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Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analogue. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

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Introduction

Chronic pain is common and debilitating with too few effective therapeutic options. Cannabinoids represent a relatively new pharmacological option as part of a multimodel treatment plan. With increasing knowledge of the endocannabinoid system [1–3] and compelling preclinical work supporting that cannabinoid agonists are analgesic [4, 5] there is increasing attention on their potential role in the management of pain [6–9]. A previous systematic review done a decade ago identified the need for further randomized controlled trials (RCTs) evaluating cannabinoids in the management of chronic pain indicating that there was insufficient evidence to introduce cannabinoids into widespread use for pain at that time [10]. A subsequent review identified a moderate analgesic effect but indicated this may be offset by potentially serious harm [11]. This conclusion of serious harm mentioned in the more recent review is not consistent with our clinical experience. In addition there have been a number of additional RCTs published since this review. We therefore conducted an updated systematic review examining RCTs of cannabinoids in the management of chronic pain.

Methods

We followed the PRISMA update on the QUORUM statement guidelines for reporting systematic reviews that evaluate health care interventions [12].

Systematic search

A literature search was undertaken to retrieve RCTs on the efficacy of cannabinoids in the treatment for chronic pain. The databases searched were: PubMed, Embase, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library (Wiley), ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline,

OAIster (OCLC) and Google Scholar. None of the searches was limited by language or date and were carried out between September 7 and October 7, 2010. The search retrieved all articles assigned the Medical Subject Headings (MeSH) *Cannabis*, *Cannabinoids*, *Cannabidiol*, *Marijuana Smoking* and *Tetrahydrocannibinol* as well as those assigned the Substance Name *tetrahydrocannabinol-cannabidiol combination*. To this set was added those articles containing any of the keywords *cannabis*, *cannabinoid*, *marijuana*, *marihuana*, *dronabinol* or *tetrahydrocannibinol*. Members of this set containing the MeSH heading Pain or the title keyword '*pain*' were passed through the 'Clinical Queries: therapy/narrow' filter to arrive at the final results set. For the pain aspect, the phrase '*Chronic pain*' along with title keyword '*pain*' was used to retrieve the relevant literature. We contacted authors of original reports to obtain additional information. Bibliographies of included articles were checked for additional references.

Inclusion and exclusion criteria

Included were RCTs comparing a cannabinoid with a placebo or active control group where the primary outcome was pain in subjects with chronic non-cancer pain. Relevant pain outcomes included any scale measuring pain, for example the numeric rating scale for pain (NRS), visual analogue scale for pain (VAS), the Neuropathy Pain Scale or the McGill Pain Scale. We excluded (i) trials with fewer than 10 participants, (ii) trials reporting on acute or experimental pain or pain caused by cancer, (iii) preclinical studies and (iv) abstracts, letters and posters where the full study was not published.

Data extraction and validity scoring

One author (ML) did the initial screen of abstracts, retrieved reports and excluded articles that clearly did not meet the inclusion criteria. Both authors independently read the included articles and completed an assessment of the methodological validity using the modified seven point, four item Oxford scale [13, 14] (Figure 1). After reading the complete articles it was clear that several additional papers did not meet inclusion criteria and these were excluded. Discrepancies on the quality assessment scale were resolved by discussion. Trials that did not include randomization were not included and a score of 1 on this item of the Oxford scale was required and the maximum score was 7.

Information about the specific diagnosis of pain, agent and doses used, pain outcomes, secondary outcomes (sleep, function, quality of life), summary measures, trial duration and adverse events was collected. Information on adverse events was collected regarding serious adverse events, drug related withdrawals and most frequently reported side effects. A serious adverse event according to Health Canada and ICH[1] guidance documents

Modified Oxford Scale
Validity score(0–7)

Randomization

0 None
1 Mentioned
2 Described and adequate

Concealment of allocation

0 None
1 Yes

Double-blinding

0 None
1 Mentioned
2 Described and adequate

Flow of patients

0 None
1 Described but incomplete
2 Described and adequate

Figure 1
Modified Oxford scale

is defined as any event that results in death, is life threatening, requires prolonged hospitalization, results in persistent of significant disability or incapacity or results in congenital anomaly or birth defects [15].

