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INVITED REVIEW

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

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Abstract An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

Keywords Cannabinoids · Chronic non-cancer pain · Neuropathic pain · Systematic review · Marijuana

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Introduction

Chronic pain is a growing public health problem affecting approximately one in five people and predicted to increase to one in three over the next two decades (Blyth et al. 2001; Moulin et al. 2002; Breivik et al. 2006). The prevalence of chronic pain is likely to increase as the population ages and as medical advances continue to improve survival related to cancer, serious injury and diseases that previously would have been fatal, such as HIV, but have left the survivors with serious neuropathic pain conditions (Lynch 2011). Currently available agents (eg. antidepressant and anticonvulsant analgesics, opioids and nonsteroidal anti-inflammatory drugs) (Finnerup et al. 2010) are inadequate to control all pain or are associated with limiting side effects (eg. most problematic being sedation with the antidepressant and anticonvulsant group, constipation with the opioids and gastrointestinal and cardiovascular effects with the NSAIDs) (Lynch 2008). There is a critical need for new treatments.

In this context, many people with chronic pain are turning to other therapies including cannabinoids (Ware et al. 2003). Due to patient demand, several nations (or states within countries) have developed programs to allow people with serious health conditions to access cannabis (marijuana) for medicinal purposes. Most of these programs (e.g., Canada, Israel, Netherlands, several US States) require physician or nurse practitioner support for the individual patient to be approved for access. Medical professionals have called for more research regarding both potential therapeutic and adverse effects of cannabinoids (Kahan et al. 2014). This is an updated systematic review of controlled trials done since the previous systematic review regarding cannabinoids in the treatment of chronic non-cancer pain (Lynch and Campbell 2011).

Methods

We conducted a systematic review following PRISMA guidelines (Liberati et al. 2009). Initially a literature search was undertaken to retrieve Randomized Control Trials (RCT) 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), LILACS, and Google Scholar. The searches were updated from the date of last search in 2010 to October 2014 and were not limited by language. The search retrieved all articles assigned the Medical Subject Headings (MeSH) *Cannabis*, *Cannabinoids*, *Cannabidiol (CBD)*, *Marijuana Smoking* and delta-9-*Tetrahydrocannabinol (THC)* as well as those assigned the Substance Name *tetrahydrocannabinol-cannabidiol combination*. Cannabidiol (CBD) is the main nonpsychotropic phytocannabinoid and delta-9-tetrahydrocannabinol (THC) the main psychoactive cannabinoid in the cannabis plant (Skaper and DiMarzo 2012). To this set was added those articles containing any of the keywords *cannabis*, *cannabinoid**, *marijuana*, *marihuana*, *dronabinol* or *tetrahydrocannabinol*. Members of this set containing the MeSH heading Pain or the keyword "*pain*" were passed through the "Clinical Queries: therapy/narrow" filter to arrive at the final results set of RCTs. The search strategy was adapted for and run in the other databases by an experienced medical librarian.

Inclusion and Exclusion Criteria

Included in this review were RCTs comparing a cannabinoid with a placebo or active control group where pain was a reported measured outcome in subjects with chronic non-cancer pain. Relevant outcomes included any scale measuring pain. This might include a numeric rating scale (NRS), a visual analog scale (VAS), the Neuropathic Pain Scale (NPS) or the McGill Pain Questionnaire. Excluded were trials where pain was not reported as an outcome, trials regarding experimental or acute pain and cancer pain, preclinical studies, abstracts, letters and posters where the full study was not published.

Data Extraction and Validity Scoring

Both authors independently read the included articles and completed the assessment of methodological validity using the modified seven point, four item Oxford scale (Fig. 1). Discrepancies on the validity assessment were resolved through discussion. Trials that did not include randomization were not included and a score of 1 or more on this item of the Oxford Scale was required.

Modified Oxford Scale

Validity score (0-7)

Randomisation

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

Fig. 1 Modified Oxford Scale

Data extracted included information about the specific population studied, number of subjects randomized and completed, outcomes, summary measures, trial duration, results and adverse events. Information about the most frequently reported or serious adverse events was extracted.

