Review Article

A selective review of medical cannabis in cancer pain management

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Abstract: Insufficient management of cancer-associated chronic and neuropathic pain adversely affects patient quality of life. Patients who do not respond well to opioid analgesics, or have severe side effects from the use of traditional analgesics are in need of alternative therapeutic options. Anecdotal evidence suggests that medical cannabis has potential to effectively manage pain in this patient population. This review presents a selection of representative clinical studies, from small pilot studies conducted in 1975, to double-blind placebo-controlled trials conducted in 2014 that evaluated the efficacy of cannabinoid-based therapies containing tetrahydrocannabinol (THC) and cannabidiol (CBD) for reducing cancer-associated pain. A review of literature published on Medline between 1975 and 2017 identified five clinical studies that evaluated the effect of THC or CBD on controlling cancer pain, which have been reviewed and summarised. Five studies that evaluated THC oil capsules, THC:CBD oromucosal spray (nabiximols), or THC oromucosal sprays found some evidence of cancer pain reduction associated with these therapies. A variety of doses ranging from 2.7–43.2 mg/day THC and 0–40 mg/day CBD were administered. Higher doses of THC were correlated with increased pain relief in some studies. One study found that significant pain relief was achieved in doses as low as 2.7–10.8 mg THC in combination with 2.5–10.0 mg CBD, but there was conflicting evidence on whether higher doses provide superior pain relief. Some reported side effects include drowsiness, hypotension, mental clouding, and nausea and vomiting. There is evidence suggesting that medical cannabis reduces chronic or neuropathic pain in advanced cancer patients. However, the results of many studies lacked statistical power, in some cases due to limited number of study subjects. Therefore, there is a need for the conduct of further double-blind, placebo-controlled clinical trials with large sample sizes in order to establish the optimal dosage and efficacy of different cannabis-based therapies.

Keywords: Medical cannabis; cancer; pain

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Introduction

Cancer patients often present with chronic pain, which may stem from direct tumour involvement, or present as a side effect of cancer treatment (1). As pain negatively impacts the physical, functional, and emotional domains of life, effective pain management strategies are essential for restoring and maintaining quality of life of cancer patients (2). Unfortunately, the current standard treatment regimens for chronic or neuropathic pain in end-stage cancer patients rely heavily on opioid analgesics, which are problematic for some patients (3,4). This can be due to a combination of factors, including differences in individual responses to these drugs, and the presence of serious side effects such as severe constipation, that may prevent the administration

of sufficient doses for pain relief (3). In addition, imprudent dosing runs the dangerous risk of patients developing dependency, or overdosing on opioids (4). Therefore, identifying alternative classes of analgesics that can effectively manage pain in cancer patients is of great importance.

Alternative pharmacological interventions include prescription medications such as acetaminophen, or nonsteroidal anti-inflammatory drugs like ibuprofen (5). Non-medicated approaches include therapies such as acupuncture, physical therapy, in addition to psychological or behavioural approaches (6). In addition to the management strategies listed above, compounds derived from the plant species Cannabis Sativa L. have demonstrated the potential to alleviate pain. The most commonly studied examples include tetrahydrocannabinol (THC), and cannabidiol (CBD) from the family of compounds known as cannabinoids (7). These compounds are commonly administered via inhalation, orally as oils or oil-filled capsules, or oromucosally via sprays containing either THC alone, or a combination of THC:CBD (8). Several pre-clinical studies have been conducted in animal models, investigating the mechanism of cannabinoid modulation of pain pathways (9,10). One of the identified mechanisms is the interaction of these compounds with one of the body's endogenous signalling systems, known as the "endocannabinoid" system (11). This system acts independently of the opioid pathway to control pain signalling, immune activation, and inflammation (11). While there is an abundance of existing anecdotal evidence of the analgesic properties of medical cannabis, its efficacy has not yet been validated through high-quality clinical studies that provide strong evidence supporting its utility in the clinical setting (12).

This selective review is an overview of clinical studies conducted historically and up until the present day that aimed to investigate the efficacy of medical cannabis in managing pain in advanced cancer patients.

