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The Effectiveness of Cannabis and Cannabis Derivatives in Treating Lower Back Pain in the Aged Population: A Systematic Review

Helen Senderovich[a] Hayley Wagman[b] Dennis Zhang[c] Danusha Vinoraj[d] Sarah Waicus[e]

[a]Department of Family and Community Medicine, Division of Palliative Care, University of Toronto, Geriatrics, Palliative Care, Pain Medicine, Baycrest, Toronto, ON, Canada; [b]Wilfred Laurier University, Waterloo, ON, Canada; [c]Department of Family Medicine, University of British Columbia, Victoria, BC, Canada; [d]Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [e]School of Medicine, Trinity College Dublin, Dublin, Ireland

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Abstract
Background/Aims: Cannabis is increasingly used in the management of pain, though minimal research exists to support its use since approval. Reduction in stigma has led to a growing interest in pharmaceutical cannabinoids as a possible treatment for lower back pain (LBP). The objective of this review was to assess the role and efficacy of cannabis and its derivatives in the management of LBP and compile global data related to the role of cannabis in the management of LBP in an aging population. ***Methods:*** A systematic review was conducted using predetermined keywords by 3 independent researchers. Predetermined inclusion and exclusion criteria were applied, and 23 articles were selected for further analysis. ***Results:*** Studies identified both significant and insignificant impacts of cannabis on LBP. Contradicting evidence was noted on the role of cannabis in the management of anxiety and insomnia, 2 common comorbidities with LBP. The existing literature suggests that cannabis may be used in the management of LBP and comorbid symptoms. ***Conclusions:*** Further research is needed to consider cannabis as an independent management option. There is a lack of evidence pertaining to the benefits of cannabis in an aged population, and thus, additional research is warranted to support its use in the aged population.

Background

Lower back pain (LBP) is a leading cause of disability globally, with damaging economic implications [1]. The 2010 Global Burden of Disease Study defined LBP as pain between the regions of the 12th rib and lower gluteal folds [2]. There is a positive association between LBP and an aging population. The aged population is defined as individuals between 65 and 79 years of age. LBP was ranked the highest of 291 conditions ranked regarding disability in the global burden of disease, surpassing the previous ranking completed <10 years prior [2]. In 1990, the USA estimated the economic burden of back pain as over 24 billion dollars, 3.2% of health-care costs [3]. Insomnia and anxiety are common comorbidities, reducing the quality of life and exacerbating the severity of LBP [4, 5]. Acute LBP is defined as 6–12 weeks of often nonspecific pain that spreads down one or both legs [6]. Persistent pain for a period of at least 3 months is termed chronic LBP [6]. In patients with dementia, this pain can be as-

karger@karger.com
www.karger.com/ger

Correspondence to:
Helen Senderovich, hsenderovich@baycrest.org

sociated with increased agitation and behavioral symptoms [7]. LBP can be categorized as organic or mechanical pain. Organic pain is caused by disease, while mechanical pain results from damage to the spinal joints, discs, vertebrae, or soft tissues [8]. Over 90% of LBP is mechanical [9]. Neuropathy arises from injury to nerve roots and is present in up to 55% of patients with chronic LBP [10, 11]. Given the prevalence of LBP among the aged, exploration of the evidence surrounding alternative treatment options, such as cannabis, to minimize potential side effects imposed by conventional treatment plans is warranted. Moreover, it may support holistic management for the aged population.

Pharmaceutical Formulations of Cannabis

Marijuana has commonly been used to alleviate chronic pain. Routes of administration include oral, inhalation, sublingual, topical, or intravenous [12]. Medical marijuana is synthetically modified cannabis used for symptom management. Cannabis is a general term referring to the products derived from the plant genus *Cannabis* [13]. The active ingredients in plant-based cannabis, termed cannabinoids, are tetrahydrocannabinol (THC) the psychoactive component and cannabidiol (CBD). Cannabinoids are widely used in pain relief and may be synthetically modified for use [14]. Dronabinol is a synthetic form of THC with the same psychoactive and pain modulation properties as the plant counterpart [15]. Pharmaceutical cannabinoids include dronabinol (brand names Marinol© and Syndros©); nabilone (a synthetic THC derivative with the brand name Cesamet©); and nabiximols (oral spray containing THC and CBD also known as brand names Cesamet© and Epidiolex©) [16]. Globally, most cannabis-based pharmaceuticals are not approved for medical use. Nabilone, Epidiolex, and dronabinol are used in Canada and the USA, while nabiximols are used in Canada, New Zealand, and Europe. Marinol© was recently withdrawn from the Canadian market by the manufacturer for unknown causes [17]. Cannabis also exists as oil and may be used in baked goods resulting in slower THC absorption, a delayed onset and a prolonged period of intoxication compared to inhalation [18]. The utilization of CBD in conditions such as epilepsy, multiple sclerosis (MS), Huntington's disease, and more, is currently being evaluated.

