Review of Current Research Regarding the use of Medicinal Cannabis for MS and MND Symptom Management

A report for Multiple Sclerosis New Zealand and Motor Neurone Disease New Zealand

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1.0. Introduction

It is important to ensure that people with Multiple Sclerosis (PwMS) and Motor Neurone Disease (PwMND) in NZ have appropriate access to the latest proven treatment options to manage their MS or MND. The purpose of this report is to:

1. Review and report on current research regarding the use of medicinal cannabis for multiple sclerosis (MS) and motor neurone disease (MND) symptom management;
2. Examine the risks and the risk/benefit profile of using medicinal cannabis; and
3. Review the current international recommendations for the safe use of medicinal cannabis for MS and MND symptom management.

2.0. Definition of Medicinal Cannabis

When discussing medicinal cannabis, it is important to define exactly what this term refers to. The term 'medicinal' refers to the situation in which cannabis is used. With respect to the proposed changes to New Zealand law[1], this refers to the use of cannabis by those with a medical need. Under the proposed changes, only those who can provide evidence that they suffer from a condition where cannabis may alleviate the pain and suffering associated with that condition and who have the written support of their medical practitioner, may apply for a Medicinal Cannabis Identification Card. This card would allow the holder to "consume, smoke or otherwise use any plant of the genus Cannabis or any preparation containing any tetrahydrocannabinols; and procure or have in his possession, an amount of any plant of the genus Cannabis or any preparation containing any tetrahydrocannabinols as agreed upon by the medical practitioner caring for the card holder and the card holder themselves"[1].

Medicinal cannabis is prepared from the dried flowering tops and leaves of the female *Cannabis* plant, which belongs to the *Cannabaceae* family. It is also commonly called medical marijuana, or herbal marijuana. For the purposes of this review, it will be henceforth referred to as medicinal cannabis. Compare this to pharmaceutical cannabis products which are those derived from the cannabis plant, in a pharmaceutical laboratory, or comprised of synthetic compounds analogous to those known to exist in the cannabis plant. They usually contain one or two of the pharmacologically active compounds (cannabinoids) which are unique to the cannabis plant; delta-9 tetrahydrocannabinol (ΔTHC) and cannabidiol (CBD). There are a multitude of randomised controlled trials which illustrate the efficacy of pharmaceutical cannabis products for a variety of symptoms. It is based on this evidence that MedSafe NZ have approved the pharmaceutical cannabis product Nabiximols (trade name Sativex) for use in New Zealand[2]. However, this review focuses on the evidence for the therapeutic benefits of medicinal cannabis.

Medicinal cannabis can be used in several different methods, each with their own risk/benefit profiles, which will be further discussed in this report. These include ingestion of the raw product, smoking, inhalation of vapour, and oral administration via tinctures and cannabis oil.

Cannabis first became a controlled drug in New Zealand in 1927, when it became listed in The Dangerous Drugs Act[3]. In 1965 New Zealand passed the Narcotics Act which banned the use of many drugs, including cannabis[4]. This was passed in accordance with international obligations under the 1961 Single Convention on Narcotic Drugs. Currently, the cannabis seed and plant is classified as a Class C illegal drug under the Misuse of Drugs Act 1975 [5]. Under this Act, it is an offence to possess, cultivate or traffic cannabis. The penal consequences for being convicted of these offences range from 3 months imprisonment and/or a $500 fine for possession of cannabis, to up to 8 years imprisonment for supply or manufacture.

Around the world, the legality of cannabis varies greatly. In some nations is it decriminalised, or small amounts for personal use are permitted. To date, in South Africa, Uruguay, Colombia, The Netherlands and Spain, cannabis is a completely legal drug. Medicinal cannabis is currently legal in Greece, Peru, Chile, Switzerland, Croatia, Italy, Macedonia, Poland, Canada, Puerto Rico, Turkey, The Czech Republic, Australia, Mexico, Germany, Israel, and some states of the USA.

The USA Food and Drug Administration (FDA) is often looked to by international governments and policy makers as a world leader in the regulation of new medicines. Despite several American State governments allowing the use of medicinal cannabis, and some allowing recreational cannabis use, cannabis remains an illegal drug at the Federal government level. The USA Drug Enforcement Administration (DEA) has classified marijuana as an illegal Schedule I drug which has no accepted medical use and will not reschedule marijuana without an official determination of the safety and efficacy from the (FDA). In order to do this, the FDA requires controlled, double-blind clinical trials. Such trials would be able to definitively prove the therapeutic benefits of cannabis. This sounds simple and logical, however rigorous clinical trials are very expensive. To offset this cost, the majority of new medicines are trialled by companies looking to patent a product, which they can then profit from. The problem with cannabis is that it is not a patentable product. Owing to this lack of potential financial rewards, few have pursued the path of carrying out research using the sophisticated, difficult, and expensive procedures required by best practice. Despite these challenges, there still exists a large amount of support worldwide to examine the potential therapeutic benefits of medicinal cannabis. This is examined in this report.

