

# Multiple Sclerosis



Presented By Dr Gull Herzberg

# **ANZCCP - Australian and New Zealand College of Cannabinoid Practitioners**

## **Medicinal Cannabis Education and Authorized Prescriber Course**

- Multiple sclerosis is a potentially progressive, autoimmune neurologic disorder of the central nervous system, resulting from an autoimmune attack on central nervous system white matter.
- Emerging disease-modifying therapies aim to control symptoms, with increasingly sophisticated immune function modulation.
- Though several environmental exposures increase the risk of developing the disease, a large fraction of overall risk is heritable and can be attributed to hundreds of common genetic variants influencing gene regulation in specific immune subsets
- There is no known cure
- It is a leading cause of neurologic symptoms in young adults.
- Multiple sclerosis (MS) is the most common chronic autoimmune disease of the central nervous system



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Review > Front Immunol. 2021 Oct 6;12:728677. doi: 10.3389/fimmu.2021.728677.

eCollection 2021.

### Infections and Multiple Sclerosis: From the World to Sardinia, From Sardinia to the World

Jessica Frau <sup>1</sup>, Giancarlo Coghe <sup>1</sup>, Lorena Lorefice <sup>1</sup>, Giuseppe Fenu <sup>1</sup>, Eleonora Cocco <sup>1</sup>

Affiliations – collapse

#### Affiliation

<sup>1</sup> Multiple Sclerosis Centre, Azienda Tutela Salute (ATS) Sardegna, University of Cagliari, Cagliari, Italy.

- increasing incidence and prevalence in geographical regions with higher latitude, in both the hemispheres
- prevalence of the disease in Sardinia is 361/100,000 inhabitants



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There are four types of multiple sclerosis:

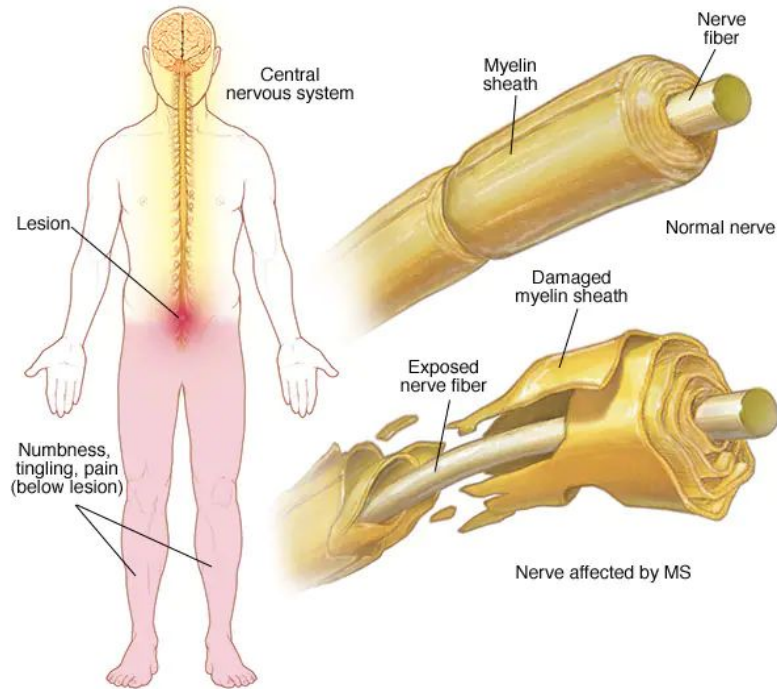
- **Clinically isolated syndrome (CIS):** When someone has a first episode of MS symptoms, healthcare providers often categorize it as CIS. Not everyone who has CIS goes on to develop multiple sclerosis.
- **Relapsing-remitting MS (RRMS):** This is the most common form of multiple sclerosis. People with RRMS have flare-ups – also called relapse or exacerbation – of new or worsening symptoms. Periods of remission follow (when symptoms stabilize or go away).
- **Primary progressive MS (PPMS):** People diagnosed with PPMS have symptoms that slowly and gradually worsen without any periods of relapse or remission.
- **Secondary progressive MS (SPMS):** In many cases, people originally diagnosed with RRMS eventually progress to SPMS. With secondary-progressive multiple sclerosis, you continue to accumulate nerve damage. Your symptoms progressively worsen. While you may still experience some relapses or flares (when symptoms increase), you no longer have periods of remission afterward (when symptoms stabilize or go away).



