moderate: dizziness, vertigo, drowsiness, fatigue, nausea, and dry mouth most common</td>
<td>Large placebo effect</td>
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(Continued)
Questionnaire. Only one of the 3 studies that assessed physical function reported an improvement in this domain. Six of the 7 studies that assessed quality of sleep found an improvement in this parameter. Only 11 of the 3 studies that measured anxiety using validated questionnaires reported an improvement in the Anxiety subscale on psychological function based on the Hospital Anxiety and Depression Scale. Five of the 6 studies that included satisfaction of participants as one of the outcomes reported positive results for this parameter. There did not appear to be a correlation between the maximum dose (48 sprays per day) allowed for nabiximols and incidence or severity of adverse effects because the dose range utilized per 24 hours by participants in studies on nabiximols was fairly low (4–11 sprays).

Adverse Effects

All 11 studies included in this review collected data on adverse effects with selective cannabinoids and study medications. The majority of reported adverse effects with selective cannabinoids were mild to moderate. The most common adverse effects with selective cannabinoids were dizziness/lightheadedness, somnolence, and dry mouth. Adverse effects usually occurred at the onset of treatment and subsided over time, indicating development of tolerance (Table 2).

We also assessed reports of severe adverse effects requiring withdrawal from the trials. These included confusion in 2 patients and headaches in 1 patient on nabilone. In a study with a crossover design, 4 participants (out of 96) on nabilone withdrew from the trial due to intolerance whereas 8 participants on dihydrocodeine ceased taking this medication. Two patients developed severe adverse events from selective cannabinoids (agitation and paranoid ideation). In another study, 11 (18%) patients withdrew from the nabiximols group because of adverse effects compared to 2 (3%) in the placebo group. All other studies demonstrated similar patient withdrawal rates between the trial arms.

There did not appear to be a correlation between the maximum dose (48 sprays per day) allowed for nabiximols and incidence or severity of adverse effects because the dose range utilized per 24 hours by participants in studies on nabiximols was fairly low (4–11 sprays).

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<th>First Author, Year</th>
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<th>Secondary Outcome(s)</th>
<th>Adverse Events</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serpell, 2014</td>
<td>Patients with &gt;30% reduction in pain (NRS compared to baseline)</td>
<td>Improvements in THC-CBD group (versus placebo) in:</td>
<td>Mild-to-moderate: dissociation and disorientation most common</td>
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<td></td>
<td>Can: 28%</td>
<td>- Sleep quality (NRS)</td>
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<td></td>
<td>Com: 16%</td>
<td>- PGI</td>
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<td>- NPS</td>
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<td>- BPI-SF</td>
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<td>- QoL (EQ-5D)</td>
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<td>- QST (dynamic allodynia)</td>
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<td>No difference between groups in:</td>
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<td>- QST (punctate allodynia)</td>
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<td>No difference between groups in:</td>
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<td>- QoL (SF-36)</td>
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<td>- QST (dynamic and punctate allodynia)</td>
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<td></td>
<td></td>
<td>Mild: fatigue, dizziness, dry mouth, nausea</td>
<td>Study was significantly underpowered</td>
<td></td>
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<tr>
<td>Lynch, 2014</td>
<td>Mean daily pain score in the last (fourth) wk of treatment</td>
<td>Improvements in nabnilone group (versus placebo) in:</td>
<td>Mild: dizziness, drowsiness, dry mouth</td>
<td>Combination of gabapentin and nabilone evaluated</td>
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<tr>
<td></td>
<td>Can: 6.0 ± 1.2</td>
<td>- PGI</td>
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<tr>
<td></td>
<td>Com: 6.4 ± 1.2</td>
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<tr>
<td>Turcotte, 2015</td>
<td>VAS for pain intensity</td>
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<td></td>
<td>Can: 3.5 ± 1.4</td>
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<td>Com: 5.6 ± 1.4</td>
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<td>VAS for impact of pain on daily activities</td>
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Table 2. Continued
Heterogeneity