Marinol© has been approved in the USA since 1985 for appetite stimulation in patients with HIV/AIDS and chemotherapy-associated nausea. Oral dronabinol exhibited little benefit in the treatment of chronic pain and failed to show much promise in the management of neurogenic pain in patients with MS [19]. With a bioavailability of 10–35%, inhaled THC has a peak plasma concentration between 3 and 10 min. However, due to hepatic first-pass metabolism, the bioavailability of THC was 6% with oromucosal administration. Peak blood concentrations were found to occur 1–5 h post-dose, with a slow and unpredictable onset [20]. Nabilone (Cesamet©), a synthetic THC analog has been shown to exhibit analgesic effects in neuropathic pain. The beneficial properties of nabilone may be attributed to its prolonged half-life and increased potency. Another synthetic THC analog, ajulemic acid (CT3, IP-751), has also shown improvement in neuropathic pain [20]. Cannador (IKF-Berlin), an orally administered pill composed of cannabis extract, has been shown to improve spasm-associated pain among patients with MS [20]. In terms of LBP treatment, management of spasm-related pain is commonly encountered in occupational injuries among laborers. Cannador may serve as an alternative treatment option for patients facing daily NSAID and salicylate consumption. Finally, Sativex, an oromucosal spray, is a combined THC:CBD formulation that acts as a CB1 partial agonist. Sativex was approved by Health Canada in June 2005 and August 2007 for neuropathic pain in MS and cancer pain unresponsive to opioids [20].

Mechanisms of Action

The human body contains 2 G-protein coupled receptors, CB1 and CB2. Binding of these G-protein-coupled receptors blocks the release of pain-inducing neurotransmitters in the central nervous system (CNS) [21]. The CB1 receptor is located in central and peripheral neurons, affecting cognition, memory, control of motor functions, and analgesia. The CB2 receptor is mainly found in immune cells, altering cytokine release and cell migration in the central and peripheral nervous systems. THC is the main bioactive ingredient in cannabis. THC binds CB1 and CB2 receptors with equal affinity mimicking the effects of endogenous cannabinoids [22, 23]. Binding these 2 receptors may attenuate neuropathic pain [24]. CB2 activation is shown to suppress acute, chronic, and neuropathic pain by stimulating the release of β-endorphin from peripheral keratinocytes [25, 26]. Endogenous endorphins subsequently act on afferent nociceptors to inhibit pain transmission. In LBP, signals from nociceptors are sent to the spinal dorsal horn and ultimately sent through ascending pathways toward somatosensory cor-

Table 1. Side effects of cannabis

Psychiatric	Neurological	Gastrointestinal	Cardiovascular	Pulmonary
Anxiety	Memory deficits	Xerostomia	Hypertension	Chronic bronchitis
Panic attacks	Learning deficits	Weight changes	Tachycardia	
Agitation	Vertigo	Appetite changes	Vascular constriction	
Palpitations	Drowsiness	Diarrhea		
PTSD	Catecholamine release	Cannabis hyperemesis syndrome		
	Ataxia			
	Cognitive impairment			

PTSD, post-traumatic stress disorder.

tices in the brain [25, 26]. CBD does not act directly on either CB1 or CB2 receptors, instead encouraging the body to make use of its own cannabinoids [24]. CBD enhances the activity of 5HT1a receptors to mediate anxiolytic and depressive symptoms. Additionally, CBD binds to inhibitory glycine a1 and a3 receptors attenuating excitatory neuronal pathways in the CNS [23]. Finally, recent studies suggest the involvement of CBD and inhibition of the adenosine receptor A2A, reducing adenosine transport [20]. The inhibition of adenosine, a well-known participant in pain and inflammatory pathways, may be another mechanism of analgesia.

THC and CBD demonstrate potential for the treatment of LBP. The neurotransmitter and cytokine inhibitory actions of THC, with the serotonergic and neuroexcitatory inhibiting properties of CBD, provide a new, plausible, means for pain management. Though THC and CBD exert separate analgesic effects, they are commonly administered together. THC inhibits PGE-2 synthesis, platelet aggregation, and stimulation of lipoxygenase, attenuating pain [19]. A major difference between THC and CBD is the psychotic-like symptoms that can be produced at high THC levels [27]. CBD is often used in conjunction with THC as hepatic first-pass metabolism of THC to 11-hydroxy-THC, the more psychoactive form, is inhibited [28]. As a result, CBD may act as a moderator of negative psychotic effects induced by THC.

Side Effects of Cannabis

A systematic review found cannabis to worsen psychiatric disorders and be positively correlated with anxiety, panic attacks, and cognitive impairments (memory and learning deficits) among patients being treated for noncancerous pain [29, 30]. Vertigo, drowsiness, ataxia, and an increase in violent outbursts were reported in patients with post-traumatic stress disorder [31, 32]. Sensations of euphoria and perceptual distortion were side effects in patients with chronic pain and anxiety [33]. Changes in weight and appetite were also noted [34]. Less commonly, long-term cannabis use may lead to cannabis hyperemesis syndrome: cyclical vomiting, abdominal pain, and dehydration [35]. Dried cannabis can cause hypertension, tachycardia, catecholamine release, and vascular constriction [33]. There have been occasional reports of adverse cardiovascular events; however, healthy individuals have minimal risk compared to older individuals with a history of similar complications [21, 36, 37]. Smoking cannabis, a possible risk factor for lung cancer, can lead to chronic bronchitis [33, 38]. However, CBD suppresses cancer growth, kills cancer cells, and prevents cancerous cells from invading tissues and spreading in the body; however, there is a paucity of safe and effective clinical trials assessing potential risk and benefits [33, 39, 38]. A patient-reported study focused on aged patients (patients older than 65 years) found that dizziness was one of the most common adverse effects of cannabis use [40]. Cognitive impairment and agitation has also been associated in aged individuals, especially with neurodegenerative comorbidities such as dementia [7]. This is particularly concerning in a frail population where dizziness may potentiate falls.

