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Review Article

Practical considerations in medical cannabis administration and dosing

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ABSTRACT

Cannabis has been employed medicinally throughout history, but its recent legal prohibition, biochemical complexity and variability, quality control issues, previous dearth of appropriately powered randomised controlled trials, and lack of pertinent education have conspired to leave clinicians in the dark as to how to advise patients pursuing such treatment. With the advent of pharmaceutical cannabis-based medicines (Sativex/nabiximols and Epidiolex), and liberalisation of access in certain nations, this ignorance of cannabis pharmacology and therapeutics has become untenable. In this article, the authors endeavour to present concise data on cannabis pharmacology related to tetrahydrocannabinol (THC), cannabidiol (CBD) et al., methods of administration (smoking, vaporisation, oral), and dosing recommendations. Adverse events of cannabis medicine pertain primarily to THC, whose total daily dose-equivalent should generally be limited to 30 mg/day or less, preferably in conjunction with CBD, to avoid psychoactive sequelae and development of tolerance. CBD, in contrast to THC, is less potent, and may require much higher doses for its adjunctive benefits on pain, inflammation, and attenuation of THC-associated anxiety and tachycardia. Dose initiation should commence at modest levels, and titration of any cannabis preparation should be undertaken slowly over a period of as much as two weeks. Suggestions are offered on cannabis-drug interactions, patient monitoring, and standards of care, while special cases for cannabis therapeutics are addressed: epilepsy, cancer palliation and primary treatment, chronic pain, use in the elderly, Parkinson disease, paediatrics, with concomitant opioids, and in relation to driving and hazardous activities.

1. Introduction

Cannabis has a history of medical application likely exceeding that of the written word, including mainstream usage in Europe and North America for a century between 1840 and 1940 [1,2]. It is only in the last century that quality control issues, the lack of a defined chemistry, and above all, politically and ideologically motivated prohibition relegated it *planta non grata*. The discovery and elucidation of the endocannabinoid system [3], coupled with a popular tidal wave of anecdotal accounts and renaissance of therapeutic clinical trials renders that *status quo ante* untenable.

One preparation, Sativex® (USAN: nabiximols), an oromucosal cannabis-based medicine with 2.7 mg of THC and 2.5 mg CBD plus terpenoids per spray has attained regulatory approval in 29 countries for treatment of spasticity in multiple sclerosis, having met the standards of safety, efficacy and consistency required of any pharmaceutical. The problem for physicians with respect to treatment with herbal cannabis remains acute, however: How does the responsible healer and medical scientist approach the desperate patient for whom conventional medicine has failed and wishes to avail themselves of a purportedly healing herb that has been an international societal outlaw for decades? The answer is simple: educational and scientific standards apply to the cannabis controversy equally with that of any other putative therapy.

Unfortunately, physicians of the world remain profoundly uneducated with respect to cannabis and the endocannabinoid system (ECS) that underlies much of its activity. A recent USA study [4] documented that 89.5% of surveyed residents and fellows felt unprepared to prescribe, while only 35.3% even felt ready to answer cannabis questions. Additionally, only 9% of American medical schools

Abbreviations: 5-HT$_{1A}$, serotonin 1A receptor; AE, adverse events; AIDS, acquired immunodeficiency syndrome; CB$_1$, cannabinoid-one receptor; CB$_2$, cannabinoid-two receptor; CBD, cannabidiol; CBDA, cannabidiolic acid; CRISP-R, Clustered Regularly Interspaced Short Palindromic Repeats; ECS, endocannabinoid system; GAP, Good Agricultural Practice; GCP, Good Clinical Practice; GMP, Good Manufacturing Practice; HIV, human immunodeficiency virus; MS, multiple sclerosis; PAH, polycyclic aromatic hydrocarbon; RCT, randomised controlled trial; THC, Δ^9-tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; TRPV1, transient receptor potential cation channel vanilloid subfamily receptor 1; USAN, United States Adopted Name

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documented pertinent clinical cannabis content in their curricula.

