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Critical Review

Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data

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Abstract: **Chronic neuropathic pain, the most frequent condition affecting the peripheral nervous system, remains underdiagnosed and difficult to treat. Inhaled cannabis may alleviate chronic neuropathic pain. Our objective was to synthesize the evidence on the use of inhaled cannabis for chronic neuropathic pain. We performed a systematic review and a meta-analysis of individual patient data. We registered our protocol with PROSPERO CRD42011001182. We searched in Cochrane Central, PubMed, EMBASE, and AMED. We considered all randomized controlled trials investigating chronic painful neuropathy and comparing inhaled cannabis with placebo. We pooled treatment effects following a hierarchical random-effects Bayesian responder model for the population-averaged subject-specific effect. Our evidence synthesis of individual patient data from 178 participants with 405 observed responses in 5 randomized controlled trials following patients for days to weeks provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated (number needed to treat = 5.6 with a Bayesian 95% credible interval ranging between 3.4 and 14). Our inferences were insensitive to model assumptions, priors, and parameter choices. We caution that the small number of studies and participants, the short follow-up, shortcomings in allocation concealment, and considerable attrition limit the conclusions that can be drawn from the review. The Bayes factor is 332, corresponding to a posterior probability of effect of 99.7%.**

Perspective: ***This novel Bayesian meta-analysis of individual patient data from 5 randomized trials suggests that inhaled cannabis may provide short-term relief for 1 in 5 to 6 patients with neuropathic pain. Pragmatic trials are needed to evaluate the long-term benefits and risks of this treatment.***

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Key words: *Cannabis, chronic pain, neuropathy, painful, polyneuropathy, meta-analysis, meta-analysis of individual patient data, Bayesian analysis, human immunodeficiency virus.*

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About 1 in 40 adults in the general population has chronic neuropathic pain, making it the most frequent condition affecting the peripheral nervous system.[52] Chronic neuropathic pain presents a heterogeneous burden with a large prevalence[12] in certain susceptible subpopulations, for example in people living with human immunodeficiency virus (HIV).[30] HIV-related distal sensory neuropathy affects every third patient.[30] Chronic neuropathic pain may result from diverse insults, including diabetes, HIV, trauma, and certain medications.[86,87] Chronic neuropathic pain remains underdiagnosed and difficult to treat.[33] Regardless of the cause, chronic neuropathic pain persists despite attempts at management with opioids, nonsteroidal anti-inflammatory drugs, anticonvulsants (gabapentin), anti-inflammatory agents, antidepressants, and complementary medicines.[33]

A recent systematic review concluded that cannabis is effective in selected neurological disorders, including multiple sclerosis, but did not address chronic neuropathic pain.[50] Considering the recent wave of cannabis legalization,[76] continued legal wrangling,[65] its widespread medicinal and recreational use,[80,88] and additional randomized controlled trials (RCTs) published on cannabis recently, we performed a meta-analysis to investigate if inhaled cannabis alleviates chronic neuropathic pain.[8,81,84] Previous (systematic) reviews did not investigate inhaled cannabis for chronic neuropathic pain or were unable to synthesize all available data, did not include recently published RCTs, and varied considerably in their inclusion criteria, study selection, and data synthesis, leading to conflicting and outdated conclusions.[13,19,23,47,50,54-56,63,67,76,79,89] As cannabis should undergo the same evidence-based review[39] as other potent prescription medications,[83] an update is needed.[81,84]

In cooperation with all primary study authors, we performed an individual patient data Bayesian[35] meta-analysis of RCTs[71] (Supplementary Box 1). Although classic meta-analysis pools aggregate data extracted from published study reports, meta-analysis of individual patient data synthesizes the original data of the individual participants obtained from the primary study authors.[75] This often gives meta-analysis of individual patient data more power.[75] We selected Bayesian evidence synthesis for the analysis, anticipating that incomplete outcome reporting, varied endpoints, limited availability of aggregate or individual patient data, and diversity of study designs with varied statistical analysis approaches would pose a formidable challenge to the classic (frequentist) methods of meta-analysis.[74] Classic meta-analysis may also underestimate the between-study variability for small numbers of trials,[24,73] leading to inaccurate inferences; Bayesian methods provide more robust estimates of between-study variance.

Objectives

We performed a Bayesian responder meta-analysis of individual patient data to study whether inhaled cannabis provides relief for chronic neuropathic pain.

Methods

We registered our protocol with PROSPERO.[5] We identified studies by a combination of electronic and manual searches (Fig 1) (Supplementary Appendix 1). We followed the recommendations of the QUORUM and PRISMA statements,[59] including the PRISMA checklist (Supplementary Appendix 2). We searched in Cochrane Central, PubMed, EMBASE, and AMED without any language restriction with a combination of free text and controlled vocabulary, using the highly sensitive search strategy.[44] We conducted a hand search in the conference abstracts from the Conference on Retroviruses and Opportunistic Infections 2011, the International AIDS Conference, and the World Congress of Pain 2010 and reference lists.

