Drugs & Aging
https://doi.org/10.1007/s40266-018-0616-5

REVIEW ARTICLE

Medical Cannabis for Older Patients

Amir Minerbi[1,5] · **Winfried Häuser**[2,3] · **Mary-Ann Fitzcharles**[1,4,5]

Abstract

Interest in the medicinal use of cannabis and cannabinoids is mounting worldwide. Fueled by enthusiastic media coverage, patients perceive cannabinoids as a natural remedy for many symptoms. Cannabinoid use is of particular interest for older individuals who may experience symptoms such as chronic pain, sleep disturbance, cancer-related symptoms and mood disorders, all of which are often poorly controlled by current drug treatments that may also incur medication-induced side effects. This review provides a summary of the evidence for use of cannabinoids, and medical cannabis in particular, for this age group, with attention to efficacy and harms. Evidence of efficacy for relief of an array of symptoms is overall scanty, and almost all study participants are aged < 60 years. The risk of known and potential adverse effects is considerable, with concerns for cognitive, cardiovascular and gait and stability effects in older adults. Finally, in light of the paucity of clinical evidence and increasing patient requests for information or use, we propose a pragmatic clinical approach to a rational dialogue with older patients, highlighting the importance of individual benefit–risk assessment and shared patient–clinician decision making.

Key Points

Evidence for the efficacy of medical cannabis for the treatment of various symptoms, including pain, sleep disturbances, mood disorders and neurological symptoms, in older adults is scanty.

Older adults have an increased risk of side effects from cannabinoids because of their impaired metabolism, decreased reserves and the potential for drug–drug interactions and comorbidities.

Despite the lack of high-quality supporting evidence, medical cannabis may provide some benefits in selected older patients.

Any use of medical cannabis in older patients should be individualized and account for the unique characteristics of each patient, including the symptoms requiring treatment, symptom severity, comorbid conditions and possible adverse effects. Patients and families should participate in clinical decisions regarding medical cannabis only after an open and informative dialogue with the treating healthcare team.

✉ Mary-Ann Fitzcharles
mary-ann.fitzcharles@muhc.mcgill.ca

1 Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC, Canada

2 Department Internal Medicine I, Klinikum Saarbrücken, Saarbrücken, Germany

3 Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany

4 Division of Rheumatology, McGill University Health Centre, Montreal, QC, Canada

5 Montreal General Hospital, McGill University Health Centre, 1650 Cedar Ave, Montreal, QC H3G 1A4, Canada

Published online: 29 November 2018

1 Introduction

Cannabis generally refers to the plant product derived mostly from *Cannabis sativa,* with use defined by the individual as either recreational or medicinal. The potential of medical cannabis as a treatment for many symptoms has gained worldwide publicity in the past decade and has been promoted by advocacy and the media, but clinical evidence is lagging. Patients with various complaints are requesting information about medical cannabis or are currently using cannabis with or without medical directive [1, 2]. There is a prevalent belief that medical cannabis is an unexplored potential treatment option for many ailments that has been ignored for decades because of its long-standing illegal status and physician bias. In addition, many older adults feel a certain familiarity with cannabis, having used it recreationally since the hippie movement of the 1970s. In the context of increasing legalization and media promotion, it can be expected that medical cannabis use will increase. Results from a US nationally representative survey in 2014 confirmed this, reporting that 5% of individuals aged > 50 years had used cannabis in the past month: 53% for recreational use, 11% for medicinal use and 36% for combined use [3]. This prevalence rate for cannabis use in the preceding year further increased to 9% of participants aged ≥ 50 years and 2.9% for those aged ≥ 65 years for the National survey on Drug Use and Health in 2015 to 2016 [4].

1.1 Why May Older Patients Consider Using Medical Cannabis?

The purported treatment effects of medical cannabis pertinent to older adults include effects on pain and sleep difficulties, motor changes such as tremor or spasticity, and mood disturbance and agitation. Although medical cannabis is not approved by health regulators and has not been subject to the rigorous testing required for pharmaceutical products, older patients may consider using it for a number of reasons. First, many symptoms, especially in older patients, may not be adequately controlled by standard drug treatments, either because of suboptimal effects of pharmacotherapies or unacceptable adverse effects. Second, belief is common that, as cannabis is a plant product, it is natural and less harmful than medications. Furthermore, there exists a potential attraction for an oral product in the form of an oil formulation of cannabis obtained from the leaves and buds of the plant but containing various amounts of the active molecules. Cannabis may be confused with hemp seed oil preparations, which are obtained by pressing hemp seeds from a *Cannabis sativa* plant but contain mostly cannabidiol and negligible amounts of Δ^9-tetrahydrocannabinol (THC), the molecule with psychoactive effects. The safety of cannabidiol is further bolstered by reports of effects in children with intractable seizures [5]. This perception of medical cannabis as a "non-drug" may be even more appealing to older patients when offered as an "elixir" or liquid medication in oil form rather than a pharmaceutical pill. Third, older patients are often advised by well-meaning family members who suggest use in a caring and empathetic manner, especially for improved quality of life or symptom relief at the end of life. Finally, abuse, as has been seen with opioids, must be considered. Patients may be coerced into obtaining prescribed cannabis that is then accessed by someone else for recreational use or diversion.

2 The History of Medical Cannabis

Although having gained worldwide attention in the past decade, cannabis has been known as a medicinal product for thousands of years for rheumatism treatment, sleep promotion and effects on pain, inflammation and "spasms". Documentation of cannabis use began with writings from ancient China about 5000 years ago and from ancient Eurasia, Egypt and Greece. From the early nineteenth century, cannabis was promoted in the UK as an analgesic and antispasmodic, and—by the early twentieth century—was marketed over the counter in the USA as *Cannabis Americana* for effects on pain, sleep and paralysis agitans and as a cough mixture [6, 7]. The USA progressively regulated cannabis in various states, culminating in the Marijuana Tax Act of 1937, and completely banned it altogether with the Controlled Substance Act of 1970 [8]. Following multiple court appeals in both the USA and Canada, these two governments have progressively implemented policies for access to medical cannabis, beginning with California's Compassionate Use Act of 1996 [8]. In 2001, Health Canada passed the Marijuana for Medical Purposes Regulations, allowing for cannabis use for severe pain associated with various conditions and for treatment of seizures [9].

There followed a rapid acceptance of cannabis as a medicinal product by regulators, with current approval in 31 states in the USA as well numerous countries in South America, Europe, Israel and Australia [10]. Israel, Canada and the Netherlands have had almost two decades of experience of medical use, with prescriptions allowed for limited indications in Israel but more liberal access in Canada and the Netherlands [11, 12]. Cannabis is currently identified as one of the 50 fundamental herbs in traditional Chinese medicine, although it remains an illegal product in the Peoples Republic of China. Further impetus to global access is the progressive decriminalization of recreational cannabis

in many countries, with legalization in nine US states and Washington, D.C. (albeit remaining illegal at the federal level), Spain and Uruguay, and recent legalization in Canada. Legalization of a product leads to increased use, as has been seen historically for alcohol and cigarettes. Therefore, it can be anticipated that patients worldwide will have easier access to cannabis and may seek treatments through usual channels or choose to self-administer. Physicians must therefore be knowledgeable of the current evidence for medical cannabis as a therapy for all patients, including older individuals.

