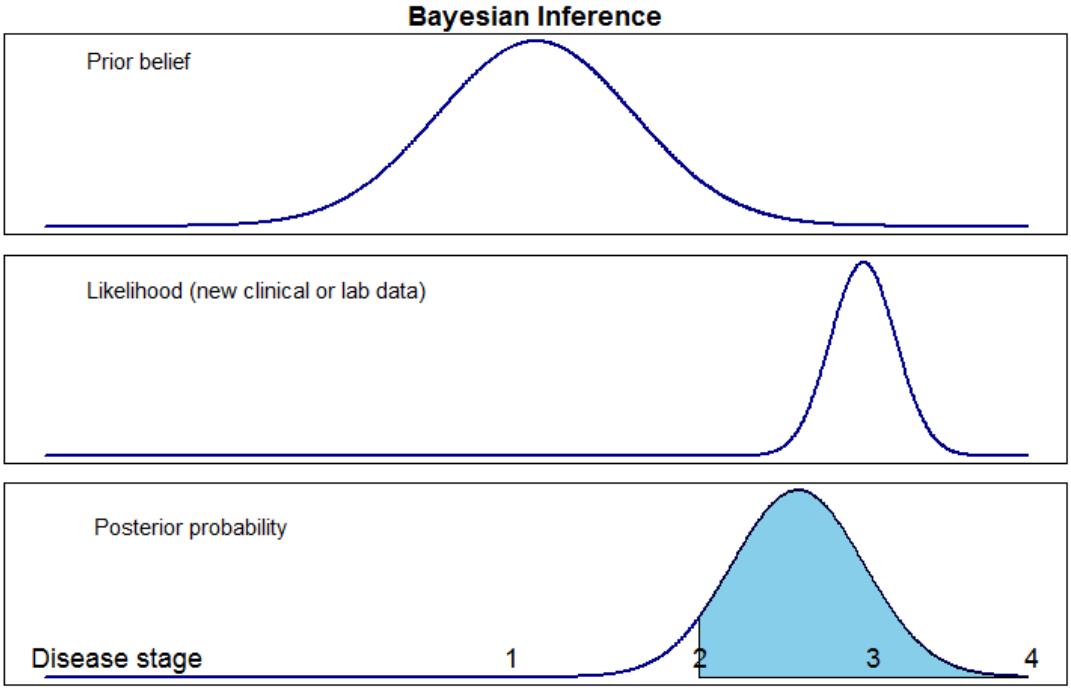
## ~~Supplemental Figures~~

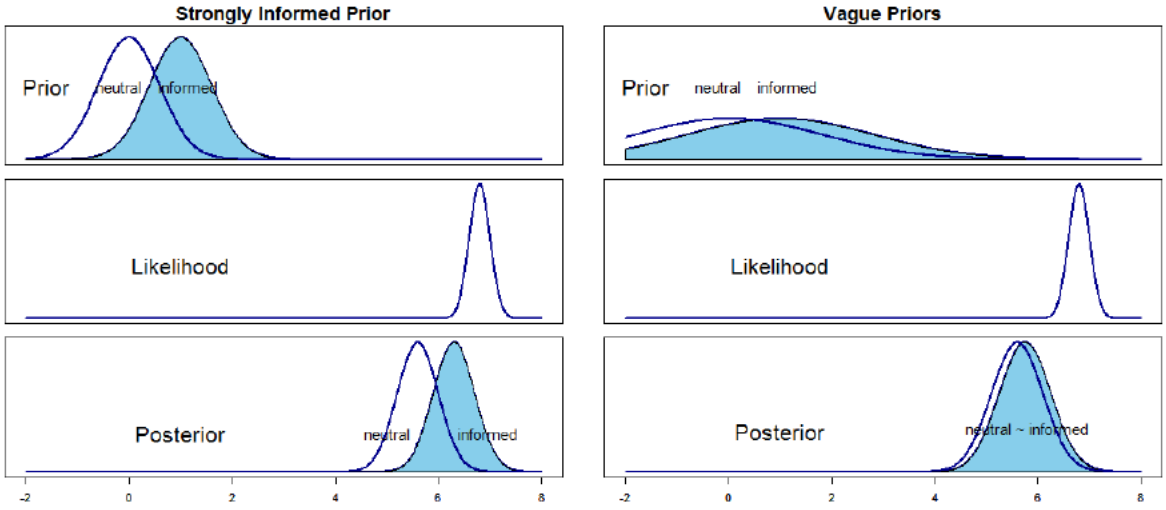
### *Supplementary Box 1: Bayesian approach to statistical inference*

We illustrate Bayesian inference in the clinical setting of cancer staging: The patient's history and physical informs a vague *prior* belief about the cancer stage, expressed as a wide probability distribution centered around 1 in the top panel. New clinical or laboratory data (termed *likelihood* in Bayesian parlance) are displayed as a probability distribution, peaked and centered on the disease stage most compatible with the new observations (middle panel). The combination of prior belief and data (likelihood) yields a posterior probability distribution reflecting the integration of prior information with new data (lower panel). The blue-shaded area shows the posterior probability that the stage is larger than 2. The *posterior* distribution becomes the new *prior,* when we update our belief with additional (imaging) information.