We considered RCTs investigating chronic painful neuropathy. We included diabetic, traumatic, and HIV-related causes. We excluded multiple sclerosis, a central rather than a peripheral pain condition. The nature of the intervention likely interfered with effective participant blinding,[3] which was therefore not required for study inclusion. We only included studies comparing inhaled *Cannabis sativa* with placebo, because inhaled whole-herb cannabis differs significantly in composition, bioavailability, and pharmacodynamics from synthetic cannabinoids.[70]

Three review authors (M.H.A., G.C., K.S.) screened the citations using explicit criteria for study exclusion. Using a standard data collection form, 2 authors (M.H.A. and G.C.) extracted the data independently, reconciling any differences by consensus. Study authors provided individual patient data.[2,31,81,84,85] We recorded details of trial design, conflict of interests, sponsors, participant

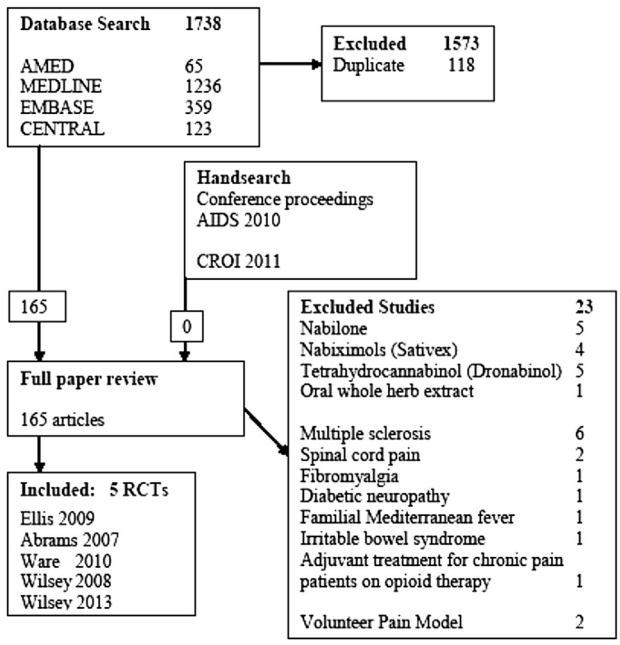

Figure 1. The QUORUM flow chart details our search in a diagram. We selected 165 articles for full review from 1738 hits in multiple electronic databases; 5 RCTs met the inclusion criteria (Abrams 2007,[2] Ellis 2009,[31] Ware 2010,[81] Wilsey 2008,[85] Wilsey 2013[84]). Excluded studies are double counted if they met more than 1 exclusion criterion, eg disease and mode of administration.

characteristics, interventions and outcome measures, inclusion and exclusion criteria, comorbidity and HIV status, cannabis provenance, dose, and mode of administration. We extracted data on attrition and on adverse effects.

We compared the proportion of patients experiencing more than 30% clinical improvement in chronic neuropathic pain assessed with a continuous patient-reported instrument (eg, the visual analog scale) at baseline and after treatment with inhaled cannabis. In essence, we dichotomized the outcome in a responder analysis, emerging as the preferred method for pain outcomes research.[28,32] We chose this patient-centered concept of minimally clinically important difference,[58] because chronic neuropathic pain, our primary outcome, is patient reported and may have a skewed distribution, with no more than 40 to 60% of patients obtaining even partial relief of their pain.[27] A statistically significant change in the population mean of a continuous pain outcome may not correspond to a clinically meaningful improvement for many individual patients.[60] In other words, large studies may detect population differences too small for individual patients to appreciate. However, responder analysis converts continuous pain outcomes to dichotomous responder data allowing a more meaningful comparison between interventions.[61,72] By convention, we classified participants as "responders" if their reduction in continuous spontaneous pain outcome (eg, VAS score) was larger than 30% after treatment.[28,32]

Two authors (G.C. and M.H.A.) independently assessed the risk of bias of the studies included according to the Cochrane Collaboration[44] on the basis of a checklist of design components and they contacted authors for missing information. We summarized this in a risk of bias graph (Fig 2) and provide detailed information in Supplementary Table 1. This comprised randomization, allocation concealment, observer blinding, intention-to-treat analysis, selective reporting, and conflict of interests. We achieved consensus by informal discussion. With inhaled cannabis interventions, blinding of patients and providers can be difficult and hence they received less weight in the evaluation of performance bias but not with regard to detection bias.

Our results are based on individual patient data obtained from primary authors who helped resolve data inconsistencies when evident. We estimated the content and the dose administered following published methods[10,57] in cooperation with the primary study authors.

We compared the reported primary outcome with the planned primary outcome in the study protocols to assess reporting bias. We explored undue sponsor influence.[44] We considered an examination of publication bias using graphical and statistical tests.[29] We investigated study heterogeneity using a χ^2 test and calculation of an I^2 analog Bayesian statistic.[44]

Data Synthesis, Statistical Modeling, and Sensitivity Analysis

We performed full Bayesian probability modeling[20] of the population-averaged subject-specific effect[90] as

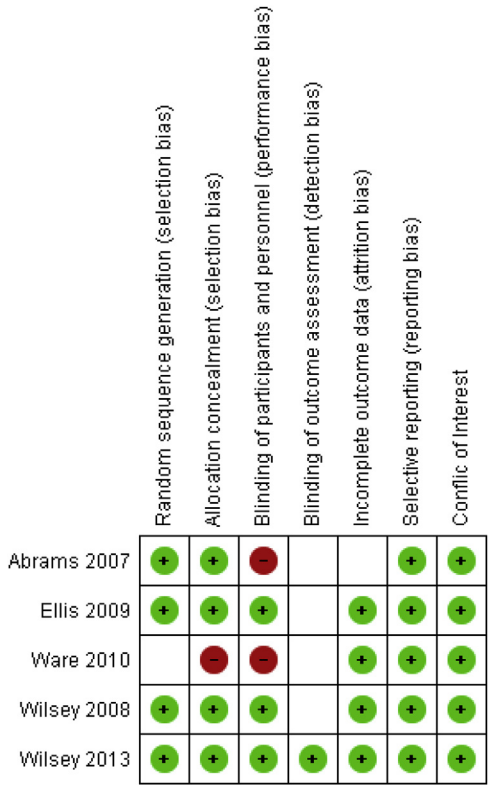

Figure 2. This summary of bias graph shows that the studies included were mostly of good quality in the domains of sequence generation, concealed allocation, incomplete outcome data, and selective reporting, and with regard to conflict of interest. However, the nature of the intervention likely interfered with effective blinding, possibly resulting in a high risk of performance bias in all studies and detection bias due to a lack of blinding of outcome observers. (Abrams 2007,[2] Ellis 2009,[31] Ware 2010,[81] Wilsey 2008,[85] Wilsey 2013[84]).