3 Physiology of the Endocannabinoid System

Knowledge of the endocannabinoid system is necessary to understand the proposed therapeutic effects of cannabinoids. As the science of cannabinoids has evolved progressively over the last half century, with many researchers contributing to the current understanding, this synopsis draws mostly on reviews in this area, rather than specifically quoting individual studies. In the early seminal studies in the 1960s, Professor Mechoulam et al. [13] isolated various cannabinoid molecules from hashish and subsequently synthesized these molecules. This system was named following the isolation of THC from the plant *C. sativa* and the observation that this molecule affected physiological signaling via receptors that were discovered in the mid-1980s [14]. This system has important functions in human physiology, is ubiquitous throughout the human body and has effects best understood for modulation of the nervous system but also impacts immune function, bone health, mood and appetite modulation, amongst others. The simplistic view is that the endocannabinoid system is the counterbalance to the acute stress response and restores the organism to equilibrium [15]. This complex interaction of molecules and ligands is not a simple on/off phenomenon and is affected by interaction between various ligands, cross reaction with non-cannabinoid receptors, and plasticity of response dependent upon local tissue characteristics or the presence of other molecules such as opioids [16]. Cloning of the cannabinoid receptor genes was soon followed by identification of endogenous ligands that could function as agonists for these receptors [15, 17, 18].

Cannabinoid receptors are found throughout the human body, with two receptors (CB_1 and CB_2) identified to date, and possible other receptors with cannabinoid off-target effects (i.e., GPR55 [19, 20]). The receptor functions are complex and involve negative coupling with adenylate cyclase via G-proteins, positive coupling to mitogen-activated protein (MAP) kinase, and regulation of calcium and potassium channels [21, 22]. Distribution of receptors is uneven, with CB_1 receptors mostly associated with neural tissue with pain-modulating effects, but also in brain areas sub-serving motor control, memory and cognition [23]. CB_2 receptors are found mostly peripherally on immunologic cells and musculoskeletal tissues, but their exact function requires clarification [24].

The endocannabinoid ligands, produced on demand by breakdown of cell membrane phospholipids, cascade in an alternative pathway to the inflammatory prostaglandin pathway [22]. Arachidonic acid, a shared progenitor of both endocannabinoids and prostaglandins, gives rise to two streams of molecules with opposing effects on inflammation and pain sensitization, among others. This leads logically to an explanation for the potential therapeutic effects for cannabinoids on physiological functions such as stress reduction, promotion of appetite and sleep, and modulation of pain and inflammation. Endocannabinoids share a short half-life period, and identified members of this class include anandamide, 2-arachidonylglycerol (2-AG), noladin, virodhamine and *N*-arachidonoyl dopamine [25].

Activity of endocannabinoids is regulated by catabolic enzymes; 2-AG is primarily degraded by monoacylglycerol lipase (MAGL) and anandamide by fatty acid amide hydrolase (FAAH) [26]. Therefore, it can be anticipated that the pharmacologic effects on catabolic enzymes can be considered as alternate therapeutic drug targets for manipulation of the endocannabinoid system.

Cannabinoids are metabolized in the liver via hepatic cytochrome P450 (CYP) enzymes with initial hydroxylation and conversion to glucuronides and biliary and intestinal tract excretion [27]. These lipophilic molecules can be deposited for a prolonged time in tissues. Cannabinoid tolerance is mediated via internalization or degradation of receptors, reduced receptor signaling or reduced receptor protein synthesis.

4 Therapeutic Cannabinoid Options

Beyond the physiological function of the endocannabinoid system, administered agents may impact this system [28]. Cannabinoids are available via two avenues: (1) herbal cannabis derived from the whole plant material, i.e., the buds, flowers and leaves, which contain many molecules, including non-cannabinoid molecules; (2) pharmaceutical preparations that are either plant derived or synthesized, with defined molecular concentrations and dosing information. The two most studied cannabinoid molecules are THC and cannabidiol. THC has mostly pain-relieving and psychoactive properties, whereas cannabidiol has additional tranquilizing and anxiolytic effects without psychoactive effects. Cannabidiol has limited affinity for cannabinoid receptors and acts mainly via the transient receptor potential vanilloid channel-1 (TRPV-1) and 5-HT_{1A} receptors [21]. Cannabidiol

enhances the signaling properties of adenosine and anandamide, has antioxidant effects, impacts immune functions, has less psychoactive properties and possibly reduces addiction [29].

4.1 Herbal Cannabis

Herbal cannabis derived from the plant *C. sativa* is the most well-known source of natural cannabinoids. Cannabis is a genus of flowering plant in the family of Cannabaceae, with the species *C. sativa* most commonly associated with medicinal use. *C. sativa* contains over 500 compounds, with over 100 cannabinoids, and with concentrations of various molecules dependent upon the strain of plant [30]. The leaves and flowers of the plant have the highest molecular concentration of THC and cannabidiol, with the concentration of THC varying from 3 to 30% and of cannabidiol from < 1 to 13% [31, 32]. Although these latter two molecules have received much attention for therapeutic effects, other molecules in the plant, including terpenes and phenolic compounds, may have physiologic affects that are largely unrecognized. There is also the intriguing concept of synergy and interaction of various bioactive molecules in the whole plant that may contribute to the therapeutic effect [33]. This hypothesized synergistic phenomenon, known as the "entourage effect," is currently only supported by anecdotal evidence [34]. These non-cannabinoid molecules may function to attenuate or augment the effects of THC or cannabidiol, alter the blood–brain barrier or even promote dermal absorption as for the terpene lipophilic compounds [33].

Medical cannabis may be inhaled by smoking or vaporizing, ingested as an oil, absorbed through mucous membranes or used topically [34, 35]. Unlike pharmaceutical preparations with defined molecular concentrations and dosing recommendations, no formal dose-finding studies for medical cannabis have been conducted, and current suggestions regarding the specific strain of *C. sativa,* optimal dosing and administration method are mostly derived from patient reports. Smoking is not recommended because of the toxic products of combustion, whereas vaporizing the dried product uses lower temperatures and is believed to be a safer administration method, as it prevents exposure to pyrolytic compounds of combustion [36].

4.2 Pharmaceutical Cannabinoid Preparations

Cannabinoids may be administered as a pharmaceutical preparation with specified molecular content, and some authors have suggested dosing recommendations [37]. Available products are mostly THC, either as a synthesized analog or as a pharmaceutical preparation from the plant product, which allows for defined amounts of drug that may be administered and tested in a controlled setting. Three pharmaceutical products are currently available, mostly in Europe and North America: dronabinol, a stereoisomer of THC; nabilone, a synthetic analogue of THC; and the oromucosal nabiximols spray, a combination of THC and cannabidiol. Cannabidiol-only formulations are also available (e.g. Epidiolex) [38]. However, in this rapidly evolving field, additional pharmaceutical preparations of cannabis are being developed worldwide and offered for use.