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- The basic pathology is thought to be auto-immune mediated damage to the myelin sheaths of the central nerves
- Demyelination of the white matter in MS is routinely demonstrated by conventional MRI techniques
- Lesions in the grey matter are also demonstrated
- The degree of cortical demyelination reflects the clinical progression of MS



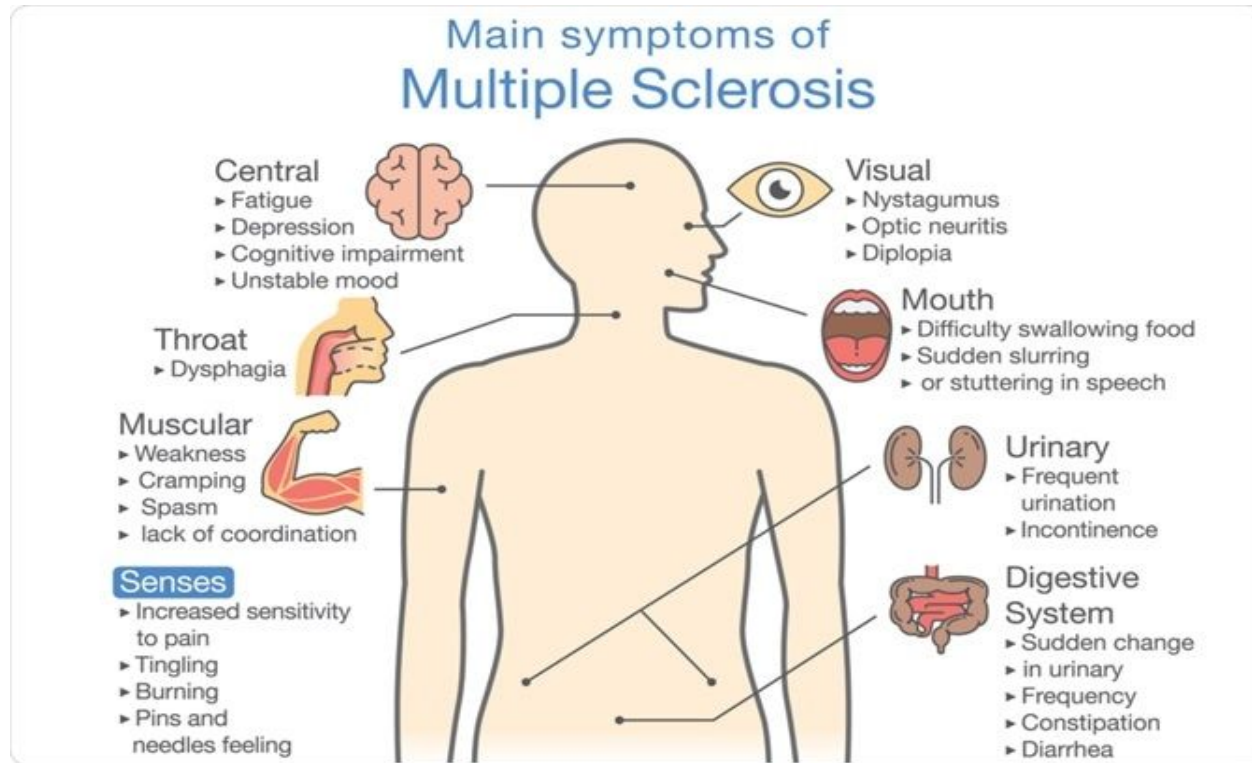
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# MS risk factors