Results

Trial flow

Eighty abstracts were identified of which 58 did not meet inclusion criteria on the initial review of records (Figure 2). Twenty-two RCTs comparing a cannabinoid with either a placebo or active control group where pain was listed as an outcome were found and full text articles were reviewed, four further studies were excluded, two because pain was not the primary outcome (Zajicek [16, 17]), one because there were fewer than 10 participants in the study (Rintala [18]). A further study was excluded because there were two studies reporting on what appeared to be the same group of participants (Salim [19], Karst [20]), in this case we included the first study in which the pain outcomes were reported (Karst). References of the included trials were reviewed for additional trials meeting inclusion criteria. This revealed no further studies. Eighteen trials met the study criteria for inclusion. We did not retrieve any unpublished data. Given the different cannabinoids, regimens, clinical conditions, different follow-up periods, and

1. International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

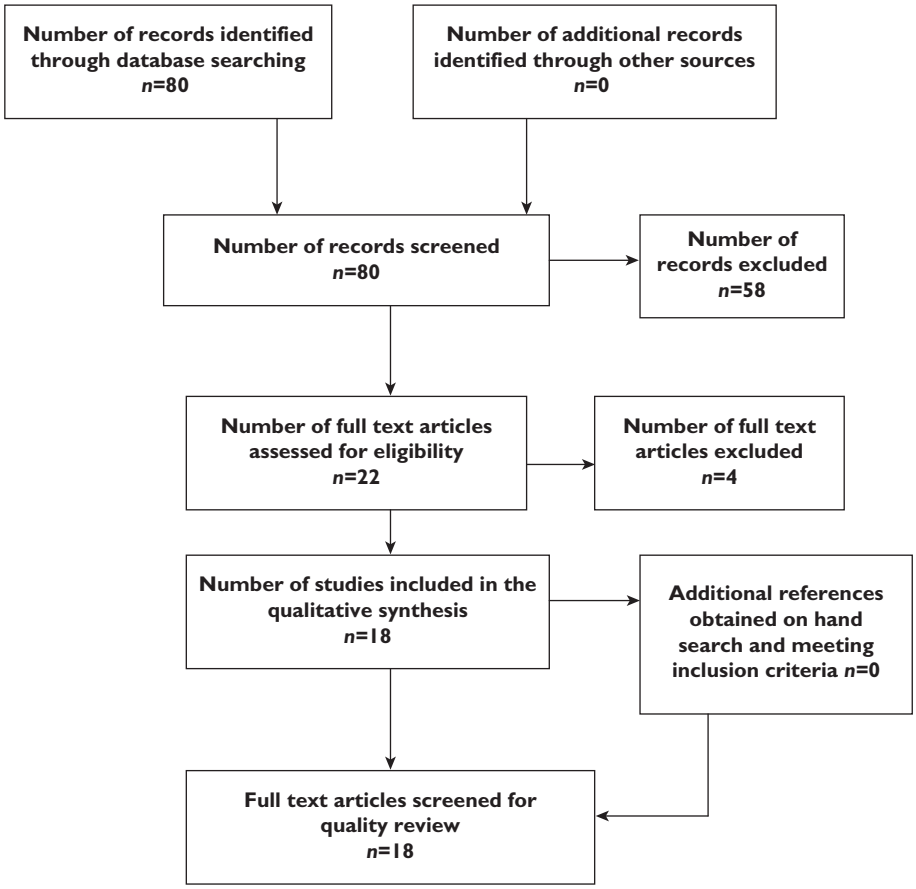

Figure 2
Flow diagram of systematic review

outcome measures used in these trials, pooling of data for meta-analysis was inappropriate. Results were therefore summarized qualitatively.