Pharmaceutical manipulation of the endocannabinoid system by other methods such as inhibition of enzymes that degrade endocannabinoids, namely FAAH and MAGL, may hold potential, especially in light of the limitations on the efficacy of exogenous cannabinoids [15, 39]. The endocannabinoid catabolic system is the focus of ample preclinical studies, but with caution in view of a catastrophic effect of a FAAH inhibitor in a phase I study [40–42]. Nevertheless, the failure of a specific trial should not be construed as an absolute failure for a class of compounds as there may yet be clinical successes for this approach in the future [42].

5 Pharmacokinetics and Pharmacodynamics of Cannabinoids

Evidence for the pharmacokinetics and pharmacodynamics of cannabinoids is limited, and available data are extrapolated from studies conducted in young healthy individuals, limiting their generalizability to older patients. Both THC and cannabidiol are highly lipophilic, resulting in low bioavailability. When inhaled, both molecules peak within a few minutes, with bioavailability in the order of 30% for both, and thereafter a rapid decline [36]. Pharmacokinetics following smoking and vaporization are comparable but can be erratic and influenced by rapidity of inhalation, duration of breath holding and other factors. The rapid rise in blood levels following inhalation may be an advantage for an immediate effect. Oral administration of the oil results in a more gradual and prolonged increase in serum level, with peak plasma concentrations of THC and cannabidiol reached within 120 min. Although the bioavailability of THC and cannabidiol is lower following oral administration because of first pass metabolism, this route likely provides a more controlled and longer lasting effect.

Metabolism of THC and cannabidiol is mainly hepatic, via cytochrome P450 isoenzymes. Metabolites are excreted in feces and urine, which could lead to half-life prolongation in patients with impaired kidney or liver function. This also raises the potential for drug–drug interactions via inhibition or induction of the cytochrome enzymes. Being highly lipophilic, THC and cannabidiol are characterized by high volumes of distribution, leading to a bi-phasic elimination curve, with a fast initial half-life and a long terminal half-life, with ranges of 24–31 h for cannabidiol and 22 h for

THC. Accumulation in adipose tissues with chronic use significantly prolongs the elimination half-life up to 2–5 days [36].

Only a few studies have explored the pharmacokinetic and pharmacodynamic effects of cannabinoids in older patients, all in the context of pharmaceutical preparations [43, 44]. Similar to other drugs, the pharmacokinetics of cannabinoids in older individuals is altered because of decreased hepatic and renal function, increasing the elimination half-lives of cannabidiol and THC, and because of the increased relative body fat, which increases the volume of distribution of lipid-soluble molecules [36, 45]. Data on pharmacodynamic interactions with other medications are lacking, but potential interactions with central nervous system depressants such as sedatives and hypnotics have been suggested, as well as interactions with cardiac stimulants, which may increase cardiac toxicity via hypertension and tachycardia.

6 The Evidence for Efficacy

Evidence for the efficacy of cannabinoids in older patients remains scanty. Even recent guidelines only mention use in older patients in a summary nature or even not at all [46–48]. The European Pain Federation position paper on cannabinoids in general for chronic pain cautioned that seniors may be more sensitive to the cannabis-related neuropsychiatric and postural hypotensive effects, leading to a recommendation of lower starting doses [46]. The quantity of evidence is larger for oral or buccal cannabis-based medicines (e.g., dronabinol, nabiximols) than for medical cannabis or for cannabis extracts, although randomized controlled trials (RCTs) failed to demonstrate a superiority of nabilone over placebo in pain relief [2]. The shortfalls of the herbal product are as follows: the THC and cannabidiol content varies in medical cannabis but is better defined in pharmaceutical preparations; the bioavailability of inhaled cannabis is more variable than for oral preparations; data are insufficient for the indication of different cannabis strains with differing THC and cannabidiol content; risk of misuse, especially diversion, is likely higher for inhaled cannabis strains with a high THC content than for oral cannabis-based medicines or for inhaled cannabis strains with a low THC content.

In a recent prospective study of older Israeli patients seen in a specialized medical cannabis clinic, 901 of the 2736 recruited participants were followed for 6 months [49]. Patients had a mean age of 75 ± 8 years, were treated for pain (67%) and cancer (61%) and had a reduction of median pain from 8/10 to 4/10 [49]. Adverse events were dizziness in 10% and dry mouth in 7%. Encouragingly, 18% of participants either discontinued opioid use or reduced the dose. The reported excellent results should be seen in the light of a number of observations: patients were seen in a designated medical cannabis clinic, raising the question of a placebo response; the study was funded by a commercial cannabis supplier; only 33% of the patients responded to the 6-month questionnaire, raising the possibility of selection bias (i.e., patients who persisted could be those experiencing fewer side effects and vice versa); a pain rating of 8/10 is extremely high for individuals with chronic pain, although cancer pain was common; almost one-fifth discontinued treatment during the 6 months of treatment; and there was no report of urine drug screening to validate adherence to treatment. Finally, a symptom of dizziness cannot be taken lightly in older adults, who are at risk of falls.

The paucity of information on cannabinoids in older patients is illustrated in a narrative systematic review that included five studies, with four studies comprising 2–19 patients and one study of chemotherapy-induced nausea and vomiting with 214 patients (mean age 47 years) [50]. Study duration was from 1 day to a maximum of 42, and active treatment was THC preparations (three studies) or combined THC and cannabidiol preparations (two studies). With a total of 17 patients studied with behavioral symptoms related to Alzheimer's disease, we challenge the authors' conclusion that cannabinoids might be useful for these symptoms. No effect was observed on dyskinesia related to Parkinson's disease (19 patients), breathlessness related to chronic obstructive pulmonary disease, or chemotherapy-induced nausea. Common side effects included sedation (36.9% in trials vs. 37.9% in observational studies), dizziness and somnolence.

6.1 Conditions Considered and the Evidence

The efficacy of cannabis in various medical diagnoses is a constant source of controversy. Thus far, published clinical studies of cannabinoids are fraught with shortcomings for many reasons. Patient populations are often heterogeneous (especially for studies of chronic pain), various pharmaceutical and herbal products are used, study duration is often short, outcome measures are inconsistent, and previous recreational use is frequent [51]. The average age of patients for all studies is between 40 and 60 years, and no study has performed subgroup analysis for older patients.

Even with these limitations, the clinician must interpret the evidence as best as possible and weigh the balance of efficacy and side effects rationally. Several extensive meta-analyses, reviews and guidance or position papers have been published in recent years, summarizing the available evidence for the efficacy and safety of cannabis and cannabinoids for various indications [46, 48, 51–53]. All reviews caution that there is a paucity of evidence for efficacy but an increased risk of harm. Generally, there is some limited evidence for an effect on pain and spasticity from multiple sclerosis and neuropathic pain, cancer-related pain, insomnia and anxiety.

Table 1 summarizes the level of evidence for the efficacy of medical cannabis in various indications.