*Supplementary Box 2: Informed versus neutral priors*

In Bayesian inference, information from outside sources can be expressed in priors [top panel]. Data is included through the likelihood (middle panel). Effect estimate (NNT), are shown in the lower panel. Strongly informed priors (shaded in blue) may shift the effect estimate, effectively driving the analysis (as shown on the left]. However, our evidence synthesis used diffuse “neutral” priors (shaded in white), which convey essentially no information. Our priors therefore exerted little influence on our pooled effect estimate (lower panel, right); the inferences are therefore robust to model choices and assumptions. Statistical results must be subjected to a sensitivity analysis to investigate if inferences depend critically on prior or model parameters choices.




## *Supplementary Box 3: Comparison of Bayes factor and posterior probability versus p-value*

Bayesians estimate the posterior probability that an intervention improves outcome, or the Bayes factor to indicate how new data shifted the probability of effect, while the classical p-value in frequentist statics only helps to reject the Null-hypothesis of no difference between interventions, but contains no information in favor or against the alternative hypothesis; our very crude juxtaposition of Bayes factors, posterior probabilities and p-values is to give readers a feel for the strength of evidence, even though on theoretical grounds such a comparison is rather problematic. A Bayes factor larger than 300 and a posterior probability of effect larger than 99% is very strong evidence of Cannabis' effect for chronic neuropathic pain.

| | Strength of the evidence <-- | Bayes Factor | Posterior Probability of Effect | p-value |
|---|---|---|---|---|
| weak | | 3 | 90% | 0.1 |

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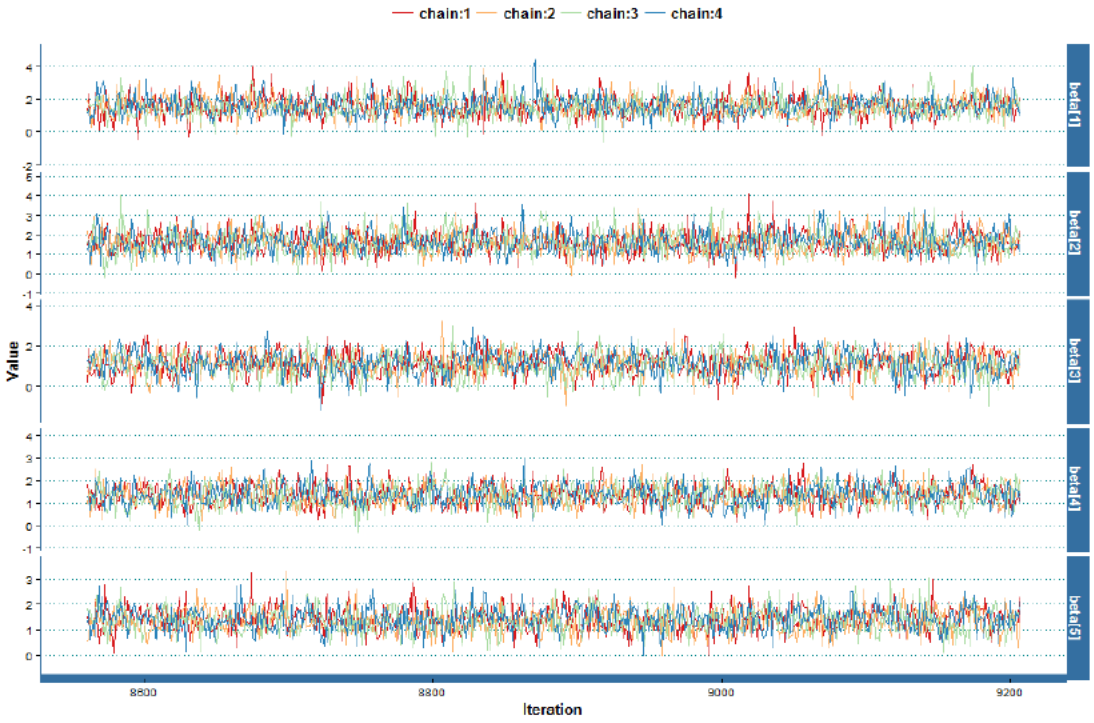
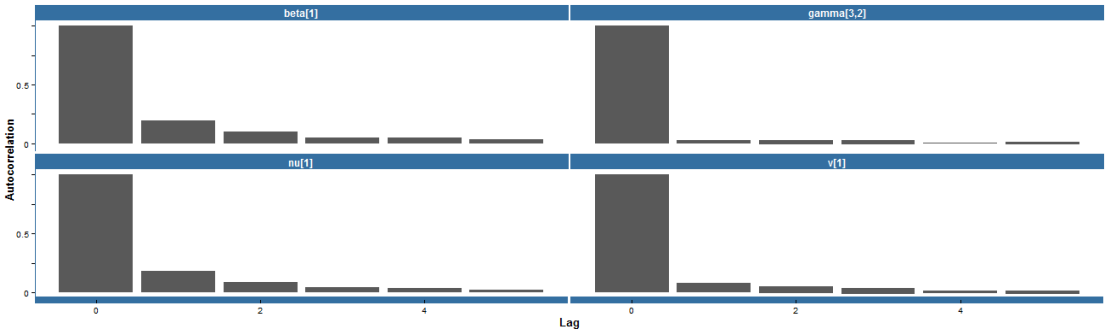
|---|---|---|---|---|
| "significant" | | 10 | 95% | 0.5 |
| strong | | 50 | 99% | 0.01 |
| very strong | | 300 | 99.9% | 0.001 |



