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REVIEW ARTICLE

Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain

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ABSTRACT

Setting. Cannabis preparations have been used as a remedy for thousands of years in traditional medicine. Clinical use of cannabinoid substances is restricted, due to legal and ethical reasons, as well as limited evidence showing benefits.

Objective. To assess the efficacy and harms of cannabis preparations in the treatment of chronic pain.

Design. Systematic review and meta-analysis of double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain. An electronic search was made in Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (TRIALS CENTRAL) of all literature published until February 2008, as well as specific web pages devoted to cannabis. Studies were cross-checked, selected, and assessed.

Results. Eighteen trials were included. The efficacy analysis (visual analog scales) displayed a difference in standardized means in favor of the cannabis arm of –0.61 (–0.84 to –0.37), with statistical homogeneity ($I^2 = 0.0\%$; $P = 0.50$). For the analysis of harms, the following Odds Ratios (OR) and number needed to harm (NNH) were obtained: for events linked to alterations to perception, OR: 4.51 (3.05–6.66), NNH: 7 (6–9); for events affecting motor function, 3.93 (2.83–5.47), NNH: 5 (4–6); for events that altered cognitive function, 4.46 (2.37–8.37), NNH: 8 (6–12).

Conclusions. Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms. More evidence from larger, well-designed trials is needed to clarify the true balance of benefits to harms.

Key Words. Cannabis; Chronic Pain; Systematic Review; Meta-Analysis

Introduction

Cannabis preparations (*Cannabis sativa*) have been used as a remedy for thousands of years [1]. The use of this plant in traditional medicine has been documented in a range of countries, extending from China to the rest of the world, for the treatment, among other things, of strained muscles, convulsions, asthma, depression, pain [2], nausea, and vomiting [3,4] or as an appetite stimulant [5,6]. At present, the possible medical applications of the plant or its natural or synthetic pharmacologically active agents are tightly restricted, both for ethical and legal reasons, and for lack of solid scientific evidence to show that

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their use can be efficacious in most of the treatments proposed [7]. Furthermore, evaluations of clinical utility require evaluations of benefits as well as harms, given potential negative effects of these substances on neurotransmitters and neuromodulators [8].

Pain is a disagreeable sensorial and emotional experience that subjects associate with tissue damage, real or potential [9]. Where the damage, and thus the attendant sensorial experience, is prolonged to the point of being unlimited, and in many cases, is accompanied by a marked psychological component, it becomes chronic pain [9]. Many chronic-pain patients are dependent upon powerful analgesics and tend to relapse into a cyclical situation of pain, inactivity, and depression.

The existence of a solid biochemical basis for a link between central cannabinoid receptors ($CB_{1\&2}$), the principal psychoactive cannabinoid THC—a natural isomer of delta-9-tetrahydrocannabinol—and pain pathways, has made clinical exploration in search of a potential analgesic use plausible [10]. Consequently, initial clinical studies based on extrapolation of results of animal research [11] have been conducted on the use of cannabinoids for pain situations. To date, however, no solid, conclusive data have emerged that would justify the use of cannabis as an alternative to the currently marketed and accepted therapeutic analgesic arsenal [12,13].

In the light of the present dearth of solid evidence on cannabis for treatment of chronic pain and the considerable controversy and media pressure surrounding the positive effects of this substance, we decided to undertake this systematic review and meta-analysis based on randomized controlled studies on the topic, with efficacy indicators interpretable from the standpoint of daily clinical practice.

Methods

Search Strategy

An electronic search was made in Medline/Pubmed, Embase, and The Cochrane Controlled Trials Register (TRIALS CENTRAL) of all literature published until February 2008, using the following search terms: "cannabis," "cannabinoids," "marijuana," "THC," "tetrahydrocannabinol," "pain," and "chronic pain." This was followed by a general Internet search, covering medical websites as well as specific pages devoted to the substance under review. The websites reviewed included those of the International Association for Cannabis as Medicine, Medical Marijuana Information Resource Centre, Center for Medicinal Cannabis Research (University of California) American Society of Clinical Oncology, Allied and Complementary Medicine Database, and GW Pharmaceutical. The search covered all languages, and was completed by cross-checking the references cited in the papers located, and consulting the registers of ongoing clinical trials: The Current Controlled Trials Register and ClinicalTrials.gov. In cases where additional information was required, authors were contacted directly for the purpose.

Study Selection

The studies selected were double-blind, randomized controlled trials having a crossover or parallel design. In the intervention group, subjects were required to have received any cannabis preparation, which at minimum contained the cannabinoid, delta-9-tetrahydrocannabinol (THC), applied by any route of administration. Studies were included that used the extract of the complete plant or the active agent—isolated and purified—whether alone or combined with other cannabinoids such as cannabidiol. Synthetic derivates of THC, such as dronabinol, nabilone, or benzopyranoperidine, a synthetic nitrogen analog of THC, were likewise included. In the control group, subjects were required to have received a placebo treatment. Subjects undergoing such interventions must have presented with chronic pain of a pathological or traumatic origin, defined as constant or intermittent pain, for a minimum of 6 months [9].

Quality Assessment

Study quality was assessed independently by two authors of this review. Although studies were not required to have a quality threshold level other than the pre-established inclusion criteria, their validity was analyzed by the Jadad scale [14]—Oxford quality scoring system—and particularly by reference to the principal biases that affect clinical trials involving health interventions, namely, selection bias, performance bias, and attrition bias. According to the study design and the methodological quality of individual study, we assessed the supporting evidence of each study using the system of determining levels of evidence and grades of recommendation for evidence based clinical guidelines of The Scottish Intercollegiate Guidelines Network [15].

Outcome Measures

The measure of efficacy chosen was the variable, "intensity of pain," as scored by numeric analog scales.

Harms were assessed by analyzing the number of adverse events experienced in each group. The adverse events were classified with respect to the specific anatomical or physiological system affected, and grouped by categories of events altering the same function.

Statistical Analysis

To study efficacy, we compiled each intervention group's initial and final means and standard deviations (SD), measured on pain scales and quantified in the same direction; based on these, we then calculated the change from baseline, and the differences between final measures for the groups studied. The included studies used different scales of pain intensity; therefore the effect of treatment was quantified as the standardized mean difference (SMD) between intervention and control groups, adding a final estimator of the overall effect size for all studies. Weighting was done by reference to the degree of study precision, using the method of the inverse of the variance [16]. For the study of harms, the effect of the treatment was quantified by means of the odds ratio (OR), thereby furnishing a final joint measure that, as with the continuous variables, indicated the size of the observed effect. All the analyses were performed by fitting both fixed- and random-effects models. Heterogeneity between studies was statistically studied using the χ^2 test and I^2 statistic [17]. Possible publication bias was ascertained by means of funnel plots.

