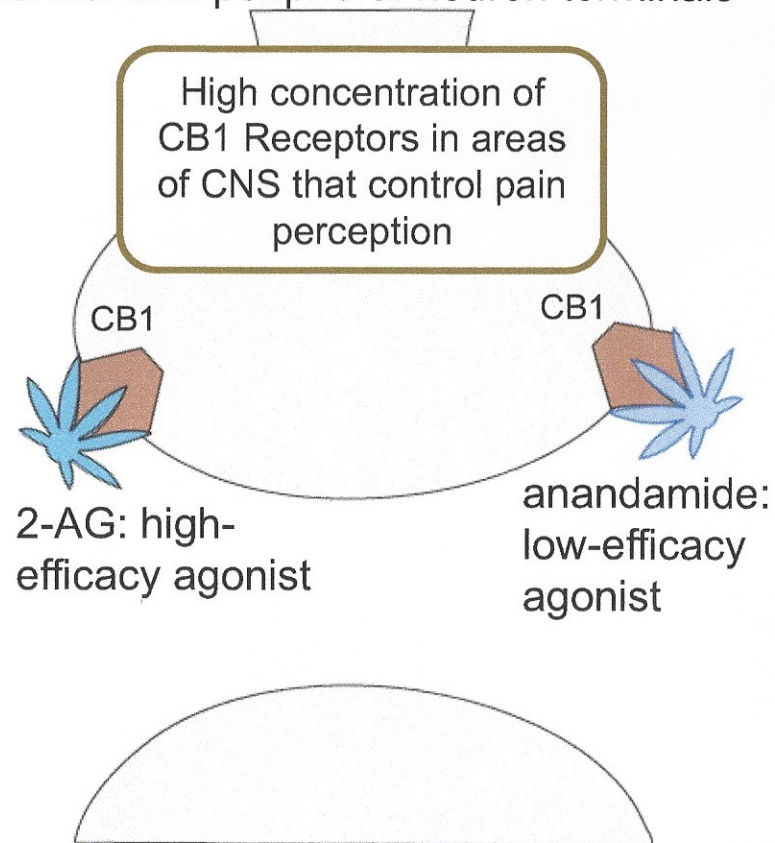


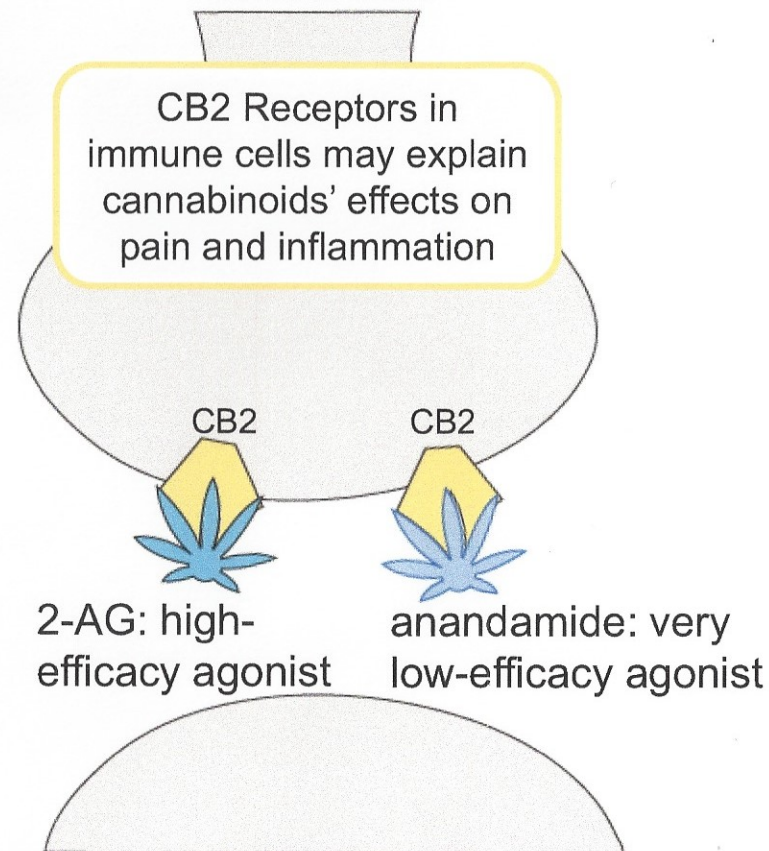
Cannabis

The Endocannabinoid System: Receptors and Ligands

central and peripheral neuron terminals