While it remains a common complaint that cannabis therapeutics lacks adequate documentation, according to a recent publication [5], scientist and clinicians are recognising the limitations of randomised controlled studies in their generalisability to populations vs. customisation of best evidence based practices for individual patients. Individualized evidence based medicine may be delivered to a patient using an N-of-1, or single clinical trial, whereby the patient is the sole unit of observation for efficacy and side effects of various interventions. This method can be applied to a medical cannabis patient to find an optimal intervention or "sweet spot" combination of plant varieties and dosage forms that provide superior symptom control.

In this article, two experienced clinicians, internist and neurologist, respectively, offer their review of the literature and personal observations that might serve as an initial guide to suggested Good Clinical Practice (GCP) as applied to cannabis. These include our opinion that cannabis medicines, whether prescription or over-the-counter, should be ideally cultivated organically according to Mendelian selective breeding techniques without the necessity of genetic modification or CRISPR technology according to Good Agricultural Practice (GAP), be extracted and processed under Good Manufacturing Practice (GMP) [6], and be made available to consumers with full information as to cannabinoid and terpenoid profiles, and certification that the material is free of pesticide [7], microbial or heavy metal contamination.

2. Cannabis pharmacology in brief

Cannabis produces phytocannabinoids (plant cannabinoids) in greatest abundance in the unfertilised female flowers in acid form, most abundantly tetrahydrocannabinolic acid-A (THCA-A) and cannabidiolic acid (CBDA), which are most frequently utilised after heating either by smoking, vaporisation, or baking in confections to produce decarboxylation of the more familiar neutral cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD) (see graphical abstract) [8].

THC is the primary psychoactive component of cannabis, working primarily as a weak partial agonist on CB_1 and CB_2 receptors with well-known effects on pain, appetite, digestion, emotions and thought processes mediated through the endocannabinoid system, a homeostatic regulator of myriad physiological functions [9], found in all chordates. THC can cause psychoactive adverse events depending on dose and patient previous tolerance. Its use is applicable for many symptoms and conditions including; pain, nausea, spasticity/spasms, appetite stimulation, anxiety, depression, post-traumatic stress disorder (PTSD), insomnia et al.

CBD, in contrast, has little affinity for these receptors directly, but rather is a negative allosteric modulator of CB_1 [10], with protean pharmacological effects on various other receptor systems including TRPV1, 5-HT_{1A}, adenosine A2A and non-receptor mechanisms (reviewed [11]), productive of analgesic, anti-inflammatory, anti-anxiety, and anti-psychotic effects among many others. CBD is non-intoxicating, and has been shown to help with similar symptoms, with added benefit as an anticonvulsant, anti-psychotic, neuroprotectant, and anti-inflammatory (including autoimmune conditions). Cannabis is a multimodal treatment. It can be used to treat multiple symptoms and conditions concurrently, which can therefore help to reduce polypharmacy burden.

There are thousands of individual cannabis types, which patients and purveyors may erroneously refer to as 'strains', whereas the preferred term is chemical variety or 'chemovar' [12]. Each chemovar contains varying concentrations of cannabinoids and other components with important pharmacological and modulatory effects include the monoterpenoids [8,11] myrcene (analgesic, sedating), limonene (antidepressant and immune-stimulating), pinene (acetylcholinesterase inhibitor alleviating short-term memory impairment from THC) and the sesquiterpenoid beta-caryophyllene (anti-inflammatory analgesic and selective full agonist at the CB_2 receptor). The relative proportions of these and other components are the primary determinants of the pharmacological effects and adverse events associated with a particular cannabis chemovar, and is critical information that should be available to patients and physicians recommending such treatment. Until recent years, the vast majority of chemovars in Europe [13] and North America [14] were THC-predominant (Type I cannabis). Contemporaneously, there has been greater interest in mixed THC:CBD (Type II) and CBD-predominant (Type III cannabis) chemovars with broader mechanisms of action and improved therapeutic indexes [12].

The acid cannabinoids have received much less research interest, but possess fascinating pharmacological properties. THCA has been noted to produce anti-inflammatory effects via antagonism of tumour necrosis factor-alpha (TNF-α) [15], to be a strong anti-emetic [16] and was recently demonstrated to be an agonist of the PPAR-γ nuclear receptor with neuroprotective effects [17], as well as anticonvulsant efficacy [18]. CBDA is also a powerful anti-emetic [19] and anti-anxiety agent [20] in rodents, and both acid cannabinoids have prominent anecdotal reports of benefit on skin and other tumors.