6.2 Non-cancer Chronic Pain, Including Musculoskeletal and Neurological Pain

The evidence for the effect of cannabinoids for chronic pain is tenuous. In a systematic review examining cannabis for chronic pain, Nugent et al. [54] reported low-strength evidence for effect in neuropathic pain and insufficient evidence in other types of pain. A Cochrane systematic review of 16 RCTs for neuropathic pain, comprising 1750 subjects receiving either cannabis medications or herbal cannabis versus placebo or analgesics, found that cannabis-based medications increased the number of patients achieving ≥ 50% improvement in pain intensity from 17% (placebo) to 21% (cannabis medications), with a number needed to treat (NNT) of 20 for 30% improvement; cannabis medicines improved response from 33 to 39% (NNT 11) [55]. Adverse events were more common with cannabis-based medications, especially relating to the nervous system, reported for 61%, with a number needed to harm (NNH) of 3; psychiatric adverse events occurred in 17% (NNH 10). The level of evidence regarding herbal cannabis was deemed too low to draw conclusions on efficacy or tolerability. The authors concluded that "the potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD [cannabidiol] oromucosal spray) in chronic neuropathic pain might be outweighed by their potential harms." Another systematic review including 47 RCTs and 57 observational studies reported similar results [56]. The combined results indicated a small added effect on pain compared with placebo estimated at 3 mm on a 100-mm visual analog scale. The NNT for 30% improvement in pain intensity was 24, and the NNH was 6. Evidence on improved sleep and patient global impression of change was deemed low quality.

6.3 Cancer-Related Pain

Pain is a common symptom among patients with cancer and cancer survivors, affecting 30–90% of individuals, depending on the diagnosis and stage [57, 58]. Pain may result from the disease itself or from medical treatments (chemotherapy, radiotherapy or post-surgical pain) or could be unrelated to the disease. Cancer-related pain differs from chronic non-cancer pain in several aspects: it is often "mixed pain", i.e., pain of more than one etiology; it may be more amenable to pharmacological treatment than chronic non-cancer pain and is often accompanied by considerable psychosocial suffering [59]. Apart from the increased prevalence of malignancy with age, age-related changes in the nociceptive system render older individuals more vulnerable to developing chronic pain. Despite the notion that cannabinoids are often considered a therapeutic option for cancer-related pain, the evidence supporting this practice is surprisingly lacking. Two RCTs of pharmaceutical cannabinoids versus placebo (cannabidiol:THC or THC extracts) in 537 subjects with intractable cancer-related pain indicated a non-significant trend towards greater pain reduction in the treatment group [60, 61]. With the average age of participants 58 and 60 years, there were no sub-analyses for older adults. In conclusion, while evidence on the efficacy of cannabinoids for cancer-related pain is scanty, evidence of effect for this indication in older adults is absent.

6.4 Sleep Disturbance

Endocannabinoids are known to play a role in circadian regulation, and exogenous cannabinoids are known to have an impact on sleep in humans, with individuals often reporting using cannabis specifically for sleep problems. Despite this, not many studies have examined the effect of cannabis on sleep. In a review published in 2017, Babson et al. [62] reported that, whereas cannabidiol may have a therapeutic potential for the treatment of insomnia (possibly via its anxiolytic effect, see below), as well as rapid eye movement (REM) sleep behavior disorder and excessive daytime sleepiness, THC may impair sleep quality over the long term. When the effect on sleep was assessed for patients with chronic pain and multiple sclerosis, the evidence for improved sleep quality and reduced sleep disturbance was of low quality [53]. Discontinuation of cannabinoids that have been used regularly may lead to a withdrawal syndrome, including interrupted sleep [63].

Table 1 Possible indications for the use of cannabinoids in older individuals, and the level of evidence supporting their use

Level of available evidence	Indication
Low-quality evidence	Neuropathic pain [54–56]; insomnia [53]; anxiety [69]
Non-statistically significant trend toward efficacy	Cancer pain group [60, 61]; spasticity associated with neurological diseases [53, 64, 66]
No evidence of efficacy	Cancer-related anorexia, nausea and vomiting [71]; chronic non-cancer pain (other than neuropathic) [54–56]

6.5 Neurological Disease

A meta-analysis examining spasticity in patients with multiple sclerosis and spinal cord injuries found that cannabinoids showed a tendency towards efficacy but without reaching statistical significance [53]. There is an impression that patient-perceived spasticity but not physician-administered measures of spasticity may be improved by cannabinoids in patients with multiple sclerosis [64]. A similar conclusion was articulated in the 2014 American Academy of Neurology's guidelines on complementary and alternative medicine in multiple sclerosis as well as a systematic review of reviews [65, 66]. The American Academy of Neurology made a level A recommendation for oral cannabis extract as effective for short-term relief of spasticity-related symptoms and pain, and Nielsen et al. [66] concluded that cannabinoids may be effective for pain and spasticity. The effect of cannabinoids for relief of symptoms of Parkinson's disease was reported in a review of ten small clinical studies with a total of 181 patients (four RCTs, two open-label studies, two patient surveys, two case series), with suggestion that some motor symptoms of Parkinson's disease, particularly levodopa-induced dyskinesia, may respond to cannabis-based therapies [67]. However, results are conflicting, and reported effect sizes are often modest [67, 68].

6.6 Mood and Agitation

Cannabinoids are known for their psychoactive properties, with particular interest in the tranquilizing and anxiolytic effect of cannabidiol, especially pertinent for anxiety and agitation in older patients. Two recent reviews explored the evidence on the efficacy of cannabinoids for psychiatric disorders [68, 69]. Lim et al. [69] reported low-quality evidence for the effect of nabilone on anxiety, and cannabidiol was found to reduce social anxiety symptoms in two small-scale studies. Studies were assessed as having a high or unclear risk of bias [69]. Several small studies of THC preparations for agitation in patients with dementia have shown mixed results [69]. Posttraumatic stress disorder, a common condition in the population and especially in veterans, is challenging to treat, with considerable anecdotes of effects from medical cannabis. A recent review of five studies concluded that the data at this time are conflicting, with current evidence limited to case reports and observational studies [70].

6.7 Palliative Care and End-of-Life Care

Cannabinoids in various forms are often considered in the context of palliative care, where the potential improvement in quality of life is weighed against the risk of adverse effects. In a systematic review and meta-analysis, including nine studies and 1561 patients (patients with cancer or HIV), there was no clinically significant difference between cannabinoids and placebo in improving caloric intake or appetite or treating symptoms of pain, nausea and vomiting or sleep problems in patients with cancer in palliative care [71]. Nor were any significant differences seen in tolerability or safety of cannabinoids versus placebo treatments in patients with cancer.

6.8 A Combined Effect on Wellbeing

A small narrative qualitative study of 19 patients aged 28–79 years treated with medical cannabis for chronic pain suggested that patients perceived the effect of cannabis as a subjective sense of return to their normal self in terms of relaxation, pain relief, improved sleep and function [72]. The authors suggested the term "restored self" as a conceptual description of the effect of medical cannabis.

7 Cautions and Contraindications

Risks associated with the use of medical cannabis in older individuals can be anticipated to be similar to those seen in younger people but possibly more pronounced in view of slower drug metabolism, interaction with concomitant medication and associated comorbidities [46]. Areas of particular pertinence for older patients include effects on cognition and psychomotor function, cardiovascular risks, mental health and elder abuse. Table 2 summarizes the important adverse effects of cannabis pertinent to older individuals.