Methods

A search of literature published on Medline between 1975 and 2017 through using key words including "cannabis", "THC", "CBD", "Nabiximol", "cancer", and "pain" was conducted. Five clinical studies that evaluated the effect of THC or CBD on controlling cancer pain were evaluated for a selective review. Information regarding the study population, interventions, pain response, and side effects was reviewed and summarised.

Results

Patient populations and selection criteria

Five studies were selected based on their evaluation of cannabinoids to manage chronic pain in advanced cancer patients. An early pilot study conducted in 1975 by Noyes *et al.* assessed pain in ten advanced cancer patients (eight women and two men, average 51 years old) (13). In a similar pain management study, Noyes *et al.* compared the effects of THC and codeine in 36 cancer patients (consisting of 26 women and 10 men) (14). Non-study medications were withheld from patients from both studies by Noyes *et al.* during the study period (13,14). Johnson *et al.* conducted a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of nabiximols and THC in patients with intractable cancer-related pain, using a well-distributed population of 177 advanced cancer patients, who recorded non-study breakthrough analgesics (15). In this study, the mean age, gender, primary disease sites, and pain classification were distributed similarly between the three treatment arms; THC, nabiximols, and placebo (15). In 2012, Portenoy *et al.* conducted a randomized, placebo-controlled, graded-dose trial involving 360 patients with advanced cancer, looking at the efficacy of THC or nabiximols. Patients were chosen based on having previously responded poorly to opioid analgesics, but were allowed to take breakthrough opioid analgesics as required (16). Patients who had received long-term methadone treatment for pain were excluded. Pain characteristics were categorized as mixed (48%), bone (24%), visceral (15%), and neuropathic (11%), and were distributed approximately equally across the study arms. Finally, Lynch *et al.* conducted a double-blind, placebo-controlled, crossover pilot trial including 16 cancer patients who had persistent neuropathic pain 3 months after their cancer treatment (17). These patients had an average 7-day pain intensity ≥4 on 0–10 NRS, stable concurrent analgesic treatment for 14 days prior to study initiation, and were not taking breakthrough analgesics.

Evaluation of pain

In the clinical studies of cannabinoids for cancer pain management included in this review, several methods of

measuring changes in pain intensity were employed. Early studies by Noyes *et al.* used a 4-point pain scoring system in which 0= absent, 1= mild, 2= moderate, and 3= severe (13,14). Since then, many studies have employed the numerical rating scale (NRS) to evaluate pain on a 0–10 scale, with "0" representing "no pain" to "10" representing "pain as bad as you can imagine". Patients with neuropathic pain studied by Lynch *et al.* completed the NRS at baseline, and the last day of each week of dosing (17). The change in NRS score from baseline to the week in which a stable dose was reached was used as the primary endpoint in determining cannabis efficacy. In the study by Johnson *et al.*, patients used the NRS in addition to recording their long-term and break-through pain medications in a pain diary (15). Portenoy *et al.* asked patients to report their average pain on the brief pain inventory (BPI), as well as through an interactive voice recording system (16). The two remaining studies used the BPI to assess change in pain as the primary endpoint (18,19).

Efficacy of interventions

Overall, four out of the five studies found that cannabis was significantly associated with a decrease in cancer-associated pain. *Table 1* presents a summary of the efficacy of THC or CBD on cancer pain.

THC oil capsules and THC, CBD oromucosal sprays

Studies included in this review assessed the efficacy of THC oil capsules, and oromucosal sprays containing THC extract, or THC:CBD extract, also known as nabiximols. Since nabiximols have CBD in addition to THC, they may potentially target more pain pathways when compared to THC extract alone.

Two early clinical studies on the efficacy of THC extract in sesame oil capsules were published by Noyes *et al.* in 1975 (13,14). The first was a pilot study that identified a correlation between higher doses of THC and increased pain relief ($P<0.001$) (13). The second study found a significant difference in pain reduction between placebo and 20 mg THC ($P<0.05$), in favour of THC treatment (14).