Primary outcome – efficacy

Eighteen trials published between 2003 and 2010 involving a total of 766 completed participants met inclusion criteria (Table 1). The quality of the trials was very good with a mean score of 6.1 on the 7 point modified Oxford scale. The majority (15 trials) demonstrated a significant analgesic effect for the cannabinoid agent being investigated. Several trials also noted significant improvements in sleep [21–24]. Treatment effects were generally modest, mean duration of treatment was 2.8 weeks (range 6 h–6 weeks) and adverse events were mild and well tolerated.

Cannabis Four trials examined smoked cannabis as compared with placebo. All examined populations with neuropathic pain and two involved neuropathic pain in HIV neuropathy [21, 25–27]. All four trials found a positive effect with no serious adverse effects. The median treatment duration was 8.5 days treatment (range 6 h–14 days).

Oromucosal extracts of cannabis based medicine (CBM) Seven placebo controlled trials examined CBM [22–24, 28–30]. Five examined participants with neuropathic pain, one rheumatoid arthritis and one a mixed group of people with chronic pain, many of whom had neuropathic pain. Six of the seven trials demonstrated a positive analgesic effect. Of note in the one trial examining pain in rheumatoid arthritis, the CBM was associated with a significant decrease in disease activity as measured by the 28 joint disease activity score (DAS28) [23].

Nabilone Four trials studied nabilone [31–34]. Three of these trials were placebo controlled and found a significant analgesic effect in spinal pain [34], fibromylagia [32] and spasticity related pain [33]. The fourth compared a daily dose of nabilone 2 mg with dihydrocodeine 240 mg in neuropathic pain. Mean baseline pain was 69.6 mm on

Table 1

Randomized controlled trials examining cannabinoids in treatment of chronic non-cancer pain

Author and date	Agent (control group)	Population (*n*) completed/randomized *design*	Core outcomes*	Summary measures used	Oxford scale score	Duration of RCT	Results (brief comments)	AEs‡	Outcome summary
Ware *et al.* [21]	Cannabis smoked 0%, 2.5%, 6%, 9.4% (placebo)	Neuropathic pain 21/23 *crossover*	NRS Pain Leeds sleep POMS	Difference in means	7	14 day treatment periods	Significantly lower average daily pain intensity on 9.4% THC (5.4) than 0% (6.1) Improved sleep No change in mood	No serious AEs Headache Dry eyes Burning sensation Dizziness Numbness Cough	+
Ellis *et al.* [26]	Cannabis smoked 1–8% (Placebo)	HIV neuropathy 28/34 *crossover*	DDS pain McGill VAS pain POMS	Median difference pain intensity change	6	5 day treatment periods	Pain reduction significantly greater with cannabis than placebo median difference in pain reduction = 3.3 DDS points, effect size = 0.60 Also proportion achieving >30% reduction greater for active 0.46 *vs.* placebo 0.18 NNT 3.5 for 30% reduction	No serious AEs Two participants experienced treatment limiting side effects most common AEs Decreased concentration Reduced salivation Fatigue sleepiness Sedation	+
Frank *et al.* [31]	Nabilone 2 mg (dihydrocodeine) 240 mg	Chronic neuropathic pain 96 *crossover*	VAS pain Hamilton depression SF-36	Difference in means	7	6 weeks	Both agents resulted in approximately a 10 mm reduction in a 0–100 mm VAS pain Baseline 69.6 mm Nabilone 59.6 mm Dihydrocodeine 58.6 mm with dihydrocodeine providing marginally better pain relief	No serious AEs Tiredness Sleepiness Sickness	+/–
Narang *et al.* [36]	Dronabinol 10, 20 mg (placebo)	Chronic pain on opioids 29/30 *crossover*	NRS pain intensity and pain relief	Difference in average pain intensity and total pain relief	7	1 day each treatment RCT 4 week open extension	Dronabinol at both doses significantly less pain and greater relief than placebo SPID –6.4 placebo, 10 mg (–17.4, $P < 01$), 20 mg (–19.7, $P < 0.01$) TOTPAR placebo (31.1), 10 mg (39.7, $P < 0.5$) 20 mg (41.7, $P < 0.01$ in both the RCT and the extension	No serious AEs Drowsiness Sleepiness Dizziness Dry mouth	+
Wilsey *et al.* [27]	Cannabis smoked 7.7%, 3.5% (placebo)	Neuropathic pain 38/44 *crossover*	VAS pain intensity Pain relief PGIC	Difference in mean pain	7	6 h sessions	Cannabis both doses significantly less pain and pain unpleasantness (combined 3.5 and 7% cannabis *vs.* placebo differences per minute –0.0035, 95% $P = 0.016$)	No serious AEs or withdrawals Feeling high Stoned Impaired greater with high dose, side effects stated to be relatively inconsequential	+
Skrabek *et al.* [32]	Nabilone 0.5–1 mg twice daily (placebo)	Fibromyalgia 40 *parallel group*	VAS pain FIQ	Difference in means	6	4 weeks treatment	Significant decrease in 10 cm VAS pain (–2.04, $P < 0.02$), total FIQ (–12.07, $P < 0.02$) and 10 point FIQ anxiety (–1.67, $P < 0.02$) with nabilone *vs.* placebo	Three withdrew due to side effects Dizziness Disorientation Nausea Poor co-ordination Drowsiness Dry mouth Vertigo Ataxia Headache	+
Abrams *et al.* [25]	Cannabis smoked 3.56% (placebo)	HIV sensory neuropathy 50/55 *parallel group*	VAS pain	Difference in Median daily pain ratings	7	5 day inpatient 7 day outpatient	Significant reduction in pain with cannabis *vs.* placebo Median reduction in pain was 34% (17% placebo) >30% relief 52% (*vs.* 24%) NNT=3.6	All side effects were mild and included Anxiety Sedation Disorientation Paranoia Confusion Dizziness Nausea	+