3. Pharmacokinetic considerations

Absorption, distribution, and metabolism determine the onset and duration of action of each dosage form. Absorption has the most variability, and is affected by product lipophilicity, bioavailability as well as the inherent organ tissue differences (i.e., alveolar, dermal vs. gastric). Cannabinoids are lipophilic and have low water solubility. Therefore, for topical or oral routes, they are best absorbed in the presence of fat, oils or polar solvents, such as ethanol. There is suggestion that newer technology such as using nano- or ionized particles or the use omega fats in carrier oil can enhance absorption; or for topicals preparations, using ingredients to mildly disrupt the skin barrier may allow greater absorption of active ingredient. Factors such as recent meals, depth of inhalation, duration of breath holding, temperature of vaporizer all affect cannabis absorption, which can vary from 20%–30% orally, up to 10–60% for inhalation [21]. Clinicians will benefit from an understanding of these factors to prescribe or recommend cannabis to enable estimation of a target quantity of dried product for their patients. See Dosing strategies and clinical pearls section for more details.

4. Modes of administration

This information is summarised (Table 1, Table 2) [7,21–27].

5. Therapeutic uses

Cannabis can be a useful tool in the treatment of many complex diseases or rare conditions which lack effective conventional therapeutic options, or where the side effects burden of such treatments outweigh the benefits, for example, central sensitivity syndromes (fibromyalgia, chronic fatigue syndrome, migraines, irritable bowel), or multiple sclerosis, neuropathic pain, and refractory nausea. An assessment of current evidence in various indications is summarised (Table 3) [28–33].

6. Dosing strategies and clinical pearls

- There is insufficient evidence to support the necessity of a trial of synthetic cannabinoids prior to initiating cannabis-based medicine treatment, unless legal availability is not an option.
- General approach to cannabis initiation is 'start low, go slow, and stay low'.
- For cannabis inhalation, patients should start with 1 inhalation and wait 15 min. Then, they may increase by 1 inhalation every 15–30 min until desired symptom control has been achieved.

Table 1
Cannabis routes of administration.

Cannabis routes of administration			
Smoking	Vaporisation	Oral	Other routes
• Most common route of administration, but not recommended (joints, bongs, pipes, etc.) • Combustion at 600–900 °C producing toxic biproducts: tar, PAH (polycyclic aromatic hydrocarbons), carbon monoxide (CO), ammonia (NH_3). • Chronic use associated with respiratory symptoms (bronchitis, cough, phlegm), but not lung cancer nor COPD (if cannabis only). • Patients may mix with tobacco increasing respiratory/cancer risk • 30–50% of cannabis is lost to 'side-stream' smoke	• Heats cannabis at 160–230 °C. Reduced CO, but not complete elimination of PAH demonstrated to date. • Vaporisation produces significantly less harmful biproducts vs. smoking. • Decreased pulmonary symptoms reported compared to smoking.	• Oils, capsules and other po routes increasingly popular due to convenience and accuracy of dosing. • Edibles (brownies/cookies) may be more difficult to dose. • Juicing and cannabis teas do not allow for adequate decarboxylation of raw plant • Nabiximols oromucosal spray is currently the only cannabis-based prescription that delivers standardised dosage of CBD/THC in a 1:1 ratio with extensive research • Tinctures and lozenges intermediate onset with limited research	• Topicals ideal for localised symptoms (dermatological conditions, arthritis), with limited research evidence • Suppositories possibly indicated for specific populations (cancer, GI symptoms, young/elderly, etc.) with variable absorption. THC-hemisuccinate may allow for best absorption with limited research. • Recreational routes include 'shatter', 'dabs', concentrates. Deliver very high doses of THC with high risk of euphoria, impairment, reinforcement, toxic psychosis, orthostatic hypotension. Inappropriate for medical application.