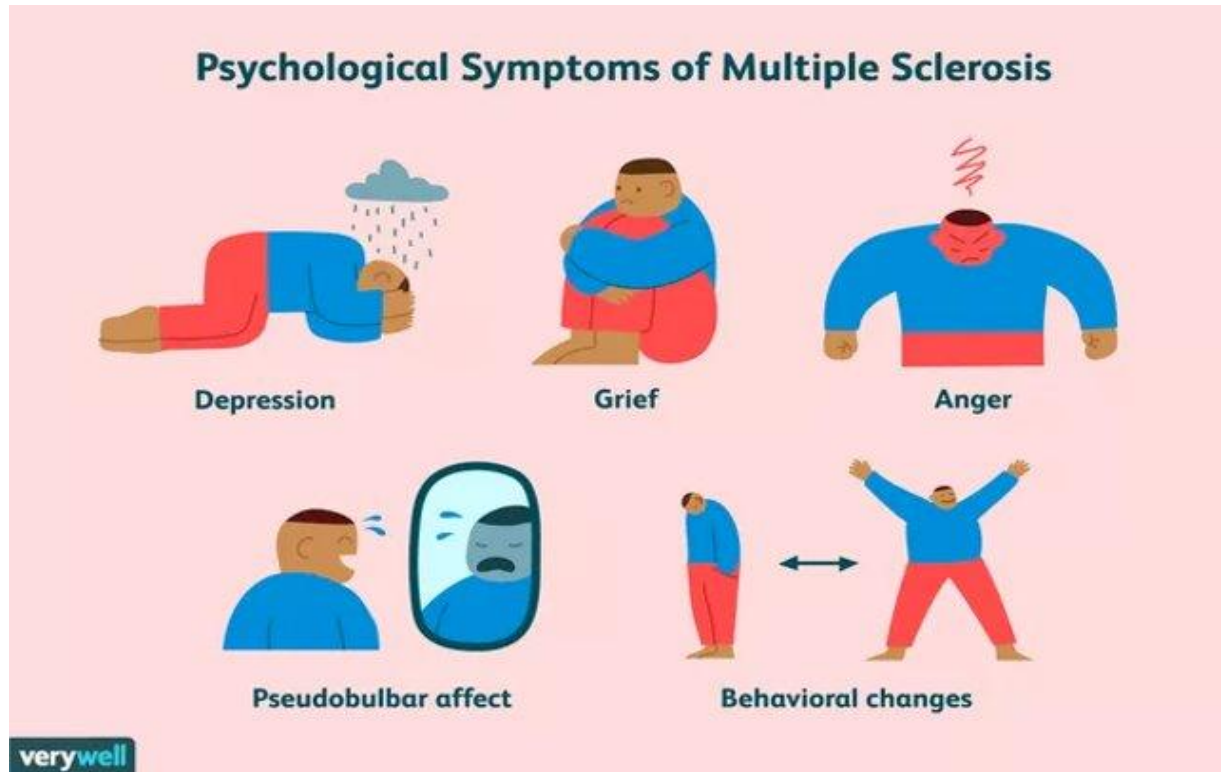
- Ethnicity (particularly the HLA loci)
- Gender (it is more common in women)
- Latitude
  - Sunlight
  - Vitamin D levels)
- Viral infections
  - ? Epstein–Barr virus (EBV),
  - ? Human herpesvirus 6 (HHV-6)
  - ? Varicella–zoster virus (VZV)
  - ? Cytomegalovirus (CMV),
  - ? John Cunningham virus (JCV)
  - ? Human endogenous retroviruses (HERVs)



# Main Symptoms



# Psychological Symptoms





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Review > Curr Neurol Neurosci Rep. 2018 Feb 13;18(2):8. doi: 10.1007/s11910-018-0814-x.

### The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews

Suzanne Nielsen <sup>1</sup>, Rada Germanos <sup>2</sup>, Megan Weier <sup>2 3</sup>, John Pollard <sup>4</sup>, Louisa Degenhardt <sup>2</sup>, Wayne Hall <sup>3</sup>, Nicholas Buckley <sup>4</sup>, Michael Farrell <sup>2</sup>

Affiliations:

#### Affiliations

- <sup>1</sup> National Drug and Alcohol Research Centre, University of New South Wales Sydney, Sydney, NSW, 2052, Australia. [suzanne.nielsen@unsw.edu.au](mailto:suzanne.nielsen@unsw.edu.au).
- <sup>2</sup> National Drug and Alcohol Research Centre, University of New South Wales Sydney, Sydney, NSW, 2052, Australia.
- <sup>3</sup> Centre for Youth Substance Abuse Research, The University of Queensland, Royal Brisbane and Women's Hospital Brisbane, Brisbane, QLD, 4006, Australia.
- <sup>4</sup> School of Medical Sciences, The University of Sydney, Sydney, NSW, 2006, Australia.