Results

Trial Flow

A total of 201 citations were initially identified through database searches. Duplicates were removed and unique citations identified through Google Scholar were added, resulting in a total of 199 citations. Research assistants and the review team screened the studies for content relevance and study design at the title and abstract level to exclude 186 results, leaving 13 trials to be screened by examining the full text. One study was excluded after reading the full text as it had not included pain as an outcome, and one was removed as it had been included in the previous review, leaving 11 studies that received quality screening and underwent data extraction (Fig. 2).

Primary Outcome-Efficacy

There were 11 randomized controlled trials published from 2010 to 2014 involving 1185 subjects that met inclusion

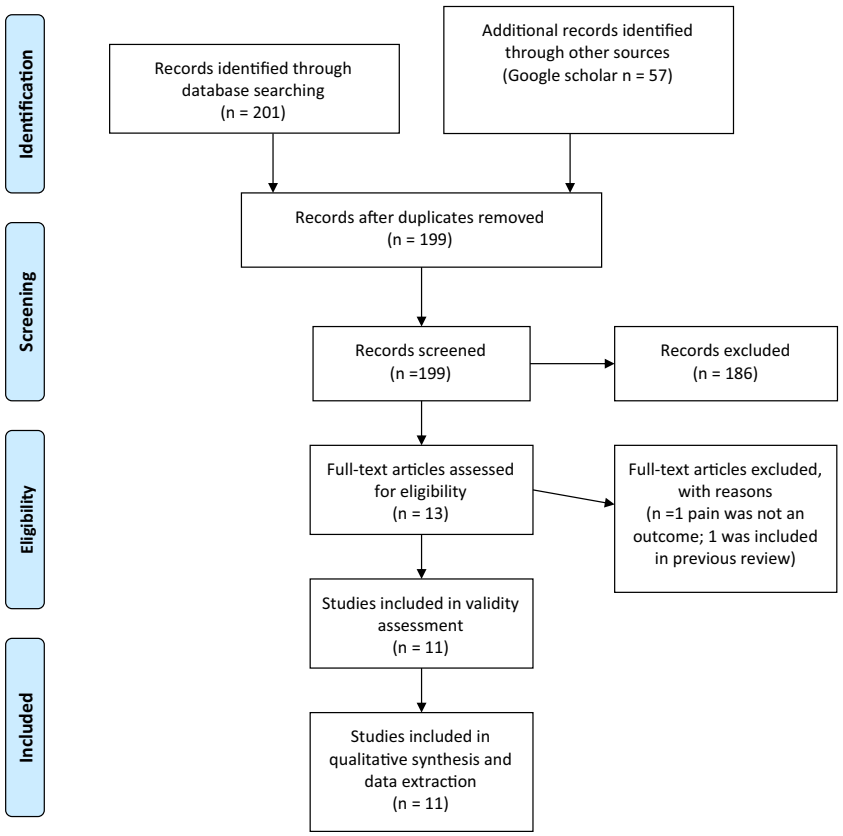

Fig. 2 PRISMA flow diagram

criteria. The quality of trials was excellent with a mean score of 7 (range 5–7) on the Modified Oxford Scale. In 7 studies pain was the primary outcome, while in 4 studies other outcomes were stated as primary outcome (sleep, headache frequency, spasticity) with pain as a secondary outcome. Overall 7 studies demonstrated that the cannabinoid under study exhibited an analgesic effect that was significantly better than the control. In 9 studies the control was a placebo, while in 2 studies the cannabinoid was compared to an active control (nabilone and ibuprofen) (Table 1).