Table 2 Major adverse effects of cannabinoids pertinent to older patients

Domain	Adverse effects pertinent to older patients
Psychomotor	Impairment in gait and stability predisposes older patients to an increased risk of falls and injuries and impairs their driving skills [75, 77, 78]
Cognitive	Impairment in short-term memory and emotional processing, which may be particularly harmful in patients with pre-existing cognitive impairment [75]
Cardiovascular	Increased risk for myocardial infarction, sudden cardiac death, arrhythmia, stroke and transient ischemic attacks [79–82]
Mental health	Increased risk of psychotic episodes (arguably more pertinent to young patients) and suicidality [84–86, 88, 90]

7.1 Cognition and Psychomotor Function

The most prevalent adverse effects of medical cannabis, particularly related to THC content, relate to cognition and executive and psychomotor function. Other than for hemp oil, which almost entirely comprises cannabidiol, most herbal cannabis products contain at least some THC. THC impairs short-term memory and emotional processing in a manner that may be modulated by cannabidiol [73]. Synthetic cannabinoids have a similar negative effect on executive function [74]. It can be anticipated that adverse cognitive effects in older adults may be more prolonged than in younger individuals. While no studies have evaluated the clinical relevance of this effect in older individuals, and specifically in patients with mild cognitive impairment or mild dementia, it is reasonable to expect that patients with low cognitive reserves may be adversely affected.

Psychomotor effects may predispose older patients to falls and injury. Choi et al. [75] reported a significant increase in injuries necessitating emergency department visits among older people consuming cannabis. This may be especially important when a cannabinoid is used at night, with the risk of balance problems in a darkened environment. This effect may be further compounded by concomitant use of other drugs with psychoactive properties such as sleep-promoting agents. Many older adults view their independence as closely linked to driving. With psychomotor effects identified in young recreational cannabis users, with effects lasting as long as 5 h, risks to the patient and society must be acknowledged [76]. Cannabis is associated with a five times greater risk of having a motor vehicle accident and a two times greater risk of a fatal or serious accident [77, 78]. Orally administered medicines may also incur increased risks because of the delay in effect, which could prompt a patient to administer additional doses, resulting in more prolonged adverse effects.

7.2 Cardiovascular Risks

Cardiovascular events are reported with increasing frequency for younger recreational cannabis users, so it can be anticipated that older adults or those with risk factors for or established cardiovascular disease will be at even higher risk [79]. As cannabis increases heart rate, blood pressure and myocardial oxygen demand, use may aggravate stable angina or trigger myocardial infarction. Increasing numbers of case reports show an association between smoked cannabis and a spectrum of acute cardio- and cerebrovascular events such as acute myocardial infarction, sudden cardiac death, arrhythmia, stroke and transient ischemic attacks [80–82]. In a study of over 2 million patients admitted in the USA with acute myocardial infarction, recreational marijuana use was a significant risk factor for infarction when adjusted for demographic factors as well as smoking and other substance abuse (adjusted odds ratio [AOR] 1.031; 95% confidence interval [CI] 1.018–1.045) [83]. Therefore, unstable cardiac disease is a relative contraindication for use.

7.3 Mental Health

Mental health must always be considered in older patients, especially in those with preexisting mental illness. Current or past mental health disorder, especially substance abuse and dependence, and psychosis are relative contraindications for use. In a systematic review of 35 longitudinal population-based studies, Moore et al. [84] examined the evidence for cannabis use and psychotic or affective mental health outcomes although a causal relationship has not been established and a bias based on self-treatment has been suggested [85]. Cannabis increased the risk of any psychotic outcome (pooled AOR 1.41; 95% CI 1.20–1.65), with findings consistent with a dose–response effect (pooled AOR 2.09; 95% CI 1.54–2.84), but findings of outcomes related to depression, suicidal thoughts and anxiety were less consistent [84]. The risk of cannabis-related psychotic episodes is thought to be most pertinent in adolescents and young adults [86].

The risk of suicidality is another concern, particularly as the prevalence of suicidal ideation and attempts increases with age [87]. With limited studies available, the current evidence points to an increased rate of death by suicide (OR 2.56; 95% CI 1.25–5.27), increased suicide ideation (OR 1.43; 95% CI 1.13–1.83) and suicide attempt (OR 2.23; 95% CI 1.24–4.00), with heavy cannabis use increasing the risk of suicide attempt (OR 3.20; 95% CI 1.72–5.94) [88]. Older men with psychotic disorders who consumed cannabis were noted to have higher odds of attempted suicide in an Australian study of 1790 individuals with psychotic disorders [89]. Addiction, although a prevalent problem of herbal cannabis use, is less likely to be an important issue for older adults, although tolerance to the product and subsequent need for increased dose may occur.

7.4 Elder Abuse

Abuse and misuse of medications prescribed for older adults is prevalent in many settings and may be particularly pertinent to medical cannabis use. Although never specifically studied in older adults, the potential for diversion of medical cannabis is a risk, especially in jurisdictions where recreational cannabis is illegal or when medical cannabis is reimbursed. Diversion of medical cannabis has been reported to occur commonly for patients admitted for psychiatric reasons and holding a medical marijuana card in Colorado [90]. An older patient may be coerced into seeking a prescription for medical cannabis by someone with an agenda

for diversion. This will be especially true for settings where medical cannabis is reimbursed.

8 Pragmatic Suggestions for Medical Cannabis Use in Older Patients

Taking all factors into consideration, we offer a pragmatic and conservative approach based on the current available knowledge and our personal clinical experience of treating older patients with medicinal cannabis. We acknowledge that physicians and other healthcare professionals may be practicing in different geographic, cultural and socioeconomic settings, all having an influence on the prescribing practice of medical cannabis. Additionally, innate personal characteristics and biases may influence the prescriber, with some being more reliant on the "evidence" and others possibly more inclined to consider a therapy with lesser evidence. A global approach to both practice suggestions as well as the dialogue with patients and caregivers will therefore differ but must be attuned to the unique needs of the individual. As patients will be requesting advice from physicians regarding cannabis use, it is a medical obligation to provide accurate information and to counsel patients with empathy. Any patient encounter regarding medical cannabis must begin with a statement that the evidence for the effect of medical cannabis is overall limited, with even less evidence for effect in older adults. Additionally, the ideal strain of cannabis, molecular content of the plant, administration method or dose is unknown. Smoking the dried product is not recommended, whereas using a vaporizer is suggested to be safer. Ingestion of a measured amount of medical cannabis oil is likely the preferred method of administration, although dosing strategies are mostly suggested on the basis of patient report rather than formal study. When considering the use of medical cannabis in an older individual, we suggest addressing a number of conceptual considerations (summarized in Fig. 1).