For the primary outcome, the $I^2$ statistic was 60% for the meta-analysis of pain NRS from all selective cannabinoid RCTs, it was 85% for comparison of mean postintervention pain scores for trials on nabilone, and 43% for comparison of mean postintervention pain scores for trials on nabiximols. These results indicate moderate-to-high heterogeneity. Several characteristics of these studies may have contributed to heterogeneity in our review including types of patient populations, timing of assessing primary outcome, and variations in dose. To explore heterogeneity, we conducted subgroups using meta-regression and a sensitivity analysis and found no significant difference based on central versus peripheral and on risk of bias.

We performed meta-regression analysis to assess whether there was a significant interaction between location of pain (central versus peripheral) and treatment effects of selective cannabinoids. We found no significant difference in effect size between studies on selective cannabinoids that enrolled participants with central pain compared to studies that enrolled participants with peripheral pain ($P = .998$ and .958 when assessed using normal and non-normal distribution assumptions, respectively).

We performed a sensitivity analysis by removing the 1 trial with a high risk of bias. This trial also reported a significant effect of depression on NP scores with patients in both arms who had more depression also had a more pronounced response to the study treatments. Meta-analysis of data from the other 9 trials on selective cannabinoids that had a low risk of bias (ie, after excluding 1 trial with a high risk of bias17) showed that the significant but clinically small reduction in pain NRS in patients with NP remained (−0.70 points; 95% CI, −1.10 to −0.31 points; $P = .0005$, $I^2 = 57\%$) (Supplemental Digital Content 3, Figure 1, http://links.lww.com/AA/B749).13–16,19–23

**Figure 3.** A, Forest plot of analgesic efficacy (pain Numerical Rating Scores) of trials on nabilone. B, Forest plot of analgesic efficacy (pain Numerical Rating Scores) of trials on nabiximols.

**Figure 4.** A, Forest plot of analgesic efficacy (pain Numerical Rating Scores) of trials on selective cannabinoids in patients with central neuropathic pain. B, Forest plot of analgesic efficacy (pain Numerical Rating Scores) of trials on selective cannabinoids in patients with peripheral neuropathic pain.
Publication Bias
We also evaluated probability of publication bias in trials on selective cannabinoids for NP. The funnel plot (Supplemental Digital Content 4, Figure 2, http://links.lww.com/AA/B750) was asymmetrical suggesting the possibility of publication bias. Although other causes including clinical heterogeneity could be responsible for this finding, we decided to perform Begg’s and Egger tests for publication bias but the P values for publication bias were nonsignificant (P = .371 and .103, respectively). This suggests that there was no publication bias. It is also important to acknowledge that there were only 10 studies in our meta-analysis and 10 is the minimum recommended number of studies for constructing a funnel plot.25,26

Recommendations
Based on the quality of the evidence included in this review and the strength of effect, it can be recommended that selective cannabinoids may be used as adjunct analgesics in patients with NP syndromes (GRADE: weak recommendation; moderate quality evidence) (Supplemental Digital Content 5, Table 3, http://links.lww.com/AA/B751). Selective cannabinoids may be associated with improvement in QoL, sleep, patients’ reports of impression of positive change, and improved sensory and pain thresholds with psychometric testing. The overall small analgesic benefit and the associated adverse effects associated with use of selective cannabinoids should be discussed with patients and their preferences and values considered before prescribing selective cannabinoids. Further research in this field is justified because there is a lack of information about appropriate dosages and duration of treatment, impact of these medications on physical and psychologic functioning, and adverse effects.