"... sufficient evidence that cannabinoids may be effective for symptoms of pain and/or spasticity in MS."



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> Med Cannabis Cannabinoids. 2021 Feb 25;4(1):21-42. doi: 10.1159/000515069.  
eCollection 2021 Jun.

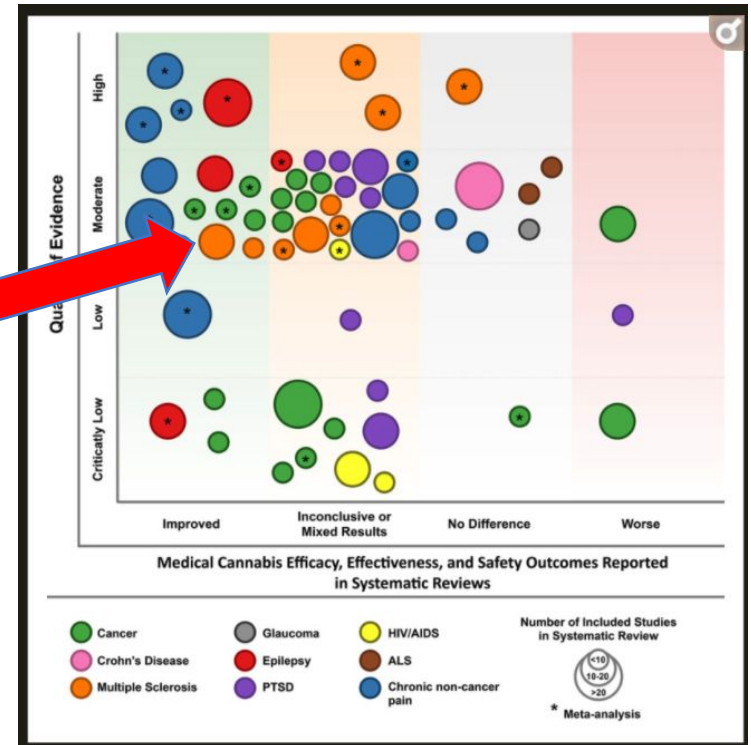
### A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019

Sebastian Jugl<sup>1 2</sup>, Aimalohi Okpeku<sup>1 2</sup>, Brianna Costales<sup>1 2</sup>, Earl J Morris<sup>1 2</sup>,  
Golnoosh Alipour-Haris<sup>1 2</sup>, Juan M Hincapié-Castillo<sup>1 2</sup>, Nichole E Stetten<sup>3</sup>, Ruba Sajdey,  
Shailina Keshwani<sup>1 2</sup>, Verlin Joseph<sup>4</sup>, Yahan Zhang<sup>1 2</sup>, Yun Shen<sup>1 2</sup>, Lauren Adkins<sup>5</sup>,  
Almut G Winterstein<sup>1 2</sup>, Amie Goodin<sup>1 2</sup>