Oromucosal sprays have been a common method of administration for cannabinoid-based medicines in clinical investigations, to date (12). Both THC extracts and nabiximols, administered oromucosally, were studied by Johnson *et al.* (15). They did not observe a significant change in mean pain score from baseline for THC spray compared to placebo, but did report a statistically significant change in favour of nabiximols treatment compared to placebo ($P=0.024$). In addition, they reported that patients taking nabiximols required significantly fewer doses of breakthrough pain medications when compared to placebo ($P=0.004$). Portenoy *et al.* found that compared to placebo, nabiximols were significantly more effective for reducing average daily pain when comparing scores from baseline to the end of the study period ($P=0.038$) (16). These findings are in contrast with the study by Lynch *et al.* in which there was no statistically significant difference between placebo and nabiximols treatment groups amongst the 16 patients experiencing cancer-related neuropathic pain (17).

Dosage

Studies assessed the efficacy of different doses of medication, or allowed patients to self-titrate up to a maximum dose, as dictated by study protocols.

Evaluation of the effect of 5, 10, 15, and 20 mg of THC in oil capsules by Noyes *et al.* found that the amount of pain relief increased with dose (13). Out of 10 patients in each cohort, 5 received substantial relief from 15 mg, and 7 patients received substantial relief from 20 mg. In the second study by Noyes *et al.*, two different THC doses of 10 and 20 mg were compared to placebo and 60 mg codeine (14). A 60 mg dose of codeine is a standard daily opioid analgesic regimen used in the management of many pain types, including cancer pain (20). A significant difference in pain reduction was observed with the administration of 20 mg THC when compared to placebo ($P<0.05$). Additionally, no significant difference in pain relief was observed when comparing the 10 mg THC cohort to those receiving 60 mg codeine ($P<0.05$). This suggests the non-inferiority of 10 mg of THC in comparison to a commonly used opioid treatment.

Evaluation of the efficacy of THC oromucosal spray by Johnson *et al.* followed a self-titration method of dosing (15). Patients who used THC sprays used an average of 8.3 sprays/day, corresponding to 22.5 mg of THC/day following dose titration up to a ceiling dose of 48 sprays/day. Patients were considered to have reached their optimal dose upon experiencing relief of pain, or the development of side-effects. The authors found the optimal dose of THC reached across patients provided greater pain relief compared with placebo as measured by the average NRS pain score reduction (THC –1.01 *vs.* placebo –0.69) however, statistical significance was not reached ($P=0.245$).

Table 1 An overview of randomized controlled trials (RCTs) involving medical cannabis for cancer pain

Reference	Year	Type of study	Total subjects	Treatment arms and doses	Duration	Outcome measure	Pain response
Noyes *et al.* (13)	1975	RCT	10 advanced cancer patients	(I) THC: 5, 10, 15, and 20 mg in oil capsules; (II) placebo	6 hours	Self-reported pain severity, pain relief, side effects, subjective effects questionnaires	Correlation between higher doses of THC and increased pain relief ($P<0.001$)
Noyes *et al.* (14)	1975	RCT	36 advanced cancer patients	(I) THC: 10 and 20 mg in oil capsules; (II) codeine: 60 mg and 120 mg; (III) placebo	6 hours	Self-reported pain severity, pain relief, side effects, subjective effects questionnaires	Significant difference in pain reduction between placebo and 20 mg THC ($P<0.05$), in favour of THC treatment; no significant difference in pain relief was observed when comparing the 10 mg THC cohort to those receiving 60 mg codeine ($P<0.05$)
Johnson *et al.* (15)	2010	RCT	177 advanced cancer patients	(I) Nabiximols: ceiling dose of 8 sprays/3-hour period (21.6 mg THC, 20 mg CBD); (II) THC: ceiling dose of 48 sprays/day (130 mg/day); average dose of 8.3 sprays/day (22.5 mg/day); (III) placebo	2 weeks	Self-reported pain score, BPI-SF, EORTC QLQ-C30; Self-recorded background medication and breakthrough analgesics	No significant change in mean pain score from baseline for THC spray compared to placebo; statistically significant change in favour of nabiximols treatment compared to placebo ($P=0.024$); patients taking nabiximols required significantly fewer doses of breakthrough pain medications when compared to placebo ($P=0.004$)
Portenoy *et al.* (16)	2012	RCT	263 advanced cancer patients	(I) Low dose nabiximols (1–4 sprays/day, or 2.7–10.8 mg THC, 2.5–10.0 mg CBD); (II) medium dose nabiximols (6–10 sprays/day, or 10.8–16.2 mg THC, 10.0–15 mg CBD); (III) high dose nabiximols (11–16 sprays/day, or 29.7–43.2 mg THC, 27.5–40 mg CBD); (IV) Placebo	5 weeks	Self-reported pain, sleep disruption, BPI-SF, EORTC QLQ-C30, MADRS; self-recorded medications for breakthrough pain	Compared to placebo, low and medium dose nabiximols were significantly more effective for reducing average daily pain when comparing scores from baseline to the end of the study period (low dose $P=0.008$, medium dose $P=0.038$); insignificant for high dose
Lynch *et al.* (17)	2014	RCT	18 cancer patients with chronic neuropathic pain after taxol-based chemotherapy	(I) Nabiximols: ceiling dose of 12 sprays/day, or 32.4 mg THC, 30 mg CBD); (II) placebo	4 weeks	Self-reported NRS-PI pain scale, SF-36, adverse events; QST	No statistically significant difference between placebo and nabiximols treatment groups

