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Are Cannabis and Cannabinoids Effective for Symptomatic Treatment in People With Multiple Sclerosis?

A Cochrane Review Summary With Commentary

Bhasker Amatya, MD, MPH, DMedSc, and Fary Khan, MBBS, MD, FAFRM (RACP), AM

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review “Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis” by Filippini et al. (<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013444.pub2/full>), published by Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group. This Cochrane Corner is produced in agreement with the *American Journal of Physical Medicine and Rehabilitation* by Cochrane Rehabilitation with views of the review summary author(s) in the “implications for practice” section.

BACKGROUND

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system with variable clinical manifestations, which often lead to a progressive functional decline.¹ People with MS can present with a wide range of complex symptoms, including spasticity, neuropathic and musculoskeletal pain, mobility restriction, ataxia, tremor, sensory loss, sphincter dysfunction, visual and cognitive impairment, etc.^{2,3} Spasticity is a common and serious feature of MS that can worsen with disease progression and lead to wide-ranging consequences, such as weakness, pain, fatigue, restricted joint range of movement, loss of dexterity, etc.^{3,4} These lead to deterioration in function, interfere with mobility, activities of daily living, and restriction in participation.⁴ Many medications for alleviation of these symptoms, especially spasticity and chronic pain, are poorly tolerated and/or are of limited benefit; therefore, patients tend to use alternative treatment, including cannabis-based medicines, referred to as plant cannabis, or its ingredients cannabinoids.^{1,4}

Recently, there has been a growing interest in the therapeutic benefit of cannabinoid-based medicines with the manufacture of several standardized medicines (such as nabiximols—Sativex, Bedrocan, Bedrobinol, etc.).¹ These have demonstrated potential to affect both pathogenic mechanisms and symptoms of MS, such as stress, sleep, mood, spasticity, and pain.^{5,6} One Internet-based survey in the United States reported that 66% of people with MS used cannabis for symptom treatment.⁷ Another survey by the UK MS Society demonstrated that 22% of respondents used cannabis to manage their MS symptoms and 7% continued using it.⁶ Furthermore, more than half of those (56%) currently using cannabis for medical purposes report benefits to outweigh its adverse effects.⁶ There are variations between countries globally in the legal authorization and use of cannabinoid-based medicines and recommendations in international guidelines on the use of cannabinoids in people with MS vary.¹

Cannabis and Cannabinoids for Symptomatic Treatment for People With Multiple Sclerosis (Review)

(Filippini G, Minozzi S, Borrelli F, Cinquini M, Dwan K, 2022).¹

What Is the Aim of This Cochrane Review?

The aim of this Cochrane Review was to assess the benefit and harm of the use of cannabinoids, including synthetic or plant-derived cannabinoids, for reducing symptoms in adults with MS.

What Was Studied in the Cochrane Review?

The review included randomized controlled trials (RCTs) of adult patients (18 yrs and over) with a confirmed diagnosis of MS (all types), using any cannabinoid (including herbal cannabis, cannabis flowers, plant-based cannabinoids, or synthetic cannabinoids) irrespective of dose, route, frequency, or duration of use, to alleviate symptoms of MS. The intervention was compared with a placebo or any active comparator for effect on chronic pain and/or functional limitations due to spasticity, adverse events, and health-related quality of life.

Search Methodology and Up-to-Dateness of the Cochrane Review?

The review authors searched studies published from inception to December 2021 from MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), CINAHL (EBSCO host), LILACS, the Physiotherapy Evidence Database (PEDro), the World Health Organization International Clinical Trials Registry Platform, the US National

From the Department of Rehabilitation and Australian Rehabilitation Research Centre, Royal Melbourne Hospital, Parkville, Australia; and Department of Medicine (Royal Melbourne Hospital), The University of Melbourne, Parkville, Australia. All correspondence should be addressed to: Bhasker Amatya, MD, MPH, DMedSc, Department of Rehabilitation Medicine, Royal Melbourne Hospital, 34-54 Poplar Road, Parkville, Victoria 3052, Australia.