3.0. The Benefits of Medicinal Cannabis for MS and MND Symptom Management

3.1. Neurodegenerative Neuromuscular Disease

Both MND and MS are neuromuscular and neurodegenerative diseases. Multiple sclerosis is a chronic demyelinating disease of the nervous system. The myelin sheath which insulates the nerve cells is attacked and its integrity compromised. The inflammation related to this, together with neurodegeneration, are responsible for a myriad of symptoms. These can vary from case to case, and by the type of MS a person has. The most common symptoms are vision impairment, muscle weakness, muscle spasms, muscle wasting, paresthesias, pain, speech impediments, tremors, dizziness, fatigue and

cognitive impairments. Because MS is not curable, treatment of MS is focused on symptom management.

Motor Neurone Disease is the collective name for a group of diseases which affect either the upper or lower motor neurons, or both. Amyotrophic lateral sclerosis (ALS) is the most common and well-known type of MND and has both upper and lower motor neuron involvement resulting in limb muscle weakness, stiffness, fasciculation and wasting. Muscles controlling speech, swallowing and breathing are often later affected. The inverse is true in progressive bulbar palsy (PBP), where the muscles which control swallowing and speech are first affected, often spreading to the limbs later. Progressive muscular atrophy (PMA) primarily causes damage to the lower motor neurons and differs from ALS and PBP in that it often progresses more slowly and has a longer survival time. Primary lateral sclerosis (PLS) is one of the rarer forms of MND and only involves the upper motor neurons only and causes weakness mainly in the lower limbs. Lifespan can be unchanged with PLS, however this form can develop into ALS.

Although both diseases are neuromuscular and neurodegenerative in nature, MS and MND have vastly different causes and mechanisms. Despite this, they have the common symptoms of muscle spasms, weakness and wasting, pain, and fatigue.

3.2. Pain

Unfortunately, chronic pain is a frequent and debilitating component of both MS[6,7] and MND[8]. Pharmacological treatment of pain in neurodegenerative neuromuscular conditions is challenging due to the many underlying pathophysiological mechanisms. Pain can be neuropathic, related to muscle spasms, nociceptive, or any combination of these[9–11].

A study of pain was conducted in 10,176 PwMS enrolled on the North American MS Patient Registry (NARCOMS)[12]. Respondents were grouped into those experiencing mild, moderate or severe pain. The study revealed that 29%, 31%, and 39% of patients (with mild, moderate or severe pain, respectively), were dissatisfied with their physicians' efforts to manage their pain symptoms. Satisfaction with physicians' efforts to manage symptoms was inversely associated with pain severity ($p < .0001$). The authors note that this dissatisfaction is partly due to the inadequate drug therapies available.

Prior to 1983, MND was not considered to be a painful condition. A landmark paper by Drake[13] helped to change the perspective of the medical profession and led to many studies investigating pain in MND. In a more recent German cross-sectional survey of patients with ALS, 78% of ALS patients reported pain[14]. And this pain was shown to have a significant effect on enjoyment of life and mood compared to age-matched controls. However, only 47% of the patients experiencing pain reported receiving treatment for it, highlighting that pain in MND is not a well understood or effectively treated symptom.

Neuropathic pain can be defined as pain arising from damage to the nervous system[15]. The management of neuropathic pain generally focuses on treating symptoms because, such as in MS and MND, the cause of this pain can often not be treated. The first line treatments for neuropathic pain are currently pregabalin (a GABA analogue), gabapentin (a GABA inhibitor), duloxetine (a serotonin-noradrenaline reuptake inhibitor) and various tricyclic antidepressants[16]. However, most of these treatments are only moderately effective, based on the high number needed to treat (NNT, the number of patients necessary to treat to obtain one responder more than the comparison treatment, usually a placebo) for obtaining 50% of pain relief[17]. Additionally, a large number of the pharmacological treatments for neuropathic pain are associated with adverse effects which limit their use in the clinical setting[12].

The practice of using cannabis to relieve pain goes back thousands of years. Now that the molecular mechanisms of how this works have been elucidated, the practice is now grounded in evidence-based medicine. In the 1980's, the cannabinoid receptor type 1 and 2 (CB1 and CB2) were discovered, opening doors for research into how cannabis acts on the brain and the possible therapeutic benefits. CB1 and CB2 are G-protein coupled receptors which are located throughout the brain and nervous system and bind to both natural, endogenous cannabinoids called endocannabinoids, and the cannabinoids present in cannabis[18]. CB-1 receptor activation suppresses the sensation of pain by influencing the release of the neurotransmitters acetylcholine, norepinephrine, gamma-amino butyric acid (GABA), glycine, dopamine, serotonin and cholecystokinin (CCK) from the presynaptic terminal. This likely occurs through reduced membrane depolarisation and exocytosis due to the modification of the calcium and potassium channels[19]. These molecular mechanisms can be seen in real life organisms, such as a mouse model of neuropathic pain. In 2014, a study showed that endocannabinoids decrease neuropathic pain-related behaviour in mice, directly through the activation of CB1 and CB2 receptors[20]. This proved that the binding of cannabinoids to their receptors caused downstream signalling events which resulted in a specific reduction in neuropathic pain.

