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คณะแพทยศาสตร์
ศิริราชพยาบาล

Evidence-based of Medical Cannabis in Epilepsy and Sleep Disorder

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EVIDENCE-BASED OF MEDICAL CANNABIS IN EPILEPSY

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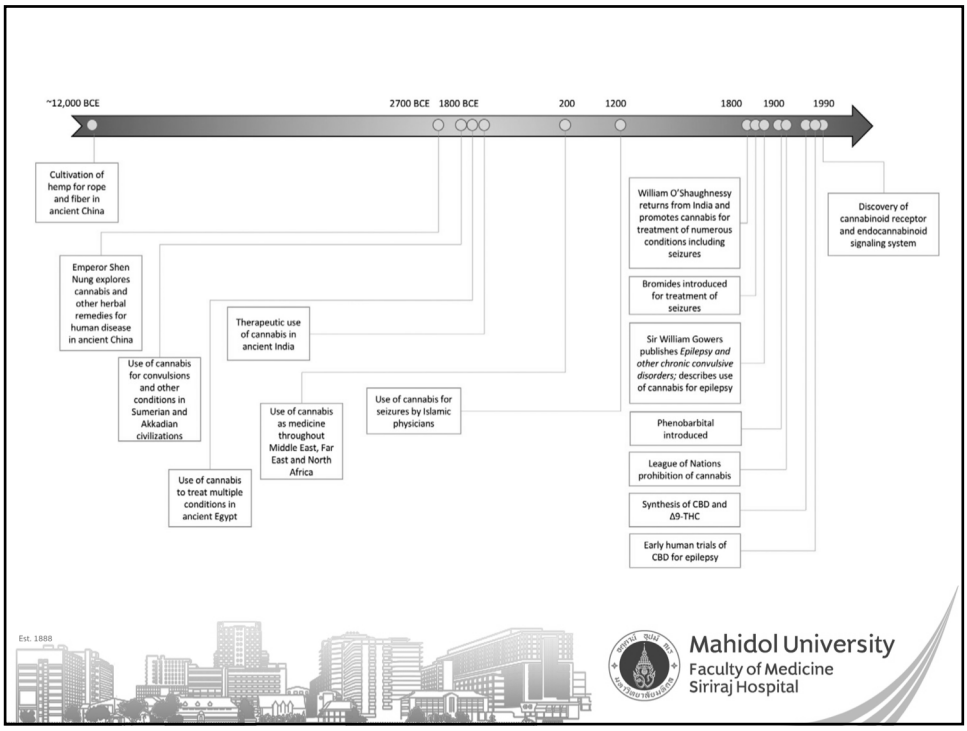

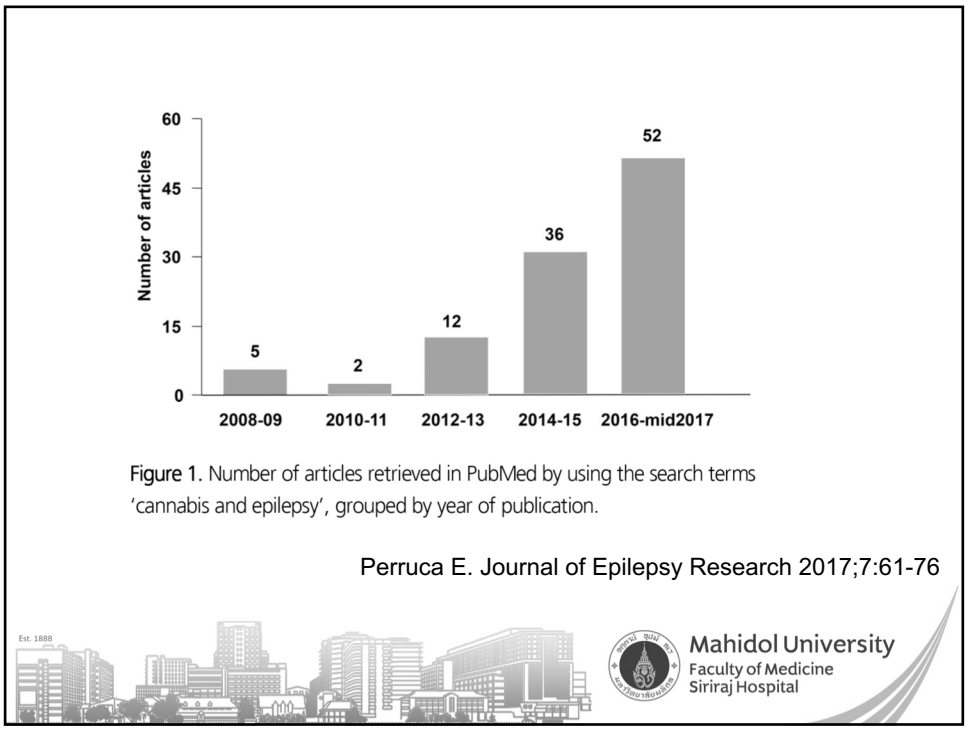

Figure 1. Number of articles retrieved in PubMed by using the search terms 'cannabis and epilepsy', grouped by year of publication.