Many chronic pain investigations have shown nonsignificant reductions in pain intensity, particularly in patients with nonneuropathic pain [12]. Cardiovascular events were recorded after cannabis use in young people, and high doses noted to precipitate myocardial infarction [41]. However, there is little evidence to support the relationship between cannabis and myocardial infarctions in the absence of pre-existing cardiac disease. Cannabis use has been correlated with anxiety, panic attacks, worsening of existing psychiatric disorders, and insom-

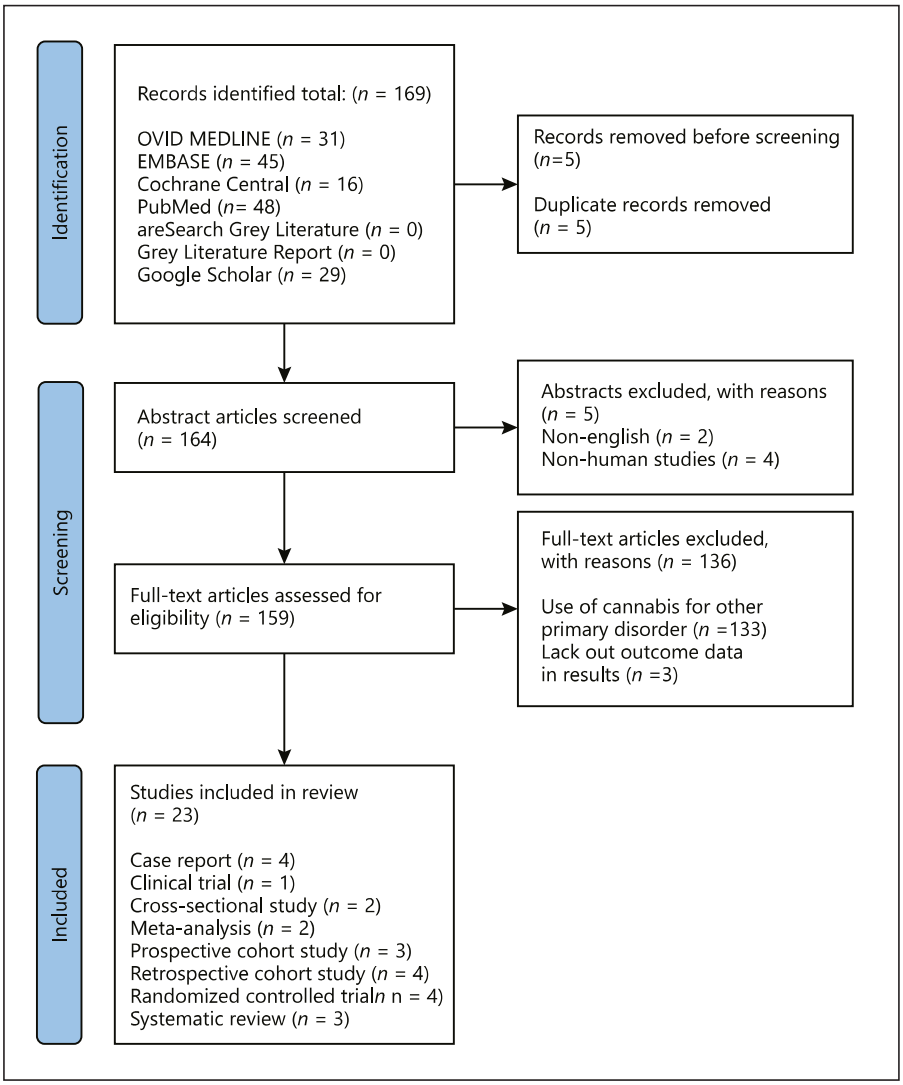

Fig. 1. PRISMA flow diagram: search history. RCT, randomized controlled trial.

nia, all of which commonly coexist in patients with LBP [29]. Acute effects of cannabis include cognitive impairment and neurocognitive deficits in learning and memory [31]. Euphoria and perceptual distortions were also noted [42]. While evidence exists supporting the use of pure CBD, and not THC, in the treatment of anxiety associated with chronic pain, there is ongoing controversy [32]. The risk of cognitive impairment is greater when THC enters the CNS rapidly in high concentrations as observed when this derivative is smoked or vaporized. Moreover, there is currently no evidence to support the use of dried cannabis for pain treatment and should only be considered in patients suffering from neuropathic pain and nonresponsive to standard treatment modalities [43]. Side effects of cannabis and its derivatives are summarized in Table 1.