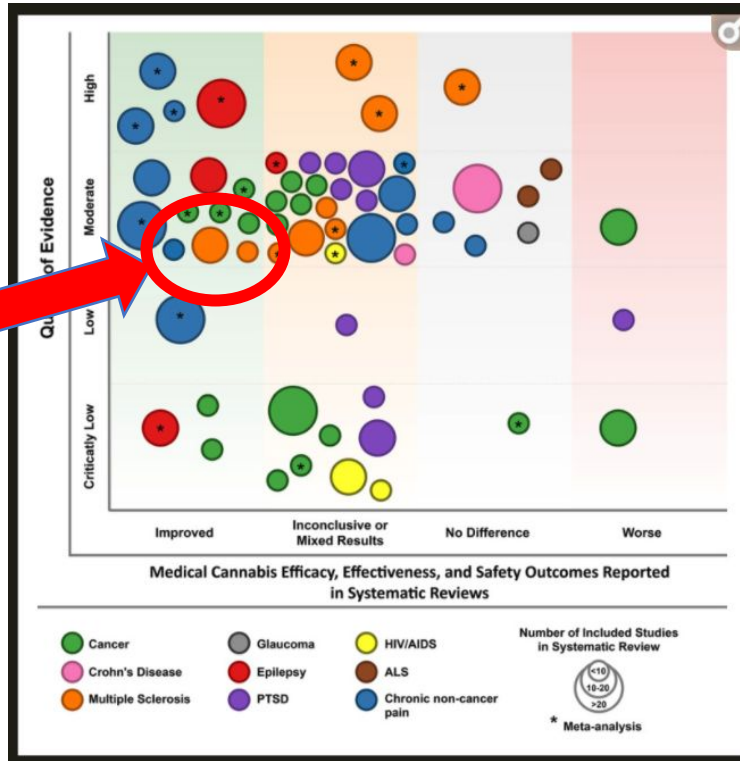
Affiliations

#### Affiliations

- 1 Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, Florida, USA.
- 2 Center for Drug Evaluation and Safety (CoDES), University of Florida, Gainesville, Florida, USA.
- 3 Occupational Therapy, University of Florida, Gainesville, Florida, USA.
- 4 Epidemiology, University of Florida, Gainesville, Florida, USA.
- 5 Health Sciences Center Libraries, University of Florida, Gainesville, Florida, USA.



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Moderate evidence  
of improved  
outcomes in MS



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> [Biomolecules](#). 2021 Jun 1;11(6):826. doi: 10.3390/biom11060826.

### Cannabinoid Activity–Is There a Causal Connection to Spasmolysis in Clinical Studies?

Daniel Joseph <sup>1</sup>, Johannes Schulze <sup>1</sup>

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#### Affiliation

<sup>1</sup> Institute of Occupational, Social and Environmental Medicine, Goethe-University Frankfurt/Main, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main, Germany.

"Current data do not support a specific spasmolytic effect; **a general decrease in CNS activity analogous to benzodiazepines** appears more likely. Whether individual patients or specific subgroups benefit from cannabinoids is unclear."



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Review > J Cent Nerv Syst Dis. 2019 Mar 11;11:1179573519831997.

doi: 10.1177/1179573519831997. eCollection 2019.

### Daily Practice Managing Resistant Multiple Sclerosis Spasticity With Delta-9-Tetrahydrocannabinol: Cannabidiol Oromucosal Spray: A Systematic Review of Observational Studies

Katja Akgün <sup>1</sup>, Ute Essner <sup>2</sup>, Cordula Seydel <sup>3</sup>, Tjalf Ziemssen <sup>1</sup>

Affiliations

#### Affiliations

- <sup>1</sup> Department of Neurology, Center of Clinical Neuroscience, University Hospital Dresden, Dresden, Germany.
- <sup>2</sup> O.MEANY Consultancy GmbH, Hamburg, Germany.
- <sup>3</sup> Almirall Hermal GmbH, Reinbek, Germany.

"...data illustrate that THC:CBD is an effective and tolerable alternative therapeutic option for patients who do not respond to conventional anti-spastic drugs and still suffer from MS **spasticity**."

"The mean recorded daily dose of THC:CBD in the publications was in the range of four to seven sprays."

Sativex: Each 100 microlitre spray contains 2.7 mg THC and 2.5 mg CBD.



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Meta-Analysis > JAMA Netw Open. 2018 Oct 5;1(6):e183485.

doi: 10.1001/jamanetworkopen.2018.3485.