DISCUSSION
This is the first SR-MA of RCTs that focuses on the analgesic efficacy of selective cannabinoids when used as adjuncts in relieving refractory central and peripheral NP of moderate-to-severe intensity. It reveals that daily doses of 2.5 to 10 mg of dronabinol, 1 to 4 mg of nabilone, and 8.3 sprays of nabiximols when administered over 2 to 15 weeks are associated with analgesic benefit compared to placebo at 2 weeks or more following initiation of treatment. The reduction in mean NRS pain scores (0–10 scale) in patients receiving selective cannabinoids compared to placebo is significant but clinically small. The quality of evidence is moderate and the strength of recommendation is weak for analgesic efficacy of selective cannabinoids in this clinical setting. Among the different selective cannabinoids, use of nabiximols and dronabinol, but not nabilone, conferred an analgesic benefit. Evaluation of subgroup results of analgesic impact of selective cannabinoids on different locations of NP (central versus peripheral) did not reveal a significant difference. For secondary outcomes, use of selective cannabinoids was associated with improvements in QoL and sleep, and enhanced patient satisfaction but the impact on physical and psychologic function was unclear. Serious adverse effects were rare with the doses of selective cannabinoids used in these trials.

The role of selective cannabinoids in relieving chronic pain has been evaluated in a few narrative reviews over the last few years but no SR-MAs on their role in NP have been reported.10,11,27–29 Conclusions of these reviews vary with 1 review suggesting that selective cannabinoids have equianalgesic effect to codeine and are associated with unwanted side effects,27 whereas a meta-analysis of trials on selective cannabinoids for MS-related pain revealed significant pain relief compared to placebo.29 Other recent systematic reviews on heterogeneous pain populations (in terms of etiologies and presentations) demonstrated analgesic superiority of selective cannabinoids and cannabis in 2 reviews31,32 or were inconclusive.32 Selective cannabinoids and cannabis preparations used in trials included in these reviews varied in formulation (eg, smoked cannabis, vaporized cannabis, fatty acid amide hydrolase inhibitors, oral mucosal sprays, and oral cannabis extracts) making it difficult to understand and establish whether there was a dose-response relationship. Our SR-MA is clinically relevant because it is the first synthesis of published data to exclusively focus on recent trials on chronic NP that involved use of selective, prescription cannabinoids.

Population Included in This Review
There was a moderate degree of clinical and statistical (60%) heterogeneity among the trials included in this SR-MA. We included trials on selective cannabinoids for patients with central NP pain because this type of pain can be extremely challenging to relieve. NP was assessed using accepted methods (clinical assessment in all studies and use of validated questionnaires for NP or QST in 1 study). However, current ability to reliably diagnose central NP is uncertain.30 One of the trials on central NP included in our SR-MA included only patients with sensory abnormalities at the maximal pain site but patients with multiple sclerosis can also have spasm-related pain.31 Spasm-related pain has been considered as nonneuropathic by some investigators.31

Efficacy of Selective Cannabinoids in Relieving Neuropathic Pain
Dose-Response Effect. Nabiximols. A self-titration dosing schedule was chosen by investigators of trials on nabiximols (THC-CBD sprays) included in our SR-MA because there is high intersubject variability in the bioavailability of nabiximols.13–18,22 The recommended dose range is between 1 and 48 sprays per day but the mean daily dose used by participants included in this SR-MA was 8.3 sprays.31 This suggests that only a few patients will progress to the upper limit of the allowed dose range. Self-titration also enables patients to achieve their individual optimum therapeutic dose by balancing analgesia against adverse effects and allowing variation of dose depending on the levels of pain and activity. However, allowing wide dose ranges makes it difficult to ascertain presence or absence of a dose-response effect. It should also be acknowledged that although the therapeutic effects of cannabis have often been attributed to THC, the second major constituent of the trial medication—CBD has been shown to have effects, which may be additive to those of THC in pain relief in animal models, and CBD also has the potential to ameliorate some of the psychoactive effects of THC.32
**Nabilone.** Nabilone is a selective cannabinoid that is administered through the oral route. Some authors have also questioned the appropriateness of trials of selective cannabinoids using oral administration due to the variability in their gastrointestinal absorption and crossover designs because of their long half-lives. The recommended daily therapeutic dose of nabilone varies from 1 to 4 mg. Of the 3 trials on nabilone included in our SR-MA, the 2 trials that reported analgesic benefit with nabilone allowed flexible dosing of nabilone (1–4 mg per day), or a fixed daily dose of nabilone of 2 mg, but another trial that also allowed a fixed daily dose of 2 mg did not report any analgesic benefit. We conclude that it is not possible to define a specific dose of nabilone that is associated with an analgesic response in patients with NP and gradual escalation of dose titrated to analgesic benefit is recommended.

