Advances in Social Sciences Research Journal – Vol.5, No.12
Publication Date: Dec. 25, 2018
DoI:10.14738/assrj.512.5864.
Silverstone, P. H. (2018). Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©): a simple evidence-based scale to determine clinical benefits and adverse events following medical cannabis use. *Advances in Social Sciences Research Journal, 5(12)* 324-334.

Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©): a simple evidence-based scale to determine clinical benefits and adverse events following medical cannabis use

Peter H. Silverstone
MB BS, MD, FRCPC, ICD.D
Professor, Department of Psychiatry, University of Alberta
Adjunct Professor, Faculty of Business, University of Alberta

ABSTRACT

Medical cannabis has been proposed to benefit patients in a wide range of conditions, including chronic pain, psychological conditions including anxiety, and sleep issues. It is available via prescription in multiple countries, and in Canada it is available legally in both stores and on-line. The range of methods by which it can be consumed are large including (1) inhalation via smoking or using vapourizers, (2) swallowed as an oil or within a food or liquid, or (3) absorbed through the skin including as a patch. As the range of products increases, a major problem is that there is no standardized scale to determine changes, both positive and negative, induced by medical cannabis products. This also means that there is no method to compare products, and the Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©) is specifically designed to address this issue. Following a comprehensive medical literature search and review, the most relevant clinical benefits and adverse events following the use of cannabis for medical purposes were determined. Following this key items were identified, with the scale being designed to measure these. The scale consists of 25 questions with each question being scored from 0 – 4, giving a range of total potential scores between 0 – 100. With the MACESS© a high score indicate a well tolerated and effective product, while a low scores indicates significant side-effects or adverse events and/or lack of positive clinical changes. It is available online and can be used for research, to measure change following prospective use in individuals or groups, and for cross-sectional information. It is intended to support both individual users and researchers examining benefits and problems with specific medical products, and can provide an easily understood single number for overall product comparisons.

Key words: Marijuana; Medical Cannabis; Safety; Clinical Study; Rating Scale

INTRODUCTION

Cannabis sativa is a plant that has long been used as a medicinal agent, with the earliest written evidence suggesting it was used in ancient Chinese medical practice from at least 2,700 BC [Ko et al, 2016]. This use is because cannabis plants contain compounds, cannabinoids, that have a variety of effects on humans and animals. Indeed, within the cannabis plant more than 100 naturally occurring cannabinoids are found. Although the focus to date has been on the psychoactive molecule delta-9-tetraydrocannabinol (THC) and cannabidiol (CBD) [Grof, 2018], other potentially clinically important cannabinoids have been identified including cannabinol [Kelly & Nappe, 2018].

Although the terms “marijuana” and “cannabis” are often used interchangeably, more recently the term “medical cannabis” has been used to refer to active components from the cannabis plant when they are used for clinical purposes. In contrast, “recreational marijuana” is a term more frequently used to refer to products primarily used for adult use including recreational

purposes. Although this is by no means completely consistent across the literature, throughout this article the term "medical cannabis" is used to describe any use for clinical purposes and "recreational marijuana" for other uses.

Regulation of medical cannabis varies widely between countries [Abuhasira et al, 2018], including Canada. However, since October 17th, 2018 it is available in Canada for any individual to purchase without prescription [Capler et al, 2017; Ko et al, 2016]. Of all purchases it is envisaged that many will be by individuals using medical cannabis for purposes of self-medication. Despite this widespread use, there is only a relatively small research base on medical cannabis itself, while research on individual products is almost completely lacking. This means it can be nearly impossible to appropriately recommend a specific medical cannabis product to a potential user. This is further complicated by the fact that there are a wide range of ways in which medical cannabis can be administered [Russell et al, 2018]. Thus, products can be smoked, inhaled after vapourization ("vaped"), swallowed as an oil (which can be an extract, or concentrate of specific cannabinoids), swallowed when included in food ("edibles"), swallowed in liquids (including in drinks containing alcohol), chewed (like gum), or used as a topical application where is it put on the skin to be absorbed (sometimes as a cream). Data from use in the USA suggests that many such routes will become commercially available in Canada and used for medicinal purposes [Caulkins et al, 2018].