### Assessment of Efficacy and Tolerability of Medicinal Cannabinoids in Patients With Multiple Sclerosis: A Systematic Review and Meta-analysis

Mari Carmen Torres-Moreno<sup>1 2</sup>, Esther Papaseit<sup>1 2</sup>, Marta Torrens<sup>3 4</sup>, Magí Farré<sup>1 2</sup>

Affiliations

#### Affiliations

- <sup>1</sup> Universitat Autònoma de Barcelona, Departament de Farmacologia, Terapèutica i Toxicologia, Cerdanyola del Vallès, Spain.
- <sup>2</sup> Hospital Universitari Germans Trias i Pujol and Institut de Recerca Germans Trias i Pujol, Servei de Farmacologia Clínica, Badalona, Spain.
- <sup>3</sup> Universitat Autònoma de Barcelona, Departament de Psiquiatria i Medicina Legal, Cerdanyola del Vallès, Spain.
- <sup>4</sup> Hospital del Mar, Institut de Neuropsiquiatria i Addiccions, Programa Addiccions, Barcelona, Spain.

"limited efficacy of cannabinoids for the treatment of **spasticity, pain, and bladder dysfunction** in patients with MS.

Therapy using these drugs can be considered as safe. "



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# Psychological Effects

- Loss of autonomy
- Anxiety
- Depression
- Strain on personal relationships
- Impact on quality of life
- Can manifest in myriad ways





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> J Neuroimmune Pharmacol. 2021 Jun;16(2):251-269. doi: 10.1007/s11481-021-09982-7.  
Epub 2021 Jan 25.

### Immunomodulatory Potential of Cannabidiol in Multiple Sclerosis: a Systematic Review

Alessia Furguele <sup>1</sup>, Marco Cosentino <sup>2</sup>, Marco Ferrari <sup>1</sup>, Franca Marino <sup>1</sup>

Affiliations — collapse

#### Affiliations

- <sup>1</sup> Center for Research in Medical Pharmacology and Center for Research in Neuroscience, University of Insubria, Via Ottorino Rossi n. 9, 21100, Varese, VA, Italy.
- <sup>2</sup> Center for Research in Medical Pharmacology and Center for Research in Neuroscience, University of Insubria, Via Ottorino Rossi n. 9, 21100, Varese, VA, Italy.  
marco.cosentino@uninsubria.it.

"Evidence in rodent models of (experimental autoimmune encephalomyelitis ) EAE **strongly supports CBD as effective**, while clinical evidence is still limited and usually negative, due to paucity of studies and possibly to the use of suboptimal dosing regimens."



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> J Neurosci. 2017 Aug 30;37(35):8385-8398. doi: 10.1523/JNEUROSCI.2900-16.2017.  
Epub 2017 Jul 27.

### 2-Arachidonoylglycerol Reduces Proteoglycans and Enhances Remyelination in a Progressive Model of Demyelination

Ana Feliú<sup>1</sup>, Itziar Bonilla Del Río<sup>2 3</sup>, Francisco Javier Carrillo-Salinas<sup>1</sup>,  
Gloria Hernández-Torres<sup>4</sup>, Leyre Mestre<sup>1</sup>, Nagore Puente<sup>2 3</sup>, Silvia Ortega-Gutiérrez<sup>4</sup>,  
Maria L López-Rodríguez<sup>4</sup>, Pedro Grandes<sup>2 3 5</sup>, Miriam Mecha<sup>6</sup>, Carmen Guaza<sup>6</sup>

“...increased 2-arachidonoylglycerol tone promotes **remyelination** in a model of progressive multiple sclerosis ameliorating motor dysfunction.”



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# Conclu sion:

There is published evidence that, in MS, Medical Cannabis can be helpful in the management of

- pain,
- spasticity and
- bladder dysfunction



So what does this mean for  
Authorised Prescriber applications?



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- The specific choice of products and starting doses is beyond the scope of this presentation.
- As with any therapeutic intervention, medical cannabis or otherwise, the clinicians knowledge, understanding and confidence in the products, their possible effects, positive or negative and communication with the patient are key to clinical effectiveness.
- In terms of the products used, there is no clinical difference in prescribing medical cannabis as an Authorised Prescriber compared with using SAS B approval process.
- Suffice to say that the option to use a reasonably wide range of dosage forms and cannabinoid concentrations, with a sense of the entourage effects of each, as far as possible, will likely enhance effectiveness and ease of prescribing, depending on the clinical indications adapted for the patient in question.