detailed in the statistical supplement (Supplementary Appendix 3). We pooled the treatment effects following a hierarchical random-effects Bayesian responder model. Kruschke[51] provided an accessible introduction to Bayesian methods in health sciences. Ashby[6] recently offered a chronological outline of applications in medicine, and Spiegelhalter et al[74] compiled the first concise overview. Gelman et al[35] described Bayesian hierarchical modeling approaches more formally. Supplementary boxes explain the basic concepts of Bayesian inference (Supplementary Boxes 1–3). The prior for the between-study variability (Cauchy) and the pooled effect estimate (normal distribution) were centered at zero with a standard deviation of 100. We preferred the Cauchy distribution over the closely related t-distribution, because the Cauchy is more robust in accommodating outliers[34,35]; these priors for our meta-analysis were uninformative and served to ensure computational convergence of the Markov chain Monte Carlo algorithm. Our priors were subsequently subjected to sensitivity analysis. Inference was implemented using a Gibbs sampling scheme to generate a computer simulation of a Monte Carlo sample from the posterior distribution in OpenBugs.[53] Our OpenBugs program code is provided in Supplementary Appendix 4. We have uploaded details on Monte Carlo Markov chain convergence, including graphs

demonstrating mixing, as supplementary material (Supplementary Figs 1 and 2). Differences in the design and quality of the studies were the focus of a sensitivity analysis. We tested the sensitivity of our results for our Bayesian model and its assumptions. We investigated our choice of prior and model parameters and reanalyzed the individual patient responder data 1) in a frequentist random-effects meta-analysis and 2) controlling for cannabis dose as an explanatory variable of the between-study variability in a meta-regression (methods and data not shown but available on request).

Reporting

We estimated the number needed to treat (NNT) and calculated the Bayes factor,[36] compared with the classic *P* values in Supplementary Box 3. We provided forest plots for the individual trials broken down by dose for the period level data (Fig 3). The reported pooled Bayesian estimate is the population-averaged subject-specific odds ratio comparing inhaled cannabis versus placebo for chronic painful neuropathy and their 95% Bayesian credible intervals ($CRI_{95\%}$), displayed as the standard diamond used for synthesized effects.[43]

Differences From the Initial Protocol

In our initial Prospero protocol registration, we considered including all types of studies, populations, and cannabis interventions. We intended to do a network analysis in 1 coherent Bayesian model. We found published aggregate data insufficient for evidence synthesis and therefore we decided to attempt an individual patient data meta-analysis, but limiting ourselves to only RCTs investigating inhaled cannabis, and updated the protocol accordingly.

Results

Our search (Fig 1) was completed in April 2014 and yielded 1738 references (1236 in MEDLINE, 359 in EMBASE, 123 in Cochrane Central, and 65 in AMED) matching the predefined search parameters. We excluded 118 duplicates and 1573 references for which we could clearly discern from the title or abstract that they were not randomized trials or did not investigate cannabis for a painful condition. Our hand search yielded no additional references. Except for the 5 studies included,[2,31,81,84,85] the remaining 163 publications studied different modes of cannabis administration or included participants with other painful conditions. No study investigated outcomes beyond 2 weeks. The characteristics of the 5 RCTs meeting our inclusion criteria are summarized in Table 1 and detailed characteristics are presented in Table 2. Important studies that were excluded are listed in Supplementary Table 2 with reasons for their exclusion.

Descriptive Characteristics of the Studies Included and the Participants

One hundred and seventy-eight middle-aged participants (approximately equal numbers of men and women) with painful neuropathy of at least 3 months duration (pain scores at least about 3/10) were enrolled in 5 RCTs executed across North America. Two trials recruited only HIV-positive individuals with HIV-related chronic painful neuropathy[1,2,31]; sexual orientation and