However, these products will vary greatly in terms of cannabinoid content, THC/CBD ratios, absorption, metabolism, and other aspects of pharmacokinetics. For this reason, each medical cannabis product should ideally be examined for its efficacy and side-effect profile in a standardized manner. Nonetheless, exemplifying some of the issues regarding standardization, even standardized laboratories can vary significantly in their reports of the actual THC/CBD ratio contained within specific products [Jikomes & Zoorob, 2018]. It is therefore clear that the need for good research is critical, and this need has been raised repeatedly with one review concluding that "with ongoing developments in legalization of cannabis in medical and recreational settings, numerous scientific, safety, and public health issues remain" [Russo et al, 2016].

The most psychoactive component of marijuana is THC, which has also been considered as responsible for most of the adverse events associated with both recreational marijuana and medical cannabis [Cohen & Weistein, 2018]. In contrast, CBD has been suggested as having medical benefits in several clinical areas, although there is a lack of high quality medical evidence [Lim et al, 2017]. This is the case even in areas where it is widely utilized, such as to treat mental health issues [Walsh et al, 2017] and in the management of chronic neuropathic pain [Mücke et al, 2018]. Not only is there a lack of high quality efficacy data, there is also a relative dearth of reliable safety and side-effect data for medical cannabis, although there is some for CBD on its own [Iffland & Grotenhermen, 2017]. Added to this there is also minimal data on possible drug interactions, despite the fact that these are highly likely with increased use [Rong et al, 2018].

Despite the lack of strong evidence, such as Phase III placebo-controlled studies, medical cannabis is increasingly available in a number of countries for clinical use. In addition to Canada this includes the UK, Australia, countries within Europe, and many US States (although it still remains illegal Federally in the US).

Experience from other jurisdictions suggests that individuals are likely to self-medicate with medical cannabis products for a wide variety of clinical reasons [Whiting et al, 2015; Abrams, 2018]. However, the most frequent use is for issues individuals who have clinical concerns

with cognition, pain, sleep, or anxiety [Park & Wu, 2017; Turna et al, 2017]. However, the lack of any safety measures for such a wide range of medical cannabis products is a major concern, which is only increased by the large variability between them. Furthermore, as more individuals will be working while also using medical cannabis, there is a need to determine possible side-effects, cognitive impacts, and their likely impact of specific products on their ability to drive vehicles and operate heavy machinery.

In terms of efficacy there have been multiple suggestions about the possible effectiveness of medical cannabis in a wide variety of medical conditions [Ko et al, 2016; Andrade, 2016]. A recent meta-analysis found that cannabinoids were associated with only modest benefits for chemotherapy-related nausea and vomiting, small and inconsistent benefits for spasticity, and inconclusive benefits for other indications such as improvement of appetite and weight, reduction in tic severity, and improvement of mood or sleep [Andrade, 2016]. They do appear to be consistently effective for some types of epilepsy [Perucca, 2017], to reduce the symptoms of post-traumatic mood disorder (PTSD), and also to reduce the use of opioids [Walsh et al, 2017].

There are also consistent findings that there may be therapeutic psychological benefits from medical cannabis [Walsh et al, 2017], which would support such a conclusion. Possible anti-psychotic benefits have also been suggested in some studies [Rohleder et al, 2016], despite the fact that development of psychosis is a well recognized risk of marijuana use, particularly when high-potency THC strains are used [Murray et al, 2017].

Nonetheless, the most consistent findings for benefits of medical cannabis are for the treatment of chronic pain (defined as being of at least 12-weeks duration), with most recent reviews reporting that medical cannabis can be effective for some patients in a variety of chronic pain conditions [Romero-Sandoval et al, 2017; Miller & Miller, 2017; MacCallum & Russo, 2018].

It is also important to note that it is likely that many future users of medical cannabis will be elderly [Mahvan et al, 2017], as they are often individuals with chronic pain and other conditions for which medical cannabis is used. Since most cannabis has been used by those aged 18-35 [Karila et al, 2014], there has been relatively little insight into this issue and little research in this group to date. Complicating this is the use of a wide variety of other medications in the elderly and so it will be important to understand what possible interactions may occur with specific medical cannabis products.