In the various analyses, studies having a parallel and crossover design were jointly meta-analyzed, entailing the use of a specific method that would take account of existing within-patient correlation in the crossover design. In the continuous measures analysis, none of the studies supplied information on the value of this correlation coefficient, which was calculated using extreme values—the furthest vs the closest possible to a parallel design—for all the crossover studies. Binary measures were analyzed using the Becker Balagtas method [18], which uses ORs and their related standard error (SE) logarithmically, applying the corresponding correction to the within-patient correlation. For these measures, the same approach was used as for continuous measures [18], with the same analyses being repeated for a correlation range of 0.1 to 0.5.

All analyses were performed using the RevMan 4.2 (The Cochrane Collaboration, Oxford, UK) [19] and STATA/SE 8.0 User for Meta-analysis (StataCorp, College Station, TX) [20] statistics programs.

Results

The manual and electronic search yielded 229 studies that had used cannabis on pain sufferers from 1975 to February 2008. Perusal of the abstracts led to 128 of these studies being directly discarded. Of the remaining 101, nine were ongoing at the date of analysis and had no data available for our study. As a result, a total of 93 complete papers were reviewed, with only 18 [21–37] of these fulfilling the criteria for inclusion in this review. Unpublished data were analyzed in three of the studies included in this review, in two cases through direct contact with the authors [28,34], and in the third through a study presented in poster format [35]. The remaining 74 were excluded for a number of reasons: 25 failed to meet the requirement of randomized clinical trial methodology; 3 displayed repeated data; 15 were conducted on healthy volunteers and 4 on subjects with acute pain; 10 had an open design; 13 used outcome measures that lay outside the stated objectives of this review; and 3 were rejected, either because not all of the initially randomized subjects presented with chronic pain or because initial pain levels in the different intervention groups were not comparable. Two further studies were excluded: one [38] because the different intervention groups did not register similar baseline pain intensity levels, something that could have been a source of bias in the results; and another because it assessed the effect of smoked cannabis [39], as it was felt that this form of administration did not meet the ethical criteria for therapeutic use (Figure 1).

Of the 18 studies included, only eight had relied on two intervention arms or groups (active agent vs placebo) [22,28,30,32–34,36,37], while the remainder had used a placebo control group and various intervention arms, using different cannabis preparations or increasing doses of the same preparation. In addition, four of the studies had included an intervention group with an analgesic drug (codeine or secobarbital) [23,26,29] excluded from the analyses of this review.

Study subjects registered differences in terms of type and aetiology of pain, but aside from these variables, all presented with chronic pain of a con-

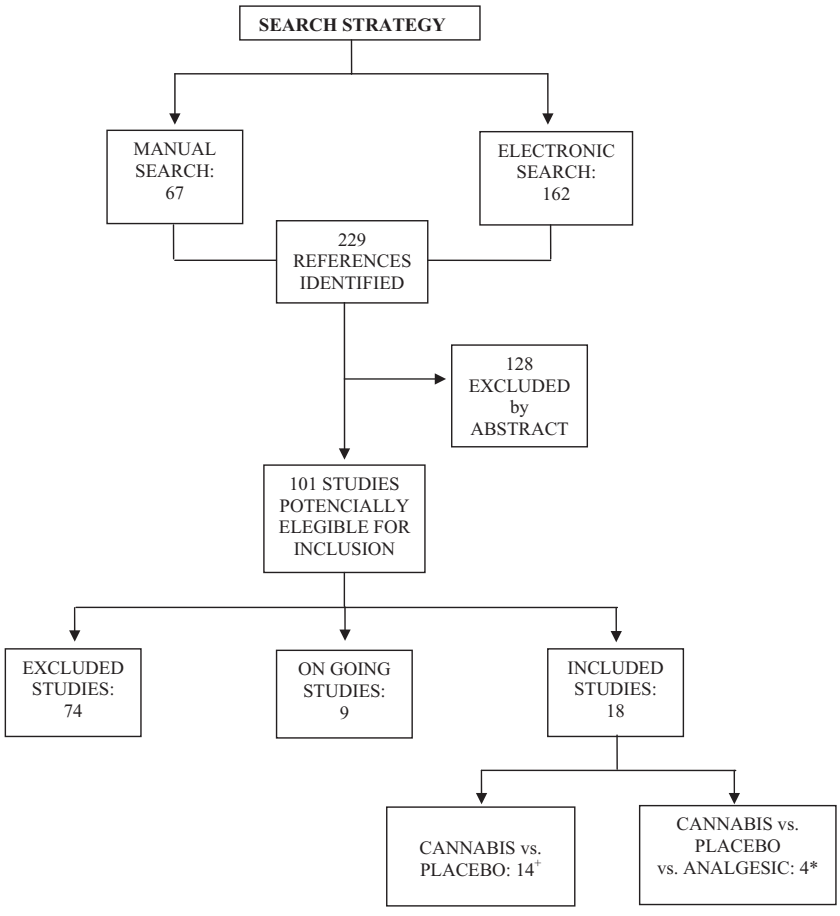

Figure 1 Flow of studies through selection process.
+ Three studies with unpublished data.
* Only placebo arms were used for comparison.

tinuous or intermittent nature and of comparable baseline intensity among the different intervention groups.

All studies but two [24,34] furnished information on the analgesic treatments permitted during the intervention period, and only seven reported on study subjects' history of prior consumption of cannabis (Table 1).

Study Quality

A summary of the methodological quality and level of evidence for each study is shown in Table 1. The studies displayed flaws with respect to control of selection bias. In most cases no information was provided regarding the concealment allocation process or the method of randomization [21–27,29,30,34–37]. This phenomenon, which is usual in small trials, increases the risk of possible selection bias [40].

All the studies were conducted on a double- or triple-blind basis. However, adequacy of blinding was not tested in any trial. Being a substance surrounded by considerable controversy in the media and in society, cannabis has a marked placebo effect, so that inadequate blinding would constitute an important source of bias in this type of study. Yet, the characteristic side effects caused by these substances render perfect masking extremely difficult.

Another important flaw in terms of study quality lay in the control of attrition bias. In 13 of the studies there were losses and withdrawals of subjects [21–23,25,27–29,31–36], and only five specified that they had been analyzed on an intention-to-treat basis [21,22,28,33,35]. These, moreover, were not conducted in accordance with the correct definition of intention-to-treat analysis, for example, instead of including all randomized subjects for whom baseline measures had been obtained in the analysis, subjects to be included were purposefully-defined as those who had remained in the trial a minimum of 3 days [21].