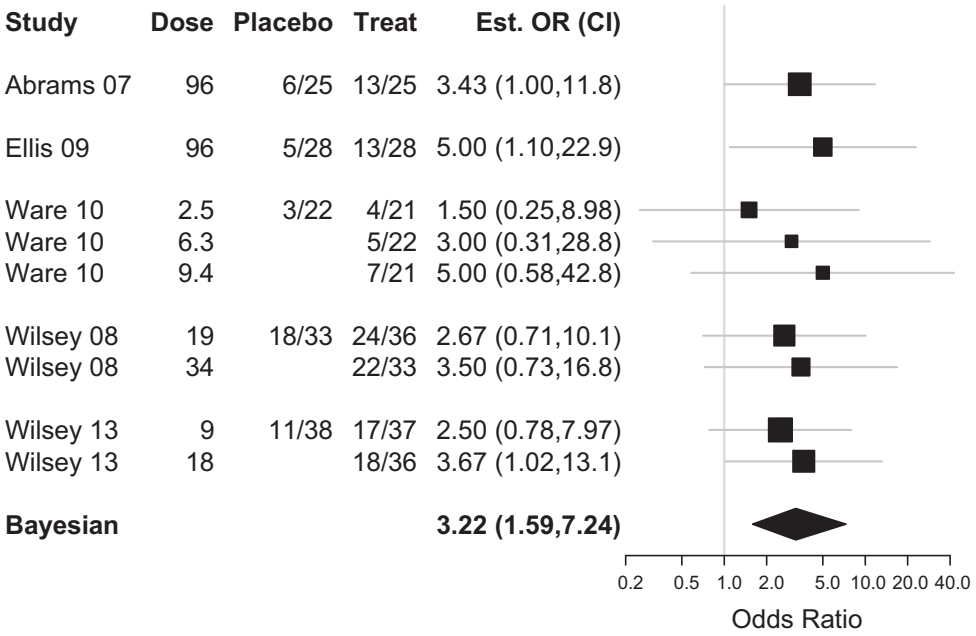

Figure 3. The forest plot displays odds ratios (with the 95% CRI indicated by horizontal bars on the log scale) to indicate their contribution to the Bayesian pooled effect estimate shown below as a diamond with the Bayesian 95% CRI. The table on the left lists the raw responder data at the study level. For Ware 2010,[81] Wilsey 2008[85] and Wilsey 2013,[84] the responder data are broken down by dose, listing the number of observed responses for each crossover period and the corresponding cannabis dose. The increased effect with increased cannabis content (evident in the period level data of Ware 2010,[81] Wilsey 2008,[85] and Wilsey 2013[84]) is additional evidence in support of the effect of cannabis on chronic painful neuropathy.

Table 1. Summary of the 5 RCTs on Inhaled Cannabis for Chronic Neuropathic Pain

Characteristic	Abrams 2007	Ellis 2008	Ware 2010	Wilsey 2008	Wilsey 2013
Neuropathy	HIV-DSPN	HIV-DSPN	Posttraumatic	Sensory	Mixed
Participants	50	34	23	38	39
Allocation	<---------- Randomized ---------->				
Intervention	<---------- Inhaled cannabis versus placebo ---------->				
Outcome	VAS	DDS	NRS	VAS	VAS
Follow-up	<---------- 5 days ---------->		2 weeks	<---------- 5–6 h ---------->	
Design	Parallel	<---------- Crossover ---------->			
Statistics	Mann-Whitney	Wilcoxon rank sum	<---------- General and linear mixed models ---------->		

Abbreviations: HIV-DSPN, HIV-related distal sensory polyneuropathy; DDS, Descriptor Differential Scale; NRS, Numerical Rating Scale.
NOTE. The cause of chronic neuropathic pain varied (including traumatic, central, diabetic, and HIV-related). Study authors used several patient-reported pain outcome instruments.

transgender data were not reported. Three trials recruited patients with neuropathy secondary to trauma,[81] spinal cord injury, diabetes mellitus, and complex regional pain syndrome.[84,85] Psychiatric disease, substance abuse, and significant cardiopulmonary disease were explicit exclusion criteria. Although previous cannabis experience was a prerequisite for inclusion for some studies,[1,2,84,85] current use was an exclusion criterion in all. Prescribed opioid use was not specified among the inclusion or exclusion criteria.

Characteristics of Interventions and Comparators

All studies investigated inhaled cannabis. The 5 studies used different doses, estimated as detailed in the Supplementary Table 3. All 5 studies used whole *Cannabis* plant provided by the US National Institute of Drug Abuse (NIDA). Cannabis was administered as prerolled cigarettes in 3 studies,[1,2,31,85] through a Volcano vaporizer in 1 study,[84] and as gelatin capsules smoked through a pipe at home in 1 study.[81] All 5 studies used identical-looking placebo as comparator. Concomitant nonstudy analgesics were permitted and continued in both arms.

Clinical Outcomes and Adverse Effects

All 5 RCTs reported continuous patient-reported spontaneous pain intensity scales as primary outcomes. We report the study level observed odds ratio (with 95% CRI indicted by vertical bars on the log scale) as a measure of their contribution to the Bayesian pooled effect estimate (shown as a diamond with 95% CRIs below) (Fig 3). The breakdown of responder data by dose suggested an increased effect with increased cannabis content.

Withdrawals due to adverse effects were rare. One case of serious adverse effects leading to withdrawal occurred in the placebo group (a case of psychosis) and 2 others in active treatment groups (hypertension and increased pain). Subjective side effects included anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, and numbness and were reported as being mild. Wilsey et al[85] reported short-term declines in attention, psychomotor performance, and learning and memory in the highest dose (7% tetrahydrocannabinol) group. Memory impairment was also seen in the placebo group and at lower doses, albeit at lower levels. Statistically significant physiological changes (such as increases in heart rate) were observed in one study[31] but not in another study.[81] Reports of euphoria or "high" were rare.[81] Psychoactive effects (such as feeling "high") were statistically significantly associated with treatment allocation in 2 studies[2,31] and increased in frequency with increasing dose[81,85]; they were mostly mild. The studies included followed patients only for days to weeks and hence did not report long-term adverse effects.