Perruca E. Journal of Epilepsy Research 2017;7:61-76

What are the anticonvulsant mechanisms of CBD?

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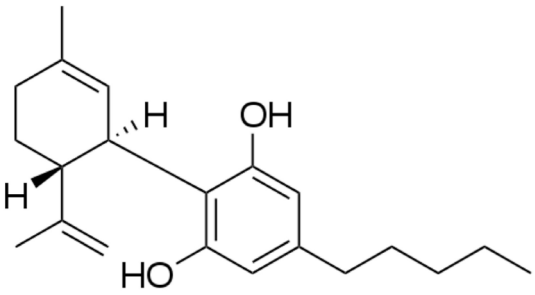
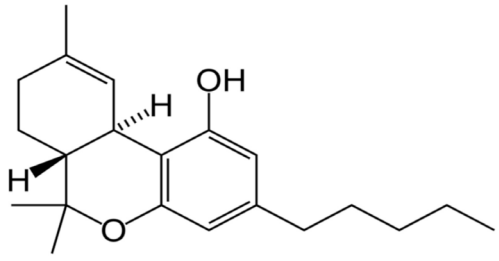


Cannabidiol (CBD)



9-Δ-tetrahydrocannabinol (THC)

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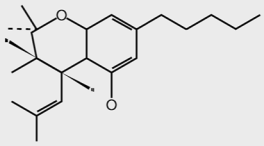
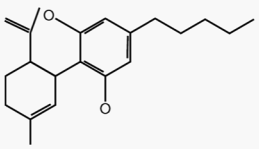
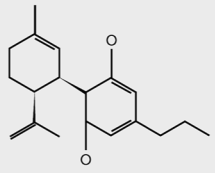
Cannabinoid	Structure	Central Nervous System Targets	Actions
Δ^9-Tetrahydrocannabinol		CB_1R	Partial agonist
		CB_2R (microglia)	Partial agonist
		TRPA1	Agonist
		TRPV2	Agonist
		TRPM8	Antagonist
		$\alpha_1\beta$ GlyR	Enhancer
		5-$HT_{3A}R$	Antagonist
		PPAR-γ	Activator
		GPR18	Agonist
		GPR55	Agonist
Cannabidiol		CB_1R	Antagonist
		CB_2R (microglia)	Antagonist
		GPR55	Antagonist
		TPRA1	Agonist
		TRPV1–3	Agonist
		TRPV4	Agonist
		TRPM8	Antagonist
		5-$HT_{1A}R$	Enhancer
		5-$HT_{3A}R$	Antagonist
		α_3GlyR	Enhancer
		PPAR-γ	Activator
		Ca_v3 ion channel	Inhibitor
		Adenosine reuptake	Inhibitor
Cannabidivarin		TRPA1	Agonist
		TRPM8	Antagonist
		TRPV4	Agonist
		TRPV1–3	Agonist
		DAGL-α	Inhibitor

N Engl J Med 2015;373:1048-58

Plant cannabinoid	Model	Efficacy
(B)		
Δ^9-Tetrahydrocannabinol	Generalized seizure (e.g., MES, PTZ, 6 Hz, 60 Hz, nicotine, and strychnine)	Y
(Δ^9-THC)	Temporal lobe epilepsy	Y
Synthetic CB1R agonists	Generalized seizure (MES, PTZ, amygdala kindling)	Y
(e.g., WIN55-212)	Partial seizure with secondary generalization (penicillin and maximal dentate gyrus activation)	Y
	Temporal lobe epilepsy	Y
	Absence epilepsy (WAG/Rij)	Mixed effect
Synthetic CB1R antagonists	Generalized seizure (MES and PTZ)	N[a]
(e.g., SR141716A)	Absence epilepsy (WAG/Rij)	N
	Partial seizures with secondary generalization (penicillin but not maximal dentate gyrus activation)	N[a]
	Epileptogenesis (juvenile head trauma but not kainic acid)	Y
Δ^9-Tetrahydrocannabivarin	Generalized seizure	Y
(Δ^9-THCV)		
Cannabidiol (CBD)	Generalized seizure (MES, PTZ, 6 Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical), and strychnine but not 3-mercaptoproprionic acid)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin but not cobalt)	Y
Cannabidivarin (CBDV)	Generalized seizure (MES, PTZ, and audiogenic)	Y
	Temporal lobe convulsions/status epilepticus	Y
	Partial seizures with secondary generalization (penicillin only)	Y
Cannabinol (CBN)	Generalized seizure (MES only)	Y

Mechanism of action of CBD

- Unlike Δ^9-THC, cannabidiol does not have its main neural effects through the activation of CB1R
- Alters neuronal excitability by other mechanisms