- Higher THC concentrations of herbal cannabis may allow utilization of lower amounts. Patients should titrate accordingly to avoid adverse events.
- THC-mediated side effects such as fatigue, tachycardia and dizziness are avoidable when starting dose is low and titration is slow.
- Slow upward dose titration promotes tolerance to psychoactive sequelae of THC, which is especially important for naïve users.
- Medical cannabis patients, in contrast to recreational users, frequently use CBD-predominant chemovars with the smallest amount of THC to get the greatest improvement in symptom control, function, and quality of life, with fewest adverse events.
- Attainment of euphoric effects is not required to attain symptom control.
- For chronic conditions and symptoms, long acting oral preparations are the mainstay of treatment.
- Vaporisation can be utilised as an add-on prn technique for episodic exacerbations of symptoms.
- CBD can balance THC side effects, especially in daytime use, or when driving is required.
- Cannabis should be stored in a safe place, or lock box in the home.
- Physicians must clearly communicate the potential risks and safety of cannabis, no differently than with any psychoactive medication. We suggest documentation in a standard 'treatment agreement' form for medical-legal purposes. (See https://www.drcarolinemaccallum.com/cannabis-resources/.)
- Patients should keep a 'symptom inventory' chart indicating response or efficacy for each cannabis product for each symptom as and aid for physicians in determining treatment response to cannabis in follow up visits. (See https://www.drcarolinemaccallum.com/cannabis-resources/.)
- Most patients use 1–3 g of herbal cannabis per day. < 5% of patients use > 5 g per day [34]. Tolerance does not develop to the benefits. Over time dose escalation is not generally observed [22,34,35]. Additional needs require reassessment.

Table 3
Levels of evidence for cannabis-based medicines in various conditions.

Cannabis and nabiximols supporting evidence	
Level of evidence	Benefits
Conclusive or substantial evidence of efficacy	• Adult chronic pain treatment • Multiple sclerosis spasticity symptoms • Chemotherapy-induced nausea and vomiting • Treatment of intractable seizures in Dravet and Lennox-Gastaut syndromes (CBD)
Moderate evidence of efficacy	• Improving outcomes in individuals with sleep disturbances associated with chronic pain, multiple sclerosis, fibromyalgia, obstructive sleep apnea syndrome • Decreasing intraocular pressure in glaucoma
Limited evidence of efficacy	• Symptoms of dementia • Symptoms of Parkinson disease • Positive and negative symptoms of schizophrenia • Symptoms of posttraumatic stress disorder • Appetite and decreasing weight loss associated with HIV/AIDS • Multiple sclerosis spasticity (clinician-measured) • Traumatic brain injury/intracranial haemorrhage associated disability, mortality, and other outcomes • Symptoms of anxiety in social anxiety disorders (CBD) • Symptoms of Tourette syndrome
Limited evidence of inefficacy	• Depressive symptoms in chronic pain or multiple sclerosis patients
Insufficient evidence of efficacy or inefficacy	• Addiction abstinence • Symptoms of irritable bowel syndrome • Cancers, including glioma • Cancer-associated anorexia, cachexia syndrome and anorexia nervosa • Symptoms of amyotrophic lateral sclerosis • Chorea and some neuropsychiatric symptoms associated with Huntington disease • Dystonia

Table 2
Administration factors in cannabis delivery methods.

Issue	Smoking/vaporisation	Oral	Oromucosal	Topical
Onset (min)	5–10	60–180	15–45	Variable
Duration (h)	2–4	6–8	6–8	Variable
Pro	Rapid action, advantage for acute or episodic symptoms (nausea/pain)	Less odor, convenient and discrete, advantage for chronic disease/symptoms	Pharmaceutical form (nabiximols) available, with documented efficacy and safety.	Less systemic effect, good for localised symptoms
Con	Dexterity required, vaporisers may be expensive, and not all are portable	Titration challenges due to delayed onset	Expensive, spotty availability	Only local effects