## *Supplementary Figure 1: Traceplots*

Representative trace plots for all model parameters were inspected visually to assess model convergence. In this supplemental figure we show representative extracts (after thinning with a factor of ten) for only a few parameters. Samples in the four chains converge and are mixing well; in conjunction with the Gelman statistic close to one, they indicated adequate convergence of our Bayesian model.




## *Supplementary Figure 2: Autocorrelation*

High correlations between long lags can indicate poor mixing. This plot of the autocorrelation combining all four chains (after thinning with a factor of ten) are shown for a few representative

parameters to illustrate lag of dependency among Markov chain samples; in other words samples separated by a few lags are practically independent.

# Supplemental Tables

**Supplementary Table 1: Details on methodological quality of included studies**

We assessed the methodological quality of included studies in the five domains of randomization, allocation concealment, blinding, dealing with missing data and conflicts of interests (as low, high risk or unclear) and substantiated our judgment in the column on the right with excerpts from the manuscripts. Randomization and allocation concealment were well described and suggested a low risk of bias. Inadequate blinding led to a high risk of performance bias in all studies. Some studies suffered from significant attrition.

| Abrams 2007 | | |
|---|---|---|
| Bias | Authors' judgment | Support for judgment |
| Sequence generation | Low risk | "Randomization was ...computer generated by the study statistician..."“Treatment was double blind." |
| Allocation concealment | Low risk | "Identical appearing placebo cannabis cigarettes,.." and "managed by an independent research pharmacist," suggests that treatment allocation could not be guessed by providers and participants before treatment started. |
| Performance bias | High risk | "Identical appearing placebo cannabis cigarettes,.." However, "Patients were required to have previous experience..." and possibly guessed their allocation with the first puff. "Research staff |

| | | |
|---|---|---|
| | | monitored patients during smoking sessions', possibly observing treatment effects. |
| Detection bias | Unclear risk | "Patients completed a diary at 8am..." Blinding of outcome assessor not described. |
| Incomplete data | Unclear risk | Loss to follow up and withdrawals of a total of five patients from both arms were described; these patients were excluded from the analysis. A per patient and an intention to treat analysis is reported including multivariate analysis of all available data, but still excluding missing data. |
| Selective reporting | Low risk | "Change in level of HIV-related neuropathic pain as recorded on a 100mm Visual Analog Scale." The reported outcomes was the primary outcome of the reported study as defined in the protocol |
| Conflict of interests | Low risk | Conflicts of interest were reported as none. The sponsor was reported with detailed information. Funded by an NIH grant, undue sponsor influence is unlikely. |

| Ellis 2008 | | |
|---|---|---|
| Bias | Authors' judgment | Support for judgment |
| Sequence generation | Low risk | "Participants were randomly assigned", "randomization was performed using a random number generator" |
| Allocation | Low risk | Allocation was performed "by a research pharmacist…, key to study |

| | | |
|---|---|---|
| concealment | | assignment was withheld from investigators until completion statistical analysis." |
| Performance bias | Low risk | Nurses titrating dose to effective pain control and tolerable adverse effects likely guessed the allocation. However the authors write that "changes in heart rate and blood pressure …[did not result] in unblinding of the investigators".<br><br>Participants: "Those receiving Cannabis rarely guessed incorrectly; … most of the subjects crossing over to active Cannabis during their second treatment correctly guessed their assignment." |
| Detection bias | Unclear risk | Care givers: "…key to study assignment was withheld from investigators until completion statistical analysis," but nurses titrating dose to effective pain control and tolerable adverse effects likely guessed the allocation. However "Changes in heart rate and blood pressure …[did not result] in unblinding of the investigators".<br><br>Participants: "Those receiving Cannabis rarely guessed incorrectly; … most of the subjects crossing over to active Cannabis during their second treatment correctly guessed their assignment."<br><br>Outcome assessor: Unclear if and how the outcome assessors were blinded, but the outcome tools make bias less likely. " |
| Incomplete data | Low risk | Loss to follow up and withdrawals were described; A per patient and an intention to treat analysis is reported which accounts for missing/lost data by multiple imputations. |
| Selective | Low risk | The reported outcomes was the primary outcome of the reported |