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Mechanisms of action of CBD

- Binding to members of the TRP family of cation channels, which antagonizes the G-protein–coupled receptor 55, leading to decreased presynaptic release of glutamate
- Activating 5-hydroxytryptophan 1A receptors
- Inhibiting adenosine reuptake

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

Devinsky O, et al. N Engl J Med 2017;376:2011-20

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Severe myoclonic epilepsy of infancy

- First described in 1982 and has been recognized as a syndrome since 1989
- The incidence: at least one in 40,000 children before the age of 7 years
- Dravet syndrome
- Intractable seizures that begin in the first year of life associated with developmental regression and cognitive impairment

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Severe myoclonic epilepsy of infancy

- Missense or nonsense mutations in the SCNA1 gene which encodes the pore-forming unit of the fast sodium channel NaV1.1 are present in over 80% of cases and are typically de novo, leading to haploinsufficiency.
- More rarely, mutations in other genes including SCN1B and SCN2A and mutations in the $GABA_A$ receptor subunit gene GABRG2.

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SMEI: clinical

- Typically seizures start around age 6 months
- Previously well children
- Prolonged, febrile and afebrile, generalized clonic or hemiclonic seizures
- Other seizure types including myoclonic, focal, and atypical absence seizures appear between the ages of 1-4 years

Brunklaus A, Zuberi SM. Epilepsia 2014; 55:979-84

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SMEI: clinical

- The epilepsy is usually not responsive to standard antiepileptic medication
- Patients then develop cognitive, behavioral, and motor impairment.

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- Randomized double-blind, placebo-controlled trial,
- 120 children and young adults with the Dravet syndrome and drug-resistant seizures
- Add on Cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo
- The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period

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Table 2. **Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.***

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

Devinsky O, et al. N Engl J Med 2017;376:2011-20

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End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	−1.0 (−1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (−0.5 to 10.3)‖		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−19.20 (−39.25 to −1.17)§		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)§		0.88

Caregiver Global Impression of Change (CGIC) scale range from 1 (very much improved) to 7 (very much worse)

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Table 4. **Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.***

System Organ Class and Preferred Term	Cannabidiol (N=61)	Placebo (N=59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

Devinsky O, et al. N Engl J Med 2017;376:2011-20

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome

Orrin Devinsky, M.D., Anup D. Patel, M.D., J. Helen Cross, M.B., Ch.B., Ph.D., Vicente Villanueva, M.D., Ph.D., Elaine C. Wirrell, M.D., Michael Privitera, M.D., Sam M. Greenwood, Ph.D., Claire Roberts, Ph.D., Daniel Checketts, M.Sc., Kevan E. VanLandingham, M.D., Ph.D., and Sameer M. Zuberi, M.B., Ch.B., M.D., for the GWPCARE3 Study Group*

Devinsky O, et al. N Engl J Med 2018;378:1888-97

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Lennox Gastaut syndrome

- Onset 1-8 years
- intractable generalized epilepsy with multiple seizure types
- mental retardation
- Slow spike and wave complexes on EEG

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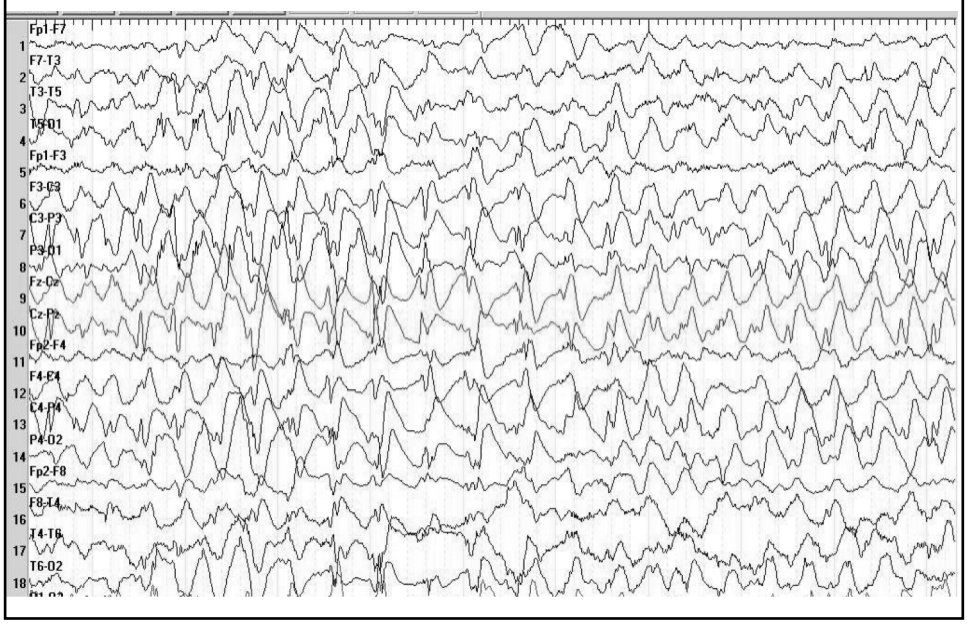

- Double-blind, placebo-controlled trial
- Patients with the Lennox–Gastaut syndrome (age range, 2 to 55 years)
- 225 patients were enrolled.
- Cannabidiol oral solution at a dose of
  - 20 mg/kg cannabidiol
  - 10 mg/kg cannabidiol
  - matching placebo
- Administered in two equally divided doses daily for 14 weeks.
- Primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period.