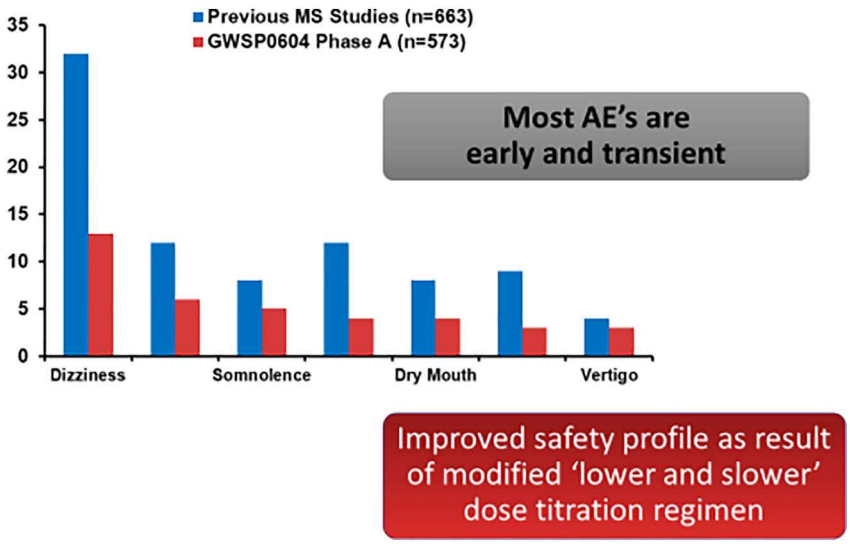

Fig. 1. Graphic comparison of nabiximols adverse events encountered in > 3% of multiple sclerosis RCT patients with rapid titration and higher dosing (blue) vs. slower titration and capping dosing at 12 sprays per day (red) (32.4 mg THC, 30 mg CBD). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

- Most patients require 6–8 sprays of nabiximols per day for symptomatic relief with a limit of 12. Above this dose, adverse events are increased without improved efficacy.
- Cannabis medicine doses must be individually determined, as this depends on underlying endocannabinoid tone.
- Use of homemade oral oils or topicals may require much higher dried cannabis than utilised for inhalation.
- CBD-predominant preparations have fewer untoward psychotropic effects, and may require higher dosing.

7. Tactics in titration

Oral THC preparation effects are usually easier to judge vs inhalation as the concentrations should be available from the producer. Vaporisation is subject to more variables which can influence estimated dose: size of chamber, depth of inhalation, breath holding, strength of THC in the chemovar, etc. Ideally, the patient would start using a THC-predominant preparation at bedtime to limit adverse events and encourage development of tolerance. However, this is not a must.

- Days 1–2: 2.5 mg THC-equivalent at bedtime. (may start at 1.25 mg if young, elderly, or other concerns).
- Days 3–4: if previous dose tolerated, increase by 1.25–2.5 mg THC at bedtime.
- Days 5–6: continue to increase by 1.25–2.5 mg THC at bedtime every 2 days until desired effect is obtained. In event of side effects, reduce to previous, best tolerated dose.

Some patients require THC for daytime use depending on their symptoms. Consider use of a more stimulating chemovar unless sedation is a desired result. Most patients dose orally two to three times per day.

Consider the following regimen:

- Days 1–2: 2.5 mg THC-equivalent once a day
- Days 3–4: 2.5 mg THC twice a day
- Increase as needed and as tolerated to 15 mg THC-equivalent divided BID-TID
- Doses exceeding 20–30 mg/day may increase adverse events or induce tolerance without improving efficacy.

Use of high doses of THC-predominant cannabis above 5 g per day are probably unjustified, except in the case of primary cancer treatment (vide infra), and suggest possible tolerance or misuse. THC tolerance may be readily abrogated via a drug vacation of at least 48 h, and preferably longer. Patients may then find that much lower doses provide symptomatic benefit equal to or better than previously experienced (see suggested regimen devised by Dustin Sulak, DO: www.healer.com).

CBD-predominant chemovars produce fewer adverse events, but there are no established dosing guidelines or maximum doses established except in psychosis (800 mg) [30]and seizure disorders (2500 mg or 25–50 mg/kg) [29]. For other indications, many patients obtain benefits with much lower doses, starting with 5–20 mg per day of oral preparations divided BID-TID, which may reduce attendant expense.

8. Contraindications

Cannabis is generally contraindicated in pregnancy and lactation, despite a long history of usage [36], and foetal/neonatal sequelae remain controversial [37,38]. It is also contraindicated in psychosis (except CBD-predominant preparations [30]). Cannabis should be utilised with caution in unstable cardiac conditions, such as angina, due to tachycardia and possible hypotension due to THC, but produces no QTc issues [39]. Use in children and teens remains the subject of debate (see below), as does its use in addiction and dependency. Smoking should be avoided in COPD and asthma.