| | | |
|---|---|---|
| reporting | | study as defined in the protocol |
| Conflict of interests | Low risk | No indication of relevant COI (Dr. Atkinson received compensation from Eli Lilly Pharmaceuticals). The sponsor was reported with detailed information. Funded by a State of California grant to the Center for Medicinal Cannabis Research (CMCR), undue sponsor influence is unlikely. |

| Ware 2010 | | |
|---|---|---|
| Bias | Authors' judgment | Support for judgment |
| Sequence generation | Unclear risk | "Eligible participants were randomized to a sequence of treatment periods based on a Latin square design." "randomly assigned"<br><br>Unlikely, but somewhat unclear as exact method of randomization is not described. |
| Allocation concealment | High risk | Allocation concealment is not well described. Did the caregivers know the sequence the participants would follow through the experiments. Could the participants guess or anticipate which treatment was next? |
| Performance bias | High risk | "double blind ... design", but outcome assessor or care giver blinding not described. Participants correctly guess allocation at the end of the trial. |
| Detection bias | Unclear | "double blind ... design", but outcome assessor or care giver |

| | | |
|---|---|---|
| | | blinding not described. |
| Incomplete data | Low risk | Loss to follow up and withdrawals were described; No ITT analysis was performed; PP analysis unreported/uncertain; missing/lost data was excluded |
| Selective reporting | Low risk | The reported outcomes was the primary outcome of the reported study as defined in the protocol |
| Conflict of interests | Low risk | No indication of relevant COI. The sponsor was reported with detailed information. Sponsor is a public entity supporting independent research; bias unlikely, undue sponsor influence is unlikely. |

| Wilsey 2008 | | |
|---|---|---|
| Bias | Authors' judgment | Support for judgment |
| Sequence generation | Low risk | "...crossover design using a web-based random-number generating program...", "Each patient received each treatment once, in random order." |
| Allocation concealment | Low risk | "The allocation schedule was kept in the pharmacy and concealed from other study personnel." "Patients were assigned to treatment after they signed a consent form." |

| | | |
|---|---|---|
| Performance bias | Low risk | Comments: “Patients and assessors were blinded to group assignments.” “Cigarettes were smoked under a standard laboratory fume hood with constant ventilation.” “A nurse supervised the participant via a closed circuit monitor...” and could hence probably not smell the agent. Unclear if participants, who had experience with Cannabis, were able to discern Verum from Placebo. Given the effect of Cannabis this is likely, but difficult to prevent completely, but this unblinding might have introduced bias. |
| Detection bias | Unclear risk | Unclear if participants, who had experience with Cannabis, were able to discern Verum from Placebo. Given the effect of Cannabis this is likely, but difficult to prevent completely, but this unblinding might have introduced bias. |
| Incomplete data | Low risk | Loss to follow up and withdrawals were described; No ITT analysis was performed; PP analysis reported; missing/lost data was excluded.<br><br>Very detailed and precise account of all patient attrition with detailed reasons, mostly likely not related to intervention. This and minimal attrition reduce the risk of bias. |
| Selective reporting | Low risk | The reported outcomes was the primary outcome of the reported study as defined in the protocol |
| Conflict of interests | Unclear/ Low risk | No statement of COI. No indication of relevant COI. The sponsor was reported with detailed information. Sponsor is a public entity supporting independent research; bias unlikely, undue sponsor influence is unlikely. |

| Wilsey 2013 | | |
|---|---|---|
| Bias | Authors' judgment | Support for judgment |
| Sequence generation | Low risk | "…in random order (using a web-based random number generating program, ''Research Randomizer'' (http:// www.randomizer.org/)..." |
| Allocation concealment | Low risk | "The allocation schedule was kept in the pharmacy and concealed from other study personnel. Patients were assigned to treatment after they signed a consent form. " |
| Performance bias | Low risk | "Patients and assessors were blinded to group assignments". "to prevent contamination of the breathing space of observers, this procedure was conducted under a standard laboratory fume hood"<br><br>**BUT:** "When subjects ''guessed'' whether they had received placebo or active study medication, participants were correct 63% of the time for placebo, 61% of the time for 1.3% THC, and 89% of the time for 3.5% THC." |
| Detection bias | Low | Outcome assessor: Stated that the outcome assessors were blinded; additionally the outcome tools make bias less likely. |
| Incomplete data | Low risk | Loss to follow up and withdrawals were described; No ITT analysis was reported; PP analysis reported; unsure/not reported how missing/lost to follow up data was accounted for |

| | | |
|---|---|---|
| | | All response observations, including information from subjects who did not complete all experimental sessions, were included in the analyses.<br><br>Considering the minimal attrition, we judge the risk of bias as low. |
| Selective reporting | Low risk | The reported outcomes was the primary outcome of the reported study as defined in the protocol |
| Conflict of interests | Low risk | Had statement of COI. No indication of relevant COI. The sponsor was reported with detailed information. Sponsor is a public entity supporting independent research; bias unlikely, undue sponsor influence is unlikely.<br><br>This material is the result of work that was supported by resources from the VA Northern California Health Care System, Sacramento, California."<br><br>"They derived direct financial support from the California legislature"<br><br>Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR), |