In the first instance, it should be determined whether symptoms could potentially benefit from a treatment trial of medical cannabis (i.e., insomnia, neuropathic pain). The quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for chronic neuropathic pain. For all other conditions, the use of cannabis-based medicines should be regarded as an individual therapeutic trial. Review the medical records to discern whether other potentially effective treatment modalities have been explored, with consideration of pharmaceutical, physical, psychological and invasive treatment options. Prior to initiation of medical cannabis, clinicians should consider a trial of pharmaceutical cannabis-based medicines [46, 48]. However, we acknowledge that availability and reimbursement of cannabis-based medicines and medical cannabis differs between countries and that local availability and reimbursement may be an important determinant of treatment choice. Consider contraindications or cautions for medical cannabis use: (1) psychiatric comorbidities, excluding patients deemed at risk for psychosis and suicidal attempts; (2) cardiovascular disease, both established and those with risk factors; (3) cognitive impairment, with risk of aggravation; (4) frailty, polypharmacy and problems of gait and balance.

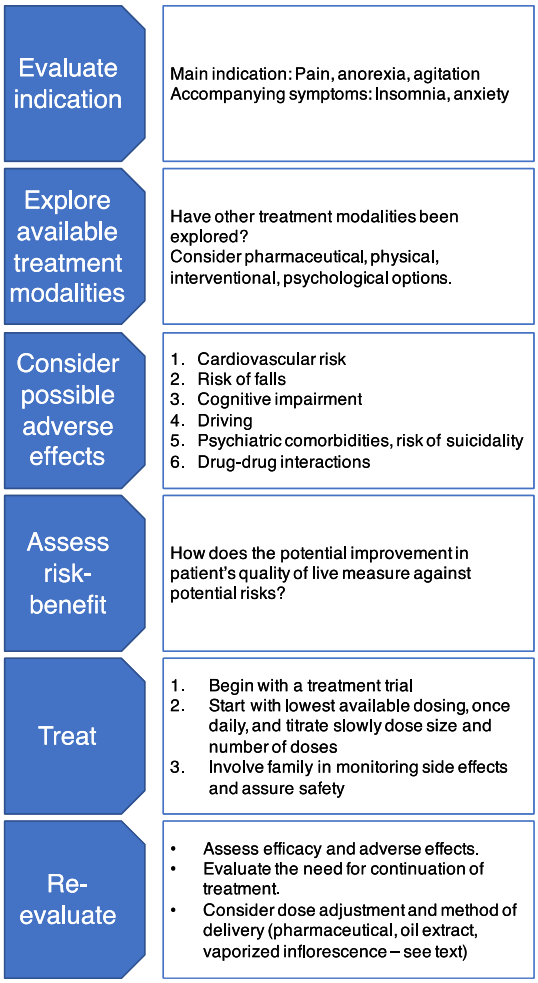

Fig. 1 A pragmatic approach to treating older patients with medical cannabis

We suggest having an open discussion of the advantages and disadvantages of medical cannabinoids with the patient, incorporating principles of shared decision making, raising possible cardiovascular and cognitive effects as well as potential effects on driving. Consider involving family members in the decision process and after the initiation of treatment, as they may be sensitive to subtle side effects of cognitive impairment and gait and balance disturbance. Patients can be directed to information brochures about medical cannabis (e.g., Dutch Office of medicinal Cannabis, 2011; Health Canada, 2016). Finally,

there should be clinical judgement of the benefit–risk profile pertinent to the individual patient characteristics, e.g., patients in a palliative care setting may be more willing to take more risks to improve quality of life than patients with longer life expectancies.

Therapy with cannabis-based medicines should only be considered by experienced clinicians as part of a multidisciplinary treatment and preferably as adjunctive medication if guideline-recommended first- and second-line therapies have not provided sufficient efficacy or tolerability. Monotherapy with cannabis-based medications should be avoided. Should the decision be taken to initiate treatment, an initial prescription of medical cannabis should be clearly defined as a treatment trial and with realistic outcome goals for therapy. Ideally, a pharmaceutical preparation should be the first choice, with the advantage of a measured dose and availability of full pharmacological documentation. Choice of currently available pharmaceutical cannabinoids is limited, not always indicated by regulatory authorities, and tend to be costly. Plant-derived preparations, while having the potential advantage of the entourage effect, are highly variable in composition and quality, and quantified cannabidiol/THC preparations are available only in some countries. The dosing and timing are best determined by the old adage "start low and go slow." If a plant-derived preparation is chosen, we suggest beginning with a strain with higher cannabidiol (10–20%) and lower THC (< 2%) content, because of the advantageous side effect profile, initially given once daily at night. Some practitioners suggest adjusting the concentration of cannabidiol and THC according to the individual patient symptoms, although this is mostly based on practice experience rather than rigorous study. Only after an individual side effect profile has been established should there be any upward titration.

Ideally, an oral oil preparation is preferred, in view of a more prolonged and stable pharmacokinetic profile. When breakthrough symptoms are of concern, inhaled doses may be considered. All patients must remain under close clinical surveillance, with a maximum testing period of 3 months. As with any other medical therapy, if the treatment fails to reach the predefined goals and/or the patient is additionally burdened by an unacceptable level of adverse effects and/or there are signs of abuse and misuse of the drug by the patient, therapy with cannabis-based medicines should be terminated. If the clinical effect is inadequate and side effects permit, an increase in dose and frequency of administration may be considered. In the event of inadequate response or unacceptable side effects, treatment must be discontinued. In selected cases, in which there is concern for diversion, prescription adherence may be verified with a urine drug screen, taking into consideration that the result may be positive for weeks following ingestion.

9 Reflections on Opioid Use

At this time, with widespread enthusiasm for medical cannabis, the medical community could look to other situations, namely opioid use, where a drug was embraced but with serious consequences to patients and society. Reflections on the history of opioid use for chronic pain could help inform treatment decisions regarding cannabinoids. Opioid prescriptions escalated in the latter part of the last century, but it took almost 30 years for the implications of opioid access to be recognized as gravely detrimental to society. In a recent systematic review of 23 RCTs of opioids for musculoskeletal pain in older patients, there was a small effect on decreasing pain intensity (standardized mean difference [SMD] −0.27; 95% CI −0.33 to −0.20) and improving function (SMD −0.27; 95% CI −0.36 to −0.18), but with a three times higher rate of adverse events (OR 2.94; 95% CI 2.33–3.72) and four times higher odds of treatment discontinuation due to adverse events (OR 4.04; 95% CI 3.10–5.25) in patients treated with opioid analgesics [91]. This led the authors to conclude that the small benefits due to opioid treatments may be outweighed by risks. The experience of opioid use and abuse can be used as a guide to inform the medical community and the public about potential concerns for medical cannabis, with obligation to critically monitor the effects of medical cannabis for both patients and society over the next few years [92].

10 Summary

The evidence to date for the efficacy of cannabinoids in general and medical cannabis in particular, for many medical conditions and symptoms is scanty. In contrast, there is considerable mounting evidence for harms, many of which are applicable to older individuals. Even in this setting of uncertainty, the overwhelming media publicity for medical cannabis will continue to drive the hopes of patients and their desire to explore this treatment option.