There are a multitude of published studies investigating the effect of inhaled cannabis on neuropathic pain. They vary in methods, outcome reporting, participant inclusion and overall quality. This variety has historically made it difficult to draw definitive conclusions about the effectiveness of cannabis as treatment for pain. In order to tackle this, a recent study compiled the data from several randomised controlled trials (RCT) to investigate if there was reliable evidence. They completed a meta-analysis of individual patient data from these trials which all investigated the effects of inhaled cannabis for the treatment of chronic neuropathic pain[21]. Usually, meta-analysis pools aggregate data taken from published study reports, however this study obtained the original data of the individual subjects obtained from the primary study authors in order to provide more power to the analysis. Data from five randomised controlled trials were included. The study classified participants as "responder" if they had a 30% or more reduction in pain scores compared to before starting treatment. An odds ratio of 3.2 was found, meaning that those who inhaled cannabis were 3.2 times more likely to have a 30% reduction in pain score, compared to those who inhaled a placebo. The NNT was found to be 5.6. Compare this to gabapentin, the current frontline therapy for neuropathic pain, which has a NNT of 7.2[17]. The lower the NNT the better, with the ideal NNT being 1, where everyone improves with treatment and no one improves with control. This type of powerful analysis proves that inhaled cannabis is an effective treatment for neuropathic pain.

Chronic pain, a symptom of both MND and MS, is well established to be associated with profound negative effects on personal, social, and psychological well-being[22–24]. A cross-sectional survey of European patients with neuropathic pain showed that this pain interferes with daily functioning, despite receiving treatment[25]. A 2016, prospective, open-label study looked at quality of life outcomes for patients using medicinal cannabis for pain[26]. A requirement of enrolment was that participants had had chronic pain for at least 3 months, and that they had either had unsatisfactory pain relief or intolerable adverse effects with at least two analgesics from two different drug classes at full dose. The participants had a mixture of neuropathic and non-neuropathic pain. Cannabis treatment was added to the participant's existing pain relief regime. Not only did 69.5% of participants report a significant reduction in pain scores, but there was also a significant improvement in quality of life. Additionally, 44% of the

participants who were taking opioids at the start of the study had completely discontinued their use by the end of the study.

The effect of cannabis on pain has also been looked at specifically in MS. Most notably is the CAMS study in which 33 neurology and rehabilitation centres in the UK participated[27]. In this large, multi-centre, randomised, placebo-controlled trial 630 PwMS were treated with either cannabis extract, ΔTHC, or placebo. Many different outcome measures were investigated, and pain was assessed after 15 weeks of treatment. When asked about pain, a statistically significant proportion of participants randomised to the cannabis extract group reported an improvement, compared to the placebo group. Following this main study, participants were invited to continue using their allocated treatment for a total of 12 months[28]. Rating scales again showed highly significant effects of cannabis extract on pain, indicating that the treatment is also effective in the longer-term.

Studies investigating cannabis in MND are few and far between. In fact, there is very little evidence even for any of the current frontline therapeutic treatments for pain management in MND. A 2013 Cochrane review illustrated this point by concluding that at the time, there were no randomised or quasi-randomised controlled trials on drug therapy for pain in ALS or MND[11]. This is largely owing to the severe nature of the disease, the rapid progression and the severely reduced lifespan that often accompanies it. The time of the PwMND is precious. Therefore, most studies and clinical trials are focused on potentially disease-modifying treatments. The treatment options for pain in MND are usually based on the experience of the physician and the efficacy shown for treatment of similar pain in other diseases. There are, however, observational studies which have looked at cannabis use in PwMND. Amtmann et al[29] showed that cannabis may be effective for pain in MND and that for those able to obtain cannabis, they found it preferable to prescription medication for managing their symptoms. However, the study noted that the biggest reason patients did not use cannabis was due to the difficulty in obtaining it, either due to legal or financial reasons or lack of safe access.

3.3. Spasticity

Spasticity in muscles is a state where the muscle is pathologically, involuntarily contracted. This causes tightness, stiffness and pain in muscles and can interfere with normal movement. These contractures can be brief spasms, or more sustained contractions. Reflexes can also be hyperactive and may persist for too long. Spasticity is a feature of both MS and MND.

The effects of cannabinoids on spasticity have been studied extensively. As early as 2000, it was discovered that cannabinoids could control spasticity in the experimental mouse model of MS[30]. And as previously discussed, the pharmaceutical cannabis-based medicine, Sativex, has now been approved for use in New Zealand by MedSafe NZ, for "persons with severe spasticity who have not responded to any other anti-spasticity medication and who show a clinically significant improvement in spasticity-related symptoms during an initial trial of therapy"[2]. There is also a large body of evidence for the use of medicinal cannabis to treat spasticity. A randomised, placebo controlled trial of smoked cannabis in PwMS was published in 2012, with the primary outcome measure being the Modified Ashworth Scale[31]. The Modified Ashworth Scale[32] is an objective ordinal scale (0–5 points) ranking the intensity of muscle tone as assessed by a physician. Participants were able to continue using their already prescribed medication for spasticity and any disease-modifying treatments they were currently using. Smoking

cannabis was shown to have a beneficial effect on treatment-resistant spasticity, with a reduction in patient scores on the Modified Ashworth Scale of an average of 2.74 points more than placebo ($p < 0.001$) being identified.