Nabilone

Nabilone is a synthetic analog of THC approved by the FDA over 25 years ago for treatment of chemotherapy induced nausea and vomiting (Pertwee 2012). Four studies examined the efficacy of nabilone. In a study of medication overuse headache (N=26/30), nabilone was superior to ibuprofen in reducing daily analgesic intake, pain intensity and level of dependence and was equally efficacious in reducing frequency (Pini et al. 2012). In a study of patients with painful diabetic neuropathy (N=25/26) nabilone was significantly more effective than placebo in reducing pain with significant improvements in secondary measures of anxiety and sleep (Toth et al. 2012). In a study using amitriptyline as an active control examining sleep with pain as a secondary measure in fibromyalgia (N=29/32), both agents improved sleep with nabilone demonstrating significantly more improvement in sleep quality on one of the sleep measures; there was no significant impact on pain, however subjects started with a relatively low mean pain score of 2.3/10 (Ware et al. 2010). In a study of MS pain (N=14/15) nabilone was demonstrated to improve pain significantly more than placebo in combination with gabapentin according to both the VAS and patient global assessment of change (Turcotte et al. 2014).

Oral Mucosal Cannabis Spray and Oral Cannabis Extract

Three RCTs examined an oromucosal cannabis spray (each spray delivers 2.7 mg of THC and 2.5 mg of CBD) and 1 examined an oral cannabis extract (doses 5–25 mg daily with CBD between 29 and 72 % that of THC). In neuropathic pain associated with allodynia (N=173/246), the oral mucosal cannabis spray demonstrated a significant analgesic effect with improvements in sleep and subject global impression of change (Serpell et al. 2014). In a study involving neuropathic pain in MS (N=297/339) oral mucosal cannabis spray demonstrated a reduction in pain compared to placebo at 10 weeks; however at 14 weeks, pain scores did not differ between the

Table 1 Results of randomized controlled trials examining cannabinoids in chronic pain

Author and date	Agent (control group)	Population (N) completed/ randomized *design*	Core outcomes	Summary measures used (eg. difference in means, responder rates)	Oxford score (bias risk)	Duration of RCT (duration of extension phase)	Results (brief comments)	Adverse Events	Outcome summary
Ware et al. (2010)	Nabilone (amitriptyline)	Fibromyalgia 29/32 *crossover*	Sleep (ISI, LSEQ) Pain (MPQ) Mood (POMS) QOL (FIQ)	Differences in means	7	2 weeks each treatment	Both agents improved sleep, with nabilone having a greater effect in improving sleep than amitriptyline on the ISI. and no significant difference from amitriptyline on pain measures	Main side effects reported drowsiness and dizziness 1 withdrew due to side effects	−
Pini et al. (2012)	Nabilone (ibuprofen)	Medication Overuse Headache *crossover* 26/30	Headache frequency (HI), intensity (VAS) and duration of headache Analgesic intake (DAI) QOL (HIT-6, SF-36) Mood (Zung depression and anxiety) Dependence (LDQ)	Differences in means	6	8 weeks each treatment	Both drugs showed improvements to baseline in all primary endpoints Nabilone was superior to ibuprofen in reducing daily analgesic intake, pain intensity and level of dependence	1 withdrew due to loss of concentration and memory on nabilone and 1 withdrew due to gastric discomfort on ibuprofen all other AEs were described as mild	+
Corey-Bloom et al. (2012)	Cannabis, smoked 4%THC (placebo)	MS *Crossover* 30/37	Spasticity (Ashworth scale) Pain (VAS)	Differences in means	5	1 supervised exposure each treatment followed 3 days	Statistically significant reduction of spasticity reduced by average of 2.74 more than placebo ($p<0.001$) Pain reduction of average 5.28/100 points more than placebo ($p=0.008$)	5 withdrew due to adverse effects (2 uncomfortable "high" 2 dizziness, 1 fatigue)	+
Huggins et al. (2012)	FAAH Inhibitor PF-04457845 (placebo) and active control)	OA *crossover* 69/74	WOMAC pain score and other subscales, pain (11-point NRS) FAAH activity in leukocytes and plasma	Differences in means	7	2 weeks each treatment	There was no significant difference in pain scores for the FAAH inhibitor There were significant decreases in FAAH activity in the presence of PF-04457845 pharmacodynamically according to 4 endogenous fatty acid amides which did increase	Well tolerated with no significant difference in AEs from placebo	−
	Nabilone	Diabetic neuropathy	Pain (NRS)		7				+