Devinsky O, et al. N Engl J Med 2018;378:1888-97

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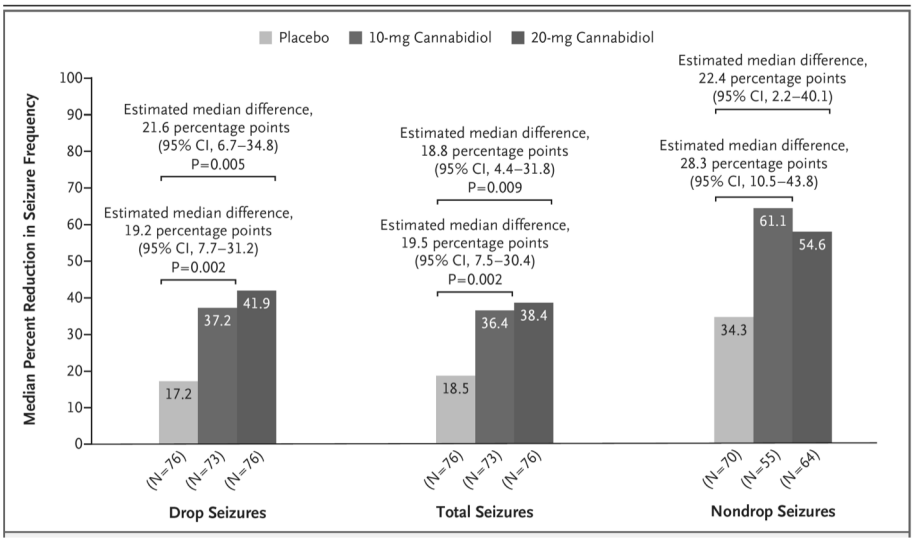
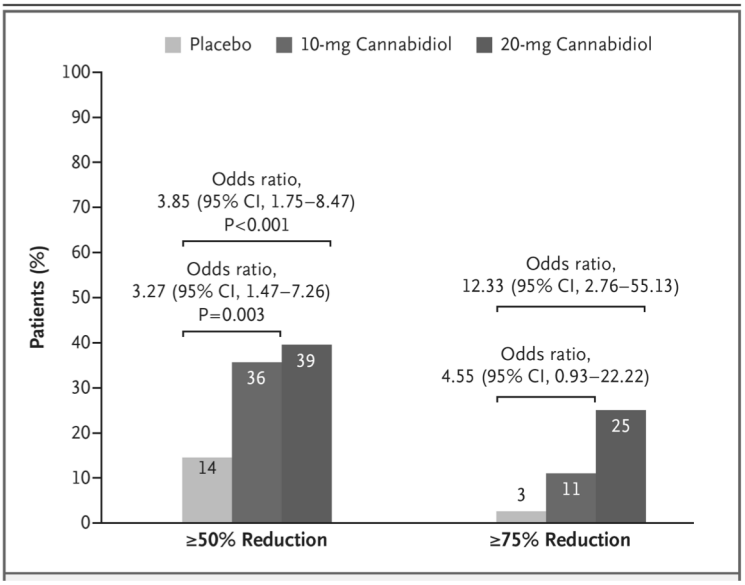
Median Percent Reductions in Monthly Seizure Frequency



Devinsky O, et al. N Engl J Med 2018;378:1888-97

Reductions of at Least 50% and 75% from Baseline in Drop-Seizure



Devinsky O, et al. N Engl J Med 2018;378:1888-97

Adverse Event	Placebo (N=76)	10-mg Cannabidiol (N=67)	20-mg Cannabidiol (N=82)
	number of patients (percent)		
Somnolence†	4 (5)	14 (21)	25 (30)
Mild	3 (4)	9 (13)	18 (22)
Moderate	1 (1)	4 (6)	6 (7)
Severe	0	1 (1)	1 (1)
Decreased appetite	6 (8)	11 (16)	21 (26)
Mild	5 (7)	8 (12)	15 (18)
Moderate	1 (1)	3 (4)	5 (6)
Severe	0	0	1 (1)
Diarrhea	6 (8)	7 (10)	12 (15)
Mild	6 (8)	6 (9)	10 (12)
Moderate	0	1 (1)	2 (2)
Upper respiratory tract infection	11 (14)	11 (16)	11 (13)
Mild	11 (14)	10 (15)	8 (10)
Moderate	0	1 (1)	3 (4)
Pyrexia	12 (16)	6 (9)	10 (12)
Mild	11 (14)	5 (7)	10 (12)
Moderate	1 (1)	1 (1)	0
Vomiting	9 (12)	4 (6)	10 (12)
Mild	9 (12)	2 (3)	10 (12)
Moderate	0	2 (3)	0
Mild nasopharyngitis	5 (7)	3 (4)	9 (11)
Status epilepticus	3 (4)	7 (10)	4 (5)
Mild	2 (3)	1 (1)	1 (1)
Moderate	1 (1)	4 (6)	3 (4)
Severe	0	2 (3)	0