9. Adverse events

Cannabis has a superior safety profile in comparison to many other medications, with no reported deaths due to overdose, due to a lack of CB_1 receptors in brainstem cardiorespiratory centres [40].

THC-mediated side effects are most pertinent and rate-limiting, and are dose-dependent. Using a 'start low and go slow' dosing strategy mitigates most adverse events of THC. Also, combining CBD with THC can further reduce those effects (Fig. 1). Patients develop tolerance to psychoactive effects of cannabis quickly over period of days, without concomitant tolerance to the benefits, and therefore maintain the same daily dose of many years [34,35], in stark contrast to opioids. A recent large review of herbal cannabis in Canada revealed no increase in serious adverse events in chronic administration, no harm on cognitive function, pulmonary function tests, biochemistry (creatinine, liver function test, and CBC) [34], confirming patterns seen in decades-long usage in the USA [35].

Common AEs are listed (Table 4) [34,41,42], and their reduction with lower doses and slow titration with nabiximols [42,43] are documented (Fig. 1).

The critical nature of dose and preparation are additionally exemplified (Fig. 2), demonstrating that whereas even 10–15 mg of pure

Table 4
Adverse events associated with cannabis-based medicines.

Side effect	Most common	Common	Rare
Drowsiness/fatigue	✓		
Dizziness	✓		
Dry mouth	✓		
Cough, phlegm, bronchitis (Smoking only)	✓		
Anxiety	✓		
Nausea	✓		
Cognitive effects	✓		
Euphoria		✓	
Blurred vision		✓	
Headache		✓	
Orthostatic hypotension			✓
Toxic psychosis/paranoia			✓
Depression			✓
Ataxia/dyscoordination			✓
Tachycardia (after titration)			✓
Cannabis hyperemesis			✓
Diarrhea			✓

oral THC may induce toxic psychosis in the naïve or susceptible individual [44], such reactions were only identified in 4 of 260 exposures to high dose nabiximols for a Phase I RCT containing 48.6 mg of THC by virtue of its CBD and terpenoid profile [39]. Extrapolation of data in Figs. 1 and 2 suggest that other Type II oral preparations may produce similar results with slow titration.

10. Drug interactions

Most drug interactions are associated with concurrent use of other CNS depressants with cannabis. Clinically, significant drug interactions have proven rare [7], and there is no drug that cannot be used with cannabis, if necessary. THC is oxidised by (CYP) 2C9, 2C19, and 3A4. Therefore, serum levels may increase with inhibitors, or decrease with enzyme inducers. Pertinent drug interaction studies are few [45,46]. Existing studies have not demonstrated toxicity/ loss of effect of concomitant medications, but still theoretically possible [47]. One exception is high dose CBD with clobazam, wherein high levels of a sedating metabolite, *N*-desmethyl clobazam will require a dose reduction for that drug [29].

11. Monitoring

Depending on the patient, they may need to be seen in follow up every 1–6 months depending on several factors such as; their familiarity with cannabis, comorbid medical conditions, ability to adhere to treatment plan instructions and keep an inventory of cannabis efficacy on individual symptoms/conditions. This should involve appropriate monitoring for efficacy (consider changing dosage routes, dose, and/or plant varieties if needed), side effects of THC, review of concomitant medication changes, and when it is appropriate to initiate a gentle drug taper to minimise withdrawal symptoms, which are rarely problematic in medicinal cannabis patients [48–50]. Finally, consider implementing validated questionnaires and quality of life assessments to allow for documentation of objective measures to capture improvement in symptoms and function.

12. Special cases

12.1. Epilepsy

Cannabis has a long traditional use in treatment of seizures [51], but has frequently been contraindicated in that context in RCTs due to the observed association of THC with proconvulsant effects in rodents at high doses. In contrast, CBD displays only anticonvulsant properties and as Epidiolex® cannabis extract, has been proven safe and effective in a variety of intractable epilepsies, such as Dravet and Lennox-Gastaut syndromes in both observational settings [52] and Phase III clinical trials [29]. Regulatory approval in the USA is expected in 2018. CBD in the latter settings has often required very high doses, as much as 2500 mg/d., whereas some clinicians have claimed similar efficacy at much lower doses when CBD is utilised in preparations containing concomitant low dose THC, THCA and even the anticonvulsant terpenoid, linalool [18].