Table 1 (continued)

Author and date	Agent (control group)	Population (N) completed/ randomized *design*	Core outcomes	Summary measures used (eg. difference in means, responder rates)	Oxford score (bias risk)	Duration of RCT (duration of extension phase)	Results (brief comments)	Adverse Events	Outcome summary
Toth et al. (2012)	(placebo)	*parallel group enriched enrollment* 37 single blind phase 25/26 double blind phase	Sleep (MOSSS) Mood (HADS) Pain (BPI) QOL (EQ-5D) Satisfaction (PTSS)	Difference in means		4 weeks single blind then 5 weeks double blind	Nabilone was statistically more effective than placebo at improving pain Responder analysis number with 30 % or greater reduction in pain was 11/13 vs 5/13 for placebo with statistically significant improvements in sleep and anxiety	Medication related confusion led to discontinuation in 2 of 37 patients, one admission to ER for assessment of delirium resolved when medication discontinued 13/37 experienced AEs in single blind phase dizziness, dry mouth drowsiness confusion mild to moderate and transient	
Zajicek et al. (2012)	Oral cannabis extract vs placebo	224/279	Muscle stiffness (NRS) Body pain, muscle spasms, sleep (NRS) Spasticity (MSSS-88) Psychological impact (MSIS-29) Walking ability (MSWS-12)	Comparison of proportions of responders between active and placebo	7	12 weeks	Significant improvement of stiffness in cannabis arm compared to placebo; improvement of pain, sleep and spasms	AEs noted more in cannabis group were dizziness, disturbance in attention, balance disorder, somnolence, dry mouth, nausea, diarrhoea, fatigue, asthenia, feeling abnormal,urinary tract infection, disorientation, confusional state and fall. 7 SAEs reported in treatment group (3 were thought to be treatment related)	+
Langford et al. (2013)	Oral mucosal Cannabis spray (placebo)	Neuropathic pain in MS 297/339 *parallel groups*	Pain (NRS-P) Pain (BPI) SGIC	Difference in means	7	14 weeks RCT 14 week open label extension	Statistically significant reduction in pain as compared to placebo at 10 weeks while at 14 weeks nabiximol group demonstrated lower pain scores but this was not statistically significant	Most common AEs dizziness, fatigue somnolence, vertigo and nausea 2 SAEs in treatment group (disorientation, suicidal ideation)	−
Wilsey et al. (2013)	Vapourized cannabis	Neuropathic pain 39/39	Pain (VAS) PGIC	Linear mixed modeling	7			Significant dose response effects of vapourized	+

Table 1 (continued)

Author and date	Agent (control group)	Population (N) completed/ randomized *design*	Core outcomes	Summary measures used (eg. difference in means, responder rates)	Oxford score (bias risk)	Duration of RCT (duration of extension phase)	Results (brief comments)	Adverse Events	Outcome summary
	(1.29, 3.53 %) versus placebo		Pain (NPS) QST Neuropsychological responses			3×6 h treatment sessions. Single exposure	Significant improvement in pain and PGIC, and certain aspects of NPS	cannabis on psychoactive effects, and neurocognitive function	
Lynch et al. (2014)	Oral mucosal Cannabis spray (placebo)	Chemotherapy induced neuropathic pain 16/18 *crossover*	Pain (NRS) QOL (SF-36)	Differences in means and responder analysis	7	4 week RCT 6 month extension	When examining whole group no statistically significant difference from placebo Responder analysis demonstrated 5 responders reporting a ≥2 point reduction in pain NNT=5	Most commonly reported adverse effects were fatigue, dizziness, dry mouth and nausea, all were mild and transient, no withdrawals due to AEs	−
Serpell et al. (2014)	Oral mucosal Cannabis spray (placebo)	Peripheral neuropathic pain with allodynia *parallel group* 173/246	Pain (NRS) Pain (NPS, BPI) Sleep (NRS) SGIC QOL (EQ-5D)	Responder rates Differences in Means	7	14 weeks	34 patients in active treatment reported a 30 % or greater reduction in pain vs 19 on placebo this was statistically significant Statistically significant improvements in sleep and SGIC	Most common adverse effects: Dizziness Distortion of taste Nausea Fatigue Most mild to moderate No treatment related SAEs 25 of 128 stopped the study medication due to AEs	+
Turcotte et al. (2014)	Nabilone adjunct to gabapentin (placebo)	MS pain 14/15	Pain (VAS) Impact (VAS) PGIC	Difference in means	7	9 weeks total (4 week titration, 5 week maintainence)	Significant improvements in pain and PGIC with nabilone in combination with gabapentin as compared with placebo with gabapentin	Most common dizziness, drowsiness dry mouth 1 withdrawal due to headache in nabilone group. No SAEs	+