In the large, previously mentioned, CAMS study which investigated the effects of cannabis on MS, although the analysis did not show significant benefit using the primary outcome measure (the Ashworth Scale), patient-reported measures for spasticity were significantly improved in the cannabis-treated group[27]. However, in the 1 year blinded follow-up to this study, there was a small significant treatment effect on muscle spasticity seen in the Ashworth score, and spasticity, spasms, pain and energy all significantly improved in patient subjective ratings[28]. Similar results were also seen in another double-blind, randomised, placebo-controlled, multicentre study investigating cannabis extract use in PwMS[33]. After 12 weeks of treatment, participants reported a 29.4% improvement in muscle stiffness, compared to those in the placebo group.

3.4. Weight loss in MND

It is well established that nutritional status is an important prognostic factor for survival in MND[34]. If weight loss results in a body mass index (BMI) below 18.5 kg/m², this leads to a 7.7 times higher mortality rate, compared to MND patients with normal weight[34]. Weight loss in MND is usually unintentional and can be caused by malnutrition, loss of appetite, cachexia, muscle atrophy or a combination of these. It is a complex problem with a severe consequence. Studies in healthy populations have shown that cannabis use is associated with increased eating[35–37] therefore cannabis has been studied as a possible therapy for loss of appetite and weight loss in several disease states. Weight loss is also an issue in HIV-positive patients and is similarly associated with poorer survival outcomes. A study of smoked cannabis and the synthetic cannabinoid dronabinol, showed that the use of both of these substances results in increased food intake in people who are HIV-positive[38]. A further study, which looked at dronabinol alone, confirmed this result for increased appetite, and showed that this change reversed the weight loss seen in 63% of patients taking dronabinol[39]. Researchers have been able to show that in HIV patients, dronabinol caused this increase in appetite and consequent weight gain by upregulating ghrelin and leptin and downregulating PYY; all hormones which are well established to control appetite[40]. It is because of this effect that the US FDA has approved dronabinol (tradename Marinol) for the treatment of anorexia associated with weight loss in patients with AIDS[41].

3.5. Disease Progression

Cannabinoids have also been implicated as agents that may slow disease progression in both MS and MND. In the experimental rat model of MS, there is a decrease in the number of CB1 receptors present in the brain[42]. And in humans, CB1 and CB2 receptors can be seen in the cell subtypes which are present in the plaques found in the brains of PwMS[43]. Another study in the rat model of MS, showed that a reduction of endocannabinoid signalling is associated with the development of the disease state in these rats[44]. The authors then showed that they could reverse this decrease in CB1 signalling by giving compounds which act on the endocannabinoid system, and in turn, reduce the amount of neurological impairment in the animals. The CB2 receptor is also implicated as a target for reducing disease progression. Mice with experimental autoimmune encephalomyelitis (EAE), the rodent model of MS,

were given Gp1a, a compound which binds to and activates the CB2 receptor, and were observed along with those given a placebo treatment. The mice who received the CB2 agonist had lower disease incidence (60 versus 100% in vehicle-treated controls), a delay in disease onset, and displayed lower clinical scores, with statistically significant differences at both early and late disease stage. The findings in these rodent studies are remarkable, but how might they translate to humans? A 2007 study compared the EAE rodent model of MS with human patients. They measured endocannabinoid levels, metabolism and binding, and physiological activities in 26 patients with MS, 25 healthy controls and also in EAE mice[45]. Both MS in humans and EAE in rodents were associated with significant alterations in the endocannabinoid system. More specifically, they found increased synthesis, reduced degradation and increased levels of an endogenous cannabinoid called anandamide (AEA) in the brains of EAE mice in the acute phase of the disease, and also in the acute MS subjects. Not only does this study confirm the validity of studying EAE rodents as a model for MS, but it also further implicated the endocannabinoid system in the progression of MS.

Rodent models of MND have also indicated a role for the endocannabinoid system in the progression of the disease. One of the genetic mutations which can cause the familial ALS version of MND is a deleterious change to the superoxide dismutase 1 (SOD1) gene[46,47]. Since this was discovered, an experimental model of MND has been generated by artificially mutating the SOD1 gene in mice, which has allowed previously impossible research to be conducted into MND. SOD1 mice develop neurological disease which mimics MND, and shortens their lifespan. A study in 2006 looked at the effects of cannabinoids on these SOD1 mice. Researchers gave synthetic cannabinoids to the mice and also altered their genes so that they would have increased levels of cannabinoids. They found that the treated SOD1 mice had stronger leg muscles, which had more surviving motor units within them; 45% more motor neurons survived; the onset of disease was delayed; and the length of survival was significantly increased compared to the untreated SOD1 mice[48]. Another study gave daily injections of a CB2 agonist after the onset of symptoms in transgenic SOD1 mice. The mice that received this treatment survived, on average, 52% longer after the onset of symptoms than SOD1 mice who received a placebo[49]. Similar results have been seen by administering ΔTHC [50] and cannabinol [51]. The scientific evidence in animals and *in vitro* was reviewed in 2010 and at that stage, was described as "so compelling that it is reasonable to think that cannabis might significantly slow the progression of ALS, potentially extending life expectancy and substantially reducing the overall burden of the disease"[52]

4.0. The Risks Associated with Medicinal Cannabis Use

When investigating a new therapeutic agent, it is important to examine the risks associated with this use. Do the potential benefits to the patient outweigh the possible harm?