Study Design

All 5 studies were randomized, placebo-controlled, and double-blind; 4 used a crossover design[31,81,84,85] and 1 study used a parallel design.[1] Duration of follow-up varied from hours[84,85] to days[2,31] or weeks.[81]

Risk of Bias in the Studies Included

We characterized the risk of bias of the studies (Fig 2 and Supplementary Table 1). Randomization and allocation concealment were well described and suggested a low risk of bias. Ineffective participant blinding might have possibly resulted in performance bias in all studies; placebo effects are likely, when participants guessed their allocation, possibly leading them to overestimate the effect of inhaled cannabis on pain. Blinding of outcome observer was well described in 1 study,[84] and the use of patient diaries as an outcome instrument led us to estimate the risk of detection bias as unclear in the remaining studies. Incomplete outcome data were well described in all studies and are detailed in Table 2. Withdrawals potentially related to treatment effects led to a high risk of bias in 1 study[81] but did not seem to be associated with group allocation in all others.[2,31,84,85] All the trials included reported their primary outcome as specified in the protocol. We investigated publication bias in a funnel plot proposed by Egger et al,[29] because with fewer studies than 10 studies, the power of the tests is insufficient to distinguish chance from real asymmetry.[44] Studies received only public funding; all authors provided detailed conflicts of interest statements.

Evidence Synthesis of Effects

Based on data from 178 patients with a total of 405 observed responses, we estimated the odds ratio for more than 30% reduction in pain scores in response to

Table 2. Detailed Characteristics of the 5 RCTs Investigating Smoked or Inhaled Cannabis for Painful Neuropathy

Study ID	Year	Journal	Pubmed ID	Trial Registry ID
Abrams 2007[2]	2007	Neurology	17296917	NCT00046722
Population	55 HIV-positive adults with symptomatic HIV-DSPN and at least 30/100 VAS, on stable pain regimen for 8 weeks before enrolment, with previous experience of smoking cannabis randomized in 2 groups of size 27/28. Our Bayesian analysis is based on 50 participants with 1 observation per patient, as provided by the primary study authors. Age (experimental, control): 50 y (SD ± 6 y), 47 y (SD ± 7 y) Gender (male/female/other): experimental 22/5/0, control 26/2/0			
Intervention	Experimental: patient smoked 1 cigarette 3 times per d as tolerated Prerolled, whole-herb *Cannabis* cigarettes were provided by NIDA and contained 3.56% Δ-9-THC. Control: identical prerolled cigarettes with the active ingredient extracted. Dose estimate: 32 mg THC per session; 96 mg THC per d			
Primary outcome	Daily pain diary recording the VAS at 8 AM for average pain during the previous 24 h			
Study methods	Randomized, double-blind (patient, outcome assessor), parallel design, placebo-controlled, single-center (university) clinical trial in San Francisco, California, starting in 2003			
Notes	Also published as an abstract at the 2nd Annual Meeting of the International Association for Cannabis as Medicine, 2005 Secondary outcomes: acute analgesic effects; long thermal stimulation Anti-hyperalgesic effects: heat-capsaicin model; profile of mood states			
Ellis 2009[31]	2008	Neuropsychopharmacology	18688212	NCT00255580
Population	34 HIV-positive adults with symptomatic HIV-DSPN and pain score >5/20 on DDS, most participants were previously exposed to potentially neurotoxic deoxy-nucleoside reverse transcriptase inhibitors; 16 started control/experimental, 18 started experimental/control. 28 participants with a total of 56 observed responses were included in the Bayesian analysis Age (all): 49.1 y (SD ± 6.9 y) Gender (male/female/other): 33/1/0			
Intervention	Experimental: patient smoked cannabis, titrating dose up or down to obtain effective pain control/tolerable adverse effects, starting at 4% and ranging between 1 and 8% Δ-9-THC concentration by weight. Prerolled, whole-herb *Cannabis* cigarettes were provided by NIDA Control: identical prerolled cigarettes with the active ingredient extracted Dose estimate: average 96 mg THC per d			
Primary outcome	Crossover difference in change of DDS 0–20 scale "a ratio scale containing 24 words describing pain intensity and unpleasantness" comparing baseline with after treatment			
Study methods	Randomized, double-blind (patient, outcome assessor), crossover design, placebo-controlled, single-center (university) clinical trial at the University of California, San Diego, California, in 2006			
Notes	Secondary outcomes: McGill questionnaire, VAS, Sickness Impact Profile, Brief Symptom Inventory, UKU side effect rating, Highness/Sedation Scale, HIV load			
Ware 2010[81]	2010	Canadian Medical Association Journal	20805210	ISRCTN68314063
Population	23 adults with non-HIV neuropathy pain of at least 3 mo duration caused by trauma or surgery defined by pain intensity score greater than 40/100 VAS, on a stable analgesic regimen, not having smoked cannabis in the preceding year. 23 participants with a total of 86 observed responses were included in the Bayesian analysis Age (all): 45.4 y (SD ± 12.3 y) Gender (male/female/other): 11/12/0			
Intervention	Experimental: NIDA and Prairie plant systems prepared 3 different potencies of THC (2.5%, 6%, 9.4%) from whole herb in gelatin capsules inhaled through a pipe Control: ethanolic extraction was used to prepare the placebo Dose estimate: 0, 1.625, 3.9, and 5.85 mg/d (average) THC per period			
Primary outcome	Average daily pain intensity on the 11-item NRS averaged over 5 treatment d (least pain value, average pain value, and worst pain value) during 4 consecutive crossover periods of 14 d each (5 treatment d and 9 washout d afterwards)			
Study methods	Randomized, double-blind (patient, outcome assessor), 4-period crossover Latin square design, placebo-controlled, single-center (university) clinical trial in McGill University, Montréal, Canada, starting in 2003			
Notes	The linear model did not consider interparticipant effects Secondary outcomes: pain quality, McGill questionnaire, sleep (Leeds Sleep Evaluation Questionnaire); mood effects, short-form Profile of Mood States; quality of life: EQ-5D health outcomes			
Wilsey 2008[85]	2008	The Journal of Pain	18403272	NCT00254761
Population	38 adults with non-HIV neuropathy (complex regional pain syndrome (type I), spinal cord injury, peripheral neuropathy, or nerve injury) with previous cannabis experience and a VAS >30/100. 38 participants with 102 observed responses were included in the Bayesian analysis Age (all): 46 y (range 21–71 y) Gender (male/female/other): 20/18/0			