Abbreviations: *BPI* brief pain inventory, *CBD* cannabidiol, *DAI* daily analgesic intake, *EQ-5D* health outcome instrument, *FIQ* fibromyalgia impact questionnaire, *HI* headache index, *HIT-6* headache impact test, *ISI* insomnia severity index, *LDQ* leeds dependence questionnaire\, *LSEQ* leeds sleep evaluation questionnaire, *MOSSS* medical outcomes study sleep scale, *MSIS-29* Multiple Sclerosis (MS) Impact Scale, *MSSS-88* MS Spasticity Scale, *MSWS-12* MS Walking Scale, *MPQ* McGill pain questionnaire, *NPS* neuropathic pain scale, *NRS-P* numeric rating scale for pain, *PGIC* patient-rated global impression of change, *POMS* profile of mood states, *QOL* quality of Life, *SF-36* Short Form-36 Quality of Life Measure, *SGIC* subject global impression of change, *THC* delta-9-tetrahydrocannabinol, *PTSS* pain treatment satisfaction scale, *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

oral mucosal cannabis spray and placebo groups (Langford et al. 2013). In a pilot study of chemotherapy induced neuropathic pain (N=16/18), NRS pain scores did not demonstrate a statistically significant difference but a responder analysis found 5 of the 16 completers reported a 2 point or greater reduction with an overall NNT=5. Given that more than a quarter of patients with this highly intractable type of pain responded to oral mucosal cannabis spray over placebo, the authors concluded further study was warranted (Lynch et al. 2014). One study examined an oral cannabis extract in multiple sclerosis with spasticity as the primary measure and pain as a secondary measure (N=224/259) and found relief from muscle stiffness pain and sleep was twice as good with the cannabis extract than with placebo (Zajicek et al. 2012).

Cannabis (Smoked or Vaporized)

Since the 2010 systematic review, there have been 2 further controlled trials examining smoked (1 trial) or vaporized (1 trial) cannabis. In neuropathic pain, cannabis containing both a lower dose (1.29 % THC) and higher dose (3.53 % THC) delivered by vaporizer demonstrated a significant analgesic response as compared to placebo with an NNT for 30 % reduction of 3.2 and 2.9 respectively for low and higher dose cannabis (Wilsey et al. 2013). In a study of MS spasticity and pain, smoked cannabis containing 4 % THC demonstrated a significant antispasticity and analgesic effect compared with placebo (Corey-Bloom et al. 2012).

FAAH Inhibitor

There was one study examining a novel fatty acid amide hydrolase inhibitor (FAAH). FAAH is one of the main enzymes known to break down the endogenous cannabinoid, anandamide, as well as noncannabinoid fatty acid amides (Cravatt et al. 2001). FAAH inhibition has been found to elicit antinociceptive effects in animal models of arthritis (Schuelert et al. 2011). In spite of promising preclinical data, the single clinical trial examining a FAAH inhibitor (PF-04457845) did not find a significant improvement in pain associated with osteoarthritis of the knee (N=69/74). Interestingly there was a significant increase in 4 endogenous fatty acids [anandamide (AEA), oleoylethanolamide (OEA), palmitoylethanolamide (PEA), and linoleoylethanolamide (LEA)], which demonstrated a biological effect, but was not associated with a reduction of pain (Huggins et al. 2012).