The biological effects of cannabinoids are mediated by two members of the G-protein coupled receptor family, cannabinoid receptors 1 (CB1R) and 2 (CB2R) [Zou and Kumar, 2018]. The CB1R is the prominent subtype in the central nervous system. Furthermore, although cannabinoids modulate signal transduction pathways and exert profound effects at peripheral sites "their psychoactive effects have largely limited their use in clinical practice." [Zou and Kumar, 2018]. In particular, THC appears responsible for most side-effects and negative outcomes from the use of cannabis [MacCallum & Russo, 2018; Rohleder et al, 2016].

Widely seen adverse events associated with the use of both recreational marijuana and medical cannabis have included anxiety, depression, psychotic symptoms, neurocognitive impairments as well as changes in appetite, nausea, lack of motivation, dry mouth, dizziness, postural hypotension, and coughing or wheezing [Allan et al, 2018; Hall & Degenhardt, 2014; Cohen & Weinstein, 2018; Murray et al, 2017].

There may also be an increase in suicidal thoughts [Karila et al, 2014] and a decrease in driving skills with an associated increased risk of motor vehicle accidents [Bondallaz et al, 2016; Karila et al, 2014]. Medical cannabis can cause cardiovascular side-effects such as tachycardia [Pacher et al, 2018] and respiratory issues, but it is uncertain if the respiratory issues are only present when medical cannabis is inhaled [Russell et al, 2018]. Longer-term use has been suggested to cause adverse effects on adolescent psychosocial development, [Karila et al 2014; Hall & Degenhardt, 2014].

The potential link between cannabinoids and psychosis is greater with earlier age of exposure to cannabinoids, childhood abuse genetic vulnerability, chronicity of use, and the use of medical cannabis with higher THC content [D'Souza et al, 2016; MacCallum & Russo, 2018; Rohleder et al, 2016; Murray et al, 2017].

Given this list of side-effects, it is therefore somewhat reassuring to note that some studies do not suggest that chronic cannabis use significantly increases the risk of anxiety disorder, major depressive disorder, or suicidal thinking [Feingold et al, 2017; Danielsson et al, 2016].

Additionally, the clinical impact of a specific product is hard to predict, since potentially negative impacts of THC may be, in part, be ameliorated by cannabidiol (CBD). It is of interest that CBD on its own has been suggested to have "anxiolytic, antipsychotic, antiemetic and anti-inflammatory properties." [Bergamaschi et al, 2011]. For this reason, CBD has been studied for possible therapeutic benefits in humans. Studies have suggested CBD may be safe but "further studies are needed to clarify reported in vitro and in vivo side effects" although the same authors note that in the past chronic use and high doses up to 1,500 mg/day of CBD were reportedly to be well tolerated in humans. [Bergamaschi et al, 2011]. Supporting this is an open label study in recreational cannabis users where they received 200 mg/day of CBD, which improved cognitive functioning with no side-effects reported [Solowij et al, 2018].

While there has been significant development in growing different strains of cannabis, specifically modified to produce varying ratio's of THC and CBD [Schachtsiek et al, 2017], there is little research evidence suggesting what the most clinically beneficial ratio might be. Strains with high THC content are used for recreational purposes, whereas those with high CBD content (usually combined with low THC content) are suggested for medical purposes. However, there is minimal clinical research to date identifying which specific THC/CBD ratio's may be safest clinically. Also, given the large number of other cannabinoids, and the possibility that some of these and/or their metabolites may have clinical impacts, it is likely to be necessary to test each individual product for both side-effects and safety since they will have significant variability. This also applies to the mode of administration (smoking, 'vaping', or any variety of oral ingestion), since it is likely that the specific method of each will alter the clinical impact [Russell et al, 2018].