**Impact of Coanalgesic Therapy**

All trials included in this SR-MA except 1 allowed continuation of existing analgesic regimes. Depriving a patient of therapies for NP during a placebo-controlled trial is debatable. Clinical practice is moving toward combination therapies due to the realization that multiple mechanisms play a role in chronic NP. Experimental studies have also shown that THC may not be an effective analgesic when used alone but it displays a pronounced synergistic effect when used with an opioid. Cannabis may also have synergistic effects with opioids with a recent publication suggesting that cannabis may be effective in weaning patients with chronic postsurgical pain from high-dose opioids.

**Impact of Selective Cannabinoids on Nonanalgesic Domains of Neuropathic Pain**

Five of the 7 trials included in this review demonstrated a positive effect on QoL despite a relatively short duration of treatment in most of the studies while 1 of 3 studies on psychologic function reported an improvement in the Anxiety subscale of Hospital Anxiety and Depression Scale. It is possible that the measures used to detect changes in mood were not adequately sensitive to detect milder degrees of psychologic impairment because potential participants who had significant psychologic morbidities were excluded from the trials. Alternatively, the paradoxical effects of THC, or the ability of CBD to block some of the psychomimetic effects of THC, may explain the lack of change in mood. Assessment of mood is important in any trial involving use of selective cannabinoids because of their known anxiolytic action, while there are also concerns about the ability of selective cannabinoids to induce psychosis and schizophrenia.

Six of the 7 studies included in our SR-MA reported better quality of sleep with selective cannabinoids while 5 out of the 6 studies that included assessment of patient satisfaction or global impression of change reported positive results. This finding, despite a lack of corresponding significant change in mood, suggests that patients felt a benefit from reduction in pain, improvement in quality of sleep, or both.

**Cannabis for Neuropathic Pain**

To ensure comprehensiveness of our efforts to evaluate role of selective cannabinoids in NP, we also reviewed the evidence for cannabis (smoked or vaporized medical marijuana) in relieving NP. We found 6 RCTs that evaluated smoked or vaporized marijuana of various strengths against placebos for treatment of NP (Supplemental Digital Content 6, Table 4, http://links.lww.com/AA/B753). Two studies enrolled patients with HIV NP, 1 study included patients with posttraumatic NP, and another 2 studies enrolled patients with NP syndromes secondary to a variety of etiologies (complex regional pain syndrome type I, thalamic stroke, spinal cord injury, peripheral neuropathy, radiculopathy, or trauma). Four studies examined peripheral NP and 2 studies examined a mix of central and peripheral NP.

**Magnitude of Analgesic Effect and Probability of Treatment Success With Selective Cannabinoids**

Our SR-MA found that selective cannabinoids were associated with a significant but small analgesic benefit of change (reduction) in pain by ~0.65 points (95% CI, –1.06 to –0.23 points; P = .002) on an 11-point NRS for pain. However, patients enrolled in the trials included in our SR-MA had moderate-to-severe refractory NP despite the use of recommended therapies. It is recognized that treatment of NP, and in particular syndromes caused by central nervous system lesions, is difficult and randomized trials evaluating treatments of central pain are limited. The pain reduction seen in this study is comparable to the effect of other drugs used in the treatment of NP conditions. A meta-analysis of more than 2700 patients with various painful conditions suggested approximately a 30% or a reduction by 2 points in the 11-point NRS for pain as being clinically significant but it notably did not include patients with NP, in which “relatively small decreases in pain intensity are often highly valued by the patients.” One trial included in our SR-MA reported that the numbers needed to treat to achieve a 50% reduction in central pain in at least 1 patient was 3.7 (95% CI, 2.2–13.0), similar to that obtained in the trial on dronabinol that was also included in our SR-MA (3.5; 95% CI, 1.9–24.8). It is important to recognize that these numbers needed to treat are significantly lower (ie, better) compared to those for some first-line medications for treatment of NP.