Some trials [25,28,31] used a run-in period. This could limit generalizability as patients who experienced early intolerable adverse events or did not respond to treatment were excluded.

Table 1 Characteristics of included studies

Study	Design (Duration)	N (Dropouts)	Pathology	Type	Intervention	Baseline Characteristics				Current Treatments	Qualiy Assessment† (Level of Evidence‡)
						Age* (years)	Female (%)	Intensity of Pain* (Scale)	Canabis Previous Use		
Berman et al., 2004 [21]	Cross-over (2w + 2w + 2w; no washout period)	48 (3)	Brachial plexus avulsion	Oromucosal spray	GW-1000-02 (2.7 mg THC/2.5 mg CBD) vs GW-2000-02 (2.7 mg THC) vs placebo	39	95.8%	7.5 (Eleven point Box Scale)	45.8% Medicinal use 60.4% Recreational use	No analgesics were prohibited. Concurrent medication stable during the study and previous 4 m	3 (1–)
Blake et al., 2006 [22]	Parallel (5w + 1w follow up)	58 (4)	Rheumatoid arthritis	Oromucosal spray	GW-1000-02 (2.7 mg THC/2.5 mg CBD) vs placebo	62.8 (9.8)	79%	Active group: 48.0* Placebo group: 50.0* (Short-Form McGill Pain Questionnaire)	2% Medicinal use 3% Recreational use	Current medication stable before and during the study: NSAIDs and prednisolone (1 m); DMARDs (3 m)	3 (1–)
Jochinsem et al., 1978 [23]	Cross-over (1d + 1d + 1d + 1d + 1d; no washout period)	37 (2)	Cancer (malignancies)	Capsules (oral administration)	BPP 2 mg vs BPP 4 mg vs codeine sulphate 60 mg vs codeine sulphate 120 mg vs placebo	57	82.8%	No information (0–100 VAS of Pain)	No information	Analgesic drugs were prohibited	2 (1–)
Johnson and Potts, 2005 [35]	Parallel (2w)	177	Cancer	Oromucosal spray	GW-1000-02 (2.7 mg THC/2.5 mg CBD) vs GW-2000 (2.7 mg THC) vs placebo	60.2 (12.3)	46%	No information (0–10 Numerical Rating Scale)	2% Medicinal use 10% Recreational use	Regular strong opioid analgesic maintenance medication	2 (1–)
Killestein et al., 2002 [24]	Cross-over (4w + 4w + 4w; 4w of washout period after every treatment period)	16 (0)	Multiple sclerosis	Capsules (oral administration)	Dronabinol (THC) (2.5 mg) vs plant extract (2.5 mg THC, CBD and other cannabinoids) vs placebo	46 (7.9)	No information	No information (0–100 VAS of Pain)	37.5%	No information	3 (1–)
Notcutt et al., 2004 [25]	Cross-over	34 (12)	Several pathologies	Oromucosal spray	2.5 mg THC vs 2.5 mg CBD vs 2.5 mg THC/ 2.5 mg CBD vs placebo	46.70 (10.08)	67.6%	No information (0–10 VAS of Pain)	64.7% Medicinal use 0% Recreational use	Current medication stable during the study and previous 4w	3 (1–)

Table 1 Continued

Study	Design (Duration)	N (Dropouts)	Pathology	Type	Intervention	Baseline Characteristics				Current Treatments	Qualiy Assessment† (Level of Evidence‡)
						Age* (years)	Female (%)	Intensity of Pain* (Scale)	Canabis Previous Use		
Noyes et al., 1975a [26]	Cross-over (1d + 1d + 1d + 1d + 1d; no washout period)	10 (0)	Cancer	Capsules (oral administration)	5 mg THC vs 10 mg THC vs 15 mg THC vs 20 mg THC vs placebo	51	No information	No information (0–3 Hourly Ratings of the severity of Pain)	No information	Analgesic drugs were prohibited	2 (1–)
Noyes et al., 1975b [26]	Cross-over (1d + 1d + 1d + 1d + 1d; no washout period)	36 (2)	Cancer	Capsules (oral administration)	10 mg THC vs 20 mg THC vs 60 mg codeine vs 120 mg codeine vs placebo	51	72.2%	No information (0–3 Hourly Ratings of the severity of Pain)	No information	Analgesic drugs were prohibited	2 (1–)
Nurmikko et al., 2007 [33]	Parallel (4w)	125 (20)	Peripheral nerve lesion	Oromucosal spray	GW-1000-02 (2.7 mg THC/2.5 mg CBD) vs placebo	Active group: 52.4 (15.8) Placebo group: 54.3 (15.2)	Active group: 55.6% Placebo group: 62.9%	Active group: 7.3 (1.4) Placebo group: 7.2 (1.5) (0–10 Numerical Rating Scale)	20%	Current stable analgesic medication	5 (1++)
Pinsger et al., 2006 [37]	Cross-over (4w + 5w wash out + 4w)	30	Pathologic status of the skeletal and locomotor system	Capsules (oral administration)	Nabilone (THC) (1–4 mg /day) vs placebo	55 (50–63)§	77%	7.8 (6.0–8.5)§ (0–10 VAS of Pain)	No information	No information	3 (1–)
Rog et al., 2005 [28]	Paralell (5w)	66 (2)	Multiple sclerosis	Oromucosal spray	GW-1000-02 (2.7 mg THC/ 2.5 mg CBD) vs placebo	49.2 (8.3)	78.8%	6.5 (1.6) (Numerical Rating Scale-11 Pain Score)	47% Medicinal use 16.7% recreational use	Neurophatic pain medication stable during the study and previous 4w	5 (1++)
Skarabek et al., 2008 [36]	Parallel (4w + 4w follow-up)	40 (7)	Fibromyalgia	Capsules (oral administration)	Nabilone (THC) (0.5–1.0 mg) vs placebo	Active group: 47.6 (9.13) Placebo group: 50.11 (5.96)	No information	Active group: 6.86 (2.14) Placebo group: 6.2 (1.46) (0–10 VAS of Pain)	No previous use for pain management	Current treatments for fibromyalgia. Not to begin any new therapies	3 (1–)
Staquet et al., 1978a [29]	Cross-over (1d + 1d + 1d; no washout period)	30 (4)	Cancer	Capsules (oral administration)	4 mg NIB vs 50 mg codeine vs placebo	No information	No information	No information (0–3 Subjective assessments of pain intensity)	No information	Analgesic drugs were prohibited	2 (1–)