Numikko *et al.* [30]	Cannabis based medicine THC/CBD (placebo)	Neuropathic pain with allodynia 125 *crossover*	NRS pain PGIC PDI HQ-12 Sleep NRS NPS	Mean change VAS pain	7	5 weeks plus open label extension option	Significantly less pain with Sativex *vs.* placebo Mean change of –1.48 Sativex *vs.* –0.52 P a 22% reduction On Sativex 26% had 30% reduction and 20% a 50% reduction *vs.* P 15% and 8% NNT 8.5 (50%) 8.6 (30%) Secondary outcomes also improved – sleep, NPS, PGIC Open label extension showed initial pain relief maintained without dose escalation or toxicity for 52 weeks	18% withdrew on Sativex *vs.* 3% on placebo No serious AEs by definition below Most described as mild Dizziness Nausea Fatigue Dry mouth But seven in Sativex group and five in placebo group graded them as 'severe' Paranoid thinking was reported in one patient while on Sativex	+
Wissel *et al.* [33]	Nabilone 1 mg day^{-1} (placebo)	Spasticity related pain in UMNS 11/13 *crossover*	11-point box test Ashworth scale for spasticity Motor ADLs	Difference in median pain	3	4 week treatment periods	Significant decrease in spasiticty related pain with reduction of median 2 points with nabilone *vs.* placebo but no significant change in spasticity according to Ashworth scale or motor or ADL	Two patients withdrew one due to a relapse felt not to be related to the nabilone, the other due to leg weakness, rest described as mild Drowsiness (2) Slight weakness legs (1)	+
Pinsger *et al.* [34]	Nabilone 0.25–1 mg day^{-1} (placebo)	Chronic pain (spinal) 30 *crossover*	VAS pain intensity Cohen QOL	Difference in median pain	3	4 week treatment periods	Significant decrease in spinal pain intensity (0.6) (0.0) $P = 0.006$ on nabilone *vs.* placebo	# leg after fall possibly related to dizziness caused by interaction of nabilone with concurrent meds during crossover Fatigue Dry mouth Dizziness	+
Rog *et al.* [22]	Cannabis based medicine THC/CBD (9.6 sprays/day 2–25) (placebo)	Central pain in MS 64/66 *parallel group*	NRS pain and sleep HADS PGIC NPS	Differences in mean intensity pain	7	4 week	Significant reductions in pain (NRS, NPS) and sleep disturbance (NRS) with CBM 3.85 *vs.* placebo 4.96 NNT=3.7 NNH=5.13 No significant changes in blood pressure, weight, haematology, blood chemistry	No serious AEs Two AEs led to withdrawal from trial (agitation and paranoia) Dizziness Somnolence Dissociation Dry mouth Nausea Weakness	+
Blake *et al.* [23]	Cannabis based medicine mean dose 5.4 sprays/day (placebo)	Rheumatoid arthritis 58 *parallel group*	NRS pain, sleep SF-MPQ DAS28	Differences in means	4	5 weeks	Significant improvements in pain on movement (difference mean/median = 0.95, $P = 0.04$ at rest, 1.04, $P = 0.01$, quality of sleep 1.17, $P = 0.02$, DAS28, 0.76, $P = 0.002$, and SF-MPQ, 3.00, $P = 0.30$ with CBM *vs.* placebo)	No serious AEs No treatment related withdrawals All mild to moderate Dizziness Lightheaded Dry mouth Nausea Two noted severe constipation Fall (two patients)	+
Berman *et al.* (2004) [24]	Cannabis based medicine THC/CBD, THC 8 sprays day^{-1} (placebo)	Neuropathic pain brachial plexus avulsion 48 *crossover*	NRS pain BS-11 for sleep quality SF-MPQ PDI	Difference in means	7	2 week treatment periods extension	Statistically significant reductions in pain (NRS) and sleep disturbance (NRS) but not to the full 2 point reduction (i.e. reduction of 0.58, $P = 0.005$ and 0.64, $P = 0.002$)	No serious AEs One drug related withdrawal feeling faint The rest mild-moderate and resolved spontaneously Dizziness Somnolence Bad taste	±
Svendsen *et al.* [35]	Dronabinol 10 mg (placebo)	Central pain in MS (24) *crossover*	NRS pain Pain relief SF36	Difference in median	7	3 weeks	Significant reductions in pain (NRS) modest reductions 1 point on a 0–10 point scale NNT for 50% relief=3.45	Dizziness Headache Tiredness Myalgia Muscle weakness Dose reduction resolved the AEs in the four who experienced 'intolerable level' of the AE Four experienced aggravation of MS, one during drug treatment, two during placebo and one during washout	+