Table 2. Continued

Study ID	Year	Journal	Pubmed ID	Trial Registry ID
Intervention	Experimental participants inhaled a total of 9 standardized cued puffs. Cannabis was harvested from whole plant and rolled into cigarettes at the University of Mississippi under supervision of NIDA ranging in strength from 0% to 3.5–7%. Control: placebo cigarettes were made from whole plant with extraction of *Cannabis* Dose estimate: 0 placebo, 19.25 (low dose, range 7–30.45), 34.3 (high dose, range 18.9–60.9) mg THC/d (session)			
Primary outcome	VAS measuring spontaneous pain relief; time effects were studied with a linear model			
Study methods	Randomized, double-blind (patient, outcome assessor), parallel design, placebo-controlled, single-center (university) clinical trial at University of California Davis Medical Center, Sacramento, California, started in November 2003			
Notes	Secondary outcomes: pain unpleasantness (VAS), heat pain threshold, Neuropathic Pain Scale, neurocognitive assessment, and plasma *Cannabis* concentration			
Wilsey 2013[84]	2013	The Journal of Pain	23237736	NCT01037088
Population	39 adults with non-HIV neuropathy due to reflex sympathetic dystrophy, peripheral neuropathy, postherpetic neuralgia, poststroke pain, multiple sclerosis, or spinal cord injury with previous cannabis exposure (16 current, 23 ex-users) and a VAS pain intensity greater than 30/100. 39 participants with 111 observed responses were included in the Bayesian analysis Age (all): 50 y (SD ± 11 y) Gender (male/female/other): 28/11/0			
Intervention	Experimental: participants used a volcano vaporizer under the flexible-dose design of Wilsey 2008. The minimum and maximum cumulative doses for each visit were 8 and 12 puffs. Cannabis was harvested at the University of Mississippi under the supervision of NIDA Control: placebo was made from whole plant with removal of cannabinoids Dose estimate: maximum of 0, 10.32, 28 mg THC/d (session), presuming they were administered the entire 800 mg dose			
Primary outcome	VAS before and after consuming vaporized cannabis			
Study methods	Randomized, double-blind (patient, outcome assessor), crossover design, placebo-controlled, single-center (university) clinical trial at the University of California, Davis, California, started December 2009			
Notes	Secondary outcomes: Patient Global Impression of Change; Neuropathic Pain Scale; WAIS-III, Hopkins Verbal Learning Test (revised), Grooved Pegboard Test			

Abbreviations: HIV-DSPN, HIV-related distal sensory polyneuropathy; SD, standard deviation; DDS, Descriptor Differential Scale; NRS, Numerical Rating Scale.
NOTE. Two trials recruited patients with HIV-DSPN, 3 included participants with neuropathies due to other causes.

inhaled cannabis versus placebo for chronic painful neuropathy as 3.2 with a Bayesian CRI (subsequently denoted with the subscript $_{CRI95\%}$) $[1.59, 7.24]_{CRI\ 95\%}$, and the NNT as 5.55 $[3.35, 13.7]_{CRI\ 95\%}$. We estimated the posterior probability of the effect of *Cannabis* for chronic painful neuropathy to be 99.7% and the Bayes factor as 332 (Fig 3). The Bayesian analog I^2 statistic was 0. The posterior probability that the between-study variability in effects was greater than what would be expected by chance is .45. Effects seemed to increase with tetrahydrocannabinol (THC) content supporting the effect of cannabis for chronic painful neuropathy as seen in the forest plot (Fig 3). Specifically, the increased effect with increased cannabis content (evident in the period level data of Ware 2010,[81] Wilsey 2008[85] and Wilsey 2013[84]) is additional evidence consistent with the effect of cannabis for chronic painful neuropathy. However, a meta-regression of cannabis dose (data not shown but available on request) did not change our estimates or inferences. The aggregate and individual data on adverse effects were too sparse to be pooled. Model convergence is documented in the supplementary material (Supplementary Figs 1 and 2).

Sensitivity Analysis

When we performed a sensitivity analysis (available on request) with regard to differences in the quality of studies, we found effect estimates and credible intervals to be robust regarding the inclusion or exclusion of any single study. Our inferences were rather insensitive to priors (between-study variance) in our Bayesian model (Supplementary Box 2). Reanalyzing the data in a frequentist random-effects meta-analysis did not change the results.

Discussion

Our evidence synthesis of individual patient data from 178 participants with 405 observations in 5 RCTs with a follow-up ranging from days to weeks (Fig 3) provides evidence that inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated (NNT 5.6 with a Bayesian 95% CRI ranging between 3.4 and 14); based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definition of at least moderate benefit,[28] inhaled cannabis improved pain by an odds ratios of 3.2 (Bayesian 95% CRI of $[1.6, 7.2]_{CRI\ 95\%}$ (Fig 3). The Bayes factor was 332, corresponding to a posterior probability of effect of 99.7%.