Devinsky O, et al. N Engl J Med 2018;378:1888-97

DOI: 10.1111/epi.14477

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results

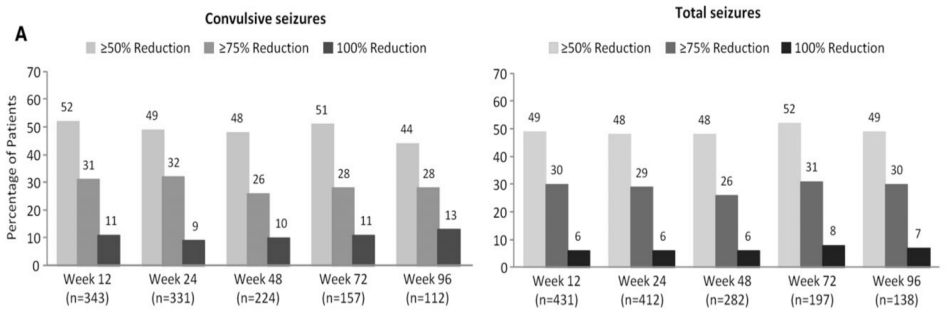
Jerzy P. Szaflarski[1] | Elizabeth Martina Bebin[1] | Anne M. Comi[2] | Anup D. Patel[3] | Charuta Joshi[4] | Daniel Checketts[5] | Jules C. Beal[6] | Linda C. Laux[7] | Lisa M. De Boer[8] | Matthew H. Wong [9] | Merrick Lopez[10] | Orrin Devinsky[11] | Paul D. Lyons[12] | Pilar Pichon Zentil[10] | Robert Wechsler[13] | on behalf of CBD EAP study group

Twenty-five US-based sites
607 patients with treatment resistant epilepsy taking stable doses of AEDs
Patients received oral CBD starting at 2-10 mg/kg/d, titrated to max. 25-50 mg/kg/d.
Efficacy endpoints:
- Percentage change from baseline in median monthly convulsive and total seizure frequency
- Percentage of patients with ≥50%, ≥75%, and 100% reductions in seizures vs baseline.

Szaflarski J, et al. Epilepsia. 2018;59:1540–48.

	Efficacy analysis set (n = 580)	Safety analysis set (n = 607)
Age, mean (range), y	13.1 (0.4-62.1)	13.2 (0.4-62.1)
Epilepsy diagnosis, n (%)		
Lennox-Gastaut syndrome	92 (16)	94 (15)
Dravet syndrome	55 (9)	58 (10)
Tuberous sclerosis complex	26 (4)	26 (4)
Aicardi syndrome	17 (3)	19 (3)
CDKL5	18 (3)	19 (3)
Doose, Dup15q, or febrile infection-related epilepsy syndromes	22 (4)	24 (4)
Other[a]	236 (41)	243 (40)
Unknown[a]	114 (20)	124 (20)
Gender, male, n (%)	302 (52)	313 (52)
Concomitant AEDs taken at baseline, median (range[b])	3 (0-10)	3 (0-10)
Convulsive seizures/28 d, median (Q1, Q3)	43 (12, 112)	–
Total seizures/28 d, median (Q1, Q3)	72 (22, 196)	–

Szaflarski J, et al. Epilepsia. 2018;59: 1540–48.



Szaflarski J, et al. Epilepsia. 2018;59:1540–48.

	CBD dose (mg/kg/d)					
	0-10 (n = 42)	>10-20 (n = 115)	>20-30 (n = 317)	>30-40 (n = 59)	>40 (n = 74)	All (N = 607)
Overall AE rate	27 (64.3)	98 (85.2)	286 (90.2)	56 (94.9)	69 (93.2)	536 (88.3)
Overall serious AE rate	4 (9.5)	31 (27.0)	112 (35.3)	19 (32.2)	33 (44.6)	199 (32.8)
AEs leading to discontinuation	5 (11.9)	6 (5.2)	17 (5.4)	2 (3.4)	1 (1.4)	31 (5.1)
AEs reported in >10% of patients in any group by MedDRA preferred term, n (%)						
Diarrhea	6 (14.3)	28 (24.3)	92 (29.0)	24 (40.7)	27 (36.5)	177 (29.2)
Somnolence	5 (11.9)	17 (14.8)	76 (24.0)	11 (18.6)	27 (36.5)	136 (22.4)
Convulsion	3 (7.1)	12 (10.4)	62 (19.6)	8 (13.6)	17 (23.0)	102 (16.8)
URTI	5 (11.9)	11 (9.6)	41 (12.9)	9 (15.3)	9 (12.2)	75 (12.4)
Decreased appetite	2 (4.8)	7 (6.1)	45 (14.2)	12 (20.3)	9 (12.2)	75 (12.4)
Vomiting	0	10 (8.7)	44 (13.9)	3 (5.1)	12 (16.2)	69 (11.4)
Fatigue	2 (4.8)	11 (9.6)	35 (11.0)	9 (15.3)	8 (10.8)	65 (10.7)
Pyrexia	1 (2.4)	9 (7.8)	40 (12.6)	5 (8.5)	8 (10.8)	63 (10.4)
Status epilepticus	1 (2.4)	8 (7.0)	21 (6.6)	4 (6.8)	11 (14.9)	45 (7.4)
Pneumonia	2 (4.8)	3 (2.6)	23 (7.3)	3 (5.1)	10 (13.5)	41 (6.8)