Objectives

This systematic review aimed to provide a comprehensive understanding of the current landscape of cannabis, its role in LBP management, and explore the following:

1. The role of cannabis in LBP management in aged populations
2. The difference in structure, mechanism of action, and efficacy of THC and CBD
3. The impact of existent routes of administration on the effectiveness of cannabis
4. The outcomes of cannabis utilization and its side-effects while managing LBP

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Table 2. Literature search on the role of cannabis and cannabis derivatives in pain management

Study	Study design	Population	Targeted symptom	Form of cannabis	Dosage	Type of pain	Author's conclusions
Deshpande et al. [30]	Systematic review	5 RCTs (total subjects: 504)	Cancer pain	THC, nabiximol	Various	Neuropathic	Low-dose medical marijuana showed potential in refractory neuropathic pain in conjunction with traditional analgesics. However, generalizability is cautioned due to a lack of high-quality evidence.
Walitt et al. [58]	Systematic review	2 RCTs (72 subjects)	FMS pain (including LBP)	Nabilone	1 mg/day	Mixed	No high-quality evidence suggesting that nabilone has value treating people with FMS. The tolerability of nabilone was low in people with FMS.
Mücke et al. [46]	Systematic review	16 RCTs studies (1,750 subjects)	Neuropathic pain in adults	Oromucosal spray of THC, CBD, nabilone, herbal cannabis, and dronabinol	Variable	Neuropathic	The potential benefits of CBM (herbal cannabis, plant-derived, or synthetic THC, THC/CBD, and oromucosal spray) in chronic neuropathic pain may be outweighed by negative SEs.
Shmagel et al. [39]	Cross-sectional study	Adults with back pain (5,103 subjects)	Chronic LBP in adults aged 20–69	Recreational and medical marijuana	Variable	Chronic LBP	Forty-six percent of adults with chronic LBP have used marijuana (undifferentiated between medical from recreational use) report pain relief
Bruce et al. [72]	Cross-sectional study	30 subjects	Chronic pain	Medical cannabis	Mixed	Mixed	MCT appeared to serve as both a complementary method for symptom management and treatment of medication SEs associated with chronic conditions. Recommended medical cannabis as an alternative method for the treatment of pain.
Hoggart et al. [66]	RCT	380 subjects	Peripheral neuropathic pain	THC/CBD spray	Various – mean doses ranged from 8.9 sprays per day to 14.2 sprays per day	Neuropathic	THC/CBD spray had beneficial properties for the majority of patients with PNP associated with diabetes or allodynia.
Issa et al. [75]	RCT	30 subjects	Chronic noncancer pain	Dronabinol	10–20 mg	Mixed	Oral dronabinol has similar psychoactive effects to smoking marijuana.
Turcotte et al. [76]	RCT	15 subjects	Neuropathic pain	Nabilone	2 mg/day	Neuropathic	Nabilone showed effective, well-tolerated combination for MS-induced neuropathic pain.
Lynch et al. [77]	RCT	16 subjects	Neuropathic pain due to chemotherapy	Nabiximol	Variable, average 800 μL/day (THC: 21.6 mg CBD: 20 mg)	Neuropathic	An average decrease of 2.6 points on an 11-point pain scale compared to 0.6 points in the placebo group. Nabiximol has potential for treating neuropathic pain.
Bestard and Toth [71]	Clinical trial	220 subjects	Neuropathic pain	Nabilone	Mixed	Neuropathic	Monotherapy or adjuvant therapy with nabilone appeared comparable to gabapentin for management of neuropathic pain.
Andreae et al. [45]	Meta-analysis	5 RCTs (total subjects: 184)	Adults with HIV and non-HIV neuropathic pain	Smoked herbal cannabis THC	2.5–96 mg THC/day	Neuropathic	Inhaled cannabis provided short-term relief for 1 in 6 patients with neuropathic pain

Table 2 (continued)