BPI-SF, Brief Pain Inventory-Short Form; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Version 3.0; MADRS, Montgomery-Åsberg Depression Rating Scale; NRS-PI, Numerical Rating Score-Pain Intensity; SF-36, 36-Item Short Form Health Survey; QST, quantitative sensory testing; RCT, randomized controlled trial; THC, tetrahydrocannabinol; CBD, cannabidiol.

In the three studies on nabiximols included in this review, self-titration was recommended up to a maximum dose of 8 sprays/3-hour period (15), and 11–16 sprays/day (16,17). In one of the studies, patients were divided into three dose groups categorized by titration ranges of mild (1–4 sprays/day, or 2.7–10.8 mg THC, 2.5–10.0 mg CBD), moderate (6–10 sprays/day, or 10.8–16.2 mg THC, 10.0–15 mg CBD), and high (11–16 sprays/day, or 29.7–43.2 mg THC, 27.5–40 mg CBD) (16). The doses found to produce significant pain relief include an average of 8.75 sprays/day (15), 1–4 sprays/day (16), and 6–10 sprays/day (16). It was observed that the high dose group of patients who utilised 11–16 sprays/day did not experience significant pain relief compared to placebo. Similarly, Lynch *et al.* found that at a high dose of an average of 8 sprays/day there was no significant pain relief observed in comparison to placebo (17).

Side effects and adverse events

Side effects reported in studies included in this review were consistent with those reported in literature investigating the use of cannabinoid-based therapies for several other indications (7). *Table 2* summarises the five most commonly reported side effects of the five studies. In both studies by Noyes *et al.*, side effects of 15 and 20 mg of THC included mental clouding (60–70%), drowsiness (70–100%), and euphoria (40–50%) (13,14). Not all side effects were experienced by all patients, and side effects tended to become more prevalent with higher doses.

Common treatment-related adverse events reported by Johnson *et al.* include somnolence (nabiximols 13%, THC 14%, placebo 10%), dizziness (nabiximols 12%, THC 12%, placebo 5%), confusion (nabiximols 7%, THC 2%, placebo 2%), nausea (nabiximols 10%, THC 7%, placebo 7%), and hypotension (nabiximols 5%, THC 0%, placebo 0%) (15). These were reportedly more frequent in patients receiving the nabiximols extract and the THC only extract, when compared with placebo. The adverse events identified by Portenoy *et al.* were significantly more frequent in the higher nabiximols dose group, whereas little difference was observed between the low dose and placebo groups (17). Lynch *et al.* identified fatigue (nabiximols n=7, placebo n=0), dry mouth (nabiximols n=5, placebo n=1), dizziness (nabiximols n=6, placebo n=0), and nausea (nabiximols n=6, placebo n=1) to be the most common side effects, which were more often observed in the treatment arm compared to placebo, although the significance of this difference was not assessed. However, patients also reported that the majority of side effects were transient and mild, and could be reduced through adjusting treatment dose. Side effects did not lead to any study drop-outs (13-17).