Table 1

Continued

Author and date	Agent (control group)	Population (*n*) completed/randomized *design*	Core outcomes*	Summary measures used	Oxford scale score	Duration of RCT	Results (brief comments)	AEs‡	Outcome summary
Wade *et al*. [28]	Cannabis based medicines HC/CBD (placebo)	MS 160 where 37 had pain as target symptom *parallel group*	VAS pain spasticity, spasms, bladder problems, tremor	Difference in means	6	6 weeks	No significant difference in pain scores (VAS) between CBM and placebo all decreased There was a significant reduction in spasticity (VAS) scores	Dizziness† Fatigue Headache Disturbance in attention Application site discomfort Mouth ulceration	–
Karst *et al*. [37]	CT-3 Synthetic analogue of THC-11-oic acid (placebo)	Neuropathic pain with hyperlagesia or allodynia 19/21 *crossover*	VAS pain Pain relief	Differences in means	7	1 week treatment periods	Significant improvement in pain intensity 3 h after study drug (-11.54 or 9.86, $P = 0.02$) §difference between CT-3 and P abated by 8 h No significant change pain relief	No serious AEs One withdrawal from excessive drowsiness Tiredness Dizziness Dry mouth Decreased concentration Sweating	+
Notcutt *et al*. [57]	Cannabis based medicine THC CBD THC/CBD (placebo)	Chronic pain 24 of 34 *'N of 1'* 2 week open/RCT 1 week Rx periods × 2 for each CBME *crossover*	VAS pain for Two worst pain symptoms BDI GHQ Sleep	Difference in medians	4	Two 1 week treatment periods or each agent	Significant reduction in pain (VAS) for THC and THC;CBD Cumulative VAS (median, interquartile range for worst pain Placebo 5.9 (2.8–7.3) CBD 5.45 (3.6–7.4) THC 4.63 (1.74–6.06) THC;CBD 4.4 (2.6–5.8 ($P < 0.001$) 9/24 had a reduction of >50%with THC or THC : CBD	No serious AEs One withdrawal due to medication AE Dry mouth Drowsiness Euphoria/dysphoria Vasovagal episode on initial dosing	+
Wade *et al*. [29]	Cannabis based medicine THC CBD THC/CBD (placebo)	Neurogenic symptoms in MS/spinal cord injury/brachial plexus injury/limb amputation 24 *'N of 1'* where 12 had target symptom of pain *crossover*	VAS pain Intoxication Alertness Appetite Happiness etc	Difference in means	7	2 week study periods	Difference in mean VAS pain between CBM and placebo = 10.3 for CBD, 10.1 for THC, $P = 0.05$ Significant reductions in pain CBD and THC but not the combination	Three withdrawals One vasovagal One intoxication One psychoactive effects marked Hypotension if given too quickly Diarrhoea Sleepiness Sore mouth	+