Staquet et al., 1978b [29]	Cross-over (1d + 1d + 1d; no washout period)	15 (0)	Cancer	Capsules (oral administration)	4 mg NIB vs 50 mg secobarbital vs placebo	No information	No information	No information (0–3 Subjective assessments of pain intensity)	No information	Analgesic drugs were prohibited	2 (1–)
Svendsen et al., 2004 [30]	Cross-over (3w + 3w washout + 3w)	24 (0)	Multiple sclerosis	Capsules (oral administration)	Dronabinol (THC) 2.5 mg vs placebo	50 (23–55)[§]	58.3%	5.5 (3.0–8.0)[§] (0–10 Numerical Rating Scale of Pain)	No information	Any analgesic drugs were prohibited except paracetamol	4 (1+)
Wade et al., 2003 [31][¶]	Cross-over (2w + 2w + 2w + 2w; no washout period)	13 (1)	Several pathologies	Oromucosal spray	2.5 mg THC/ 2.5 mg CBD vs 2.5 mg CBD vs 2.5 mg THC vs placebo	No information	No information	5.6 (3.3) (0–100 VAS of Pain)	No information	Current medication stable during the study	4 (1+)
Wade et al., 2004 [32][¶]	Parallel (6w)	37 (1)	Multiple sclerosis	Oromucosal spray	GW-1000-02 (2.7 mg THC/ 2.5 mg CBD) vs placebo	Active group: 51.0 (9.4) Placebo group: 50.4 (9.3)	Active group: 58.7% Placebo group: 65%	No information (0–100 VAS of Pain)	No information	Current medication stable during the study and previous 4w	3 (1–)
Wissel et al., 2006 [34]	Cross-over (4w + 1w wash out + 4w)	13 (2)	Chronic upper motor neuron syndrome	Capsules (oral administration)	Nabilone (THC) (1 mg) vs placebo	44.84 (14.38)	69.2%	Active group: 5.7 (2.7) Placebo group: 5.4 (2.7) (11-Point-Box Test (pain rating))	No information	No information	3 (1–)

* Mean (SD).
† Jadad scale.
‡ Scottish Intercollegiate Guidelines Network (SIGN) classification of evidence.
§ Medians (25%–75% percentiles).
¶ Studies for multiple sclerosis and several pathologies. We only used patients referring chronic pain before randomization.
1++: Randomized controlled trials (RCTs) with a very low risk of bias.
1+: RCTs with a low risk of bias.
1-: RCTs with a high risk of bias.
BPP = benzopyranoperidine; THC = delta-9-tetrahydrocannabinol; CBD = cannabidiol; NIB = Synthetic nitrogen analogous of THC; d = day; w = week; m = month; NSAIDs = Nonsteroidal anti-inflammatory drugs; DMARDs = Disease-modifying anti-rheumatic drugs; VAS = visual analog scale.

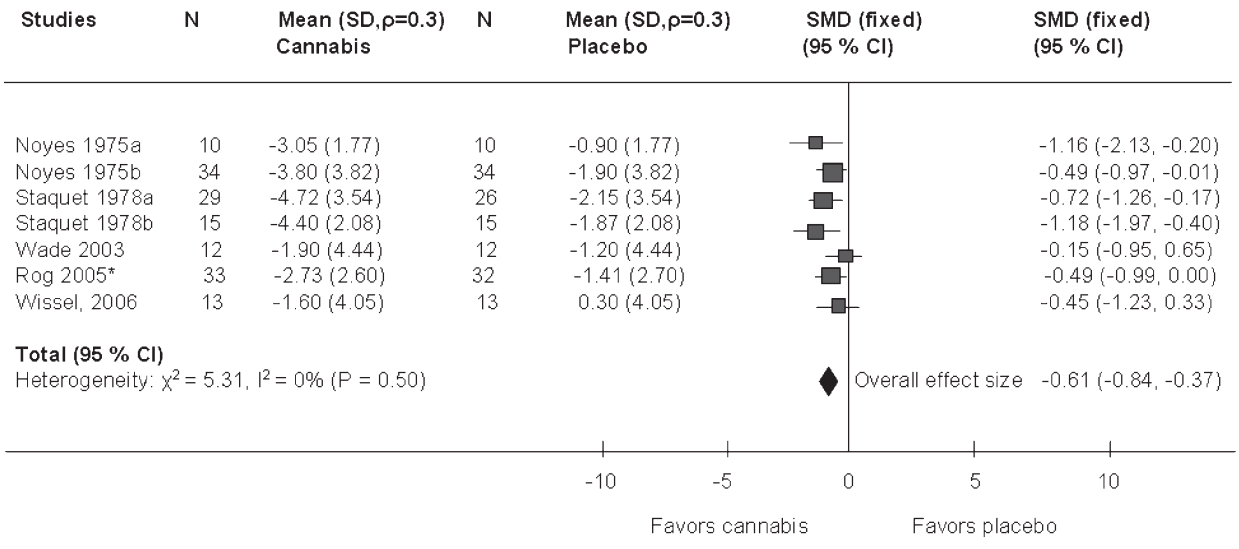

Figure 2 Meta-analysis of efficacy: intensity of pain by visual analog scale (VAS).
* Parallel design.
SD = standard deviation; ρ = within-patients coefficient; SMD = standardized mean differences; CI = confidence interval.

Lastly, studies varied considerably in how outcomes were assessed and reported. Specifically, several studies expressed data as median values [22,25,30,37], without standard deviations [21,32,33,35], or as nonquantitative data [23,24]. With regard to harms, several studies failed to report independent data for patients with pain as their primary symptom [31,32], or failed to discuss the adverse effects of treatment [23]. This heterogeneity in the trials meant that some studies included in this review could not be analyzed quantitatively.

Quantitative Analysis

Efficacy

Measured in terms of the change from the baseline intensity of pain, registered an SMD for a fixed-effects model of –0.61 (–0.84 to –0.37), using an intra-subject correlation coefficient of $\rho = 0.3$ in the crossover studies. All the studies yielded results in the same direction, and no statistical heterogeneity was in evidence ($I^2 = 0.0\%$; $P = 0.50$) (Figure 2). The analyses were repeated using a correlation range of 0.1–0.5, without registering statistically significant changes. Sufficient data were not obtained for conducting a final measures analysis—without baseline data being taken into account—among the different treatment arms under study. Funnel plot showed no sign of asymmetry, so examination of possible publication bias failed to yield positive results.

Of the 18 studies included, only one analyzed the intensity of pain as a dichotomous variable, defining response as a reduction of 50% or more in the score compared with baseline, so it was not possible to carry out this analysis.

