Cannabinoids and Cognition in Multiple Sclerosis

Learning objectives

- Differentiate the effects of cannabis vs. specific cannabinoids on adult cognitive processes
- Discuss how multiple sclerosis affects cognition
- Summarize the data regarding the impact of cannabis on cognition in persons with multiple sclerosis

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Differentiating the effects of cannabis vs cannabinoids on adult cognition

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Cannabis and specific cannabinoids have different impacts on cognition

Cannabis (also known as marijuana) contains more than 500 components, of which over 100 cannabinoids have presently been identified[1]

Two of these have been the subject of scientific investigation into their pharmacological properties: THC and CBD[1]

THC is the primary psychoactive cannabinoid in cannabis. As THC concentrations have intensified in cannabis, adverse effects after acute or prolonged may be exacerbated[2]

In recent years, a potential protective effect against certain negative psychological effects from THC has been shown in some studies investigating CBD[1]

CBD, cannabidiol; THC, Δ-9 tetrahydrocannabinol.

1. Lafaye G, et al. *Dialogues Clin Neurosci*. 2017;19:309–16; 2. Volkow ND, et al. *N Engl J Med.* 2014;370:2219–27.

Regulated cannabis products vs. unregulated dispensary products

Regulated products	Unregulated products
Rigorously tested for safety and efficacy[1]	Generally untested for effectiveness and safety[1]
Manufactured under strict conditions – the exact composition is known; no contaminants[1]	Variable processing – composition uncertain; contamination likely[1–4]
Stored under controlled conditions[1]	Stored under variable conditions[5]
Accurately labelled[1]	Labelling most likely inaccurate[6]
Prescribed by physicians[1]	Recommended only; non-prescribed[7]

Regulated cannabis products – FDA-approved or seeking FDA approval; Unregulated cannabis products - NOT FDA-approved nor seeking FDA approval;
1. Russo EB. *Front Pharmacol*. 2016;7:309; 2. Raber et al, *J Toxicol Sci*. 2015;40:797–803; 3. McKernan K *F1000Res*. 2016;5:2471; 4. Busse F, et al. *N Engl J Med.* 2008;358:1641–2; 5. Thomas BF, ElSohly M. Waltham:Elsevier;2016;37–65; 6. Vandrey R, et al. *JAMA.* 2015;313:2491–93. 7. Haug NA, et al. *Cannabis Cannabinoid Res.* 2016;1.1:244–51.

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Cannabinoids and cognition: findings from human trials

THC administration

Impaired emotional processing[1]

Impaired verbal learning and memory[2,3]

Impaired working memory performance[2]

CBD administration

CBD administration might improve emotional processing accuracy[1]

Pre-dosing with oral CBD prior to acute THC ameliorates THC-induced verbal learning and memory deficits in some studies, but not in others[2,4]

CBD and THC administration

THC impairs Sternberg Memory Task performance but not when combined with CBD[5–7]

No effect on working memory was observed in naïve patients taking a mixture of THC and CBD[8]

CBD, cannabidiol; THC, Δ-9 tetrahydrocannabinol.

1. Hindocha C, et al. *Eur Neuropsychopharmacol*. 2015;25:325–34; 2. Englund A, et al. *J Psychopharmacol.* 2013;27:19–27; 3. Englund A, et al. *J Psychopharmacol.* 2016;30:140–51; 4. Morgan CJA, et al. *Transl Psychiatry.* 2018;8:181; 5. Hunault CC, et al. P*sychopharmacology (Berl).* 2009;204:85–94; 6. Theunissen EL, et al. *Psychopharmacology (Berl).* 2015;232:343–53; 7. Schoedel KA, et al. *Hum Psychopharmacol.* 2011;26:224–36; 8. Filbey F, et al. *Neurology Rev.* 2020; June supplement.