We infer that this effect applies equally across chronic painful neuropathies of different causes (eg, diabetic and traumatic chronic painful neuropathy or HIV-related distal sensory neuropathy). The effects are remarkably homogeneous across studies (Bayesian I^2 analog = 0%) (Table 1). Dose dependency further supports the notion of a cannabis effect on neuropathy (Fig 3 and Supplementary Table 3). Our results (NNT 5.6 $[3.4, 14]_{CRI\ 95\%}$) suggest that inhaled cannabis may be about as potent as gabapentin (Cochrane Review

update: NNT 5.9 [4.6, 8.3]$_{CI\ 95\%}$ for diabetic neuropathy, Moore 2014[62]). The NNT of inhaled cannabis could potentially rival currently available therapeutics for chronic neuropathic pain,[82] whose NNT typically range well above 8, if there is any evidence at all.[15,21,25] However, we caution that our findings await confirmation in long-term pragmatic community-based trials. Our findings are remarkable considering the dearth of effective treatment options for chronic painful neuropathies or chronic pain in general.[49]

Our Review Enhances the Existing Literature on Treatment for Chronic Neuropathic Pain

Our evidence synthesis contradicts, updates, or complements the finding of several older and more recent reviews on cannabis by providing a meta-analysis for chronic neuropathic pain,[13,14,85] by updating evidence,[13-16] or by broadening the scope. We were able to include recent RCTs, not published or accessible to the previous reviews by Campbell, Phillips, Iskedjian, Lutge, or Lynch.[19,47,54,55,67] Compared with previous studies,[67] our meta-analysis of individual patient data and the inclusion of additional and recent clinical trials, which augmented the power to detect an effect, if it existed, and amplified the confidence in the pooled effect estimate (NNT = 5.6) by shrinking the 95% CRI,[2,3,12] our posterior probability of the short-term effects of inhaled cannabis is now very high (99.7%). Our analysis complements the recent evidence synthesis of cannabis for certain other neurological conditions by the American Academy of Neurology, which did not investigate cannabis for chronic neuropathic pain,[49] and supports another narrative review (published after submission of this manuscript) with a meta-analysis of individual patient data,[45] which concluded that "Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence."

Strength

Meta-analysis of Individual Patient Data Increased the Power of our Meta-analysis

We performed an individual patient meta-analysis. Unlike conventional meta-analysis based on published aggregate data, meta-analysis of individual patient data synthesizes the individual participants' original data obtained from the studies' principal investigators.[43] Meta-analysis of individual patient data is arguably the gold-standard of evidence synthesis,[71,75] not just because it allows for detailed data checking but because meta-analysis is often not feasible using only summary data. Synthesizing the diversity of reported outcomes of studies on inhaled cannabis for chronic painful neuropathy was a significant challenge for previous reviews.[13-16] In our review insufficient published outcome data and variations in design and outcome reporting would have led to the exclusion of relevant trials, because the published aggregate data lacked the necessary detail for pooling in a meta-analysis.[4,84,85]

The meta-analysis of individual patient data and the inclusion of additional recently published RCTs increased the power of our evidence synthesis and greatly increased the confidence in the effect of inhaled cannabis for chronic neuropathy compared with previous reviews.[46,54,55,67] The Bayesian posterior probability of more than 99.7% indicates the very high likelihood that inhaled cannabis is effective in the short term for 1 in 5 or 6 patients with chronic neuropathic pain (Supplementary Box 1), unlike the classic *P* value, which indicates how unlikely the observed outcomes data are given a null hypothesis of no effect. To our knowledge, this is the first Bayesian meta-analysis of individual patient data in medicine.[6]

The Observed Short-Term Effect of Inhaled Cannabis Is Meaningful for 1 in 5 or 6 Patients With Chronic Neuropathy

Our responder analysis is showing a statistically significant and minimal clinically important difference for 1 in 5 to 6 patients, an effect measure easily understood by patients, payers, and providers alike.[58] Responder analysis has been advocated for patient-reported outcomes in chronic pain trials to distinguish a minimal but statistically significant difference between groups on a population basis from a clinically meaningful effect for the individual participant.[28,60,61] Our cutoff for a meaningful response (>30%) is 1) grounded in what patients themselves judge to be important improvement[32] and 2) based on expert consensus (IMMPACT).[58] Based solely on frequentist hypothesis testing, responder analysis may miss the goal, while losing power.[72] Our Bayesian meta-analysis of individual patient data allowed us to calculate a posterior probability of effect larger than 99.7%.

Limitations

Effects Are Consistent Across Different Causes and Populations

We pooled data from populations with chronic painful neuropathy of different causes and in different populations. We included HIV-related distal sensory polyneuropathy, posttraumatic, complex regional pain syndrome, peripheral and diabetic peripheral neuropathy, and patients with and without previous exposure to cannabis. Similar approaches were also taken by authors of previous reviews on cannabis for chronic painful neuropathy.[13-16] Evidence synthesis across distinct but closely related painful neuropathies is reasonable because their clinical course and pathological mechanism are considered similar and receive uniform treatment recommendations[9,64]; Indeed, the "etiological factors responsible for driving the mechanisms are not disease specific" and "disease diagnosis is not helpful in selecting the optimal pain therapy".[86,87] Even if the absence of evidence for heterogeneity constitutes no evidence for clinical homogeneity,[44] the consistency and uniformity of the effect of inhaled cannabis on chronic neuropathic pain across different causes and