*__Examples:__
__Pain: NRS, VAS other scale__
- At least 50% pain reduction
- At least 30% pain reduction
- Patient global impression
- Other key measures, sleep,

†side effects were for the whole group.
‡Adverse events:
__Note serious adverse events defined by:__
- results in death
- is life threatening
- requires or prolongs inpatient hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defects

Clinical Research in Canada; Edition; January 1, 2006, Book 11; Section title; Guidance for Industry, Clinical Safety Data Management : Definitions and Standards for Expedited Reporting (ICH-E2A); definition is on page 3 of this section, under the heading of 'Serious Adverse Event or Adverse Drug Reaction'
§The larger difference in the group receiving CT-3 first.
DDS, descriptor differential scale, ratio scale 24 words describe pain 0–20; PGIC, patient global impression of change; POMS, profile of mood states; PDI, Pain Disability Index; HADS, Hospital anxiety and depression scale; SF-MPQ, McGill Pain Questionnaire, short form; DAS28, 28 joint disease activity score; UMNS, Upper Motor Neuron Syndrome; TOTPAR, total pain relief; SPID, sum pain intensity difference; BDI, Beck Depression Inventory; GHQ, General Health Questionnaire.
#means fractured.

the 100 mm VAS and dropped to 59.93 mm for participants taking nabilone and 58.58 mm for those taking dihydrocodeine [31].

Dronabinol Two trials involved dronabinol. The earlier trial found that dronabinol 10 mg day^{-1} led to significant reduction in central pain in multiple sclerosis [35], a subsequent trial found that dronabinol at both 10 and 20 mg day^{-1} led to significantly greater analgesia and better relief than placebo as adjuvant treatment for a group of participants with mixed diagnoses of chronic pain on opioid therapy [36].

THC-11-oic acid analogue (CT-3 or ajulemic acid) Two studies reported on various aspects of this trial examining ajulemic acid in a group of participants with neuropathic pain with hyperalgesia or allodynia [37, 38]. Nineteen of 21 completed the trial. It was found that ajulemic acid led to significant improvement in pain intensity at 3 h but no difference at 8 h as compared with placebo.