The acute and chronic effects of cannabis on human cognition

Cognitive domain	Acute use	Chronic use
Verbal learning and memory	✓ ✓ ✓	✓ ✓ ✓
Working memory	✓ ✗	✓ ✗
Other memory function	✓	✓ ✗
Attention	✓ ✓ ✓	✓ ✓ ✓
Psychomotor function	✓ ✓ ✓	✓
Planning, reasoning, interference control and problem solving	✓ ✗	✓ ✗
Verbal fluency	✗	✓ ✗
Decision making	✓ ✗	✓ ✗

✓ ✓ ✓ Strong and largely consistent evidence for impairment

✓ ✗ Mixed evidence

✓ Weak evidence for impairment, being based on only a small number of studies

✗ Little or no evidence for impairment

The results of these studies are limited by the fact that the molecular content of cannabis is unknown.
Adapted from: Broyd SJ, et al. *Biol Psychiatry*. 2016;79:557–67.

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Neuroimaging metrics of the effects of cannabinoids on cognition

THC administration

Verbal learning and memory
Decreased striatum and lateral prefrontal cortex activity[1]

Working memory
Decreased cerebellum, frontal, parietal and temporal cortices activity[1]

Attention
Attenuated P300 event-related allocation potential[1]

CBD administration

Verbal learning and memory
Increased striatum and lateral prefrontal cortex activity[1]

CBD, cannabidiol; THC, Δ-9 tetrahydrocannabinol.
Filbey F, et al. *Neurology Rev*. 2020; June supplement.

Limitations of current research and published data

Preclinical evidence

Clinical evidence is limited and preclinical models comprise the majority of the current evidence base[1–3]

Non-standardized product

Numerous other chemicals present in cannabis products[4]

Unregulated cannabis preparations are not characterized for cannabinoid composition, consistency and potency[4]

Clinical evidence

Unclear from existing research whether there is a specific ratio of THC and CBD where the beneficial effects of this combination outweigh the potential risks to cognition[5]

Most human trials are not controlled for duration of use, potential other drug use and potential underlying neuropsychiatric differences[5]

CBD, cannabidiol; THC, Δ-9 tetrahydrocannabinol.

1. Murphy M, et al. *Cannabis Cannabinoid Res*. 2017;2:235–46; 2. Vann RE, et al. *Drug Alcohol Depend*. 2008;94:191–8; 3. Todd SM, et al. *Eur Neuropsychopharmacol*. 2017;27:132–45. 4 Russo EB. *Front Pharmacol*. 2016;7:309; 5. Filbey F, et al. *Neurology Rev*. 2020; June supplement.

Cognitive decline in MS

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Prevalence of cognitive decline in MS

Cognitive decline is defined as a score where performance falls less than **1·5 SD** below normative expectation[1]

Can occur in the early stages of MS even without other neurological deficits[2]

Approximately **35%** of patients with clinically isolated syndrome[3]

Approximately **45%** of patients with relapsing-remitting MS[3]

Approximately **80%** of patients with secondary progressive MS[3]

MS, multiple sclerosis; SD, standard deviation.

1. Schinka JA, et al. *Am J Geriatr Psychiatry.* 2010;18:684–91; 2. Glanz BI, et al. *Mult Scler*. 2007;13:1004–10; 3. Ruano L, et al. *Mult Scler*. 2017; 23:1258–67.

Specific cognitive domains impaired in MS

- Visual memory (54–56%)
- Cognitive processing speed (27–51%)
- Verbal memory (29–34%)
- Executive function (15–26%)
- Visuospatial processing (22%)

Representative sample of 291 adult patients with any type of MS

MS, multiple sclerosis.
Benedict RH, et al. *J Int Neuropsychol Soc*. 2006;12:549–58.