Harms

The papers included in this review chiefly yielded data on adverse events affecting the central nervous system (CNS) and gastro-intestinal system (GIS), so that two different meta-analyses were performed, using intra-subject correlation coefficient ranges of 0–0.5 as above, for all the crossover studies. The results displayed no statistical change in response to a change in the coefficient used. Overall between-studies heterogeneity only appeared, for some outcomes, as from the use of a coefficient ≥0.5. This is probably due to the considerable rise in the precision of the intra-study measure. Data are shown with a within-patient correlation of 0.3.

CNS-related Events

For events related to mood disturbances, we observed an OR for cannabis-based intervention groups of 4.11 (1.33–12.72), with a heterogeneity test statistic of $I^2 = 0\%$; $P = 0.79$; NNH = 8 (5, 19) for euphoria and 2.56 (0.66–9.92); $I^2 = 0\%$; $P = 0.49$; NNH = 29 (16, 253) for dysphoria (Figure 3).

Events linked to alterations in perception (blurred vision, visual hallucinations, tinnitus, dis-

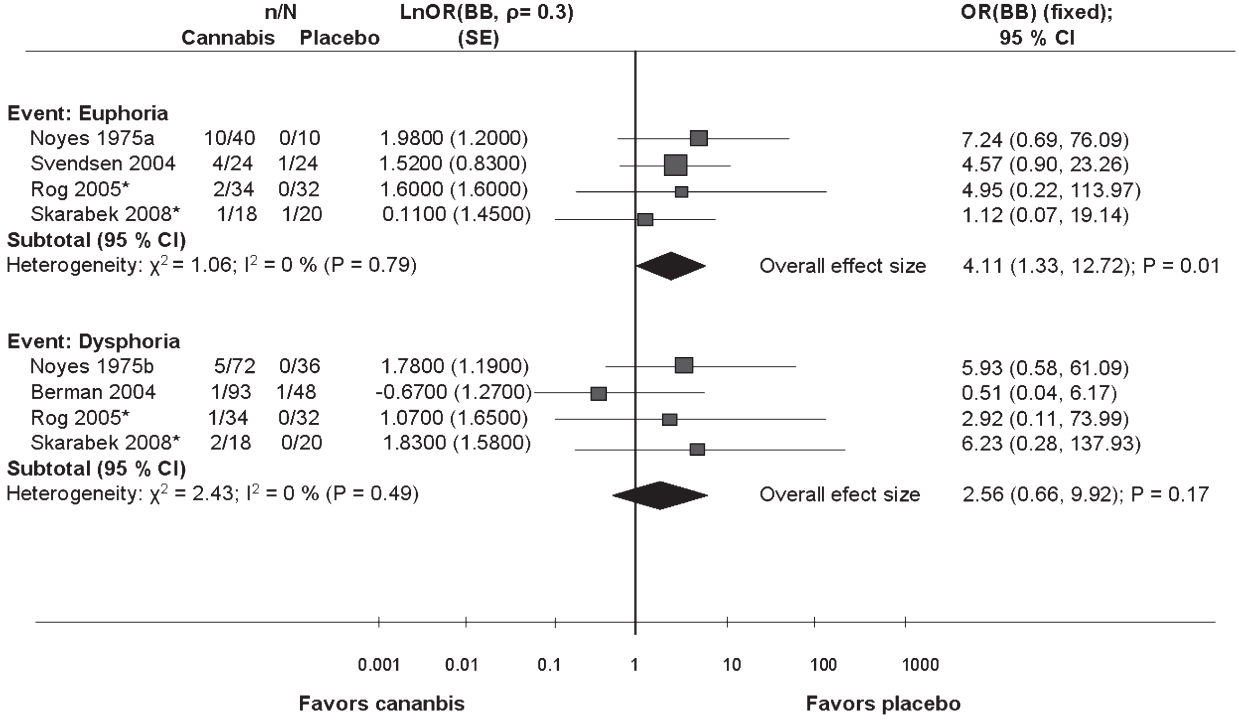

Figure 3 Meta-analysis of events related to mood disturbances.
* Parallel design.
OR = odds ratio; SE = standard error; CI = confidence interval; ρ = within-patients coefficient; BB = Becker Balagtas method.

orientation, confusion, dissociation, acute psychosis) displayed a risk, for cannabis groups of 4.51 (3.05–6.66), with $I^2 = 2.8\%$; $P = 0.42$; NNH: 7 (6–9) (Figure 4).

For events affecting motor function (speech disorders, ataxia, muscle twitching, numbness), the risk for the intervention groups was 3.93 (2.83–5.47), with $I^2 = 0\%$; $P = 0.68$; NNH: 5 (4–6) (Figure 5).

For events that altered cognitive function (impaired memory, disturbance in attention, disconnected thought) in these same intervention groups, the respective figures were: 4.46 (2.37–8.37), with $I^2 = 0\%$; $P = 0.99$; NNH: 8 (6–12) (Figure 6).

Although a high level of homogeneity of the results has been identified, a stratified subgroup analysis of the following variables was performed: study quality (assessed as ≤3 vs >3 on the Jadad scale), study design (parallel vs cross-over), chronic pain type (cancer pain vs noncancer pain), and route of drug administration (capsules vs sublingual spray). In all the included studies the results were essentially the same as those obtained in the global analysis, with a very similar size of effect. Only in a few cases where the number of included studies was reduced, and therefore with a limited global sample size, was the statistical significance lost. As such the analysis that was most affected were those made with respect to change in mood, where the process of stratification lead to the majority of the meta-analysis being performed on a minimal number of two to three studies, whereas *P* values of 0.19 were obtained for studies with a quality of ≤3 and 0.47 for studies with a parallel design for "euphoria" as the adverse event. For the event "dysphoria" a $P = 0.98$ was obtained for drugs administered as a sublingual spray, $P = 0.55$ in studies with patients with noncancer pain, $P = 0.46$ combined with cross-over studies alone, $P = 0.20$ with parallel studies alone, $P = 0.23$ with a study quality of ≤3, and $P = 0.52$ with studies with a quality >3. For the rest of the events, the results did not vary following stratification of the variables, with the exception of statistical significance, where a *P* value of 0.08 was observed for events related with alteration in perception, following a meta-analysis of the six studies that used drug administration in the form of a sublingual spray.