**Central Versus Peripheral Neuropathic Pain**

Meta-analysis of data on analgesic impact of selective cannabinoids on central and peripheral NP suggested a small analgesic benefit in patients with central NP only but meta-regression analysis revealed that the location of pain did not influence analgesic efficacy of selective cannabinoids. The pathologic mechanisms of NP in these 2 locations may be different with sensitization in spinal cord and brain playing a more important role in central NP. Pain associated with brachial plexus injury and multiple sclerosis, although considered to be central, can have different phenotypes (related to spasms, plaques in the central nervous system, and musculoskeletal pain). These factors may explain the reason for 1 of the trials in our SR-MA that found a lack of analgesic benefit with nabilone over dihydrocodeine in a population with central and peripheral NP syndromes secondary to a variety of etiologies.
Crossover trial design was used for all 6 studies except 1. All studies had similar participant inclusion criteria as studies on selective cannabinoids included in our SR-MA.

Overall bias was low in these 6 studies on cannabis (Supplemental Digital Content 8, Table 6, http://www.lww.com/AA/B754). Interventions in all 6 studies were of short duration (up to 5 days). Dose of THC per day ranged from 1.875 to 34 mg. Similar to the RCTs on selective cannabinoids included in our SR-MA, cannabis preparations were used as an adjunctive medication in the 5 studies. All studies demonstrated significant pain reduction with cannabis compared to placebo. Diversity in methodology and reporting of pain intensity ruled out the prospect of performing a meta-analysis. Similar to selective cannabinoids, escalation in strength of THC for cannabis has not clearly been demonstrated to provide superior analgesia and result in worsened neuropsychologic performance.

Secondary outcomes for improvement in anxiety and depression/mood were reported with cannabis in 23,34,45 of 30,45,46 studies. One study also reported improvement in sleep. QST testing was performed in 3 studies and there was no evidence of change in thresholds toward normal in any of these studies. Two studies reported higher participant satisfaction with cannabis. Finally, almost all adverse events relating to the interventions were considered mild to moderate. Adverse effects were similar to effects with selective cannabinoids, and only 1 study reported that a single participant withdrew due to psychosis. Detailed results for 5 out of 6 of these RCTs have been recently published in a narrative review.

**Adverse Effects of Selective Cannabinoids**

It is unclear whether use of selective cannabinoids is associated with significant adverse effects. Data on this aspect may be affected by the type of selective cannabinoid, its dose, and the comparator used in a trial. A review of 31 studies on adverse effects of medical cannabinoids revealed an increase in nonserious adverse events when compared to placebo. However, 1 trial included in our SR-MA reported that the number of patients with adverse events decreased during active treatment. Observation may be due to increasing tolerance to the drug over time but 17% of the patients were not able to tolerate the maximum allowed dose of dronabinol or other selective cannabinoids. This observation also suggests that adverse effects may prevent attainment of therapeutic levels of selective cannabinoids.

Long-term safety data in use of selective cannabinoids and cannabis for NP are limited. A recent long-term safety review of nabilone use for posttraumatic stress disorder patients cited 2 of our included studies (limited by a trial duration of only 9 weeks) and highlighted similar adverse effects. Data from an open-label follow-up for 1 year of 104 patients with multiple sclerosis who were taking nabiximols (mean of 6.2 sprays/day) for spasticity reported predominantly gastrointestinal adverse effects. Twenty-one of 22 reported adverse effects were considered nonserious, while 1 was serious due to fall resulting in fracture. A 1-year safety study on cannabis (average 2.5 g/day) with 12.5% THC for pain reported an increased risk of nonserious adverse events and risk of chronic bronchitis.