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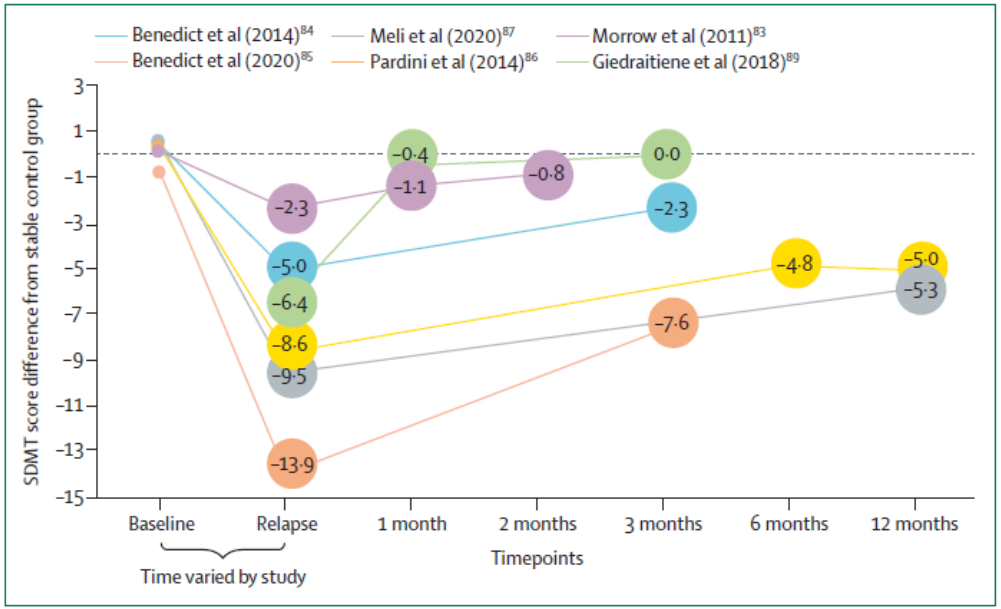
Decline and recovery in patients with MS with cognitive relapse



SDMT difference in change from baseline between matched* patients with GdE-defined relapsing disease and stable disease

*The relapsing and stable groups are generally well matched at baseline with the difference in SDMT scores ranging from –0·7 to 0·6.
GdE, Gadolinium-enhanced; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test.
Benedict RHB, et al. *Lancet Neurol*. 2020;19:860–71.

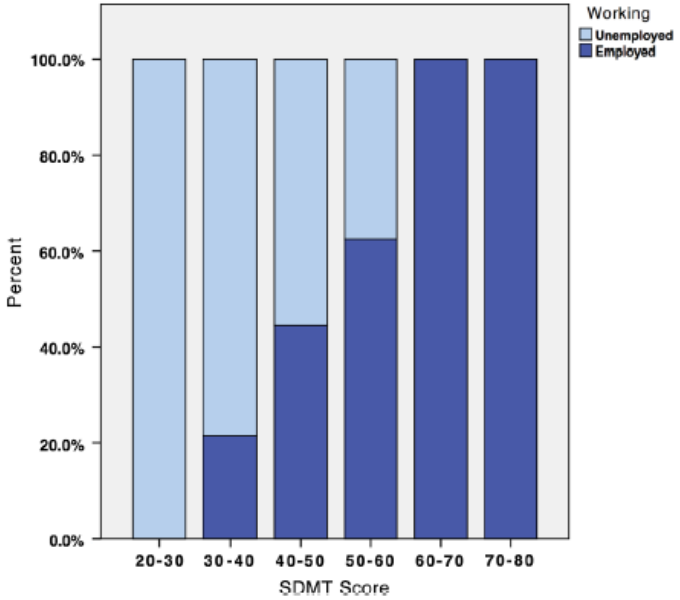
Cognitive impairment and employment in MS

Cognitive relapses can have a negative impact on daily function including employment[1,2]

Increased SDMT scores are a significant predictor of unemployment[1]

A case study of a 53-year old man with 13 GdE lesions, highlighted that he was receiving criticism from his employers for errors and formal discipline for poor performance[2]

Despite the resolution of GdE lesions after 6 months, he still demonstrated partial cognitive impairment[2]



Rates of employment with increasing performance on SDMT[1]

GdE, Gadolinium-enhanced; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test.