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- The range of medical cannabis products and their entourage effects is potentially vast
- Product choice will depend on"

- Content

- THC
- CBD
- Other cannabinoids
- Terpenes

- Dosage form

- Which will affect delivery method

- Concentration

- Cost



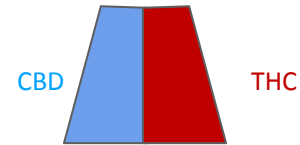
Product prescription



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# Dosing for symptoms

- **Option 1-** mild/ moderate symptoms
- balanced 1:1 (THC:CBD) oral/ sublingual cannabis preparation
- **Titrate accordingly- 1mg to 15mg CBD/THC BD or TDS**
- **Option 2-** moderate to severe symptoms
- Titrate accordingly-- “Split Protocol”- CBD and THC oral/ sublingual cannabis preparation (2 separate bottles)
- **BD dosing – 30-50mg CBD BD / 5-30mg THC BD**
- **TDS dosing – 20-35mg CBD TDS / 5-30mg THC TDS**
- **Option 3-** Add inhaled/ vaporized cannabis for BREAKTHROUGH symptoms
- Titrate accordingly- **0.1-0.5g BD/ TDS PRN vaporized cannabis**



With thanks to Dr John Teh

# Disease Modulation?

Review > Cannabis Cannabinoid Res. 2021 Jun;6(3):196-210. doi: 10.1089/can.2020.0183.

Epub 2021 May 24.

## Therapeutic Prospects of Cannabinoids in the Immunomodulation of Prevalent Autoimmune Diseases

Xandy Melissa Rodríguez Mesa <sup>1 2</sup>, Andrés Felipe Moreno Vergara <sup>1 3</sup>,  
Leonardo Andrés Contreras Bolaños <sup>1 2</sup>, Natalia Guevara Moriones <sup>1 3</sup>,  
Antonio Luis Mejía Piñeros <sup>2</sup>, Sandra Paola Santander González <sup>1 2</sup>

“CBD was found to be one of the main modulators of the immune response. This molecule decreased the number of Th1 and Th17 proinflammatory cells and the production of the proinflammatory cytokines, interleukin (IL)-1, IL-12, IL-17, interferon (IFN)- $\gamma$ , and tumor necrosis factor alpha, in mouse models of MS...”



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# CBD Dosing in Multiple Sclerosis

> [CNS Drugs](#). 2021 Mar;35(3):265–281. doi: 10.1007/s40263-021-00807-y. Epub 2021 Mar 22.

## Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome

Simona Lattanzi <sup>1</sup>, Eugen Trinka <sup>2 3 4</sup>, Pasquale Striano <sup>5</sup>, Chiara Rocchi <sup>6</sup>, Sergio Salvemini <sup>6</sup>,  
Mauro Silvestrini <sup>6</sup>, Francesco Brigo <sup>7 8</sup>