Study	Study design	Population	Targeted symptom	Form of cannabis	Dosage	Type of pain	Author's conclusions
Busse et al. [63]	Meta-analysis	96 RCTs (total subjects: 26,169)	Chronic noncancer pain	Nabilone	Nonspecific	Mixed (non-cancer pain)	Comparison of opioids with nabilone suggested that the benefit for pain and functioning may be similar, based on low to moderate quality evidence
Ware et al. [62]	Prospective cohort study	431 subjects (215 cases and 216 controls)	Chronic noncancer pain	Herbal cannabis (THC)	12.5 mg THC±1.5%	Mixed (non-cancer pain)	Herbal cannabis exhibited a reasonable safety profile with patient use of 1 year. There was no difference in risk of serious adverse events (adjusted incidence rate ratio = 1.08, 95% confidence interval = 0.57–2.04) between control and THC groups.
Capano et al. [70]	Prospective cohort study	97 subjects	Chronic pain patients	CBD and THC-rich soft gels	2 soft gel/day (CBD: 15.7 mg THC: 0.5 mg)	Mixed	CBD could significantly ($p < 0.05$) reduce opioid use and improve chronic pain and sleep quality among patients who are currently using opioids for pain management.
Eisenberg et al. [74]	Prospective cohort	8 subjects	Chronic neuropathic pain	Syqe inhaler device THC	15.1 mg single dose	Neuropathic	A significant reduction in pain intensity was noted 20 min post inhalation ($p = 0.001$) back to baseline in 90 min while using Syqe inhaler devices as a smokeless delivery system of medicinal cannabis. Low variation in THC pharmacokinetic profile of maximum serum concentration was noted.
Hickernell et al. [67]	Retrospective study	81 subjects	Postsurgical pain	Dronabinol	10 mg	Nociceptive	Dronabinol group consumed less opioid morphine equivalents; however, it did not reach statistical significance. No SEs of dronabinol were reported. Future research into the role that dronabinol has on post-arthroplasty patients is recommended.
Liu et al. [69]	Retrospective study	310 subjects	Postsurgical pain	Nonspecific cannabinoid	Nonspecific	Nociceptive	Cannabinoid use was associated with higher pain scores and a poorer quality of sleep in the early postoperative period in patients undergoing major orthopedic surgery.
Cameron et al. [73]	Retrospective study	104 subjects	Insomnia, nightmares, chronic pain, and harm reduction	Nabilone	4 mg/day	Mixed	Nabilone improved nightmares and insomnia and has potential to be a safe, effective treatment for concurrent disorders in seriously mentally ill correctional populations on top of chronic physical pain.
Wendelmuth et al. [54]	Retrospective study	93 geriatric patients	Palliative and nonpalliative pain	Dronabinol	1.4–12.5 mg THC/day	Mixed (palliative and nonpalliative pain)	52.5% geriatric patients achieved pain relief. Dronabinol is suggested to be an effective, low-risk treatment option to be considered early in therapy.
Cuñetti et al. [64]	Case report	7 subjects	Chronic pain post-transplant	CBD	100 mg/day	Mixed chronic	CBD was well-tolerated with no severe SEs. Results in pain control were optimal in 2 patients, 4 had a partial response in the first 15 days, and in one, there was no change. Longer follow-up studies are recommended

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Table 2 (continued)

Study	Study design	Population	Targeted symptom	Form of cannabis	Dosage	Type of pain	Author's conclusions
Russo et al. [65]	Case report	20 subjects (10 with neuropathic pain)	Pain in MS	Nabiximol (Sativex)	800 μL/day (THC: 21.6 mg CBD: 20 mg)	Neuropathic	One month of drug administration in MS patients with neuropathic pain successfully reduced pain rating and improved quality of life. Sativex may be effective in improving MS-related neuropathic pain in the short-term.
Maida and Corban [68]	Case report	3 cases	Wound related pain	Topical cannabinoid cream	1 mL BID	Nociceptive	Clinically significant analgesia associated with reduced opioid utilization occurred in all cases. Topical cannabinoids have the potential to improve pain management in patients with wound pain.
Yeung et al. [78]	Case report	1 subject	Geriatric patient with chronic LBP	CBD baked taken orally	10–20 mg/day	Chronic LBP	Patient reported pain relief from taking an oral CBD food product. Pain dropped from 10 to 2 after 3 years of treatment based on 10 units pain scale.

AE, adverse event; CBM, cannabis-based medicine; CI, confidence interval; FMS, fibromyalgia syndrome; MS, multiple sclerosis; MCT, medicinal cannabis; QoL, quality of life; RCT, randomized controlled trial; RA, rheumatoid arthritis; VAS, Visual Analog Score; PNP, peripheral neuropathic pain; CBD, cannabidiol; THC, tetrahydrocannabinol; LBP, lower back pain.

Table 3. Results RCTs of cannabinoids in the treatment of pain syndromes

Study	Drug	Subject number, *n*	Indication	Trial duration	Results
Hoggart et al. [66]	THC/CBD spray	380 subjects	Peripheral neuropathic pain	38 weeks	The pain numerical rating scale showed a decrease in score over time in patients from a mean of 6.9 points (baseline in the parent studies) to a mean of 4.2 points (end of open-label follow-up). The proportion of patients who reported at least a clinically relevant 30% improvement in pain continued to increase with time (up to 9 months)
Issa et al. [75]	Dronabinol	30 subjects	Chronic noncancer pain	Unclear	The 10 and 20 mg dronabinol doses had significantly elevated pain relief scores over time on 4/5 subscales versus placebo ($p < 0.05$). Average daily morphine use, total pain relief (TOTPAR), age, sex, and baseline pain level were not significant covariates. ARCI peak effects at 2 h were similar to peak effects of smoked marijuana at 30 min ($p = 0.80$, 10 mg = low strength, 20 mg = high strength)
Turcotte et al. [76]	Nabilone	15 subjects	Neuropathic pain	9 weeks	There was a significant decrease in the visual analog pain scale ($p < 0.01$). The adjusted rate of decrease for both outcomes was statistically greater in nabilone versus placebo study group. Nabilone was well tolerated, with dizziness/drowsiness most frequently reported
Lynch et al. [77]	Nabiximol	16 subjects	Neuropathic pain	4 weeks	There was no statistically significant difference between the treatment and the placebo groups on the NRS-PI. A responder analysis demonstrated that there were 5 participants who reported a 2-point or greater reduction in pain that trended toward statistical significance with the number needed to treat equal 5

ARCI, addiction research center inventory; NRS-PI, pain intensity numeric rating scale; CBD, cannabidiol; THC, tetrahydrocannabinol; RCT, randomized controlled trial.