Recreational use of cannabis suggests that it has some potential for dependence. Heavy, regular recreational cannabis smoking at a young age in vulnerable subjects may also be associated with an increased risk of subsequently developing schizophrenia. It is also believed that mental illness may be aggravated by cannabis. For this reason, patients with a history of significant psychiatric illness were excluded from trials included in this SR-MA. This limits the generalizability of results of these trials and of this SR-MA because patients with significant levels of pain often have coexisting mood disorders.

**Limitations of Current Evidence**

Despite our rigorous attempts to identify all current evidence, there remain several unanswered questions regarding efficacy of selective cannabinoids in patients with NP. We are unable to comment on the ideal proportions of THC and CBD in nabiximols preparations because there is a significant variation in amounts of THC and CBD content used in trials. The dose per administration and daily maximum limits also differed across RCTs in our SR-MA. Furthermore, analgesia was assessed over a wide range of time periods after initiation of study interventions. The diagnosis of NP was primarily clinical and other means of diagnosis including QST and validated questionnaires were not used consistently. Finally, the effect of selective cannabinoids on physical disability, psychological disability, sleep, and on QoL was also not assessed rigorously.

**Suggestions for Future Research**

Future RCTs conducted with larger enrollment may be able to better quantify the analgesic potential of selective cannabinoids for NP. One particular concern regarding selective cannabinoids is the variability in content, dosing, and route of administration. Analgesic impact and adverse effects of different proportions of THC and CBD should be assessed in trials. It is important to evaluate the efficacy of this intervention in NPs of various etiologies (central and peripheral) that cause moderate-to-severe pain intensities. Diagnosis needs to be standardized and confirmed through the use of validated NP questionnaires (eg, Douleur Neuropathique 4 questionnaire, Leeds assessment of neuropathic symptoms and signs).

Synthesized data from our SR-MA showed that nabiximols may have an analgesic effect, whereas nabilone may not relieve NP. To further understand the analgesic potential of selective cannabinoids, we propose a multicenter RCT on patients with NP with 4 treatment arms: CBD, THC/CBD, nabilone, and placebo. We propose these 4 groups because it may yield further insight in the debate concerning which selective cannabinoid provides greater analgesic effect. The sample size for this trial would be at least 70 patients per group (ie, 280 patients in all) for an expected difference between pain NRS (0–10 scale) means of 1.8 and the within-group SD of 3. This sample size has been determined to give a 90% chance of rejecting the null hypothesis of no difference between means at an α of .0125 and using a Bonferroni adjustment to the size of the test to compensate for multiple comparisons. Pain scores should be measured at multiple time intervals after initiation of intervention: acutely (eg, at 1–2 weeks after initiation of therapy), intermediate (eg, at 1 month), and long-term.
(eg, at 3, 6, 12 months and beyond). Stratification of patient data based on degree of pain relief would allow for reporting of proportion of significant versus limited responders to the intervention and further isolate patient characteristics that are more responsive to the intervention. Important secondary outcome measurements to include in this proposed trial are as follows: emotional functioning, physical functioning, patient satisfaction with treatment (all assessed using validated questionnaires), and meticulous attempts to identify and record adverse effects. These recommendations are in accordance with the core outcome domains of the IMMPACT guidelines for designing clinical trials to evaluate interventions for chronic pain conditions.

CONCLUSIONS
There was moderate quality evidence to suggest nabiximols is effective in reducing NP. There was no significant difference on the analgesic impact of selective cannabinoids on different locations of NP. Selective cannabinoids may have a role as coanalgesic therapy for refractory NP. Challenges to overcome in subsequent studies include ensuring that trials are blinded (patients, clinical team, data collectors and assessors, data analysts) with standardization of pain diagnosis, length of treatment, assessment of dose-response, homogeneity of patient population, and inclusion of QoL indicators.

DISCLOSURES
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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

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