In the case of the GIS, a risk was in evidence for cannabis-based intervention groups in all catego-

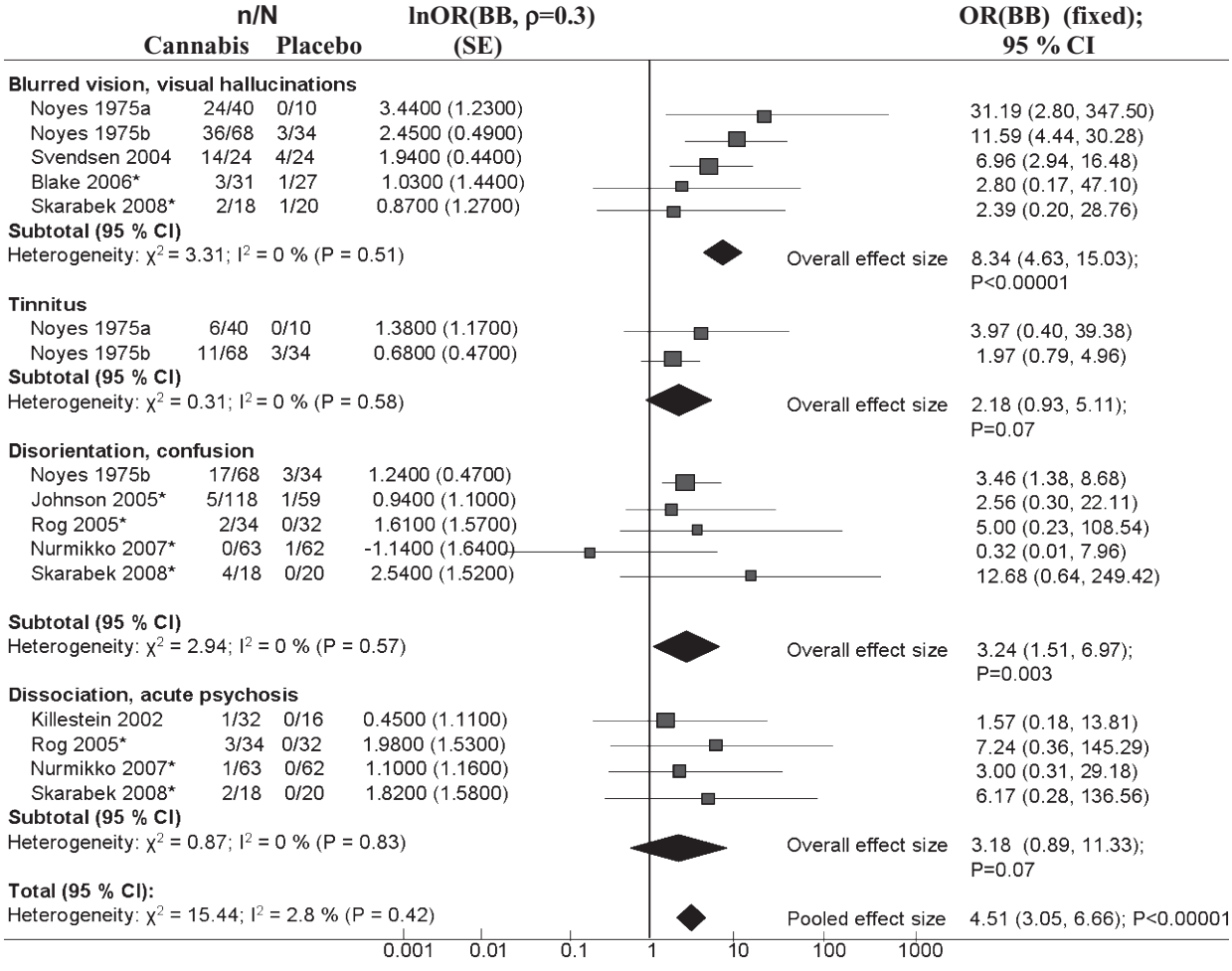

Figure 4 Meta-analysis of events linked to alterations in perception.
* Parallel design.
OR = odds ratio; SE = standard error; CI = confidence interval; ρ = within-patients coefficient; BB = Becker Balagtas method.

ries of events analysed, that is, nausea, vomiting, increased appetite, dry mouth, dysgeusia or bad taste, abdominal pain, dyspepsia, and diarrhea. No quantitative results are shown as heterogeneity between studies was observed in the data analysis.

All the analysis were performed following both a fixed and random effect model. No differences were observed between the size of the effect between both models.

Lastly, meta-analyses were conducted to ascertain possible differences in the results, using ORs and relative risk, and assuming all the studies to be parallel. The results obtained, though obviously registering slight differences on the measure of association being changed, displayed no significant change vis-à-vis the remaining analyses reported. The overall correlation obtained by using either the 0.1 or 0.5 intra-subject correlation coefficient criterion was greater than 0.8. This homogeneity across the analyses is rendered perfectly evident, on referring to the figures shown and seeing that the variables analysed plot similar trends for all studies.

Discussion

This systematic review found evidence of efficacy in the use of cannabis therapy for patients with chronic pain. Yet we also found a high number of serious adverse events in the very short term, principally at the level of the central nervous system.

The results recorded in this systematic review and meta-analysis clarify the existing controversy as to both the efficacy and harms associated with