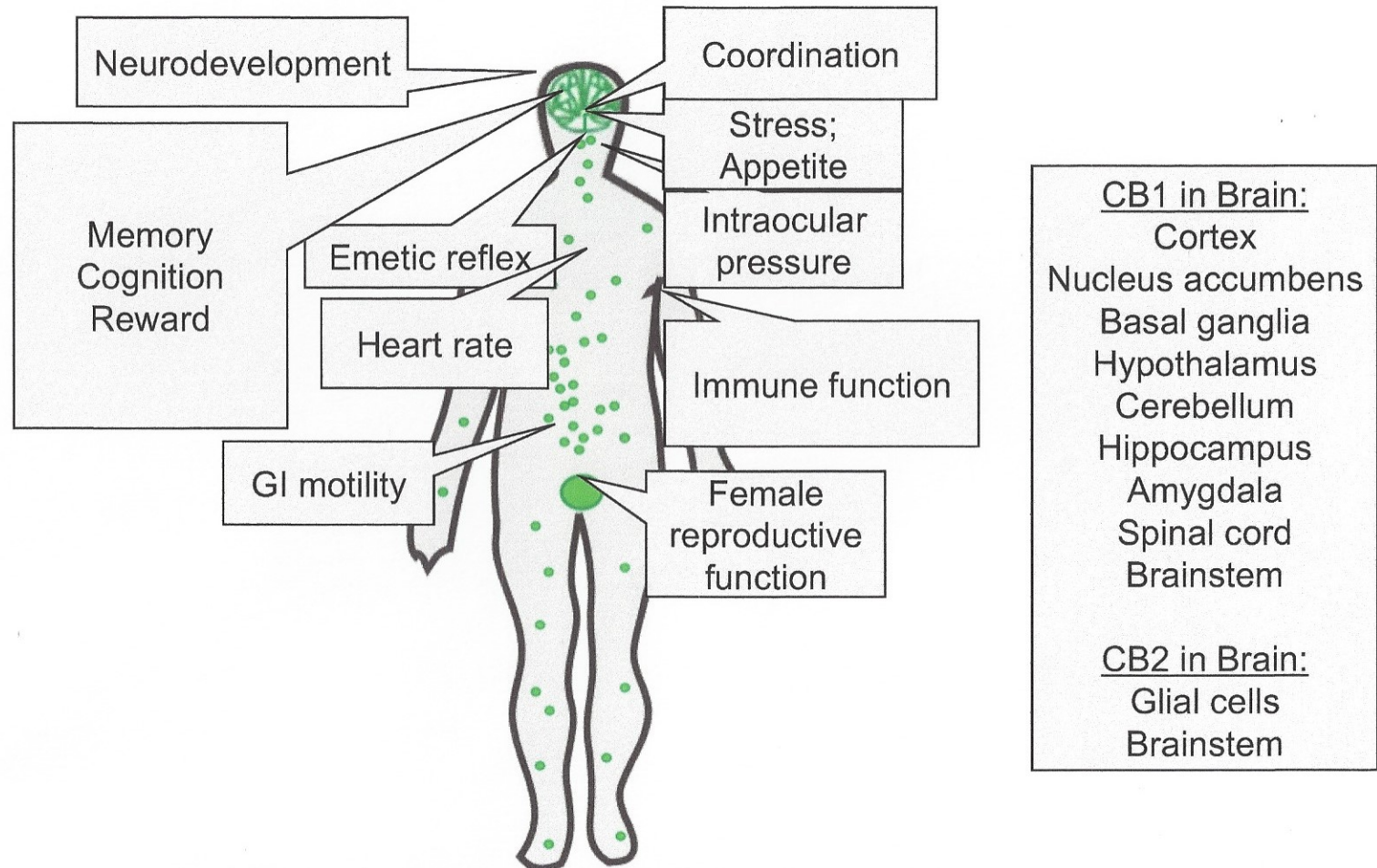
immune cells



Abrams DI et al. Clin Pharmacol Ther. 2011;90(6):844-51;
Walker JM et al. Life Sci. 1999;65(6-7):665-73.