1. Campbell J, et al. *Postgrad Med J.* 2017;93:143–7; 2. Benedict RHB, et al. *Lancet Neurol.* 2020;19:860–71.

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Cannabis and cognition in persons with MS

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Regulated cannabis products vs. unregulated dispensary products

Regulated products	Unregulated products
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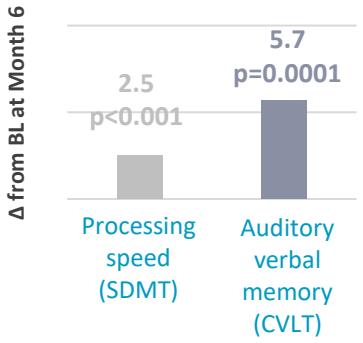
Studies of cannabis on cognition in MS as a primary endpoint

Regulated cannabis

Alessandria et al.[1]

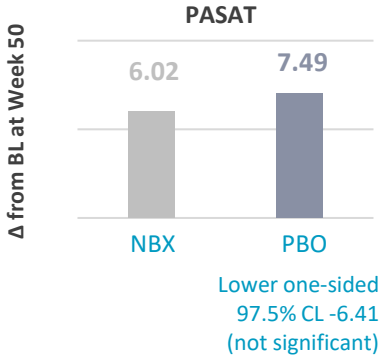
Prospective pilot study of the long-term effects of nabiximols on cognition, mood and anxiety



Safety not assessed

Vachova et al.[2]

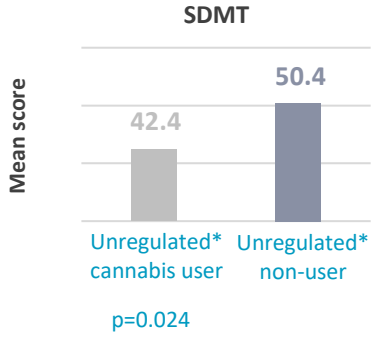
Long-term impact of nabiximols on cognitive function and mood in MS patients with spasticity



Vertigo, dry mouth, asthenia, fatigue, dizziness, muscle spasticity and euphoric mood (≥3% with NBX vs PBO)

Honarmand et al.[3]

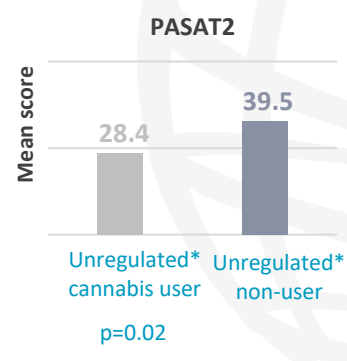
Cross-sectional study of the cognitive abilities of patients with MS using and not using cannabis



Safety not assessed

Pavisian et al.[4]

Cross-sectional study of the cognitive abilities of patients with MS using and not using cannabis



Safety not assessed

Unregulated cannabis

*Regulated cannabis products – FDA-approved or seeking FDA approval; Unregulated cannabis products - NOT FDA-approved nor seeking FDA approval;
Nabiximols is not currently approved for any indication in the United States. Nabiximols is being studied for MS spasticity and is not being studied for cognition
AE, adverse event; BL, baseline; CVLT, California Verbal Learning Test; MS, multiple sclerosis; NBX, nabiximols; PASAT, Paced Auditory Serial Addition Test; PBO, placebo; SDMT, Symbol Digit Modalities Test.

1. Alessandria, et al. *Clin Neurol Neurosurg*. 2020;196:105990; 2. Vachová M, et al. *J Mult Scler*. 2014;1:122; 3. Honarmand K, et al. *Neurology*. 2011;76:1153–60; 4. Pavisian B, et al. *Neurology*. 2014;82:1879–87.

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Studies of cannabis on cognition in MS as a secondary endpoint