This report was prepared by the Department of Rehabilitation Medicine, Royal Melbourne Hospital, Australia.

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Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

The views expressed in the summary with commentary are those of the Cochrane Corner author(s) (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

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Institutes of Health clinical trial register, the European Union Clinical Trials Register, and the International Association for Cannabinoid Medicines databank. The citation lists of included studies and relevant reviews were scrutinized for additional references.

What Are the Main Results of the Cochrane Review?

The review included 25 RCTs with 3763 participants, of these 2290 received cannabinoids. Most studies were conducted in Europe between 2002 and 2018. The participants' age ranged between 18 and 60 years, with 50%–88% women. Thirteen RCTs evaluated nabiximols (Sativex—oromucosal spray with a plant-derived combination of tetrahydrocannabinol and cannabidiol), five studies oral synthetic cannabinoids, three studies oral tetrahydrocannabinol extract of *Cannabis sativa*, and one study inhaled herbal cannabis.

The review findings show that cannabinoids compared with placebo:

- significantly reduce spasticity (5 RCTs, 1143 participants; odds ratio, 2.51; 95% confidence interval [CI], 1.56–4.04; moderate-certainty evidence)
- show some beneficial effect on chronic neuropathic pain (1 RCT, 48 participants; odds ratio: 4.23; 95% CI, 1.11–16.17; very low-certainty evidence)
- high number of participants discontinued treatment (21 RCTs, 3110 participants; odds ratio, 2.41; 95% CI, 1.51–3.84; low-certainty evidence)
- possibly improve patient global impression of health status (8 RCTs, 1215 participants; odds ratio: 1.80; 95% CI, 1.37–2.36; moderate-certainty evidence) but have little or no effect on health-related quality of life (8 RCTs, 1942 participants, standardized mean difference, 0.08; 95% CI, 0.17–0.02; low-certainty evidence)
- may increase nervous (7 RCTs, 1154 participants, odds ratio, 2.61; 95% CI, 1.53–4.44), and psychiatric disorders (6 RCTs, 1122 participants; odds ratio, 1.94; 95% CI, 1.31–2.88; low-certainty evidence)

What Did the Authors Conclude?

The authors concluded that cannabinoids (nabiximols) probably reduce the severity of spasticity in the short-term in people with MS. Its effect on chronic neurological pain and health-related quality of life is uncertain; however, it may increase treatment discontinuation due to adverse events, nervous disorders, and psychiatric disorders.

What Are the Implications of the Cochrane Evidence for Practice in Rehabilitation?

Multiple sclerosis is a complex condition requiring a longer-term comprehensive transdisciplinary approach to disease

management, which incorporates both nonpharmacological and/or pharmacological modalities.² The use of cannabinoid-based medicines to alleviate MS-related symptoms (such as spasticity, pain, etc.) is increasing.^{7–9} However, clinical practice guideline recommendations and evidence from published literature are varied and/or inconclusive.¹ Rehabilitation professionals manage various MS-related symptoms and provide information to patients (and families) about the potential benefit and harm from cannabinoid usage for symptomatic treatment of MS.

Most of the included studies are on cannabinoids in this review and show moderate evidence suggesting nabiximols (Sativex) as an add-on therapy to other antispasticity medications likely results in a reduction of perceived severity of spasticity in people with MS at 6–14 wks and may not increase serious harmful effects when compared with placebo.¹ The effect of cannabinoids on chronic neurological pain and health-related quality of life is uncertain. The possible adverse events from longer-term use of these medicines include cognitive impairment, nervous and psychiatric disorders.¹

From the clinical perspective, the use of cannabinoids should be considered when other pharmacological and rehabilitation treatments are not effective in patients with moderate to severe spasticity. The treating clinicians need to comprehensively evaluate both short- and long-term adverse effects and consider the risk of drug intolerance, possibility of abuse, and liability when prescribing these medicines to people with MS. Furthermore, robust trials need to evaluate both short- and long-term adverse effects of cannabinoids for clinical application.

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