AE, adverse event; CBD, cannabidiol; MedDRA, Medic
respiratory tract infection.

Szaflarski J, et al. Epilepsia. 2018;59:1540–48.

ANNALS of Clinical and Translational Neurology
Open Access

RESEARCH ARTICLE

A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome

Bláthnaid McCoy[1,2], Laura Wang[3], Maria Zak[1], Sameer Al-Mehmadi[1], Nadia Kabir[1], Kenda Alhadid[1], Kyla McDonald[4], Grace Zhang[4], Rohit Sharma[1], Robyn Whitney[1,2], Katia Sinopoli[4] & O. Carter Snead III[1]

[1]Division of Neurology, the Hospital for Sick Children, Toronto, Canada
[2]Department of Pediatrics, University of Toronto, Toronto, Canada
[3]Department of Pharmacy, Hospital for Sick Children, Toronto, Canada
[4]Department of Psychology, the Hospital for Sick Children, Toronto, Ontario, Canada

- To establish dosing and tolerability of TIL-TC150 - a cannabis plant extract produced by. Tilray®, (100 mg/mL CBD and 2 mg/mL THC) in children with Dravet syndrome.
- Assess impact of therapy on seizures, EEG and QoL

- Nineteen patients with Dravet syndrome
- 20-week intervention
- Mean dose achieved was 13.3 mg/kg/day of CBD (range 7–16 mg/kg/day) and 0.27 mg/kg/day of THC (range 0.14–0.32 mg/kg/day).

McCoy B, et al. Ann Clin Trans Neurol 2018; 5: 1077–88

	Pre-intervention	Primary end point	*P*-Value
Seizure Diary – median. (IQR) or mean (SD)[2]			
Seizure count (motor)	17.0 (31)	5.0 (26)	0.006[1]
Myoclonic jerks (days)	5.0 (16)	0.5 (5)	0.031[1]
Seizure free days, mean (SD)	11.89 (9.48)	18.32 (8.78)	0.008[1]
24-h EEG data – median. (IQR)[3]			
Spike-per-Second	0.09 (0.11)	0.06 (0.05)	0.022[1]
Number of seizure/24 h	0 (1)	0 (2)	0.953

McCoy B, et al. Ann Clin Trans Neurol 2018; 5: 1077–88

Consensus and Controversies

Form	Preparation	Epilepsy type	Evidence
CBD	99% cannabidiol and less than 0.10% Δ9-THC (Epidiolex®)	Dravet syndrome Lennox Gastaut syndrome	RCTs
CBD		Other syndrome Focal epilepsies	Not enough evidence
CBD/THC	100 mg/mL CBD and 2 mg/mL THC (TIL-TC150)	Dravet syndrome	Some evidence
Other forms of Cannabis extracts			Not enough evidence

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Adverse effects

- Common side effects:
  - sleepiness, diarrhea, fatigue, decreased appetite
- Serious adverse events:
  - elevated liver enzyme, infection, status epilepticus
- CBD has drug interactions (CYP inhibitor) with other AEDs eg. clobazam, carbamazepine, phenytoin

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EVIDENCE-BASED OF MEDICAL CANNABIS IN SLEEP DISORDER

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Cannabis and sleep

- The cannabis plant contains over 60 cannabinoids.
- Delta-9-Tetrahydrocannabinol (THC) is mainly responsible for the psychotropic effects
- Mediated mostly by cannabinoid CB1-receptors, found in high concentrations in the frontal cortex, cerebellum and basal ganglia

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Cannabis and sleep

- CB1- receptors activate a variety of signal transduction pathways and interact with numerous neurotransmitters and neuromodulators
- Acute effects of cannabis:
  - mild euphoria, talkativeness, intensification of sensory experiences, difficulty concentrating, altered time perception, relaxation and drowsiness

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Cannabis and sleep

- Interpretation of the available PSG studies of cannabis effects is difficult due to several limitations
- heterogeneity of administered dosage, time and route of administration, amount of THC, the extent of previous drug consumption (possibly leading to withdrawal effects or to tolerance)

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Table 2 Studies investigating the effect of smoked marijuana and oral THC upon sleep