12.2. Cancer

The anti-emetic effects of THC in association with cancer chemotherapy have long been known and a synthetic form was approved for such use in the USA in 1985. Benefits as a palliative for sleep [53], and particularly for opioid-resistant cancer pain have also been demonstrated in two Phase II clinical trials of nabiximols [54,55], but unfortunately were not proven definitively in subsequent Phase III studies. Cancer pain remains an indication in Canada under a Notice of Compliance with conditions.

Cannabis has also been an historical primary treatment for cancer [2], with extensive basic science documentation of its cytotoxic effects with cytopreservative effects on normal cells. Initial trials and case reports support the acute need for more formal investigation [56–59]. Thousands of patients worldwide are pursuing such treatment, most often without benefit of appropriate medical monitoring. Both basic science [60,61] and anecdotal clinical reports suggest that cannabis-based treatment is most effective in conjunction with conventional approaches, whether chemotherapy or radiation. High doses (up to 1000 mg/d), preferably of mixed phytocannabinoids (as in cannabis extracts), for up to 3 months may be required to eradicate some malignancies, but emphasis is required that this approach remains

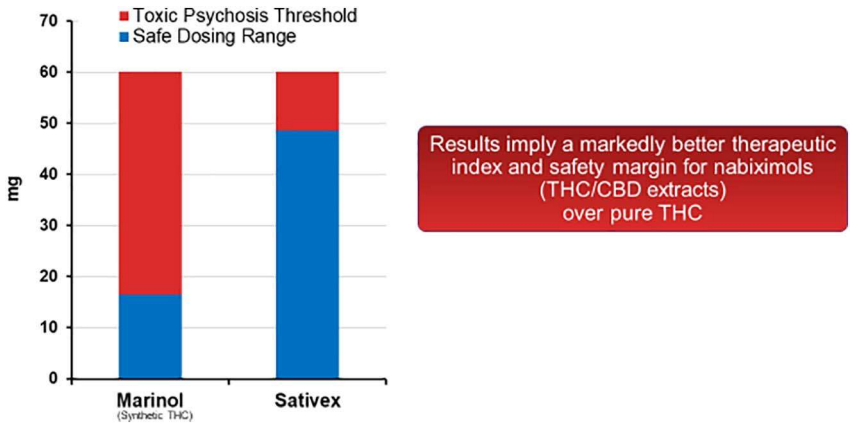

Fig. 2. Graphical comparison of threshold dosing of THC vs. nabiximols producing toxic psychosis.

anecdotal without benefit of large published RCTs. High doses of THC-containing preparations require slow titration over 2 weeks to induce tolerance to psychoactive sequelae. There is some anecdotal evidence supporting use of acid cannabinoids in much lower doses, and CBDA may improve the pharmacokinetics of CBD [47]. Prolonged maintenance of cannabis therapy, at some lower dosage may be similarly required to prevent recurrences. It should be borne in mind that 'cure' of cancer can only be claimed after a 5-year interval without evidence of tumour. Further objective evidence is needed to support adjunctive cannabis-based medicine treatment of cancer.

12.3. Pain

Cannabis treatment has not generally been useful in relation to treatment of acute pain [62]. In contrast, both THC and CBD-predominant cannabis preparations have proven safe and effective in numerous RCTs of chronic non-cancer pain, whether somatic or neuropathic, peripheral or central (reviewed [22]) and examination in national programs, as in Canada [34].

12.4. The elderly

Whereas vigilance toward adverse events, particularly attributable to polypharmacy are necessary in the elderly patient, monitoring of adverse events with nabiximols reveal no specific increased susceptibility to problems in this age group [42]. THC has been used to advantage to treat agitation in dementia [32], and the neuroprotective effects of it and CBD portend to offer possible advantages in this, and related pathologies [63]. Slow titration is required to avoid AEs, including falls and orthostatic hypotension.

12.5. Parkinson disease

CB_1 receptors are densely expressed in the basal ganglia, and cannabis has shown variable efficacy in various clinical studies [64]. Additional investigation is required, however, to establish the optimal composition of components. Anecdotal surveys suggest that acid cannabinoids given orally over prolonged intervals (3 months) may be necessary to achieve clinical improvement [65]. Slow titration is required.