Taking all current information it is clear that the use of medical cannabis for therapeutic purposes can pose potential risks to users. Examining this in a standard manner for a wide variety of products is important to allow meaningful comparisons regarding the risks to individuals. All information to date strongly indicates the need for an appropriate scale specifically designed to determine both positive clinical benefits as well as adverse events when using specific medical products. It was recognition of this major need that led to the development of the Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©). Such a scale needs to be able to measure changes with treatment, and for some specific clinical symptoms (such as sleep or anxiety) needs to be able to detect both positive clinical benefits, as well as when adverse events occur, as both have been reported.

METHODOLOGY

The goal of the research was to identify adverse events associated with the use of medical cannabis. In particular, the focus was on those adverse events that were (1) frequent, or (2) which were uncommon but could cause significant distress, or (3) which were severe and posed potentially serious clinically outcomes (even if very infrequent).

A PubMed search was carried out, limited to the past 10 years, using the following MESH terms: "Cannabis"[All Fields] OR "Medical Marijuana"[All Fields] AND "adverse effects"[All Fields] (n=3,670). The research particularly focused on those Phase III double-blind placebo-controlled treatment studies since these were most likely to have more rigorous measures (using MESH terms (phase[All Fields] AND III[All Fields] AND ("double-blind method"[MeSH Terms] OR ("double-blind"[All Fields] AND "method"[All Fields]) OR "double-blind method"[All Fields] OR ("double"[All Fields] AND "blind"[All Fields]) OR "double blind"[All Fields]) AND ("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields]) AND controlled[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND "studies"[All Fields] AND ("cannabis"[MeSH Terms] OR "cannabis"[All Fields])).

In addition to these articles, further information was gained from the Cochrane Database which has 21 reviews which include the term “cannabis” in the title, abstract, or keyword, and which were published between 2006 to 2018. Of these we particularly focused on the 9 reviews the examined the use of cannabis for treatment.

RESULTS

The search involving Phase III studies only generated a total of 559 articles for assessment, as well as some additional publications in the Cochrane Database which were not included in this number. It should be noted that this number of publications also included poster presentations and not just full peer-reviewed articles. It should also be noted that many of these studies excluded cannabis-naive patients (i.e those who had never had cannabis before), and also many excluded many patients with a past psychiatric history [e.g. Wilsey et al, 2013]. Thus, while the goal was to understand likely side-effects of medical cannabis use to better design a measuring scale, in terms of the percentage occurrence of adverse events these studies are likely to have underestimated the number of these that would occur in a larger population. Many of such individuals will not have had medical cannabis previously, and may therefore be more susceptible to adverse events.

From these studies the range of adverse effects as previously specified was determined, (1) frequent, or (2) uncommon but may cause significant distress, or (3) severe and posed potentially serious clinically outcomes (even if very infrequent. Publications were also examined to determine possible adverse events that were not included in any of these three groups (such as infrequent but minor adverse events). Additionally, before finalizing any scale it was recognized that is was also important to capture potential positive clinical changes in the subject areas of primary interest (pain, anxiety, sleep). From all of the above, it was determined that there were 12 groups of symptoms that should be included in the scale (Table 1).

To obtain external validation, we presented this list to a group of clinicians with extensive experience of prescribing medical cannabis for a variety of clinical purposes. We asked these individuals if we had missed any clinical benefits or adverse events when using medical cannabis. They confirmed that this list captured both the medical benefits and the adverse events that they experienced in the vast majority of patients. Also of note was that feedback from this group clarified that in the vast majority of cases both clinical benefits and adverse

events are evident within the first 3 days, and therefore this is an appropriate time for assessment of change.

Once this list of subject areas (Table 1) was validated, a more detailed list of questions was captured (Table 2).

SOPHISTICATED SCALE DESIGN

Designing electronic questionnaires can be complex (Minto et al, 2017), and a number of factors can increase the reliability and efficacy, particularly when used in clinical trials (Edwards, 2010). These issues were addressed in the current scale design. Specifically, questions are divided into one of 5 groups, each which have 5 questions. All questions within a specific group are either 'positive' (i.e. the best outcome is 4) or 'negative' (i.e. the best outcome if 0). The groups of questions are randomized to minimize an order effect, thus each time an individual repeats the questionnaire the questions will be in a different order.