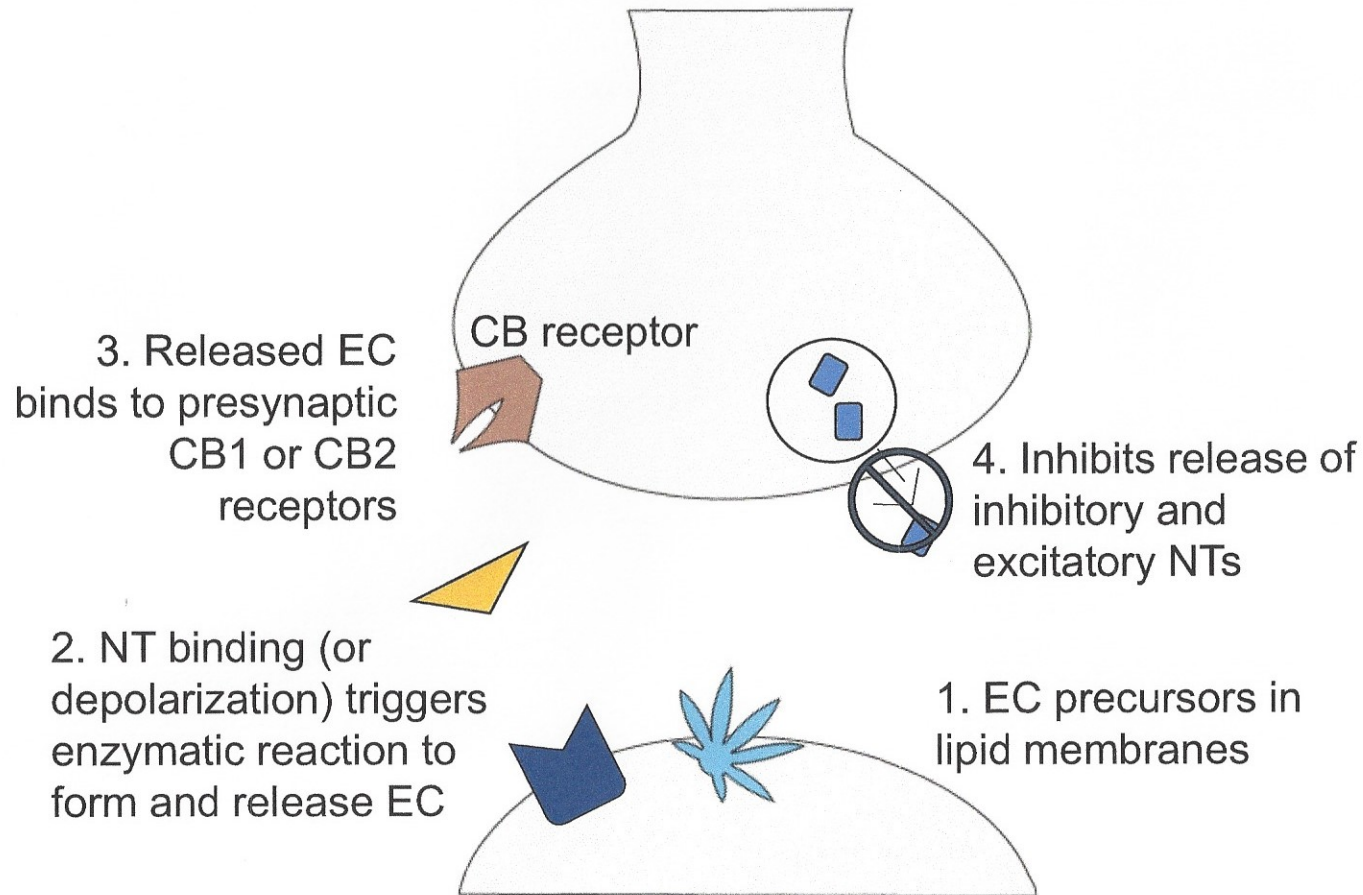
2-AG: 2-arachidonylglycerol

The Endocannabinoid System Regulates:



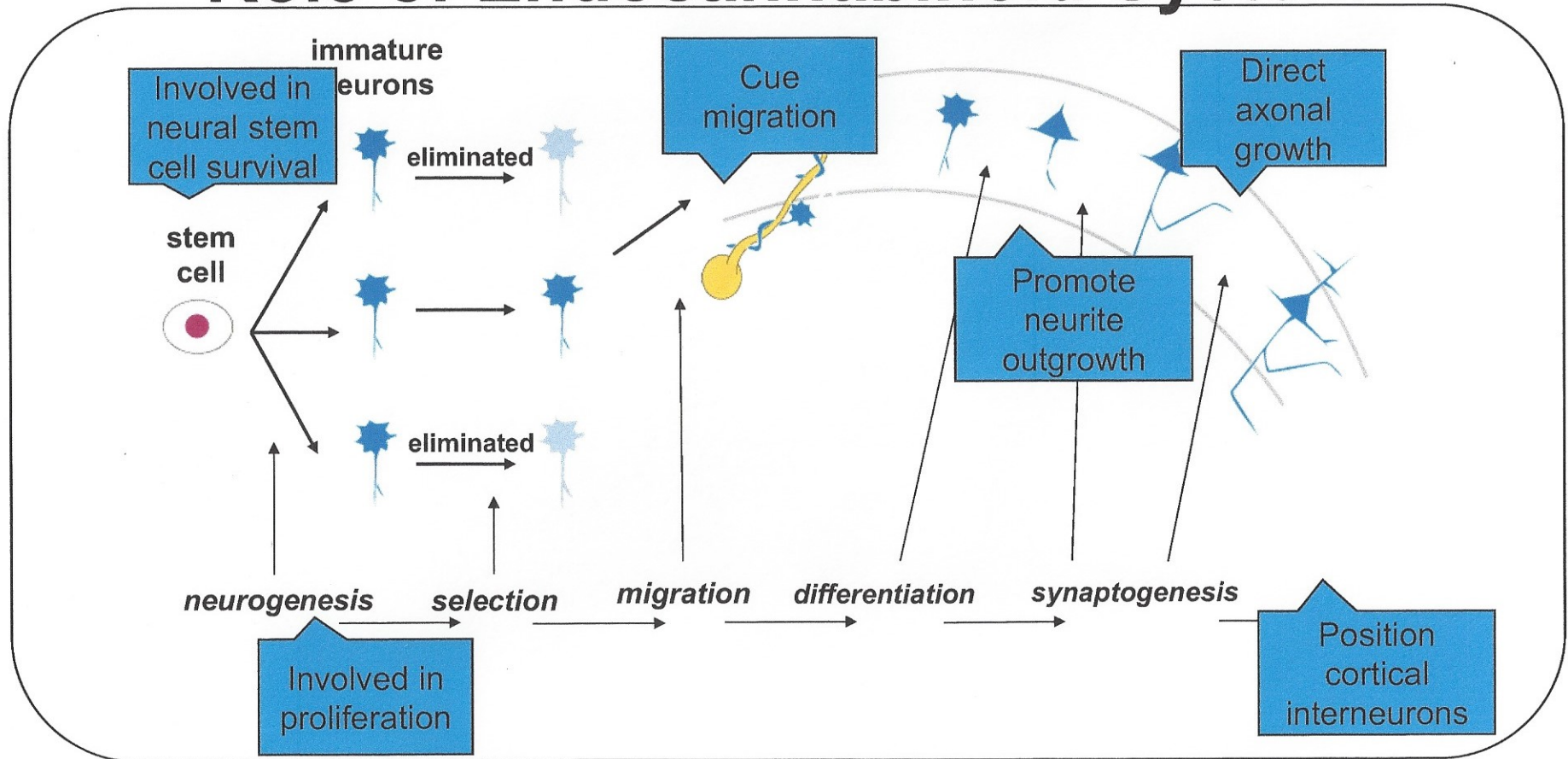
<http://www.fundacion-canna.es/en/endocannabinoid-system;>
Lu et al. Biol Psychiatry 2016;79:516-25.