Study	Subjects (no.)	Intervention	Major findings
Gillin et al.[42]	3 psychiatric pts	40 mg THC	↓ REM sleep
Kales et al.[47]	4 naive, 4 chronic users	Smoked marijuana	↓ REM sleep. Recovery: REM rebound
Freemon[48]	2	20 mg THC	↓ REM %. Recovery: ↑ wakefulness, ↓ REM latency
Pivik et al.[65]	6	<20 mg THC	↓ WASO. Recovery: ↓ Stage 1, ↓ REM latency
Cousens and DiMascio[38]	9 insomniacs	10–30 mg THC	↓ Sleep onset latency
Bobon et al.[43]	1 psychiatric pt	20 mg Δ-8-THC	↑ Wakefulness, ↑ REM latency
Hosko et al.[44]	7 (2 naive, 1 heavy user)	20 mg THC	No consistent alterations
Pranikoff et al.[52]	30 chronic users	Smoked marijuana until "high"	↑ Stage 2, ↓ Stage 4 compared to abstinent users
Barratt et al.[45]	12	2 marijuana cigarettes (1.6% THC)	Acute: ↑ SWS, chronic administration: ↓ SWS. Withdrawal: ↓ SWS
Feinberg et al.[46]	7 chronic users	70–210 mg THC	↑ Stage 4, ↓ REM density, ↓ REM sleep. Withdrawal: ↑ SOL, ↓ SWS, REM rebound
Tassinari et al.[41]	8 (7 naive)	70 mg THC	↑ Stage 2, ↓ REM sleep
Feinberg et al.[50]	4 chronic users	Marijuana extract (70–210 mg THC)	Low dosage: ↑ Stage 4, ↓ REM density. Withdrawal: ↑ SOL
Karacan et al.[53]	32 chronic users	Usual pattern of marijuana use	↑ REM %, ↑ SOL
Freemon[51]	2	30 mg THC	Chronic administration: ↓ SWS. Withdrawal: ↑ wakefulness, ↓ SWS
Nicholson et al.[47]	8	15 mg THC, 5 mg THC+CBD, 15 mg THC+CBD	15 mg THC: ↑ sleepiness next morning. 15 mg THC+CBD: ↑ wakefulness, ↓ Stage 3, ↑ sleepiness next morning
Walther et al.[89]	6 pts with dementia and nighttime agitation	2.5 mg THC	↓ Nocturnal motor activity

Abbreviations: CBD, cannabidiol; MSLT, multiple sleep latency test; PSG, polysomnography; pts, patients; SOL, sleep onset latency; SWS, slow wave sleep; THC: Δ-9-tetrahydrocannabino

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Sleep Medicine Reviews 2008; 12: 381-9

Cannabis withdrawal and sleep

- Anger and irritability, anxiety and nervousness, restlessness, weight loss, sleep difficulty and strange dreams are frequently reported marijuana withdrawal effects
- Occur within 24-72 h of discontinuation of cannabis use and persist for 6-7 weeks
- Resumption of cannabis use attenuates sleep disturbances

Sleep Medicine Reviews 2008; 12: 381-9

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Angarita *et al. Addict Sci Clin Pract (2016) 11:9*
DOI 10.1186/s13722-016-0056-7

Addiction Science & Clinical Practice

REVIEW Open Access

Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review

Gustavo A. Angarita, Nazli Emadi, Sarah Hodges and Peter T. Morgan*

	Alcohol		Cocaine		Cannabis		Opioids	
	Early Abs	Late Abs	Early Abs	Late Abs	Early Abs	Late Abs	Early Abs	Late Abs
Sleep latency	?	↑	?	↑	↑	?	↑	↑
Total sleep time	?	↓	?	↓	↓	↓	↓	↓
Slow wave sleep	?	↓	↓	↓	↓	?	↓	↓
REM sleep	?	?	?	↓	↑	↓	↓	?
REM latency	?	?	↓	?	↓	?	↑	?

Early Abs Early Abstinence or acute withdrawal

Late Abs Late Abstinence or subacute withdrawal

? Insufficient data or conflicting results across studies

Angarita et al. Addict Sci Clin Pract 2016; 11:9

REVIEW

Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of *Sativex*®, a Cannabis-Based Medicine

by **Ethan B. Russo***[a])[b]), **Geoffrey W. Guy**[a]), and **Philip J. Robson**[a])

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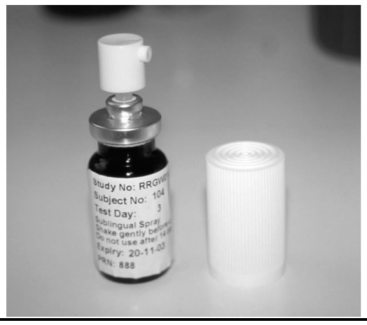