Design/patients/intervention	Cognitive endpoints	Results
Randomized, double-blind, placebo-controlled, crossover Patients with MS spasticity (n=17) NBX vs. PBO[1]	PASAT (secondary)	No significant mean difference in change from baseline between NBX vs. PBO on PASAT (42.4 vs. 43.0; p=0.79) Mouth dryness, fatigue, drowsiness and/or slower thinking, and dizziness and vertigo (≥3% with NBX vs. PBO)
Randomized, double-blind, placebo-controlled, parallel group Patients with MS and central pain (n=66) NBXs vs PBO[2]	BRB-N (10/36 spatial recall, SDMT, PASAT, Word Generation List, SRT) (secondary)	Significant difference in mean change from baseline between NBX vs. PBO in the long-term component of SRT (-0.09 vs. 5.7; p=0.009); no significant difference between groups for all other cognitive measures Dizziness, somnolence, dry mouth, dissociation, weakness (≥3% with NBX vs. PBO)
Randomized, double-blind, placebo-controlled, crossover Patients with MS spasticity (n=57) THC:CBD vs. PBO[3]	PASAT and digit span of the WAIS-R intelligence scale (secondary)	Significant improvement from baseline to trial end for PASAT (20.8 vs. 37.0; p=0.0003) and digit span of WAIS-R test (12.1 vs. 13.7; p=0.0014), no significant difference between THC:CBD vs. PBO Nausea/feeling sick (≥3% in THC:CBD vs. PBO); dizziness, euphoria/"high", difficult concentrating >8% for both THC:CBD and PBO
Randomized, double-blind, placebo-controlled Patients with MS (n=160) NBX vs. PBO[4]	SOMC Test and AMIPB (secondary)	No significant mean difference between NBX vs. PBO on AMIPB (1.90 vs 2.10; p=0.90) and SOMC (data not provided) Dizziness, disturbance in attention, fatigue, somnolence, disorientation, feeling drunk, vertigo, diarrhea, mouth ulceration (≥3% with NBX vs. PBO)
Randomized, double-blind, placebo-controlled, crossover Patients with MS spasticity (n=37) Cannabis vs. PBO cigarette[5]	PASAT (secondary)	Significant reduction from baseline in PASAT scores with cannabis vs. PBO (-8.32 vs. 0.35; p=0.003) Dizziness, headache, fatigue, nausea and feeling 'too high' (≥3% with cannabis vs. PBO)

Nabiximols is not currently approved for any indication in the United States. Nabiximols is being studied for MS spasticity and is not being studied for cognition

AE, adverse event; AMIPB, Adult Memory and Information Processing Battery; BRB-N, Brief Repeatable Battery of Neuropsychological test; CBD, cannabidiol; MS, multiple sclerosis; NBX, nabiximols; SOMC, Short Orientation-Memory-Concentration test; PASAT, Paced Auditory Serial Addition Test; PBO, placebo; SAE, serious adverse event; SDMT, Symbol Digit Modalities Test; SRT, Selective Reminding Test; THC, Δ-9 tetrahydrocannabinol; VAS, visual analogue scale; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

1. Aragona M, et al. *Clin Neuropharmacol*. 2009;32:41–47; 2. Rog DJ, et al. *Neurology*. 2005;65:812–9; 3, Vaney C, et al. *Mult Scler*. 2004;10:417–24; 4. Wade DT, et al. *Mult Scler*. 2004;10:434–41;
5. Corey-Bloom J, et al. *CMAJ*. 2012;184:1143–50.

Discontinuing unregulated cannabis: impact on cognition in MS

Patients[1]

40 patients with MS using cannabis since MS diagnosis

Assignment

Cannabis continuation or discontinuation groups for 28 days

Outcomes

Assessments of memory, processing speed and executive function

Outcome	Mean (SD) score at Day 28		
	Cannabis continuation	Cannabis withdrawal	P value
SRT-LTS	26.9 (10.81)	44.9 (8.58)	<0.05
10/36	13.3 (5.34)	24.7 (3.13)	<0.05
PASAT3	31.3 (5.96)	48.1 (7.36)	<0.05
PASAT2	23.2 (5.10)	37.3 (6.62)	<0.05
SDMT	37.3 (6.47)	51.9 (10.95)	<0.05
COWAT	37.5 (4.81)	45.2 (6.60)	<0.05

The results of these studies are limited by the fact that the molecular content of cannabis is unknown.

BL, baseline; COWAT, Spatial Total Recall Test; D, day; PASAT, Paced Auditory Serial Addition Test; MS, multiple sclerosis; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SRT-LTS, Selective Reminding Test-Long Term Storage;

1. Feinstein A, et al. *Brain*. 2019;142(9):2800–12.