Secondary outcome – level of function

Several trials included secondary outcome measures relating to level of function. Two trials examining cannabis based medicines included the Pain Disability Index (PDI) [24, 30]. Numikko found that six of seven functional areas assessed by the PDI demonstrated significant improvement on CBM (–5.61) as compared with placebo (0.24) (estimated mean difference –5.85, $P = 0.003$) in 125 participants with neuropathic pain while Berman [24] noted no significant difference from placebo in 48 participants with central pain from brachial plexus avulsion. Two studies included the Barthel index for activities of daily living (ADL) [28, 33] and noted no significant improvement in ADLs with nabilone for spasticity related pain [33] or with CBMs for multiple sclerosis [28]. In one trial examining nabilone for the treatment of fibromyalgia the FIQ [39] demonstrated significant improvement as compared with placebo. This measure includes a number of questions regarding function in several areas including shopping, meal preparation, ability to do laundry, vacuum, climb stairs and ability to work. The FIQ also includes questions relating to pain, fatigue, stiffness and mood. The total scores presented in this study were not presented separately so the reader cannot be certain. However given that the majority of questions relate to function it is likely that there were some improvements in function.

Drug related adverse effects

There were no serious adverse events according to the Health Canada definition described above and in Table 1, The most common adverse events consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration. Other adverse events included poor co-ordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria and dysphoria. Adverse effects were generally described as well tolerated, transient or mild to moderate and not leading to withdrawal from the study. This is a significant difference from the withdrawal rates seen in studies of other analgesics such as opioids where the rates of abandoning treatment are in the range of 33% [40]. Except where specifically noted in Table 1 there was no specific mention of whether adverse effects caused limitations in function. The most severe treatment related event in the entire sample was a fractured leg related to a fall that was thought to be related to dizziness [34]. Details regarding specific trials are presented in Table 1.

Discussion

Efficacy and harm

All of the trials included in this review were conducted since 2003. No trials prior to this date satisfied our inclusion criteria. This review has identified 18 trials that taken together have demonstrated a modest analgesic effect in chronic non-cancer pain, 15 of these were in neuropathic pain with five in other types of pain, one in fibromyalgia, one in rheumatoid arthritis, one as an adjunct to opioids in patients with mixed chronic pain and two in mixed chronic pain. Several trials reported significant improvements in sleep. There were no serious adverse events. Drug related adverse effects were generally described as well tolerated, transient or mild to moderate and most commonly consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration.

Limitations

The main limitations to our findings are short trial duration, small sample sizes and modest effect sizes. Thus there is a need for larger trials of longer duration so that efficacy and safety, including potential for abuse, can be examined over the long term in a greater number of patients. It is also important to recognize that cannabinoids may only reduce pain intensity to a modest degree. It remains for the patients to decide whether this is clinically meaningful.

The context of chronic pain

Pain is poorly managed throughout the world. Eighty percent of the world population has no or insufficient access to treatment for moderate to severe pain [41]. Chronic pain affects approximately one in five people in the developed world [42–46] and two in five in less well resourced countries [47]. Children are not spared [48, 49] and the prevalence increases with age [43, 50]. The magnitude of the problem is increasing. Many people with diseases such as cancer, HIV and cardiovascular disease are now surviving their acute illness with resultant increase in quantity of life, but in many cases, poor quality of life due to persistent pain caused either by the ongoing illness or nerve damage caused by the disease after resolution or cure of the disease. In many cases the pain is also caused by

the treatments such as surgery, chemotherapy or radiotherapy needed to treat the disease [51–53].

Chronic pain is associated with the worst quality of life as compared with other chronic diseases such as chronic heart, lung or kidney disease [50]. Chronic pain is associated with double the risk of suicide as compared with those living with no chronic pain [54].

In this context, patients living with chronic pain require improved access to care and additional therapeutic options. Given that this systematic review has identified 18 RCTs demonstrating a modest analgesic effect of cannabinoids in chronic pain that are safe, we conclude that it is reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well. Of special importance is the fact that two of the trials examining smoked cannabis [25, 26] demonstrated a significant analgesic effect in HIV neuropathy, a type of pain that has been notoriously resistant to other treatments normally used for neuropathic pain [52]. In the trial examining cannabis based medicines in rheumatoid arthritis a significant reduction in disease activity was also noted, which is consistent with pre-clinical work demonstrating that cannabinoids are anti-inflammatory [55, 56].

Conclusion

In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting on pain and level of function are required.

Competing Interests

The authors have no competing interests.

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