Extremely limited published  
evidence

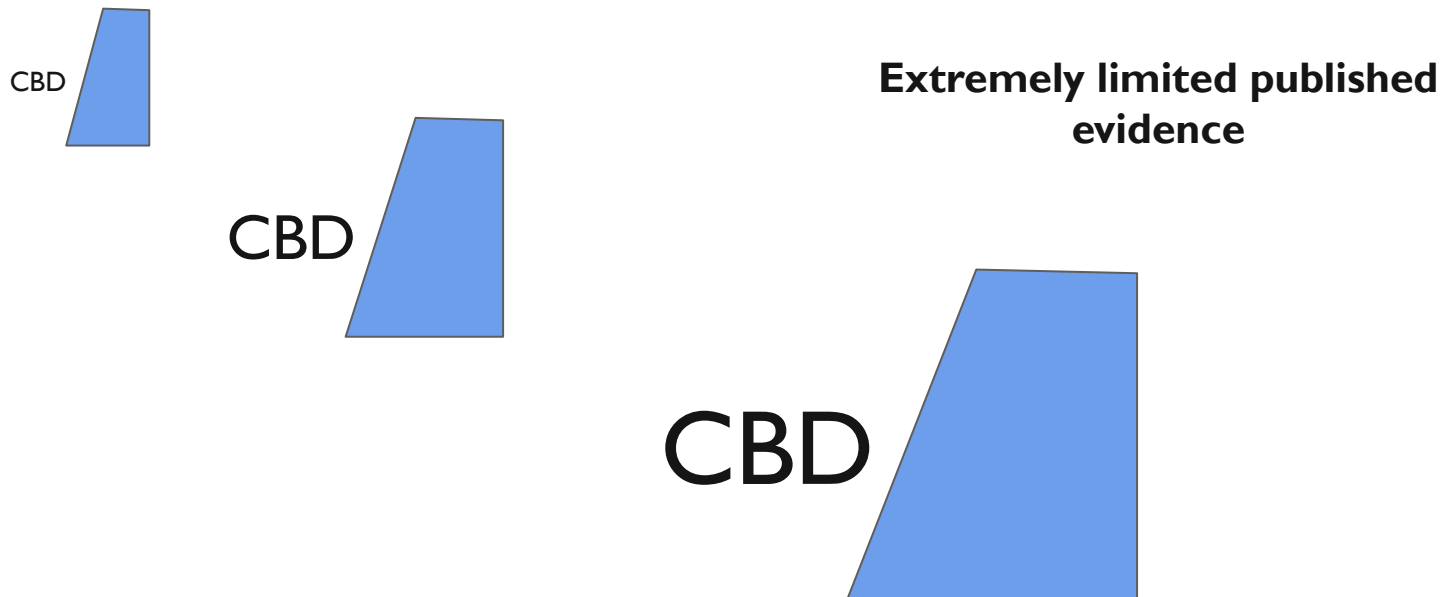
“...purified CBD was administered at dosages up to **50 mg/kg/day**.”



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# **CBD Dosing in Multiple Sclerosis**



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Australian Government  
Department of Health  
Therapeutic Goods Administration

### Medicinal cannabis products by active ingredients

Proportion of cannabidiol (CBD) content compared with the total cannabinoid content



- Category 1: CBD medicinal cannabis product (CBD  $\geq$  98%)
- Category 2: CBD dominant medicinal cannabis product (CBD  $\geq$  60% and  $<$  98%)
- Category 3: Balanced medicinal cannabis product (CBD  $<$  60% and  $\geq$  40%)
- Category 4: THC dominant medicinal cannabis product (THC 60% - 98%)
- Category 5: THC medicinal cannabis product (THC  $>$  98%)



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Australian Government  
Department of Health  
Therapeutic Goods Administration

### Medicinal cannabis products by active ingredients



Within each category there are a range of dosage forms:

1. Capsule
2. Herb, dried for vaporisation
3. Oral Liquid
4. Inhalation
5. Inhalation, pressurised (Metered Dose Preparation)
6. Spray, solution
7. Tablet
8. Pastille
9. Wafer
10. Topical



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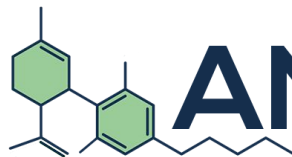
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1. Capsule
2. Herb, dried for vaporisation
3. Oral Liquid
4. Inhalation
5. Inhalation, pressurised (Metered Dose Preparation)
6. Spray, solution
7. Tablet
8. Pastille
9. Wafer
10. Topical



Product prescription



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Dear Dr Herzberg,

Notice of decision to grant an authority under subsection 19(5) of the Therapeutic Goods Act 1989  
(Authorised Prescriber Scheme) in relation to:

Product **AP Estab. Hx-**Category 1-CBD medicinal cannabis product (CBD $\geq$ 98%)  
- - Capsule



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Dear Dr Herzberg,

**Notice of decision to grant an authority under subsection 19(5) of the *Therapeutic Goods Act 1989* (Authorised Prescriber Scheme) in relation to:**

**Product:** Category 5-THC medicinal cannabis product (THC greater than 98%) - - Herb, dried (for vaporisation)



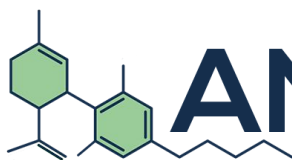
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8. <https://www.verywellhealth.com/emotional-symptoms-in-multiple-sclerosis-4588077>
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