**Supplementary Table 2: Characteristics of excluded studies**

We list important excluded studies with reasons for their exclusion. Most excluded RCTs investigated the effect of Cannabis on a different disease or condition (upper part of the table), used a different mode of administration of cannabis or a different pharmacological preparation. In the lower portion, for completeness, we list non-clinical studies.

| Reason for exclusion | Author/Year | Pubmed ID | Details |
|---|---|---|---|
| **Studies excluded investigating other conditions than chronic neuropathic pain** | | | |
| Cannabinoids for multiple sclerosis | Zajicek 2003 | 14615106 | Cannabis administered orally |
| | Vaney 2004 | 15327040 | Cannabis-extract capsules |
| | Svendsen 2004 | 15258006 | Dronabinol |
| | Rog 2005 | 16186518 | Whole-plant cannabis-based extract |
| | Conte 2009 | 18603457 | Neurophysiological study |
| | Wade 2004 | 15327042 | Sativex |
| **Studies excluded investigating other interventions than inhaled cannabis** | | | |
| Dronabinol | Holdcroft 1997 | 9165969 | Familial Mediterranean fever. |
| | Rintala 2010 | 20855984 | pain after spinal cord injury |
| | Hagenbach 2007 | 17043680 | |

| | | | |
|---|---|---|---|
| | Narang 2008 | 18088560 | adjuvant treatment for chronic pain patients on opioid therapy |
| | Wong 2011 | 21803011 | irritable bowel syndrome |
| Nabilon | Wissel 2006 | 16988792 | spasticity-related pain |
| | Pinsger 2006 | 16855921 | skeletal and loco-motor system |
| | Karst 2003 | 14519710 | chronic neuropathic pain |
| | Frank 2008 | 18182416 | |
| | Skrabek 2008 | 17974490 | Fibromyalgia |
| Sativex | Rog 2005 | 18035205 | multiple sclerosis |
| | Wade 2004 | 15327042 | |
| | Berman 2004 | 15561385 | brachial plexus avulsion |
| | Selvarajah 2010 | 19808912 | diabetic neuropathy |
| **Non-clinical studies excluded** | | | |
| Experimental pain | Wallace 2007 | 18073554 | intradermal capsaicin model |
| | Roberts 2006 | 16375890 | thermal stimuli to investigate the interaction of cannabis with morphine |

**Supplementary Table 3: Cannabis dosing in included studies**

We detail how we arrived at our estimate of cannabis dose administered for each study in this table. Estimating the administered dose of inhaled cannabis is difficult, because many factors can influence the amount of THC per cigarette, most particularly whether the material is dry or freshly picked. The dose delivered likely differs from what is actually ingested.

| Study | Duration | Dose | Quantity and THC % | THC Dose (approximate) |
|---|---|---|---|---|
| Abrams | 5 days | 3 times/day | 3.56% THC from each 0.9 g cigarette. | 32 mg THC per session<br>96 mg THC per day |
| Ellis | 5 days<br>2 periods | 4 times/day | Active strengths ranged from 1% to 8% D-9-THC concentration by weight. Started at 4% and titrated down if adverse events to 1% or up to 8% if lack of effect. | Weight unknown |

| | | | | |
|---|---|---|---|---|
| Ware | 5 days<br><br>4 periods | TID at home<br><br>13 doses/5 days | Strength 0%, 2.5%, 6.0% and 9.0%<br><br>Wt: (25 mg/dose x 13 doses)/5 days=avg 65 mg/day | 0, 1.625, 3.9 and 5.85 mg/day (average) THC |
| Wilsey | Session length – 6 hours | 3 sessions.<br><br>Hr 1: 2 puffs<br><br>Hr 2: 3 puffs<br><br>Hr 3: 4 puffs; cumulative, 9 puffs<br><br>(recovery at hours 5-6) | Intervention - high-dose cannabis (7% delta-9-THC), low-dose cannabis (3.5% delta-9- THC), and placebo cigarettes.<br><br>Weight – "The mean (range) consumption of cigarettes was 550 mg (200–830 mg) during the low-dose sessions and 490 mg (270–870 mg) for the high-dose sessions." | 0<br><br>19.25 (low dose, range 7-30.45)<br><br>34.3 (high dose, range 18.9-60.9) mg THC/day (Session) |
| Wilsey (2012) | Session:<br><br>6 hours;<br><br>3 sessions. | Hr 1: 4 puffs<br><br>Hr 3: 4-8 puffs<br><br>ange of 8 to 12 puffs how many increased # of | Intervention – Placebo (0 mg) Low-dose cannabis (1.29%), medium-dose cannabis (3.5%).<br><br>Weight – 0.8 g of cannabis | Maximum of 0, 10.32, 28 mg THC/day (Session), presuming they were administered the entire 800 mg dose. |

| | | |
|---|---|---|
| | | puffs?)<br><br>-- recovery at hours 5-6 |

Estimation of cannabis dose in included studies: Participants likely ingested variable doses of cannabis. The cannabis content per cigarette depends on the part of the plant it is derived from and if material is dry or freshly picked. The amount of cannabis actually ingested may vary with the delivery mode. Participants titrated the dose to effect (Azorlosa 1992).