Adverse Events

All studies included specific information on adverse effects; detailed findings are presented in Table 1. The adverse effects seen with all cannabinoids were similar with drowsiness or fatigue reported most frequently and dizziness, dry mouth, nausea and cognitive effects reported in most trials. In the vast majority the adverse effects were mild to moderate in severity, transient and well tolerated. Regarding serious adverse events (SAEs); in a study of oral cannabis extract in 279 patients with MS there were 3 adverse events described as serious and medication related, these included urinary tract infection, head injury and interstitial lung disease (Zajicek et al. 2012). In a study examining nabilone in treatment of 37 patients with diabetic neuropathy one patient was seen in the emergency room for assessment of delirium which resolved when the medication was discontinued (Toth et al. 2012) and in a study of the oral mucosal cannabis spray in 339 patients with neuropathic pain associated with MS there were 2 SAEs in the treatment group (suicidal ideation and disorientation) (Langford et al. 2013).

Discussion

Efficacy and Harm

This is an update to a previous systematic review examining RCTs using cannabinoids for treatment of chronic non-cancer pain. The current review found 11 RCTs published since our last review, 7 of which demonstrated significant analgesic effects by the cannabinoids studied. Several trials also reported benefits in sleep and 2 of the MS trials also demonstrated benefits in muscle stiffness and spasticity. Drug related adverse effects consisted primarily of fatigue, dizziness, dry mouth, nausea and disturbances in cognition and were mild to moderate, transient and generally well tolerated. The findings of the current review extend and are consistent with those from the previous review (Lynch and Campbell 2011) such that combined there are a total of 22 of 29 RCTs demonstrating that cannabinoids demonstrate a modest analgesic effect and are safe in the management of chronic pain.

Limitations

The main limitations to these findings are that most of the trials were of short duration, with relatively small sample sizes and modest effect sizes. There is a need for larger and longer trials to confirm efficacy signals shown by the smaller ‘proof of concept’ studies, and for longer term monitoring of patients using cannabinoids for long term safety considerations. Currently available cannabinoids only appear to reduce pain to a

modest degree, similar to all medications currently available for the treatment of chronic pain.

One message from this review is that it is perhaps ill-advised to treat all cannabinoids the same; talk of "medical marijuana" often lumps all these compounds and formulations together. In fact there are very important pharmacokinetic differences between modes of delivery (e.g., oral versus inhaled), differences in cannabinoid profiles (e.g., the presence of CBD in different amounts), and source of cannabinoid (plant based complex botanicals versus synthetic single molecules). Such diversity of approach is welcomed as each study adds value to the overall weight of evidence that cannabinoids as a drug class have analgesic potential, but distinctions must be made when citing these studies to ensure that the conclusions are not drawn more widely than is justified.

The decision as to whether the degree of pain relief obtained from using cannabinoids is clinically meaningful will remain a decision based on informed decision making between the patient and their health care provider; however we feel that cannabinoids have demonstrated sufficient analgesic potential to be included in serious discussions around therapeutic options in the treatment of chronic pain.

Conclusions

In summary the current systematic review provides further support that cannabinoids are safe, demonstrate a modest analgesic effect and provide a reasonable treatment option for treatment chronic non-cancer pain.

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Conflict of Interest ML is a founding director of Panag Pharm Inc and is medical advisor to Abide Therapeutics both start up companies focused on development of nonpsychotropic cannabinoids for treatment of pain and other health conditions, she also sits on the Board of the Canadian Consortium for the Investigation of Cannabinoids (CCIC) a nonprofit organization dedicated to research and education on cannabinoids.

MW has received a grant from Prairie Plant Systems for a clinical trial of cannabis for pain management. MW is Executive Director of the Canadian Consortium for the Investigation of Cannabinoids (CCIC), a nonprofit organization dedicated to research and education on cannabinoids.

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