4.1. Dependence

Although cannabis is anecdotally thought to be non-addictive, users can develop substance dependence[53]. Substance dependence is a brain-based disorder characterised by compulsive use, inability to desist in the face of negative consequences, and withdrawal symptoms upon cessation[54]. Although the mechanisms mediating this addiction are not clearly elucidated, ΔTHC has been shown to stimulate dopamine release[54], a feature common to all addictive substances. Other studies have shown

that cannabis affects areas of the brain's addiction centres[55,56]. Cannabis withdrawal is listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) as a "substance-related and addictive disorder"[57] with the following criteria:

Table 1. DSM-5 Cannabis Withdrawal Diagnosis Criteria

Criterion A	Cessation of cannabis use that has been heavy and prolonged
Criterion B	Three or more of the following develop within several days after Criterion A. (a) Irritability, anger, or aggression; (b) nervousness or anxiety; (c) sleep difficulty; (d) decreased appetite of weight loss; (e) restlessness; (f) depressed mood; and (g) at least one of the following physical symptoms causing significant distress: stomach pain, shakiness/tremors, sweating, fever, chills, and headache.
Criterion C	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Criterion D	The symptoms are not due to a general medical condition and are not better accounted for by another disorder

American Psychiatric Association (2013). DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th ed.)

It is important to note that the not all cannabis users develop dependence. In fact, the percentage of users who develop dependence is relatively low compared to other drugs; approximately 9.1% of cannabis users develop dependence[58]. This is compared to 31.9% for tobacco users, 15.4% for alcohol users, 23.1% for heroin and 16.7% for cocaine[58]. It is also important to highlight that the risk of developing dependence is related to the age of the user at first use. Compared to people who first use cannabis at an age of 18 or over, those who start using cannabis younger than 18 have a 2-4 times greater risk of developing dependence within 2 years of their first use[59]. This increased risk is thought to be linked to the fact that the areas of the brain which that underlie addiction and are responsible for processing stress, reward, and executive function are still developing in the adolescent[54].

4.2. Impairment

In the short term, use of cannabis is associated with impaired short-term memory, impaired motor coordination and altered judgment[60]. These acute effects are transient and are seen in the time period where the individual is intoxicated (that is, feeling 'stoned' for around 5–120 minutes following use). These effects are largely caused by the ΔTHC component of cannabis[61], and are largely attenuated by the CBD component[62]. Because it is the ΔTHC which produces the "high", the breeding of illegal cannabis has focused on increasing the proportion of this within the plant, whereas CBD content has decreased to negligible levels. In the UK[63] and Australia[64], high-potency cannabis containing ~15% ΔTHC and less than 0.1% CBD is predominant. It is for this reason that driving a motor vehicle is not recommended while under the influence of cannabis. There is a proven relationship between the blood ΔTHC concentration and performance in controlled driving-simulation studies. A low dose of cannabis was found to be associated with increased speed and lateral position variability (weaving on the road), while a higher dose of cannabis was associated with decreased mean speed, increased mean and variability in headways (distance between vehicles) and longer reaction time[65]. According to a meta-analysis of driving and cannabis use studies, the overall risk of a driver being involved in a motor vehicle accident if intoxicated by cannabis is twice that of a driver who is not[66].

4.3. Cognitive Impairment

Both MND and MS can cause cognitive impairment. Frontotemporal dementia can occur with MND or alone and causes damage to nerve cells which can result in deterioration in behaviour and personality, language disturbances, or alterations in muscle or motor functions[67]. Cognitive impairment occurs in 40-65% of PwMS and typically involves complex attention, information processing speed, (episodic) memory and executive functions[68]. There is some evidence that cannabis use may worsen cognitive problems. A small study conducted cognitive function and neuropsychological tests in 25 PwMS who were regular cannabis users and 25 PwMS who did not use it at all. In the cannabis use group, 72% of the sample used cannabis daily, 24% weekly, and the remaining subject reported bi-weekly use. The cannabis users were found to perform significantly worse on measures of information processing speed, working memory, executive functions and other cognitive functions. Those who used cannabis were twice as likely to be considered cognitively impaired, than non-users[69]. It should be noted that although the study found a statistical difference between the two groups, only a very small sample size was used. Also, it is important to consider that 18 out of 25 subjects in the cannabis user group had used cannabis the evening prior to the testing.