Methods

A systematic review was conducted by 3 independent researchers utilizing PubMed, OVID MEDLINE, Cochrane Central, and EMBASE. Additional non-peer-reviewed sources were searched, including Google Scholar, CareSearch Grey Literature, and Grey Literature Report. Eligibility assessment was performed by independent reviewers, and disagreements were resolved by consensus. A data extraction excel sheet was developed to compile and summarize relevant studies. Duplicates were removed before applying the inclusion and exclusion criteria. Inclusion criteria were established in line with the study objective, where relevant articles underwent data extraction and analysis.

Inclusion Criteria

Articles written in English language from January 2010 to September 2020, with an emphasis on the use of cannabis or its derivatives for the management of LBP, statistically significant human studies with ($p < 0.05$), and studies that explored chronic pain in older adults were included. The PICO tool was used to guide the keywords used in the search. All study designs were evaluated. The MeSH term *aged* is defined as "a person 65 years or older." A full search history can be found in Figure 1. The keywords used are as follows: "Low Back Pain," "THC," "CBD," "Cannabis," "Dronabinol," and "Cannabidiol" and "Aged."

Exclusion Criteria

Studies with nonhuman subjects, written in a language other than English, used cannabinoids for a primary purpose other than pain management, those reporting no outcomes, and duplicates between databases were excluded.

Search Results

Relevant articles underwent data extraction and analysis. A search yielded 169 references (31 in Medline, 45 in Embase, 16 in Cochrane Central, 48 in PubMed, 29 in Google Scholar, 0 in CareSearch Grey Literature, and 0 in Grey Literature Report) that matched predefined search parameters. Five articles were removed before abstract screening due to duplication. 164 article abstracts were screened, 2 were excluded as non-English, and 4 were excluded as nonhuman studies. There were 159 full-text articles assessed with 133 articles being excluded as cannabis treatment was being used for another primary disorder other than LBP, and 3 articles were excluded for a lack of reported outcome. There were 23 articles that met the final inclusion criteria, which included 3 case reports, 1 clinical trial, 2 cross-sectional study, 2 meta-analyses, 3 prospective cohort studies, 4 retrospective cohort studies, 4 randomized controlled trials (RCTs), and 3 systematic reviews found in Figure 1. Demographic (e.g., age range, sample size, and symptoms), cannabis treatment (form of cannabis, dosage, and duration), and the outcomes (pain relief and side effects) were extracted from reviewed studies. Pain reduction was the primary measure of efficacy in the studies. Corroborative themes were also identified and the authors responsible for the contributing research were cited and summarized in Tables 2 and 3. The Cochrane Risk of Bias Tool was used in reviewed studies to assess bias in RCTs found in Table 4.

Results

Supporting Evidence for Cannabis Use in LBP

Medical cannabis has been suggested to treat LBP acutely. A systematic review conducted by Deshpande et al. [30] found the majority of patients with neuropathic pain treated with medicinal cannabis had a clinically significant decrease in pain (>2 points on a 10-point scale). Another systematic review examined a different form of cannabis such as oromucosal sprays containing THC, CBD, nabilone, herbal cannabis, and dronabinol used to treat adults, including the aged population with neuropathic pain suggested that all cannabis-based medicines pooled together reduced pain intensity and improved sleep problems and psychological distress compared with placebo [44].

Three of the 4 RCTs reported beneficial properties of cannabis and cannabis derivatives on LBP. Hoggart et al. [45] examined 380 patients with peripheral neuropathic pain administering oromucosal THC/CBD mixed spray over 38 weeks. There were clinically relevant improvements of at least 30% throughout the 38-week study [45]. Mean doses ranged from 8.9 sprays to 14.2 sprays per day [45]. An RCT conducted by Issa et al. [46] examined 30 subjects with chronic noncancer pain administering 10 and 20 mg of dronabinol revealed a significant decrease in pain ($p < 0.05$) compared to placebo. Turcotte et al. [47] treated 15 patients with 2 mg/day of nabilone for neuropathic pain revealed that nabilone had a significant group and time interaction in decreasing pain, measured by the Visual Analog Scale (VAS) for pain ($p < 0.01$) when compared to placebo (Table 3).

A meta-analysis conducted by Busse et al. [48] examined the efficacy of opioids in comparison to different treat-

Table 4. Risk of bias in RCTs

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	random sequence generation	allocation concealment	blinding of participants and personnel	blinding of outcome assessor	incomplete outcome data	selective reporting
Hoggart et al. [66]	Low	High	High	High	High	Low
Issa et al. [75]	Low	Low	High	Low	Low	Low
Turcotte et al. [76]	Low	Low	Low	Low	Low	Low
Lynch et al. [77]	Low	Low	Low	Medium	Low	Low

RCT, randomized controlled trial.

ments such as nonsteroidal anti-inflammatory drugs and nabilone. They found evidence suggesting only minimal difference between opioids and nabilone efficacy for pain relief ($p = 0.77$) when measured using the VAS for pain [48].