# Supplementary Appendix 2

*Prisma Checklist*

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Inhaled cannabis for chronic neuropathic pain: an individual patient data meta-analysis | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | **Background:**<br><br>Chronic neuropathic pain, the most frequent condition affecting the peripheral nervous system, remains under-diagnosed, devastating and very difficult to treat. Inhaled cannabis may alleviate chronic neuropathic pain.<br><br>**Objective:**<br><br>Our objective was to synthesize the evidence on inhaled cannabis for chronic neuropathic pain.<br><br>**Methods:**<br><br>We performed a systematic review and an individual patient data meta-analysis. 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 to placebo. We pooled treatment effects following a hierarchical random-effects Bayesian responder model | 3 |

| | | | |
|---|---|---|---|
| | | for the population averaged subject specific effect.<br><br>**Results:**<br><br>Our evidence synthesis of individual patient data from 178 participants with 405 observed responses in five randomized controlled trials provides strong evidence that inhaled cannabis alleviates chronic neuropathic pain for one in every five to six patients treated (NNT 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 small number of included studies and participants, shortcomings in allocation concealment and considerable attrition somewhat weaken our conclusions.<br><br>**Discussion:**<br><br>Our individual patient data meta-analysis suggests that inhaled cannabis is effective for chronic painful neuropathy with a number needed to treat (NNT) of 5.6 (95% Bayesian credible interval 3.4, 14). The Bayes factor is 332 corresponding to a posterior probability of effect of 99.7%. This suggests very strong evidence. Inhaled cannabis should be considered for symptomatic treatment in chronic neuropathic pain. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | About one in forty adults in the general population suffers from chronic neuropathic pain, the most frequent condition affecting the peripheral nervous system [57], chronic neuropathic pain presents a | 5 |

heterogeneous burden with a large prevalence [14] in certain susceptible subpopulations, for example in people living with HIV [33]. Chronic neuropathic pain affects every third patient [33, 70, 81]. CNP may result from diverse insults, including diabetes, HIV, trauma, and certain medications [96, 97]. Chronic neuropathic pain remains under-diagnosed, devastating and very difficult to treat [37]. Regardless of etiology, chronic neuropathic pain persists despite attempts at management with opioids, NSAID, anticonvulsants (gabapentin), anti-inflammatory agents, antidepressants and complementary medicine approaches [37].

A recent systematic review concluded that cannabis is effective in selected neurological disorders, including multiple sclerosis, but did not address chronic neuropathic pain [55]. Considering the recent wave of cannabis legalization[83], the continued legal wrangling [69], its widespread medicinal and recreational use[87, 98] and additional randomized controlled trials [RCT] published on cannabis recently, we performed a meta-analysis to investigate if inhaled cannabis alleviates chronic neuropathic pain [88, 92,9]. Previous (systematic) reviews did not investigate inhaled cannabis for chronic neuropathic pain or were unable to synthesize all available data, didn't include recently published RCTs and varied considerably in their inclusion criteria, study selection and data synthesis, leading to conflicting and outdated conclusions [15, 21, 26, 51, 55, 59-61, 67, 73, 83, 86, 99]. As cannabis should undergo the same evidence-based review as other potent prescription medication [91], an update was urgent [88, 92].

| | | | |
|---|---|---|---|
| Objectives | 4 | We performed an individual patient data Bayesian responder meta-analysis to study if inhaled cannabis provides relief for chronic neuropathic pain. | 6 |
| **METHODS** | | | |
| Protocol and registration | 5 | We registered our protocol with PROSPERO. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42011001182<br><br>In our initial Prospero protocol registration we considered to include all types of studies, populations and cannabis interventions. We intended to do a network analysis in one coherent Bayesian model. We found published aggregate data insufficient for evidence synthesis and decided to attempt an individual patient data meta-analysis, but limiting ourselves to only RCTs investigating inhaled cannabis. | 6 +10 |
| Eligibility criteria | 6 | We considered RCTs investigating chronic painful neuropathy. We included diabetic, traumatic and HIV-related etiologies. We excluded multiple sclerosis, a central rather than a peripheral pain condition. The nature of the intervention likely interfered with effective participant blinding [4] and which was therefore not required for study inclusion. We only included studies comparing inhaled Cannabis Sativa to placebo, because inhaled whole herb cannabis differs significantly in composition, bioavailability, and pharmacodynamics from synthetic cannabinoids [76]. | 7 |
| Information sources | 7 | We identified studies by a combination of electronic and manual searches (Figure 1) (Appendix 1). We followed the | 6 |