Discussion

The paucity of clinical data available on medical cannabis for treatment of cancer pain is partly due its classification as a schedule I agent by the Controlled Substances Act in 1970, which restricted its investigation as a potential medical product (8). However, the few studies that were produced on the use of medical cannabis for cancer pain management have results that suggest it does possess therapeutic potential, and is at least worthy of further investigation.

There is a lack of dosing guidelines for the use of cannabinoid-based therapies in clinical practice. The ideal dosage would be one that provides effective pain management, but does not produce intolerable side effects. However, there are challenges in establishing this optimal dose in the advanced cancer patient population. One of these is inter-patient variability, in keeping with results from studies on narcotics and other prescription analgesics. As optimal doses were found to vary from patient to patient, physicians need to understand how to determine the correct dosage when prescribing to a new patient. In addition, advanced cancer patients are likely to present with complex symptomologies that make it difficult to accurately assess side effects derived from cannabis treatments, and are often taking multiple concurrent medications. That said, a number of these studies reported that observed side-effects tended not to be treatment-limiting, and could be controlled through dose titration, with pain relief in as little administration of 2.7–10.8 mg THC in combination with 2.5–10.0 mg CBD (17). This highlights the importance of establishing and validating a titration protocol that will allow researchers to identify effective and tolerated dosages in a safe and controlled manner.

Several studies presented in this review were underpowered due to small sample sizes, with three out of the five studies reviewed enrolling less than 50 patients. Therefore, the generalizability of the results may be limited, and future studies on medical cannabis are warranted to establish its efficacy and side effect profile in the cancer pain population. This includes additional efforts to identify the efficacies of specific cannabis compounds and their combinations, as well as ideal methods of administration through the assessment

Table 2 Summary of most common side effects

Most common side effects (reference), number of patients	Percentage of patients experiencing side effect in each treatment arm (%)				
Noyes *et al.* (13), n=10	THC (20 mg)	THC (15 mg)	THC (10 mg)	THC (5 mg)	Placebo
Drowsiness	100	70	50	70	30
Slurred speech	80	80	40	40	20
Blurred vision	70	70	40	20	0
Mental clouding	60	70	40	50	20
Dizziness	60	40	40	20	10
Noyes *et al.* (14), n=34	THC (10 mg)	THC (20 mg)	Codeine (60 mg)	Codeine (120 mg)	Placebo
Dizziness	97	59	59	24	26
Sedation	94	71	50	47	29
Dry mouth	76	74	65	59	35
Blurred vision	65	41	24	12	9
Mental clouding	53	32	24	12	9
Johnson *et al.* (15), n=177	Nabiximols	THC	Placebo	–	–
Somnolence	13	14	10	–	–
Dizziness	12	12	5	–	–
Nausea	10	7	7	–	–
Vomiting	5	7	3	–	–
Confusion	7	2	2	–	–
Portenoy *et al.* (16) n=263	Nabiximols (all dose)	Placebo	–	–	–
Nausea	22	13	–	–	–
Dizziness	19	13	–	–	–
Neoplasm progression	18	14	–	–	–
Disorientation	17	1	–	–	–
Vomiting	16	8	–	–	–
Lynch *et al.* (17), n=18	Nabiximols	Placebo	–	–	–
Fatigue	39	0	–	–	–
Dry mouth	28	6	–	–	–
Dizziness	33	0	–	–	–
Nausea	33	6	–	–	–
Increased appetite	11	0	–	–	–

THC, tetrahydrocannabinol.

of relevant endpoints. Subsequent clinical trials should also consider the differences in cannabinoid pharmacokinetics and pharmacodynamics among individuals. Moreover, standardized and validated evaluation and reporting of cannabis-associated side effects is warranted in order to enable more accurate comparisons across studies.

Ultimately, this will contribute to the development of clinical guidelines for the dosing and administration of cannabis as a pain medication for the large population of cancer patients in need of pain management, particularly those for whom alternative analgesics are insufficient, intolerable, or unsafe.

Conclusions

Current research shows that there is a potential role for medical cannabis in cancer pain management. However, the scale and quality of studies conducted to date are somewhat limited (12). Therefore, further research is needed to establish the efficacy of medical cannabis, either as an alternative to opiates or as an adjunctive therapy, and to identify the most appropriate methods of administration to achieve optimal therapeutic efficacy with minimal side effects.

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Footnote

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