12.6. Paediatrics

Use of cannabis as medicine in children remains another forbidden territory [1], but as in any other context, the relative risks and benefits must be weighed. Recent review has supported efficacy in nausea secondary to chemotherapy and in seizures [66]. It should be stated emphatically that there is a world of difference scientifically and ethically between judicious administration of low doses of cannabinoids for therapeutic purposes as compared to chronic use of high-dose THC for recreational purposes by teenagers. Even synthetic THC has been used to advantage in children with severe static encephalopathies with spasticity and seizures in Germany where warranted [67,68]. Historical data [1] and modern experience in treatment of nausea secondary to chemotherapy [69] support the fact that children under the age of 10 are remarkably resistant to psychoactive sequelae of THC, and are able to tolerate doses, when necessary, that might be more problematic in the adult patient.

In those at risk, younger age of first cannabis use is associated with earlier onset of schizophrenia and bipolar disorder and worse outcomes [70,71]. CBD-predominant preparations, and even THCA, may be a useful therapy for children (or adults) with severe developmental/self-harm, schizophrenia, seizures, brain tumors, refractory or rare diseases. In these conditions, CBD (with low or no THC) may be more efficacious with fewer AEs than traditional therapies. (i.e., opioids, antiepileptic etc). Risks and benefits need to be considered.

12.7. Opioid and other addictions

Nineteenth century observations of the use of cannabis with opioids [72,73] attested to its additive analgesic benefits, reduction of adverse events and even benefit to withdrawal symptoms. This has been supported by basic science investigation [74], and a variety of observational studies [75–77] and epidemiological evidence of decreased opioid overdose mortality in US states with medical cannabis access [78], as well as lowered costs for analgesics including opioids in such states in the Medicare (elderly) [79] and Medicaid (low-income) [80] populations. An intriguing finding from a long-term safety study of nabiximols in survivors of a Phase IIA trial of cancer pain non-responsive to optimised opioids showed no increase in cannabis dosing requirements over ensuing months, without the expected escalation of opioid requirements with continued disease progression and eventual demise [81]. Studies do not report an increase in opioid serum levels when used with cannabis [82].

12.8. Driving and safety sensitive occupations

It is important to include evaluation of social and occupational history during a medical cannabis consultation. This may include determining if a patient works outside the home, has a safety sensitive occupation, drives a motor vehicle, engages in childcare, etc. A reasonable and conservative cannabis regimen for this patient population would be CBD-predominant preparations during working hours, and THC-predominant ones after work or before sleeping.

Patients should not drive or utilise power tools or heavy equipment until accustomed to the effects of the medicine [7]. It is recommended that driving should be avoided for 4 h after inhaled cannabis use, 6 h after ingested cannabis use, or 8 h if euphoria was experienced. If a patient feels impaired, regardless of cause, they should not be driving or working safety sensitive jobs.

In clinical practice we have observed that medical cannabis patients, using daily, appropriate low doses of THC develop tolerance and experience minimal if any impairment, as has been documented for multiple sclerosis patients [83]. There are no serum assays that enable measurement of impairment due to THC accurately. Urine toxicology tests metabolites of THC which merely indicate THC ingestion sometime in the past two to three weeks. The authors believe a combination of neurocognitive testing, along with physical examination or performance specific activities to capture reaction time, coordination, balance, decision making et al. will prove more valuable in comparison to bodily fluid THC levels.

12.9. Standard of care

The authors believe that the standard of care for cannabis is no different than that for any speciality in the practice of medicine. The requirements are: examination of prior medical records whenever available, a comprehensive history and physical, a thorough discussion of the pros and cons of cannabis, plans for appropriate follow-up care, proper documentation of the consultation, and appropriate communication with other care-givers.

13. Conclusions

As cannabis-based medicines return to mainstream usage, it is essential that clinicians gain a greater understanding of their pharmacology, dosing and administration to maximise therapeutic potential and minimise associated problems. With standardised modern products, and educated caregivers, these are worthy and attainable goals.

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in the public, commercial, or not-for-profit sectors.

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