| | | | |
|---|---|---|---|
| | | recommendations of the QUORUM and PRISMA statements (Moher, Liberati, Tetzlaff, & Altman, 2010). We searched in Cochrane Central, PubMed, EMBASE and AMED without any language restriction with a combination of free text and controlled vocabulary, employing the highly sensitive search strategy (Higgins JPT, 2011). We conducted a hand search in the conference abstracts of the Conference on Retroviruses and Opportunistic Infections 2011, the International AIDS Conference and the World Congress of Pain 2010 and reference lists. | |
| Search | 8 | Appendix 1 | #3 |
| Study selection | 9 | Three review authors (MHA, GC, KS) screened the citations using explicit criteria for study exclusion (Supplementary Table 2: Characteristics of excluded studies). | 7 |
| Data collection process | 10 | Using a standard data collection form, two authors (MHA & GC) extracted the data independently, reconciling any differences by consensus. Study authors provided individual patient data [3, 35, 89, 93, 95]. | 8 |
| Data items | 11 | We recorded details of trial design, conflict of interests, sponsors, participant characteristics, interventions and outcome measures, inclusion and exclusion criteria, comorbidity and HIV status, cannabis provenience, dose and mode of administration. We extracted data on attrition and on adverse effects. | 8 |
| Risk of bias in individual studies | 12 | Two authors (GC and MHA) independently assessed the risk of bias of included studies according to the Cochrane Collaboration [48] on the basis of a checklist of design components and contacted | 8 |

| | | | |
|---|---|---|---|
| | | authors for missing information (Supplementary Table 1: Details on methodological quality of included studies). This comprised randomization, allocation concealment, observer blinding, intention-to-treat analysis, selective reporting and conflict of interests. We achieved consensus by informal discussion. In inhaled cannabis interventions, blinding of patients and providers can be difficult and hence received less weight in the evaluation of performance bias, but not with regard to detection bias. | |
| Summary measures | 13 | We compared the proportion of patients having a more than 30% clinical improvement in chronic neuropathic pain assessed with a continuous patient reported instrument (e.g. the Visual Analogue Scale) comparing baseline to post-treatment with inhaled cannabis. In essence, we dichotomized the outcome in a responder analysis, emerging as the preferred method for pain outcomes research (Dworkin, 2009; Farrar, Troxel, Stott, Duncombe, & Jensen, 2008). We chose this patient centered concept of minimally clinically important difference (MCID) (McGlothlin & Lewis, 2014), because chronic neuropathic pain, our primary outcome, is patient reported and may have a skewed distribution, with no more than 40–60% of patients obtaining even partial relief of their pain (Dworkin, 2007) : a statistically significant change in the population mean of a continuous pain outcome may not correspond to a clinically meaningful improvement for many individual subjects (Moore, Derry, & Wiffen, 2013). In other words, large studies may detect population differences too small for individual patients to appreciate. However, responder analysis | 7 |

| | | | |
|---|---|---|---|
| | | converts continuous pain outcomes to dichotomous responder data allowing a more meaningful comparison between interventions (Moore, 2010; Snapinn & Jiang, 2007). By convention, we classified participants as "responder" if their change in the continuous spontaneous pain outcome (e.g. VAS score) was larger than 30% (Dworkin, 2009; Farrar, , 2008). | |
| Synthesis of results | 14 | We pooled treatment effects following a hierarchical random-effects Bayesian responder model… We estimated the number needed to treat (NNT) and calculated the Bayes factor (Goodman, 2005), compared to the classical p-values in supplementary Box 3. We provided a forest plots for the individual trials broken down by dose (Figure 3). The Bayesian analogue i-square statistic was 0. | 9 + 10 + 14 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | 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 1997 should at least include 10 studies because with fewer studies the power of the tests is insufficient to distinguish chance from real asymmetry | 8 |
| Additional analyses | 16 | We tested the sensitivity of our results to our Bayesian model and its assumptions: We investigated our choice of prior and model parameters and reanalyzed the individual patient responder data (a) in a frequentist random effects meta-analysis and (b) controlling for cannabis dose as an | |

| | | | |
|---|---|---|---|
| | | explanatory variable of the between study variability. | |
| **RESULTS** | | | |
| Study selection | 17 | Our search (Figure 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 1573 references, including 118 duplicates. Our hand search yielded no additional references. | 10 |
| Study characteristics | 18 | We summarized the characteristics of the five RCTs meeting our inclusion criteria (Table 1: Summary of included studies) and detailed their characteristics (Table 2: Detailed characteristics of included studies)… | 10 |
| Risk of bias within studies | 19 | We characterized the risk of bias of included studies (Figure 2: Summary of risk of bias graph; Supplementary table 1: Details on methodological quality of included studies)… | 12 |
| Results of individual studies | 20 | 178 middle aged participants, (approximately equal numbers of men and women) with painful neuropathy of at least three months duration (pain scores at least about 3/10), were enrolled in five RCTs executed across North America. Two trials recruited only HIV+ individuals with HIV-related chronic painful neuropathy (Abrams, 1998; Abrams, 2007a; Ellis, 2009a); sexual orientation and transgender data were not reported. Three trials recruited patients with neuropathy secondary to trauma (Ware, | 10 |