4.4. Mental Illness

The link between cannabis use and mental illness has long been discussed. However, it is a very difficult topic to study for multiple reasons. Namely; it is difficult to predict who might develop a mental illness irrespective of cannabis use; assessing levels of cannabis use based on participant self-reported data is unreliable; and creating a study with random assignment to heavy cannabis use as the experimental condition is unethical. One randomised controlled trial in laboratory conditions, which allocated healthy participants to one dose of ΔTHC, showed that it can induce transient psychotic-like experiences[61]. However, these experiences resolved within a few hours and rarely caused distress, in contrast to psychotic disorder where experiences are prolonged and impairment often substantial. The association between cannabis and psychosis has not yet been proven to be causal. And cannabis use is neither necessary nor sufficient on its own to cause psychotic disorder as the risk factors for this multifactorial, complex disease are not deterministic. However, there is an association, and this must be examined. In epidemiological studies, cannabis use has been linked to an increased risk of developing psychotic disorders[70]. Several studies have shown an increased risk for the development of schizophrenia in cannabis users, including New Zealand's own Dunedin Birth Cohort Study. In the Dunedin Study, cannabis use by age 15 was associated with an increase in schizophreniform disorder at age 26, with a weaker association in those first using between age 15 and 18[71]. Similar associations have been seen in the Swedish Conscript Study where a dose-response relationship was discovered between cannabis use by age 18 and incident schizophrenia by age 45[72]; and in the California Hospital Study where a large association was found between diagnosis of cannabis use disorder and risk of later hospitalisation for schizophrenia when compared to a cohort of subjects who were hospitalised for appendicitis[73].

4.5. Risks Associated with Smoking

The most common method of cannabis use is inhalation of smoke from compacted and rolled leaves, similar to a cigarette. This poses a potential health risk as cannabis smoke contains a mixture of chemicals similar to those found in tobacco smoke. Although cannabis smoke does not contain nicotine, it does contain known carcinogens, such as ammonia, hydrogen cyanide, nitric oxide, aromatic amines, and hydrocarbons[74]. Despite this, epidemiologic evidence linking cannabis smoking and lung cancer is sparse. The best evidence comes from a large Swedish cohort study. In this study 49,321 men aged

between 18 and 20 years old were selected and followed for the rest of their lives. This particular analysis examined the risk of heavy cannabis use (defined as use of cannabis more than 50 times over the 40-year period of follow up) and lung cancer after 40 years of follow up. This "heavy" cannabis smoking was significantly associated with more than a twofold risk of developing lung cancer over the 40-year follow-up period[75]. Importantly, this risk is despite statistical adjustment for baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status. An increase in other respiratory symptoms are also seen in cannabis smokers. In the US National Health and Nutrition Examination Survey (NHANES III) study, both cannabis and tobacco smokers had increased likelihood of experiencing respiratory symptoms[76]. When adjusted for tobacco use, age, gender and current asthma, cannabis smokers were 2 times more likely to have chronic cough, 1.89 times more likely to have chronic phlegm and 2.98 times more likely to have wheezing. Strikingly, the cannabis users had rates of respiratory symptoms comparable to those of tobacco smokers who were 10 years older. These symptoms are likely caused by the smoke affecting the bronchial mucosa. A study which examined endobronchial biopsy specimens of habitual cannabis smokers showed that smoking of cannabis caused at least as extensive histological pathologic changes in the tracheo-bronchial mucosa as smoking tobacco, including potential premalignant cellular changes[77].

4.6. Contaminants

Because cannabis is a crop, it has the potential for contamination by microorganisms and fungi, pathogenic organisms which can cause possible infections. Toxigenic and pathogenic species of fungus have been found on even dispensary-grade cannabis samples in the USA[78]. And there have been a reported case of a marijuana smoker contracting pulmonary fungal infections[79], however this was in an immunocompromised patient. In addition, other adulterants such as pesticides and fertilisers can compromise the purity of the marijuana. One toxicology study found that pesticides were present in one third of all samples tested[80]. The most common was paclobutrazol, a pesticide which is not registered with the US Environmental Protection Agency (EPA) as safe to use on food crops. Even if pesticides which are approved for use on food crops are used, there are additional considerations when applied to the medicinal cannabis situation. Because of the way that cannabis is smoked or heated to be vaped, this could change the availability of the pesticide and many medicinal cannabis patients could be more susceptible to the toxic effects of these compounds due to their illnesses.

5.0. The Risks versus the Benefits of using Medicinal Cannabis

5.1. Clinical Trials Adverse Events

All medicines have potential risks and benefits. It is important to weigh the potential risks against the potential benefits to ensure that patients enjoy access to therapeutic agents which are safe and effective. One of the ways this is done in clinical trials of new medicines is to monitor the adverse events which occur in the subjects during the experimental treatment. This is best practice dictated by the International Conference on Harmonisation, Good Clinical Practice (ICH-GCP), which all clinical trials must adhere to[81]. An adverse event (AE) is defined as “Any untoward medical occurrence in a patient or

clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment". All AEs in clinical trial participants must be recorded and reported. AEs are classified as serious (SAEs) or minor, then determined to be related, or not, to the investigational product.

An excellent study which examined cannabis-related AEs is the aforementioned meta-analysis by Andreae et al[21]. This study compiled the data from several randomised controlled trials that investigated the effects of inhaled cannabis for the treatment of chronic neuropathic pain, then completed a meta-analysis of individual patient data from these trials. The study included five RCT's comprising 178 participants. They noted that from all of the RCT's, there were only three participants who withdrew from the trials due to AEs. One of those was from the placebo group, and the other two withdrew due to hypertension and increased pain, respectively. Side effects reported by the participants treated with inhaled cannabis included anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness and numbness, and were all described as mild.