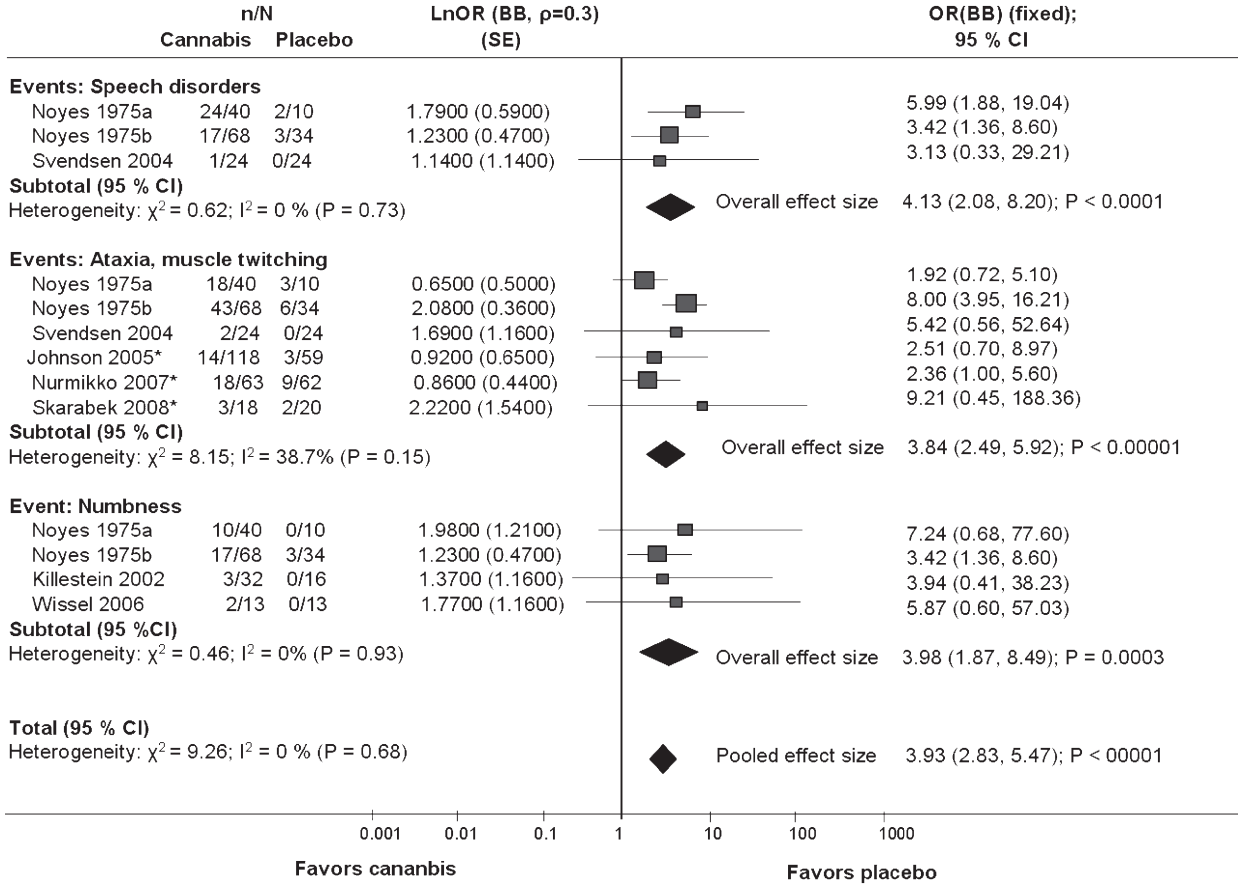

Figure 5 Meta-analysis of events affecting motor function.
* Parallel design.
OR = odds ratio; SE = standard error; CI = confidence interval; ρ = within-patients coefficient; BB = Becker Balagtas method.

the therapeutic use of cannabinoids, in the context of one of the conditions on which most research has been done with such compounds [41]. In terms of efficacy, this substance displays a positive and moderate short-term trend toward a reduction in the intensity of pain in chronic patients, but the same cannot be said for the harms. In this case, the results call into question the possibility of this therapy being efficacious over long periods of time in a medical condition as demanding of therapeutic intervention. This study, with trial interventions lasting a mean of 25 days, yielded an OR of above four for a number of these adverse events (cognitive function, motor function, and alterations in perception) and an OR of above three for mood disturbances. For visual alterations, the number needed to harm could be close on three.

Methodological Considerations

Most of the studies included in this review had a crossover design. Yet this design may not be the most appropriate for clinical assessment of cannabinoid compounds if a correct wash-out period is not taken into consideration [42], a period that was excessively short in an appreciable percentage of studies evaluated in this review. Furthermore, this lack of a correct washout period in the studies means that the results of the meta-analyses shown might be less extreme than they were in real life, due to the carry-over effect on the placebo interventions, in terms both of efficacy and adverse events, of the groups that began the trials in the active agent intervention.

Mention should also be made of the high number of sources of variability among the studies included in this review. While all the patients included in the studies presented with chronic pain—with differences in aetiology and type—the same was not true of the study designs, interventions and doses. This was why joint analysis of studies having parallel and crossover designs was performed on the basis of intra-subject adjust-

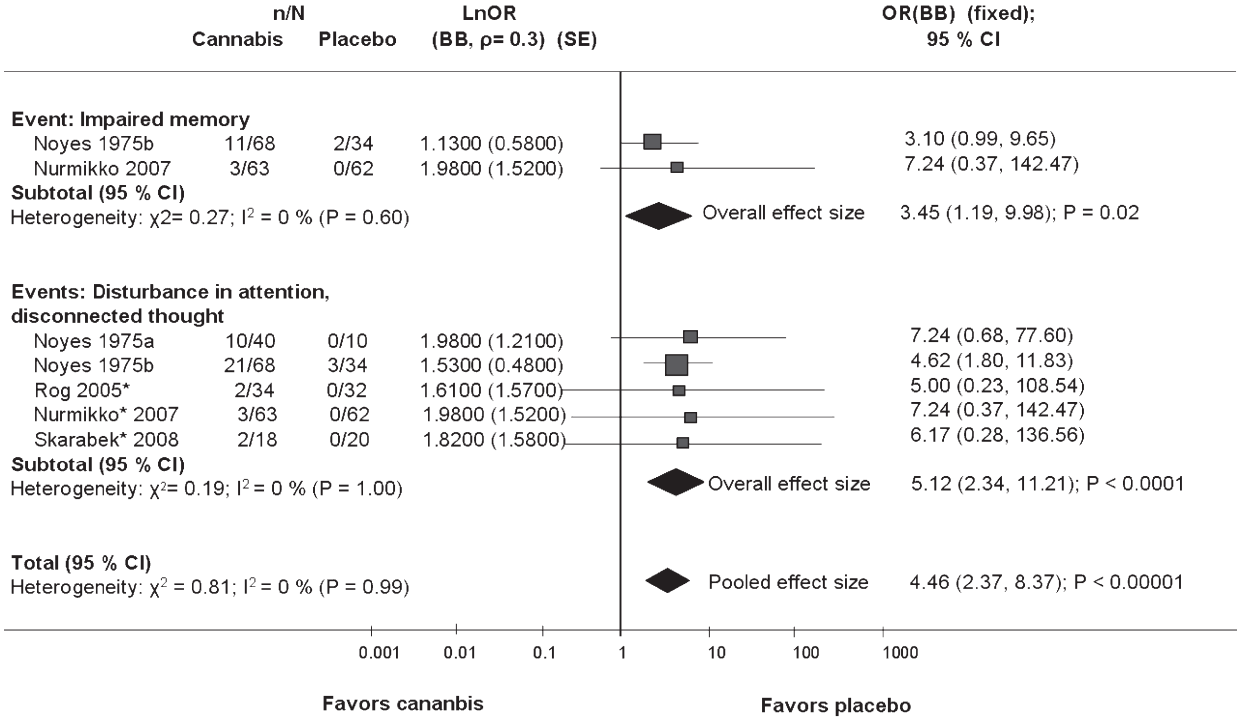

Figure 6 Meta-analysis of events that altered cognitive function.
* Parallel design.
OR = odds ratio; SE = standard error; CI = confidence interval; ρ = within-patients coefficient; BB = Becker Balagtas method.

ments in the latter to offset the effect of the same subjects crossing over to different intervention arms [18]. There being no data published by the studies, a correlation range of 0.1–0.5 was used on the assumption that any higher level of correlation (>0.5) might even question the validity of the trials *per se* at an individual level. Insofar as the interventions were concerned, we chose studies that used the cannabinoid THC (natural or synthetic) in the arm comparing the active agent to placebo; not only is THC the plant's most abundant active agent, but it is also the one that is most widely used in clinical practice and displays the greatest analgesic and psychoactive properties [43,44]. Lastly, with respect to dosage, different dose ranges were pooled to prevent the effect of the intervention being overestimated as a result of analyses always being conducted by reference to the same placebo groups. Nevertheless, the results showed—statistically and graphically—great homogeneity between studies, rendering it unnecessary for comparisons by subgroup to be performed for this variable. The high degree of homogeneity among the studies included could be due to the relatively short duration of the intervention. With longer duration interventions, a greater trend toward heterogeneity among analyzed variables would be expected, possibly reflecting differences in the efficacious dose range, the principle active agent used or individual patient's characteristics. At present, no possible dose-response relationship can be established.