| | | | |
|---|---|---|---|
| | | 2010a), spinal cord injury, diabetes mellitus and complex regional pain syndrome (Barth Wilsey, 2013; Wilsey, 2008a). Psychiatric disease, substance abuse and significant cardiopulmonary disease were explicit exclusion criteria. While prior cannabis experience was a prerequisite for inclusion for some studies (Abrams, 1998; Abrams, 2007a; Barth Wilsey, 2013; Wilsey, 2008a), current use was an exclusion criterion in all. Prescribed opioid use was not specified among the inclusion or exclusion criteria.<br><br>All studies investigated inhaled cannabis. The five studies used different doses, estimated as detailed in the Supplementary Table 3. All five studies used whole Cannabis plant provided by the US National Institute of Drug Abuse (NIDA). Three studies administered cannabis as pre-rolled cigarettes (Abrams, 1998; Abrams, 2007a; Ellis, , 2009a; Wilsey, 2008a), one through a Volcano vaporizer (Barth Wilsey, 2013) and one as gelatin capsules smoked through a pipe at home (Ware, 2010a). All five studies used identical looking placebo as comparator. Concomitant non-study analgesics were permitted and continued in both arms.<br><br>Figure 3: Forest plot of cannabis effects on chronic painful neuropathy | |

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| Synthesis of results | 21 | Based on data from 178 patients with 405 total observed responses, we estimated the odds ratio for a more than 30% reduction in pain scores in response to inhaled cannabis versus placebo for chronic painful neuropathy as 3.2 with a Bayesian credible interval (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 effect of Cannabis for chronic painful neuropathy to be 99.7% and the Bayes factor as 332 (Figure 3: Forest plot of cannabis effects on chronic painful neuropathy). | 13 |
| Risk of bias across studies | 22 | 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, where participants guessed their allocation. Blinding of outcome observer was well described in one study[92], and the use of patient diaries as 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 lead to high risk of bias in one study [88], but did not seem to be associated with group allocation in all others [2, 34, 92, 94]. All included trials reported their primary outcome as specified | 12 |

| | | | |
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| | | in the protocol. | |
| Additional analysis | 23 | When we performed a sensitivity analysis (available on request) with regards to differences in the quality of studies, we found effect estimate and confidence interval 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: Informed versus neutral priors). Reanalyzing the data in a frequentist random effects meta-analysis did not change the results. | 14 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Our evidence synthesis of individual patient data from 178 participants with 405 observations in five RCTs with a follow up ranging from days to weeks (Figure 3: Forest plot), provides strong evidence that inhaled cannabis alleviates chronic neuropathic pain for one in every five to six patients treated (NNT 5.6 with a Bayesian 95% credible interval ranging between 3.4 and 14); | 14 |
| Limitations | 25 | Even if the absence of evidence for heterogeneity constitutes no evidence for clinical homogeneity [48], the consistency and uniformity of the effect of inhaled cannabis on chronic neuropathic pain across different etiologies and populations, further enhances our confidence in the generalizability of our findings [53]. Yet, | 18 |

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| | | our meta-analysis can only be as strong as the underlying data (Table 1 and Table 2) and the methodological quality (Figure 2: Summary of bias graph; Supplementary Table 1: Details on methodological quality); the small number of included studies, their small number of participants and shortcomings in allocation concealment[46] and attrition (Table 2: Detailed characteristics of included studies) somewhat weaken our conclusions. We find that the use of an active placebo to mimic the psychotropic effects of experimental treatments, while improving blinding, does not necessarily improve the evidence regarding effectiveness in a pragmatic clinical setting, but acknowledge the risk of performance bias[76]. Meta-analyses of sparse data can be unstable[42, 71]; 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 [48, 82]. | |
| Conclusions | 26 | While the quality of the evidence for an effect of inhaled cannabis on chronic neuropathic pain is strong, studies only followed their patients for a maximum of two weeks and we acknowledge the risk of performance bias [12]. Long-term pragmatic trials are very likely to have an important impact on our confidence in the sustained benefits (or potential harms) of inhaled cannabis as a treatment of chronic neuropathic pain in the community. While the cost of inhaled cannabis is likely to be low, | 20 |

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| | | medicinal cannabis continues to be controversial, (indeed illegal in many jurisdictions) and patients may vary in their preferences to inhale cannabis, especially as long as it remains stigmatized. Balancing these arguments, the authors come to a weak GRADE recommendation[43] to include inhaled cannabis in guidelines as a consideration for the symptomatic treatment of chronic neuropathic pain until pragmatic long-term RCTs can be conducted in the community. Individual titration may allow for the best balance of beneficial to adverse effects. | |
| **FUNDING** | | | |
| Funding | 27 | This work was supported by the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), through CTSA grant numbers UL1TR000086, TL1RR000087, and KL2TR000088), the Center for Drug Evaluation and Research (CDER) through grant number R01-AT005824 and in part by Grant 5R01AT5824 from the National Center for Complementary and Alternative Medicine (NCCAM). Supported by the University of California Center for Medicinal Cannabis Research and NIH Grant 5-MO1-RR00083. Its contents are solely the responsibility of the authors and do not necessary represent the official view of the NCCAM, NCRR or NIH. | 2 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
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