AEs can also be examined from another previously mentioned study, the CAMS study[27]. In this large, multi-centre, randomised, placebo-controlled trial, cannabinoids were trialled for the treatment of spasticity and other symptoms related to MS. 611 participants were followed for 15 weeks and the numbers of serious AEs were similar across the treatments, with slightly more events seen in the placebo group. Some of the serious AEs reported were MS relapse, urinary tract infection, pneumonia, blocked insertion of suprapubic catheter and a grand mal seizure. The authors stated that most of these events were expected given that the study population was people with MS, rather than healthy subjects. As might be expected from a large clinical trial, there were a large number of minor AEs reported. In the groups randomised to active treatment, these were frequently dizziness or light-headedness, increased appetite and dry mouth; common known side effects of cannabis. Gastrointestinal effects, such as constipation and diarrhoea were also reported at more frequency in the groups on active treatment, compared to those on placebo. It is important to note that a tolerance to the common known side effects of cannabis can be developed over time. After repeated smoked or oral doses, tolerance is rapidly acquired (in two to 12 days) to many of its adverse effects, such as cardiovascular, autonomic, and many subjective and cognitive effects[82]

5.2. Identifying High Risk Groups

In order to mitigate any risks to medicinal cannabis users, it is important to establish high risk groups of potential users.

History of Mental Illness

As previously discussed in Section 4.4, cannabis use is associated with an increased risk of mental illness, although no direct causal links have been found. In this classic chicken-or-egg situation, it is difficult to elucidate whether people with mental illness are more likely to use cannabis because of the mental illness, or whether the cannabis use induces the mental illness. Regardless, cannabis has been shown to exacerbate the symptoms of schizophrenia and psychosis. In an early study of people receiving treatment for schizophrenia, subjects who were using cannabis during the 6-month observation period presented with a significantly higher degree of delusional and hallucinatory activity than those who did not[83]. This was also seen in a prospective cohort study of cannabis using and non-cannabis using

patients with schizophrenia over a year of observation[84]. Significantly more and earlier psychotic relapses occurred in the cannabis-abusing group and there was a dose-related effect where those who used more, had worse outcomes. Similar results are seen when examining cannabis and psychosis. Cannabis use is associated with an earlier age at onset of psychotic disorders[85] and with an increased risk of psychosis for people with an established vulnerability to psychosis than for those without one[86]. The current Data Safety Sheet for Sativex, an approved cannabis-based medicine, states that it is contraindicated in "patients with any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition"[2]. Based on the evidence examined in this report, this would be an appropriate guideline to also apply to medicinal cannabis use.

Age of First Use

As described earlier, in the Dunedin study participants were grouped by the age of first use of cannabis[71]. The finding that participants who used cannabis by age 15 had a greater association with schizophreniform disorder than those who used by age 18 suggests that there may be an age range for which people are more sensitive to risk. A similar age association was seen in the Swedish Conscript Study where a dose-response relationship was discovered between cannabis use by age 18 and incident schizophrenia by age 45[72]. There is also evidence that early use could impair the development of the adolescent brain. A study of early cannabis users showed that initiation of cannabis use prior to the age of 16, was predictive of impaired reaction time on a task of sustained attentional processing[87]. In 2003, Pope et al. also found that early-onset cannabis use was related to poorer performance on verbal memory and fluency tasks, as well as verbal IQ[88]. A study which looked at adults who met criteria for cannabis abuse compared users who started using cannabis prior to 15 years of age with late-onset users and non-user controls. They showed that early-onset users demonstrated poorer performance on tasks of sustained attention, impulse control, and executive functioning compared to both non-users and late-onset users[89]. These effects can also be seen in brain scans of early-onset users. Morphometry changes in grey matter tissue, changes in white matter tract integrity and abnormalities of neural functioning such as increased brain activation and changes in neurovascular functioning have been shown in the brains of adolescent cannabis users[90].

Given this evidence of poorer outcomes for early-onset cannabis users, and what is known about brain development in adolescents, it is reasonable to apply a minimum age limit to medicinal cannabis use.

Table 2 below outlines the potential benefits and risks of medicinal cannabis use for PwMND and PwMS. It also describes some risk management strategies for the established risks of use.

Table 2. Potential Benefits, Risks and Risk Management Strategies for Medicinal Cannabis Use

POTENTIAL BENEFIT	POTENTIAL RISK	RISK MANAGEMENT STRATEGY
Pain Relief	**Dependence**	• Limit access to only those 18 and over
Improvement in Spasticity	**Impairment**	• Regulate the proportion of ΔTHC acceptable in cannabis plants for medicinal use • Ensure that driving under the influence of cannabis remains illegal
Slowing of Disease Progression	**Cognitive Impairment**	
Increased Appetite and Weight Gain	**Worsening Mental Illness**	• Ensure that medicinal cannabis use is contraindicated in people with a history of schizophrenia and psychosis • Limit access to only those 18 and over
	Risks to Lung Health from Smoking	• Recommend cannabis be vaped, ingested, or used in a tincture, rather than smoked
	Contaminants	• Establish regulations which ensure medicinal cannabis is grown in contaminant free conditions

6.0. International Recommendations

As more and more countries are legalising the use of medicinal cannabis, this has compelled some of the leading MS and MND organisations worldwide to develop position statements regarding its use.