The conundrum of effect of cannabinoids can be understood for a number of reasons. Clinical trials have mostly been short, often with heterogeneous patient populations, especially for chronic pain, and with variable outcome measures. Cannabinoid preparations are diverse and cannot be regarded as a single drug. The molecular concentrations of THC and cannabidiol of pharmaceutical and plant-based preparations differ, with the plant product containing a myriad of other molecules (e.g., the entourage effect, see Sect. 4.1). The shortcomings of studies partially explain the lack of convincing conclusions of

cannabinoid effects in general, with even less data available for medical cannabis. In this setting of low-level evidence for efficacy and safety for medical cannabis and their increasing use, there has been a move to develop cannabis registries. While lacking the rigorous design of clinical trials, registries may provide real-world data on many aspects of medical cannabis use. We do acknowledge that the lack of convincing evidence for efficacy of a treatment does not necessarily mean it is ineffective; however, in the twenty-first century, use of any remedy cannot be driven by advocacy and anecdote alone. Finally, it must be recognized that the medical cannabis industry has huge financial potential, with echoes of both the cigarette and the opioid industry.

11 Conclusion

As interest in the clinical use of medical cannabis and cannabinoids surges worldwide, the evidence for efficacy and safety in older patients remains scant. While one may argue that the level of evidence for many other commonly used treatments, especially in the fields of pain and palliative care, is similarly weak, clinicians rightly remain uncomfortable when evidence is lacking. Despite this lack of evidence, patients will increasingly wish to open a dialogue regarding medical cannabis. Physicians must be as informed as possible, remain empathetic, and approach treatment decisions regarding medical cannabis use in a collaborative manner. When symptoms affect quality of life, especially for older individuals, it is understandable that patients may wish to accept some degree of risk, even if outcome is not guaranteed. Irrespective of the current level of evidence for medical cannabis, buoyed by media and advocacy, medical cannabis is a current reality, and clinicians must take an active role in ensuring competent patient care.

Author contributions All authors participated in the writing of this manuscript.

Compliance with Ethical Standards

Conflict of interest AM and WH have no conflicts of interest. MAF has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, UCB Canada, Palladin Labs, and Pfizer in the last 3 years.

Funding No sources of funding were used in the preparation of this manuscript.

References

1. D'Souza DC, Ranganathan M. Medical marijuana: is the cart before the horse? JAMA. 2015;313(24):2431–2.
2. Hauser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management—an overview of systematic reviews. Eur J Pain. 2018;22(3):455–70.
3. Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: marijuana use patterns in adults, U.S., 2014. Am J Prev Med. 2016;50(1):1–8.
4. Han BH, Palamar JJ. Marijuana use by middle-aged and older adults in the United States, 2015–2016. Drug Alcohol Depend. 2018;1(191):374–81.
5. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med. 2017;376(21):2011–20.
6. Leal-Galicia P, Betancourt D, Gonzalez-Gonzalez A, Romo-Parra H. A brief history of marijuana in the western world. Rev Neurol. 2018;67(4):133–40.
7. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: ancient times to the 1980s. Epilepsy Behav. 2017;70(Pt B):298–301.
8. Haffajee RL, MacCoun RJ, Mello MM. Behind schedule—reconciling federal and state marijuana policy. N Engl J Med. 2018;379(6):501–4.
9. Lucas PG. Regulating compassion: an overview of Canada's federal medical cannabis policy and practice. Harm Reduct J. 2008;28(5):5.
10. Bogdanoski T. Accommodating the medical use of marijuana: surveying the differing legal approaches in Australia, the United States and Canada. J Law Med. 2010;17(4):508–31.
11. Ablin J, Ste-Marie PA, Schafer M, Hauser W, Fitzcharles MA. Medical use of cannabis products: lessons to be learned from Israel and Canada. Schmerz (Berlin, Germany). 2016;30(1):3–13.
12. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur J Clin Pharmacol. 2013;69(8):1575–80.
13. Bicher HI, Mechoulam R. Pharmacological effects of two active constituents of marihuana. Arch Int Pharmacodyn Ther. 1968;172(1):24–31.
14. Howlett AC. The cannabinoid receptors. Prostaglandins Other Lipid Mediat. 2002;68–69:619–31.
15. Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. Philos Trans R Soc Lond B Biol Sci. 2012;367(1607):3353–63.
16. Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. Brain Res Rev. 2009;60(1):255–66.
17. Mechoulam R, Hanus LO, Pertwee R, Howlett AC. Early phytocannabinoid chemistry to endocannabinoids and beyond. Nat Rev Neurosci. 2014;15(11):757–64.
18. Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, International Union of Basic and Clinical Pharmacology. LXXIX, et al. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev. 2010;62(4):588–631.
19. Henstridge CM. Off-target cannabinoid effects mediated by GPR55. Pharmacology. 2012;89(3–4):179–87.
20. Henstridge CM, Balenga NA, Kargl J, Andradas C, Brown AJ, Irving A, et al. Minireview: recent developments in the physiology and pathology of the lysophosphatidylinositol-sensitive receptor GPR55. Mol Endocrinol. 2011;25(11):1835–48.
21. Howlett AC. A short guide to the nomenclature of seven-transmembrane spanning receptors for lipid mediators. Life Sci. 2005;77(14):1522–30.
22. Cravatt BF, Lichtman AH. The endogenous cannabinoid system and its role in nociceptive behavior. J Neurobiol. 2004;61(1):149–60.
23. Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol. 2001;63(5):569–611.