Three prospective cohort studies examined different forms of cannabis found different levels of efficacy in relieving pain. Capano et al. [49] examined CBD- and THC-rich soft gels in 97 patients with chronic pain and found CBD could significantly ($p < 0.05$) reduce opioid use and improve chronic pain and sleep quality. Ware et al. [50] who examined the safety profile of herbal cannabis compared to controls who did not use cannabis for 431 patients with chronic pain and concluded that herbal cannabis had a reasonable safety profile and higher pain relief over a 1-year range. Eisenberg et al. [51] who examined THC use with an inhaler device in 8 patients with chronic neuropathic pain, revealed a significant reduction in pain intensity 20 min post-inhalation ($p = 0.001$) which was back to baseline in 90 min.

When examining geriatric populations exclusively, a retrospective study conducted by Wendelmuth et al. [52] specifically assessed palliative care populations with chronic pain treated with dronabinol and revealed that 52.5% of geriatric patients achieved pain relief over a range of 1.5–12.5 mg of THC per day. Additional comorbid mental health disorders were assessed by Cameron et al. [53] when nabilone was administered for chronic pain. It was found that 4 mg/day of nabilone in addition to relief of pain also improved nightmares, insomnia, and other mental health disorders [53].

Multiple forms and doses of cannabis were assessed in 4 different case reports revealed different benefits. Russo et al. [54] who examined chronic neuropathic pain in 20 patients (10 had neuropathic pain) with MS administering nabiximol, revealed that 1 month of 800 μL/day of nabiximol successfully reduced pain rating and improved the quality of life in all 10 subjects. Cuñetti et al. [55] who examined chronic post-transplant pain in 7 subjects who received 100 mg/day of CBD revealed that 6 out of 7 patients had a positive partial response in improvement of pain control [55]. Topical cream was assessed in 3 patients with nociceptive pain by Maida and Corban [56] who revealed clinically significant analgesia ($p < 0.05$) associated with 1 mL of topical cannabinoid cream, which reduced opioid utilization in all 3 patients. An alternative oral form where 10–20 mg of CBD baked into a food product was assessed in one 87-year-old geriatric patient with chronic LBP by Yeung et al. [57] who observed pain relief from 10/10 on a pain scale to 2/10 after 3 years of treatment consuming baked goods of CBD. These studies provide promising evidence that chronic pain among the aged may be treated with a combination of low-dose opioid and cannabis, if not entirely with cannabis.

In general, medical cannabis is reported to be the highest utilized substance for LBP for adults, including the aged population [39]. A cross-sectional study examined chronic LBP in 5,103 individuals and found that 46% of individuals had used recreational cannabis for pain management [39]. A more recent cross-sectional study conducted by Bruce et al. [58] examined the use of medical cannabis on chronic pain relief in adults including the aged population and revealed that medical cannabis was effective and complementary to pharmacological analgesics in pain management and treatment of side effects associated with chronic pain.

Opposing Evidence for Cannabis Use in LBP

When analyzing the effects of THC solely, the negative side effects were more prominent than those in CBD treatment. A systematic review examined nabilone treatment for fibromyalgia, including LBP, finding conflicting results [59]. This critical review suggested that studies superficially claimed that nabilone is a safe treatment. There was a high prevalence of adverse side effects such as dizziness, nausea, dry mouth, and drowsiness not solely related to cannabis but also to other existent comorbidities

in those affected with fibromyalgia. As a result, it was concluded that the efficacy of nabilone had no value in complex pain disorders [59]. The route of administration seemed to limit efficacy when cannabis was inhaled. A meta-analysis examined smoked herbal cannabis as a treatment for chronic neuropathic pain found only short-term relief for 1 in 6 patients in HIV and non-HIV patients [60].

Chronic pain induced surgically revealed conflicting results with regards to response to cannabis. A retrospective study conducted by Hickernell et al. [61] examined the efficacy of dronabinol in postsurgical nociceptive pain for 80 patients who received 10 mg of dronabinol revealed that there were fewer opioids needed for controlling the pain. However, this study did not reach statistical significance for the efficacy of dronabinol for pain relief compared to opioids. In contrary, Liu et al. [62] examined the response to cannabinoids of postsurgical pain revealed that cannabinoid use was associated with higher pain scores and a poorer quality of sleep in the early postoperative period in patients who underwent major lumbar orthopedic surgery.

Risk of Bias

The Cochrane Risk of Bias tool and the Jadad scales were used to assess risk of bias in included RCTs. This may have contributed to inaccuracies in the assessment of study quality. Pooled data from the 5 RCTs could not be statistically analyzed due to small sample sizes. Discrepancies between the study design and small sample sizes make it difficult to generate conclusions with certainty. The risk of bias can be seen in Table 4. With multiple forms and routes of administration for treatment of chronic pain with cannabinoids, there is concern around insufficient evidence as a result of inconsistency among studies reviewed and lack of a standardized approach to evaluate outcomes [63]. In general, preference for cannabis held by patients may exceed its clinical effectiveness.