Chemistry and Biodiversity 2007;4:1729

Drug	Clinical indication	Subject number (N)	Trial duration	Results/reference
Cannabis (smoked)	HIV neuropathy	50	5 days	>30% pain reduction *vs.* placebo ($p=0.04$), sleep NA [62]
Cannador	Spasticity in MS	419	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$), sleep ($p=0.025$) [63]
Cannador	Post-herpetic neuralgia	65	4 weeks	No benefit observed on pain, sleep NA [64]
Cannador	Post-operative pain	30	Single doses, 1 day each	Decreasing pain intensity with increasing dosage ($p=0.01$). Sleep NA formally. One complaint of sleep disturbance [65]
Sativex	Neurogenic pain	20	Series of 2-week N-of-1 crossover blocks	Improvement with *Tetranabinex* and *Sativex* on VAS pain *vs.* placebo ($p<0.05$), symptom control best with *Sativex* ($p<0.0001$). *Sativex* improved sleep quality ($p=0.041$) [66]
Sativex	Chronic intractable pain	24	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$). Sleep duration and quality both improved ($p=0.0001$) [67]
Sativex	Brachial plexus avulsion	48	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with *Tetranabinex* ($p=0.002$) and *Sativex* ($p=0.005$) over placebo. *Sativex* improved sleep disturbance ($p=0.017$) and sleep quality scores ($p=0.019$) [68]
Sativex	Central neuropathic pain in MS	66	5 weeks	Numerical Rating Scale (NRS) analgesia improved ($p=0.009$), sleep disturbance ($p=0.003$) *vs.* placebo [61]
Sativex	Peripheral neuropathic pain	125	5 weeks	Improvements in NRS pain levels ($p=0.004$), dynamic allodynia ($p=0.042$), sleep disturbance ($p=0.001$) *vs.* placebo [69]
Sativex	Rheumatoid arthritis	56	5 week	Improvements over placebo morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), DAS-28 ($p=0.002$), and SF-MPQ pain at present ($p=0.016$), sleep quality ($p=0.027$) [70]

Chemistry and Biodiversity 2007;4:1729

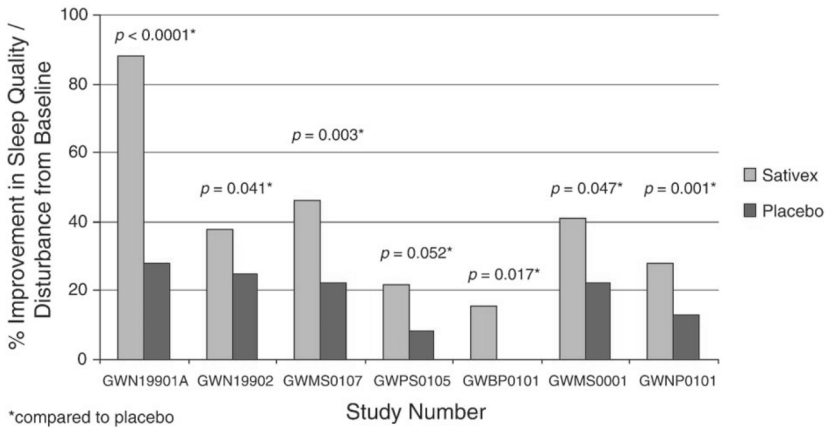

Fig. 2. *Compendium of results of* Sativex *on sleep in earlier Phase II–III RCTs in multiple sclerosis* (MS) *and intractable chronic pain*

Chemistry and Biodiversity 2007;4:1729

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

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IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder

CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

JAMA. 2015;313:2456-73

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Depression	1 (66)	Nabiximols	Placebo	Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks	Mean difference (95% CI), 0.15 (−1.0 to 1.31)	Placebo	NA	Very low
	1 (182)	Nabiximols	Placebo	Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks	Mean difference (95% CI), 1.90 (−0.22 to 4.02)	Placebo	NA	Very low
	1 (160)	Nabiximols	Placebo	Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks	Mean difference (95% CI), 0.69 (−0.76 to 2.14)	Placebo	NA	Very low
Anxiety disorder	1 (24)	Cannabidiol	Placebo	Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes	Mean difference, −16.52 *P* value = .01	CBM	NA	Very low
Sleep disorder	1 (22)	Nabilone	Placebo	Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks	Mean difference, −19.64 *P* value = .02	CBM	NA	Low
	8 (539) In other indications	Nabiximols (7), THC/CBD (1)	Placebo	Sleep quality NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.58 (−0.87 to −0.29)	CBM	33	Very low
	3 (1637) In other indications	Nabiximols (3)	Placebo	Sleep disturbance NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.26 (−0.52 to 0.00)	CBM	64	Very low

JAMA. 2015;313:2456-73

Summary

- Acute effects of cannabis include relaxation and drowsiness
- Studies on effects of cannabis on sleep structure are still difficult to interpret due to several limitations
- Irritability, sleep difficulties and strange dreams occurs with cannabis withdrawal

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Summary

- Improvement in sleep quality was reported in clinical studies of cannabis for pain and spasticity
- To date, the evidence based of clinical use of cannabis for patients with insomnia and sleep disorder is still limited

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