The National MS Society in the USA states that:

> *"The Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved. In addition, the Society supports advancing research to better understand the benefits and potential risks of marijuana and its derivatives as a treatment for MS."*[91]

They also state:

> *"The National MS Society supports the ability of people living with MS to make an informed choice about their treatments, including the use of medical marijuana, with their MS health care providers. Recognizing that additional research is still needed, we are evaluating ways we can*

> *remove the barriers to allowing research on medical marijuana at the federal level, which is complex due to government restrictions. We advocate in support of legalizing medical cannabis at the state level."*[91]

In 2010, the MS International Federation's *In Focus* magazine published an issue covering complementary and alternative therapies. Although the articles appeared to support the use of cannabis for MS symptoms and potential disease-modifying effect, a prominent editorial statement at the beginning of the magazine explained that the *"the views and opinions expressed may not be the views of MSIF"* and that the information is provided to assist people in making their own decisions[92]. On their website, MS International Federation group cannabis as a complementary or alternative medicine (CAM) and state that *"If you are considering taking a CAM instead of, or in combination with, a conventional therapy, we recommend that you discuss this with your treating physician."*[93]

In Australia in 2016, the Victorian Government passed The Access to Medicinal Cannabis Bill, 2016[94]. MS Australia (MSA) and MS Research Australia made a joint submission to the review that preceded the passing of the bill, and MSA was represented at the public hearings. On their website, MSA state that:

> *The review report was completed in August 2015, and released by the Victorian Government in October 2015. The report quotes extensively from our joint submission and the 42 recommendations in the report were in keeping with the approach of MSA to this issue. In short, people with MS were top of the list of those in exceptional circumstances, for whom medicinal cannabis would be allowed.*[95]

Upon the passing of the bill, MS Australia's National Policy Officer Andrew Giles, said:

> *"We are very pleased that the Victorian Government has responded in this way and further pleased to have been able to make such a positive contribution to this landmark decision to help expand the treatment options available to people with MS. Together with the welcome announcements made earlier this year by the Australian Government regarding action to ensure medicinal cannabis is available, we're keen to see a broadening of treatment options to people living with MS in all states and territories across the nation."*[95]

The MS Society of Canada also group cannabis as a complementary or alternative medicine and do not endorse, nor discourage its use, but provide the following information:

> *In MS, marijuana is generally used to manage MS pain and spasticity. Although marijuana is not an approved medicine or treatment in Canada, Health Canada has granted access to dried marijuana for medical reasons to individuals who are supported by their prescribing physicians. In addition, Health Canada approved the use of the cannabis-derived drug Sativex® (GW Pharmaceuticals) to treat MS-related pain. Large well-controlled studies are ongoing to determine if there is a role for marijuana or its chemical derivatives in the treatment of MS-related symptoms.*[96]

Multiple Sclerosis Trust, a UK based patient support organisation, published the following quote on their website from the Director of Service Development, Amy Bowen:

"The MS Trust does not endorse or condone the use of illegal cannabis. We do recognise how difficult MS pain and muscle spasticity can be. We want to ensure that everyone with MS is able to see an MS specialist team who can advise them on the medicines, therapies and self-care strategies to help improve these difficult and burdensome symptoms. We also recognise that people with MS will make their personal health and lifestyle choices, but this should never be because they were not able to access the specialist care they need."[97]

MND Australia have a clearly defined position on medicinal cannabis:

MND Australia recognises that there is insufficient evidence on the safety and efficacy of medicinal cannabis in MND. It is important that further, well-designed scientific studies are conducted to investigate the effects of cannabis on people living with MND.

MND Australia believes any drug must have been proven to be safe and to improve health outcomes of people living with MND before it is made available for widespread use.

People living with MND have the right to accept, refuse, or discontinue treatment or intervention within the legal framework of the person's state or territory to ensure choice, control and the best quality of life possible, including access to preservation of personal dignity and to humane care, without discrimination.

MND Australia and the State MND Associations will continue to work collaboratively to ensure that therapies that have been proven to be safe and effective are made available to people living with MND in Australia as quickly as possible.

As an active member of the International Alliance of ALS/MND Associations, MND Australia will continue to monitor the latest research related to medicinal cannabis and make this information available to the MND community in Australia as we learn more.[98]

The following organisations may provide some information about medicinal cannabis, but have no published position on its use; The ALS Association of America, The International Alliance of ALS/MND Associations, American Association of Neuromuscular & Electrodiagnostic Medicine, World Federation of Neurology, European Network to Cure ALS (ENCALS), ALS Hope Foundation in the USA, Motor Neurone Disease Association in Great Britain, Northeast Amyotrophic Lateral Sclerosis Consortium in the USA, The Muscular Dystrophy Association in the USA, The ALS Research Forum (USA), European Multiple Sclerosis Platform and ALS Canada.

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