Discussion

While our investigation provides some evidence on the effectiveness of cannabis and its derivative in the treatment of LBP and comorbid conditions, further research is required. Only 5 small RCTs (n = 214, 12, 17, 4, 2) reported data on the efficacy and safety of cannabinoids among patients older than 65 years, separately [64]. There appears to be greater benefit in the utilization of THC derivatives for the suppression of acute, chronic, and neuropathic pain in the management of malignant and nonmalignant pain, while CBD derivatives may be better suited for comorbid symptoms of anxiety and insomnia [45]. The negative psychoactive effects of THC has been documented in older adults, where agitation, dizziness, and fatigue are heightened, limiting the utilization of the THC for this group [57]. A lack of investigation into these benefits as they pertain to a geriatric population makes it difficult to conclude whether cannabis or its derivatives may benefit an aged population.

Compared to conventional treatments such as pharmacotherapy or physical therapy, a small analgesic benefit with the use of selective cannabinoids was seen in a review of current RCTs [65]. Cannabis extract is noted as a possible treatment in MS for the management of pain and muscle stiffness [66]. The findings are consistent with the current literature. An RCT of 30 patients aged 65 years who were treated with cannabis for LBP >6 months revealed a significant reduction in pain intensity and an improvement in the quality of life [40]. Cannabis may be trialed as adjunctive therapy for neuropathic pain, where there has been a failure of response to standard analgesic modalities (i.e., opioids, anticonvulsants, and antidepressants) [47]. Furthermore, a recent meta-analysis conducted by Velayudhan et al. [67] examined 6,217 patients aged 50 years and older on the safety and tolerability of cannabis and its derivatives. It was found that THC was associated with side effects and that THC and CBD combinations were less tolerable for patients older than 65 and 75 years; however, when results were pooled, it was generally concluded that cannabis-based medicines were safe to use in aged individuals [67].

Limitations

This review revealed a lack of available evidence on the role of cannabis and it's derivatives in older population. The outcomes described by some of the studies were not statistically significant. The reviewed trials were of short duration, and there was no standardized approach; variable dosages of cannabis and its derivatives were used, and it was noted a lack of appropriate reporting of outcome measures. Only a handful of identified studies exceeded 50 participants. These small sample sizes and short duration of treatment limited the statistical power of the reviewed studies and created difficulties with drawing the conclusions that could be generalized to the geriatric population. The lack of statistical significance and small sample size of some of the studies limit the ability to assess the true efficacy of cannabis in baked goods. Moreover, individuals older than 65 years were typically excluded from RCTs because the harm of

novel drugs normally outweighs the benefit. Thus, no studies exclusively explored the use of cannabis and its derivatives in the geriatric population. Additionally, some studies did not focus solely on LBP. Disorders such as fibromyalgia and MS were driving LBP in some studies. This limited the ability to compare the cause of LBP.

Future Directions

Future studies should focus on comparing cannabinoids to the existing gold standard pain reduction techniques in lieu of previously comparing to the placebo. Differences in analgesic effects among various administration methods of THC and CBD along with recommended ratios are currently unclear and remain a research priority. Studies focusing on the role of cannabis in pain and anxiety reduction are warranted as current evidence is contradictory. Further studies are required to determine the benefits of the combined use of opioids and/or other drugs with cannabinoids in the treatment and management of neuropathic pain [68]. Research evaluating the effects of cannabinoids solely in geriatric populations, given a complete absence of high-quality studies is needed.

Conclusion

This review examined the efficacy of numerous types of cannabis for the management of LBP in the aged population. In general, pain is a multifaceted and subjective phenomenon. It is often difficult to quantify with questionnaires. THC derivatives such as dronabinol and nabilone revealed more side effects due its psychoactive chemical properties. Treatments with higher levels of CBD such as CBD and nabiximol revealed fewer negative psychotic effects. Negative side effects of CBD and THC included dizziness, nausea, dry mouth, and poor sleep quality. Special consideration is needed in older adults due to polypharmacy, slower pharmacokinetic properties, and comorbid conditions. However, the benefits may outweigh the risks when cannabinoids and its derivatives are administered especially in PC palliative care, where the goals of care are comfort, symptoms control, and improvement in the quality of the remaining life. Cannabinoids may be an effective, low-risk treatment for patients with chronic pain. Anxiolytic effects of cannabinoids in the aged population are important as it can reduce the need for opioids and other pharmacological analgesics. Alternative routes in addition to traditional inhalation showed success which included oral derivatives of cannabinoids, such as baked goods, topical creams, soft gels, and oromucosal sprays. All forms of cannabinoids have shown considerable pain reduction for aged patients. It is important to have various routes of administration to achieve clinically significant pain reduction which can be useful in aged population and in palliative care settings. Cannabinoids and its derivatives may be utilized as an alternative or adjuvant for chronic pain in aged people, especially when standard analgesic modalities alone have failed.

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Statement of Ethics

The authors declare this research complies with the guidelines of the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Helen Senderovich was responsible for the conception, design, drafting, clinical revisions, and final approval of the version to be published. Helen Senderovich is accountable for all aspects of the published work. Hayley Wagman was responsible for drafting of the manuscript and interpretation of the data. Dennis Zhang was responsible for drafting of the manuscript and interpretation of the data. Danusha Vinoraj was responsible for drafting of the manuscript and interpretation of the data. Sarah Waicus was responsible for drafting of the manuscript, interpretation of the data, and critical revisions of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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