An exhaustive search was made to complete this study, which included several diverse standard databases as well as grey literature, and unpublished data, although the small size of the majority of the included studies made it impossible to exclude the possibility of a publication bias even though the specific result was not significant according to the funnel plot analysis. The difficulty of detecting publication bias when sample sizes are small constitutes a limitation in this study, particularly as the obtained results could vary slightly with respect to the real situation found in the clinical practice.

The studies included in this review were mainly pilot trials seeking an initial trend or direction in support of or against the efficacy of cannabis in chronic pain, rather than a therapeutic approximation of efficacy. Consequently, these studies suffer from important methodological flaws in terms of subject assignment to the different intervention

groups, follow-up procedure, and possible outcome reporting bias, as was mentioned above when analyzing their quality. Accordingly, these points will have to be taken into account during the design phase of future clinical trials that focus on the clinical efficacy of this substance.

Clinical Implications

Cannabis and its derivates have displayed therapeutic properties for a range of disorders. On the one hand, there is evidence of anti-emetic properties for the treatment of the nausea and vomiting that ensue as side effects of chemotherapy. This evidence comes from meta-analysis of randomized clinical trials [3,4] that in the same way of this study, show positive results for the efficacy of cannabinoid compounds compared with placebo and habitual anti-emetic treatments, and which also report adverse events of different severity with results which are statistically significant against cannabinoid compounds. On the other hand, although no meta-analysis or quantitative studies have been published that provide solid conclusions regarding the efficacy and/or safety of pharmacological interventions based on cannabinoid compounds for the treatment of other pathologies, other published clinical studies exist that have reported a hyperphagic effect in the regulation of hunger and treatment of anorexia-cachexia syndrome [5,6], a reduction in the spasticity that accompanies diseases such as multiple sclerosis [45], and a decrease in intraocular pressure for treatment of patients with glaucoma [46].

With respect to treatment of chronic pain with these substances, existing knowledge has been drawn from extrapolation of results yielded by animal studies [11,47] or small clinical trials, which in some cases, have reported contradictory findings [31,32]. Insofar as a synthesis of results is concerned, the nature of the systematic reviews published until now has been qualitative [7,12,13], or quantitative solely for neuropathic pain, with special attention paid to the compound's efficacy rather than to its adverse events [48]. This new systematic review has, however, been able to meta-analyze the studies included and report the effects found from a quantitative stance, with overall risk estimators that are easily interpretable in clinical practice. Special care is thus called for as regards the harms of this intervention. Added to the speed at which these events appear is the severity of some of them: in longer-term trials (4–5 weeks), for instance, cases of acute psychosis were observed [24,28,33,36], with percentages of naive subjects ranging from 36.3% to 80% in these studies. Although this variable failed to attain statistical significance in our analysis, there is nevertheless evidence of a dangerous trend indicating that the lack of a significant result is only a question of statistical power. Indeed, this finding is especially remarkable, bearing in mind the fact that epidemiological studies have highlighted the relationship between recreational use of cannabis and psychosis [49,50] and the association of long-term heavy cannabis use and harmful effects on brain tissues [51]. Moreover, prior to randomization a number of the studies reviewed had an open phase [25,28,31] in which all subjects took the active agent: such a phase would thus screen out subjects with low tolerance to the substance and reduce any adverse events during the trial in the remainder. Hence, when it comes to extrapolating their results to daily clinical practice, such studies might well be overestimating the intervention's efficacy and underestimating its adverse events.

None of the studies included reported information regarding the potential addictive effect of these substances on the studied patients. This effect has probably not been studied in the included RCTs as the patients were not followed after the study and that the study was performed in a duration (average: 25 days) insufficient for the manifestation of these signs. As a suggestion for future studies, it would be convenient to perform an adequate follow up of patients, to study the medium to long term development of adverse events with these substances, among them addictive effects, which represent one of the principle concerns regarding the legalization and standardization of their use.

When analyzing their results, future trials will have to make due allowance for previous use of cannabis by study subjects, whether for therapeutic or recreational purposes. Due to their liposoluble nature, cannabis and its derivates tend to accumulate in adipose tissue. This, in turn, acts as a reservoir that continuously releases them, possibly resulting in more potent effects in regular users [41]. For other effects, however, cannabis has shown a certain degree of tolerance with the passage of time, and larger doses would be required to achieve the same intensity of effect as in nonconsumers [52]. Most of the studies did not permit consumption during a period of 1–3 months preceding the trial, but this period is probably insufficient to eliminate the differences among regular, sporadic, and nonconsumers. Fur-

thermore, 11 of the studies furnished no information on prior consumption.

Most of the studies assessed were silent as to prognosis of pain [53] and subjects' ranking on the World Health Organisation analgesic scale [54]. This, coupled with the dearth of randomized clinical trials that compare the effect of cannabis and its derivates against other analgesics enjoying scientifically proven efficacy and standard use in clinical practice, means that, even though it may display efficacy, this systematic review cannot categorize cannabis as a future first-, second-, or third-line treatment against pain. The undertaking of efficacy or equivalence studies using known analgesic treatments—gold standards—and pragmatic result measures—time until the need for alternative treatment—as comparisons would furnish information on the role that cannabis might play in the present therapeutic arsenal. Such studies undertaken in the medium and long term would, moreover, afford clarity as regards the pharmacological parameters that would ensure a better benefit-risk ratio in the form of more beneficial preparations, doses, or administration routes for each type of patient.

In conclusion, currently available evidence indicates that treatment of chronic pain based on cannabinoid compounds would entail more risk than benefit, including the risk of the appearance of events in which the pain—if it is of low intensity—might even come to pose a secondary problem in the subject. Nevertheless, the antinociceptive effects of this substance constitute an open avenue for study and research aimed at developing a future line of analgesics efficacious in certain types of patients, based on and subject to specific doses and administration routes.

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