The online nature and design of the scale includes the use of internal logic. Question groups are presented to individuals in variable order, with between 'positive' and 'negative' groups of answers. This will minimize issues with automatic completion, and the inbuilt internal logic will allow data from those who have contradictory answers to be disregarded. For example, in question 12 if individuals score 0 ("Did you find that you are **less hungry** than usual during the past 3 days ?") but score positively on question 13 ("Did you find that you are **more hungry** than usual during the past 3 days ?") it will prevent the data from the individual being considered in any subsequent data analysis. The question order is also varied randomly at each time they individual sees the MACESS© to minimize any biases that could potentially be caused by effects of question order on the results.

DISCUSSION AND CONCLUSIONS

This novel scale, the Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©), is designed to help address the medical information gap when using medical cannabis. More specifically, such a scale can help both individual consumers and those who recommend products by identifying the likely clinical benefits and side-effects when using specific medical cannabis products. It can also provide a common framework for clinical research studies and for users of medical cannabis to allow comparisons between products . It is available for potential individual users of medical cannabis, pharmacists, medical cannabis retailers, and for medical cannabis producers. It is intended that open access to the data, and frequent peer-reviewed publications and medical information will allow useful clinical comparisons to be made

The design of the scale, including the inbuilt logic and variance of question order mitigates many of the potential biases that occur with most electronic questionnaires and scales. At this time there are no other similar instruments. The simplicity of the MACESS©, combined with a single scoring number, will also allow easy comparisons between products. As noted, the scale consists of 25 questions with each question being scored from 0 – 4, giving a range of total potential scores between 0 – 100. With the MACESS© a high score indicate a well tolerated and effective product, while a low scores indicates significant adverse events and/or lack of positive clinical changes. It is available online and can be used to measure change following prospective use as well as for cross-sectional information. It is intended to both users and researchers examining benefits and problems with specific medical products, and can provide an easily understood single number for overall product comparisons.

References

Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. Eur J Intern Med. 2018 Mar;49:2-6.

Abrams DI. The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report. Eur J Intern Med. 2018 Mar;49:7-11.

Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, Lindblad AJ, Korownyk C, Kolber MR. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Can Fam Physician. 2018 Feb;64(2):e78-e94.

Andrade C. Cannabis and neuropsychiatry, 1: benefits and risks. J Clin Psychiatry. 2016 May;77(5):e551-4.

Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011 Sep 1;6(4):237-49.

Bondallaz P, Favrat B, Chtioui H, Fornari E et al. Cannabis and its effects on driving skills. Forensic Sci Int. 2016 Nov;268:92-102.

Caulkins JP, Bao Y, Davenport S, Fahli I, Guo Y, Kinnard K, Najewicz M, Renaud L, Kilmer B. Big data on a big new market: Insights from Washington State's legal cannabis market. Int J Drug Policy. 2018 Jul;57:86-94.

Capler R, Walsh Z, Crosby K, Belle-Isle L, et al. Are dispensaries indispensable? Patient experiences of access to cannabis from medical cannabis dispensaries in Canada. Int J Drug Policy. 2017 Sep;47:1-8.

Cohen K, Weinstein A. The Effects of Cannabinoids on Executive Functions: Evidence from Cannabis and Synthetic Cannabinoids-A Systematic Review. Brain Sci. 2018 Feb 27;8(3). pii: E40.

D'Souza DC, Radhakrishnan R, Sherif M, Cortes-Briones J, et al. Cannabinoids and Psychosis. Curr Pharm Des. 2016;22(42):6380-6391.

Edwards P. Questionnaires in clinical trials: guidelines for optimal design and administration. Trials. 2010;11:2.

Galgatte UC, Jamdae VR, Aute PP, Chaudhair PD. Study on requirements of bioequivalence for registration of pharmaceutical products in USA, Europe, and Canada. Saudi Pharm J. 2014 Nov;22(5):391-402 Grof CPL. Cannabis, from plant to pill. Br J Clin Pharmacol. 2018 Apr 27.

Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, et al. Mild Cognitive Impairment. Lancet. 2006; Apr;3679518;1262-1270

Hall W, Degenhardt L. The adverse health effects of chronic cannabis use. Drug Test Anal. 2014 Jan-Feb;6(1-2):39-45.

Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017 Jun 1;2(1):139-154.

Ivy SP, Siu LL, Garrett-Mayer E, Rubinstein L, Approaches to Phase 1 Clinical Trial Design Focused on Safety, Efficiency, and Selected Patient Populations: A Report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee Clin Cancer Res. 2010 Mar 15;16(6):1726-36.

Jikomes N, Zoorob M. The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products. Sci Rep. 2018 Mar 14;8(1):4519.

Kelly BF, Nappe TM. Toxicity, Cannabinoids. StatPearls Publishing; Treasure Island (FL): 2018.

Ko GD, Bober SL, Mindra S, Moreau JM. Medical cannabis - the Canadian perspective. J Pain Res. 2016 Sep 30;9:735-744.

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 Nov 30;15(4):301-312.

MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19.

Mahvan TD, Hilaire ML, Mann A, Brown A, et al. Marijuana Use in the Elderly: Implications and Considerations. Consult Pharm. 2017 Jun 1;32(6):341-351.

Miller RJ, Miller RE. Is cannabis an effective treatment for joint pain? Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 107(5):59-67.

Minto C, Vriz GB, Martinato M, Gregori D. Electronic questionnaires design and implementation. Open Nurs J. 2017; 11: 157–202.

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018 Mar 7;3:CD012182.

Murray RM, Englund A, Abi-Dargham A, Lewis DA, Di Forti M, Davies C, Sherif M, McGuire P, D'Souza DC. Cannabis-associated psychosis: Neural substrate and clinical impact. Neuropharmacology. 2017 Sep 15;124:89-104.

Pacher P, Steffens S, Haskó G, Schindler TH, Kunos G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. Nat Rev Cardiol. 2018 Mar;15(3):151-166.

Park JY, Wu LT. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. Drug Alcohol Depend. 2017 Aug 1;177:1-13.

Perucca E. Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? J Epilepsy Res. 2017 Dec 31;7(2):61-76.

Rohleder C, Müller JK, Lange B, Leweke FM. Cannabidiol as a Potential New Type of an Antipsychotic. A Critical Review of the Evidence. Front Pharmacol. 2016 Nov 8;7:422. eCollection 2016.

Romero-Sandoval EA, Kolano AL, Alvarado-Vázquez PA. Cannabis and Cannabinoids for Chronic Pain. Curr Rheumatol Rep. 2017 Oct 5;19(11):67.

Rong C, Carmona NE, Lee YL, Ragguett RM, Pan Z, Rosenblat JD, Subramaniapillai M, Shekotikhina M, Almatham F, Alageel A, Mansur R, Ho RC, McIntyre RS. Drug-drug interactions as a result of co-administering Δ9-THC and CBD with other psychotropic agents. Expert Opin Drug Saf. 2018 Jan;17(1):51-54.

Russell C, Rueda S, Room R, Tyndall M, et al. Routes of administration for cannabis use - basic prevalence and related health outcomes: A scoping review and synthesis. Int J Drug Policy. 2018 Feb;52:87-96.

Russo EB. Current Therapeutic Cannabis Controversies and Clinical Trial Design Issues. Front Pharmacol. 2016 Sep 14;7:309.

Sanford AM. Mild Cognitive Impairment. Clinics in Geriatric Med. 2017 Aug;33(3);325-337.

Schachtsiek J, Warzecha H, Kayser O, Stehle F. Current Perspectives on Biotechnological Cannabinoid Production in Plants. Planta Med. 2018 Mar;84(4):214-220.

Shram MJ. Differences in the in vitro and in vivo pharmacokinetic profiles of once-daily modified-release methylphenidate formulations in Canada: examination of current bioequivalence criteria. Clinical Therapeutics. 2012, 34 (5), 1170–1181.

Silverstone PH. Concise assessment for depression (CAD): a brief screening approach to depression in the medically ill. J Psychosom Res. 1996 Aug;41(2):161-70.