populations, further enhances our confidence in the generalizability of our findings.[48] Yet, our meta-analysis can only be as strong as the underlying data (Tables 1 and 2) and the methodological quality (Fig 2 and Supplementary Table 1); the small number of studies included, their small number of participants, and shortcomings in allocation concealment[42] and attrition (Table 2) limit our ability to draw firm conclusions. The small numbers of studies found in each subgroup precluded a formal study of publication bias. A graphical analysis or the test proposed by Egger et al[29] should at least include 10 studies because, with fewer studies, the power of the tests is insufficient to distinguish chance from real asymmetry.[44] We find that the use of an active placebo to mimic the psychotropic effects of experimental treatments, although it improves blinding, does not necessarily improve the evidence regarding effectiveness in a pragmatic clinical setting, but it does acknowledge the risk of performance bias.[70] Also meta-analyses of sparse data can be unstable[38,66]; however, our evidence synthesis is based on individual patient data from all included trials, the best available source of evidence, short of a large RCT.[44,76]

Cannabis Dose and Mode of Administration May Influence Pain Relief

Estimating bioavailable cannabis is difficult. Many factors influence the amount of THC per cigarette, particularly whether the material is dry or freshly picked (Supplementary Table 3). The dose delivered likely differs from what is actually ingested[69]; we validated our dose estimates with the primary authors of the studies included. In the forest plot of the raw responder data, a higher dose seems to be associated with a stronger effect (Fig 3). Our sensitivity analysis controlling for cannabis dose only marginally improved the precision (data not shown); hence, at the individual patient level, the dose differences did not explain the differences in effect. This may effectively reflect the individual dose titration.

We cannot comment on long-term adverse effects because the available trials followed their patients for a maximum of 2 weeks.[3] Recently, several authors have raised concerns about driving while intoxicated, withdrawal, addiction, adverse cardiovascular, pulmonary and cognitive effects, especially in the developing brain, although several of these misgivings remain contentious.[11,16,17,26,37,40,47,68,77,83,88] Extrapolating from recreational use is problematic and the risk-benefit balance differs when pain is medically intractable. Clearly, we need to learn more about the benefits and risk associated with long-term cannabis use.

Our Bayesian Meta-analysis Is Robust to Parameter Choices and Model Assumptions

Bayesian methods are sometimes critiqued for their presumed subjectivity, but the short-term effects of inhaled cannabis for about 1 in 5 patients with chronic neuropathic pain are robust and independent of our mode of evidence synthesis. Our assumptions are modeled explicitly and tested.[14] Priors for our meta-analysis were uninformative in order to minimize subjectivity and just served to ensure computational convergence. As detailed in the results and illustrated in Supplementary Box 2, when subjected to sensitivity analysis, our findings were robust to the choice of parameters and models. Unsurprisingly, running a frequentist analysis resulted in similar estimates, except that the CRIs of our Bayesian estimate were more conservative because they were based on more cautious between-study variance estimates. Obviously, the Bayesian approach provides a posterior probability (99.7%; for the short-term benefits of inhaled cannabis for about 1 in 5 patients with chronic neuropathy), an inference not possible in the frequentist paradigm.[74] The result of any meta-analysis will critically depend on this estimate of the between-study variance. Our between-study variability estimation was more conservative than the classic random-effects approach promoted by the Cochrane Collaboration,[43] which itself is more conservative than the often employed fixed effects model. Indeed, the continued debate on fixed versus random-effects models, concerns about assumptions, and underestimation of between-study variability[24] demonstrate that the classic "frequentist" statistical approach is also not free of subjectivity.[78] The use of subjective model parameters destroys the illusion of objectivity in "frequentist" as well as in meta-analysis.[78] Our Bayesian approach transparently included any subjective choice explicitly in our model and subjected all to sensitivity analysis.[22,66]

Recommendations for Future Research

We lack long-term pragmatic clinical trials to determine if the effects of cannabis on chronic painful neuropathy are sustained and durable, if cannabis use is feasible in the community given the associated stigma,[1,18] if cannabis can be safely prescribed in vulnerable and young populations,[26,77] and if long-term adverse effects outweigh the benefits of inhaled cannabis.[11,40,47,68,77] Although the cost of inhaled cannabis is likely to be low, medicinal cannabis continues to be controversial (indeed illegal in many jurisdictions) and patients may vary in their preferences on inhaling cannabis, especially as long as it remains stigmatized. We need to investigate if individual titration allows for the best balance of beneficial to adverse effects. The effects of cannabis for other conditions should equally be explored in publicly funded rigorous RCTs. Solid clinical evidence may facilitate selective prescribing, prevent misuse, and reduce opioid-related harms.[41]

Conclusions

Our meta-analysis of individual patient data suggests that inhaled cannabis results in short-term benefits for chronic neuropathic pain with an NNT of 5.6 [3.4, 13]$_{CRI95\%}$ (Fig 3). We lack evidence regarding sustained long-term benefits and risks in the community setting. The small number of studies and participants included in the analysis (Table 1) and the risk of detection and

performance bias weaken our ability to draw firm conclusions (Fig 2). In our responder analysis of the proportion of patients with at least 30% reduction in chronic pain as the minimal clinically important difference, a meaningful improvement at the individual patient level was found for about 1 in every 5 to 6 patients treated.[27,58] This effect on chronic painful neuropathy is consistent across diverse causes, all hitherto resistant to available treatments (Table 1). To our knowledge, ours is the first Bayesian meta-analysis of individual patient data. The Bayesian modeling approach may be flexibly extended to other fields and questions where variance in outcome reporting hampers the classic approach to meta-analysis.[6,7,78]

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Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2015.07.009.

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