24. Croxford JL, Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? J Neuroimmunol. 2005;166(1–2):3–18.
25. Howlett AC. Cannabinoid receptor signaling. Handb Exp Pharmacol. 2005;168:53–79.
26. Ligresti A, Cascio MG, Di Marzo V. Endocannabinoid metabolic pathways and enzymes. Curr Drug Targets CNS Neurol Disord. 2005;4(6):615–23.
27. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol. 2006;147(Suppl 1):S163–71.
28. Savage SR, Romero-Sandoval A, Schatman M, Wallace M, Fanciullo G, McCarberg B, et al. Cannabis in pain treatment: clinical and research considerations. J Pain. 2016;17(6):654–68.
29. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol. 2002;42(11 Suppl):11S–9S.
30. Gould J. The cannabis crop. Nature. 2015;525(7570):S2–3.
31. Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, et al. Potency trends of Delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci. 2010;55(5):1209–17.
32. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. Biol Psychiatry. 2016;79(7):613–9.
33. Andre CM, Hausman JF, Guerriero G. *Cannabis sativa*: the plant of the thousand and one molecules. Front Plant Sci. 2016;7:19.
34. Grof CPL. Cannabis, from plant to pill. Br J Clin Pharmacol. 2018;84(11):2463–7.
35. Romero-Sandoval EA, Fincham JE, Kolano AL, Sharpe BN, Alvarado-Vazquez PA. Cannabis for chronic pain: challenges and considerations. Pharmacotherapy. 2018;38(6):651–62.
36. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of Cannabinoids. Br J Clin Pharmacol. 2018;Jul:12.
37. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–9.
38. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791–802.
39. Starowicz K, Di Marzo V. Non-psychotropic analgesic drugs from the endocannabinoid system: "magic bullet" or "multiple-target" strategies? Eur J Pharmacol. 2013;716(1–3):41–53.
40. Kerbrat A, Ferre JC, Fillatre P, Ronziere T, Vannier S, Carsin-Nicol B, et al. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. N Engl J Med. 2016;375(18):1717–25.
41. Lowin T, Straub RH. Cannabinoid-based drugs targeting CB1 and TRPV1, the sympathetic nervous system, and arthritis. Arthritis Res Ther. 2015;17:226.
42. Kaur R, Sidhu P, Singh S. What failed BIA 10-2474 phase I clinical trial? Global speculations and recommendations for future phase I trials. J Pharmacol Pharmacother. 2016;7(3):120–6.
43. Ahmed AI, van den Elsen GA, Colbers A, van der Marck MA, Burger DM, Feuth TB, et al. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: a randomized controlled trial. Eur Neuropsychopharmacol. 2014;24(9):1475–82.
44. Ahmed AI, van den Elsen GA, Colbers A, Kramers C, Burger DM, van der Marck MA, et al. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. Psychopharmacology. 2015;232(14):2587–95.
45. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571–84.
46. Hauser W, Finn DP, Kalso E, Krcevski-Skvarc N, Kress HG, Morlion B, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain. 2018;22(9):1547–64.
47. Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. Can Fam Physician. 2014;60(12):1083–90.
48. Allan GM, Ramji J, Perry D, Ton J, Beahm NP, Crisp N, et al. Simplified guideline for prescribing medical cannabinoids in primary care. Can Fam Physician. 2018;64(2):111–20.
49. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med. 2018;49:44–50.
50. van den Elsen GA, Ahmed AI, Lammers M, Kramers C, Verkes RJ, van der Marck MA, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing Res Rev. 2014;14:56–64.
51. National Academies of Sciences E, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.
52. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of systematic reviews for medical cannabinoids: pain, nausea and vomiting, spasticity, and harms. Can Fam Physician. 2018;64(2):e78–94.
53. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313(24):2456–73.
54. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med. 2017;167(5):319–31.
55. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018;7(3):CD012182.
56. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;May:25.
57. Breivik H, Cherny N, Collett B, de Conno F, Filbet M, Foubert AJ, et al. Cancer-related pain: a pan—European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009;20(8):1420–33.
58. Webb JA, LeBlanc TW. Evidence-based Management of cancer pain. Semin Oncol Nurs. 2018;34(3):215–26.
59. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database Syst Rev. 2013;22(7):CD003868.
60. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manag. 2010;39(2):167–79.
61. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–49.
62. Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. Curr Psychiatry Rep. 2017;19(4):23.
63. Gates P, Albertella L, Copeland J. Cannabis withdrawal and sleep: a systematic review of human studies. Subst Abus. 2016;37(1):255–69.

64. Rice J, Cameron M. Cannabinoids for treatment of MS symptoms: state of the evidence. Curr Neurol Neurosci Rep. 2018;18(8):50.
65. Yadav V, Narayanaswami P. Complementary and alternative medical therapies in multiple sclerosis—the American Academy of Neurology guidelines: a commentary. Clin Ther. 2014;36(12):1972–8.
66. Nielsen S, Germanos R, Weier M, Pollard J, Degenhardt L, Hall W, et al. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. Curr Neurol Neurosci Rep. 2018;18(2):8.
67. Stampanoni Bassi M, Sancesario A, Morace R, Centonze D, Iezzi E. Cannabinoids in Parkinson's disease. Cannabis Cannabinoid Res. 2017;2(1):21–9.
68. Noel C. Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders. Ment Health Clin. 2017;7(1):29–38.
69. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clin Psychopharmacol Neurosci. 2017;15(4):301–12.
70. Shishko I, Oliveira R, Moore TA, Almeida K. A review of medical marijuana for the treatment of posttraumatic stress disorder: real symptom re-leaf or just high hopes? Ment Health Clin. 2018;8(2):86–94.
71. Mucke M, Weier M, Carter C, Copeland J, Degenhardt L, Cuhls H, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexia Sarcopenia Muscle. 2018;9(2):220–34.
72. Lavie-Ajayi M, Shvartzman P. Restored self: a phenomenological study of pain relief by cannabis. Pain Med. 2018;Sep:12.
73. Colizzi M, Bhattacharyya S. Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. Curr Addict Rep. 2017;4(2):62–74.
74. Cohen K, Weinstein A. The effects of cannabinoids on executive functions: evidence from cannabis and synthetic cannabinoids—a systematic review. Brain Sci. 2018;8(3):10.
75. Choi NG, Marti CN, DiNitto DM, Choi BY. Older adults' marijuana use, injuries, and emergency department visits. Am J Drug Alcohol Abuse. 2018;44(2):215–23.
76. Mensinga TT, de Vries I, Kruidenier M, Hunault CC, van den Hengel-Koot IS, Fijen JW, et al. A double-blind, randomized, placebocontrolled, cross-over study on the pharmacokinetics and effects of cannabis: Nationaal Vergiftigingen Informatie Centrum; 2006. Report no.: RIVM 267002002.
77. Beirness DJ, Beasley EE, Boase P. A comparison of drug use by fatally injured drivers and drivers at risk. In: Proceedings of the the 20th international conference on alcohol, drugs and traffic safety T-2013; Brisbane, Australia: International Council on Alcohol, Drugs, and Traffic Safety (ICADTS). 2013.
78. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ. 2012;344:e536.
79. Singh A, Saluja S, Kumar A, Agrawal S, Thind M, Nanda S, et al. Cardiovascular complications of marijuana and related substances: a review. Cardiol Ther. 2018;7(1):45–59.
80. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014;113(1):187–90.
81. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. Stroke. 2015;46(3):852–6.
82. Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;371(9):879.
83. Desai R, Patel U, Sharma S, Amin P, Bhuva R, Patel MS, et al. Recreational marijuana use and acute myocardial infarction: insights from nationwide inpatient sample in the United States. Cureus. 2017;9(11):e1816.
84. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319–28.
85. Feingold D, Weiser M, Rehm J, Lev-Ran S. The association between cannabis use and mood disorders: a longitudinal study. J Affect Disord. 2015;1(172):211–8.
86. Ragazzi TCC, Shuhama R, Menezes PR, Del-Ben CM. Cannabis use as a risk factor for psychotic-like experiences: a systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences. Early Interv Psychiatry. 2018;Jun:21.
87. Oh DJ, Park JY, Oh M, Kim K, Hong J, Kim T, et al. Suicidality-based prediction of suicide attempts in a community-dwelling elderly population: results from the Osan Mental Health Survey. J Affect Disord. 2015;15(184):286–92.
88. Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. J Affect Disord. 2016;195:63–74.
89. Waterreus A, Di Prinzio P, Badcock JC, Martin-Iverson M, Jablensky A, Morgan VA. Is cannabis a risk factor for suicide attempts in men and women with psychotic illness? Psychopharmacology. 2018;May:16.
90. Nussbaum AM, Thurstone C, McGarry L, Walker B, Sabel AL. Use and diversion of medical marijuana among adults admitted to inpatient psychiatry. Am J Drug Alcohol Abuse. 2015;41(2):166–72.
91. Megale RZ, Deveza LA, Blyth FM, Naganathan V, Ferreira PH, McLachlan AJ, et al. Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials. J Pain. 2018;19(5): 475:e1–24.
92. Hauser W, Finnerup NB, Moore RA. Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: a methodological and political minefield. Pain. 2018;May:25.