Solowij N, Broyd SJ, Beale C, Prick JA et al. Therapeutic Effects of Prolonged Cannabidiol Treatment on Psychological Symptoms and Cognitive Function in Regular Cannabis Users: A Pragmatic Open-Label Clinical Trial. Cannabis Cannabinoid Res. 2018 Mar 1;3(1):21-34.

Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety. 2017 Nov;34(11):1006-1017..

Wakim PG, Rosa C, Kothari P, Michel ME. Relation of study design to recruitment and retention in CTN trials. Am J Drug Alcohol Abuse. 2011 Sep;37(5):426-33.

Walsh Z, Gonzalez R, Crosby K, S Thiessen M et al. Medical cannabis and mental health: A guided systematic review. Clin Psychol Rev. 2017 Feb;51:15-29.

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73.

Wilsey B, Marcotte TD, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013 Feb; 14(2): 136-148.

Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int J Mol Sci. 2018 Mar 13;19(3). pii: E833.

Table 1: Main groups of Potential Clinical Benefits and Adverse Events

1. Change in measures of Pain
2. Change in measures of Sleep
3. Change in measures of Anxiety
4. Change in measures of Depression
5. Paranoia / Psychosis
6. Cognitive changes
7. Poor Motivation / Low energy
8. Nausea / Gastro-intestinal Issues
9. Change in Appetite / Weight
10. Dry Mouth
11. Dizzyness / Postural Hypotension
12. Coughing / Wheezing

Table 2: Detailed question list for the Medical Assessment of Cannabis Efficacy and Side-effects Scale (MACESS©)

Question number	Thinking about the past 3 days:	Number of answer options	Range of possible scores
1	Did you experience significant **pain** during the past 3 days ?	5	0 - 4
2	Did the pain keep you **up at night** during the past 3 days ?	5	0 - 4
3	What was the most **severe** pain you have experienced AT ANY TIME during the past 3 days ? *NB - individuals able to mark a number from 0 - 10. Scoring converted (0 = converted score of 0; 1,2,3= converted score of 1;* 4,5 = converted score of 2; 6,7,8 = converted score of 3; 9,10 = converted score of 4)	11 (0-10)	0 - 4
4	Could you fall asleep easily during the past 3 days ?	5	0 - 4
5	Could you stay asleep easily during the past 3 days?	5	0 - 4
6	Did you feel you get enough sleep during the past 3 days ?	5	0 - 4
7	Did you feel anxious during the past 3 days ?	5	0 - 4
8	Did you get panic attacks or physical symptoms of anxiety during the past 3 days ?	5	0 - 4
9	Did anxiety stop you doing your regular activities during the past 3 days ?	5	0 - 4
10	Did you feeling depressed or sad during the past 3 days ?	5	0 - 4
11	Did you lose interest in your usual activities during the past 3 days ?	5	0 - 4
12	Did you find that you are less hungry than usual during the past 3 days ?	5	0 - 4
13	Did you find that you are more hungry than usual during the past 3 days ?	5	0 - 4
14	Did you feel more nausea (feeling physically sick) than usual during the past 3 days ?	5	0 - 4
15	Were you been concerned that people were trying to follow you, spy on you, or harm you at any time during the past 3 days ?	5	0 - 4
16	During the past 3 days did you have any unusual experiences, such as hearing sounds or voices when others couldn't ?	5	0 - 4
17	Over the past 3 days have you felt your memory is worse, or that you are forgetting things more often ?	5	0 - 4
18	Over the past 3 days have you found it harder to concentrate than usual ?	5	0 - 4
19	Do you think it has been harder to carry out your regular tasks because of your memory or concentration over the past 3 days ?	5	0 - 4
20	Have you found it harder to motivate yourself to do things over the past 3 days ?	5	0 - 4
21	Have you found that your mouth felt more dry than usual over the past 3 days ?	5	0 - 4
22	Have you felt more dizzy or lightheaded in general over the past 3 days ?	5	0 - 4

23	Have you found that when you stand up over the past 3 days you are more likely to get dizzy or lightheaded ?	5	0 - 4
24	Have you found that you are coughing or wheezing more over the past 3 days ?	5	0 - 4
25	Overall, are you feeling better or worse during the past 3 days ?	5	0 - 4
Total possible range of scores			0-100