The Endocannabinoid System: Retrograde Neurotransmission



EC: endocannabinoid
NT: neurotransmitter

Pre- and Postnatal Neurodevelopment: Role of Endocannabinoid System

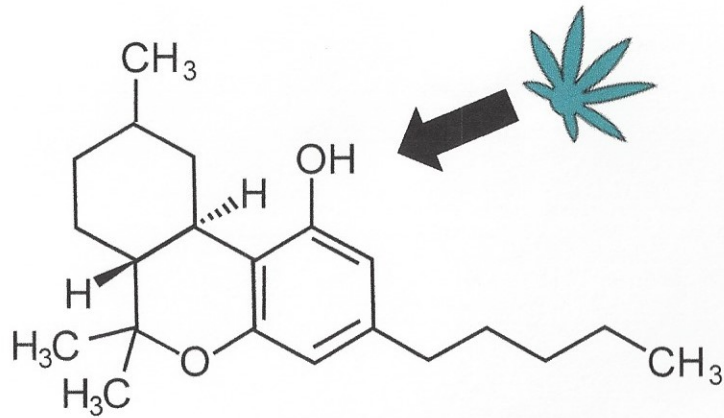


Stahl SM. Stahl's Essential Psychopharmacology. 3rd ed. 2008; Zhou Y et al. Int J Biochem Cell Biol 2014;47:104-8; Maccarrone M et al. Nat Rev Neurosci 2014;15(12):786-801.

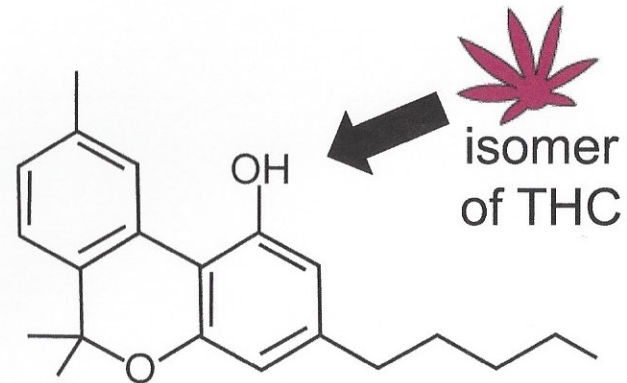
THC

vs.

Cannabidiol



Psychoactive
anxiogenic

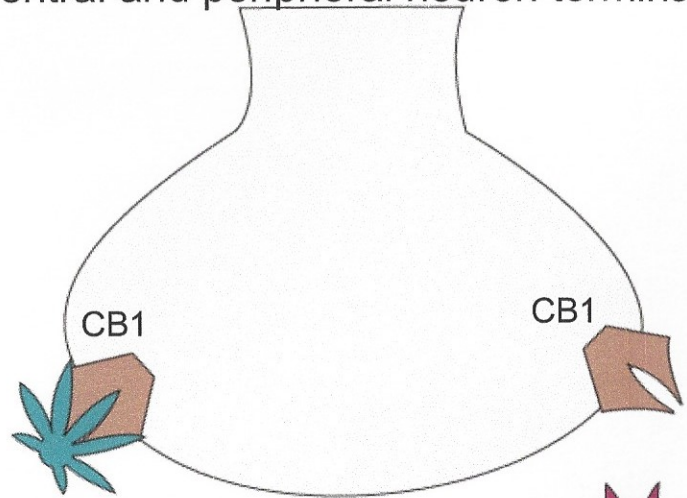


NOT psychoactive
anxiolytic
anticonvulsant
under investigation by
NIDA and NIH for
therapeutic uses

Greydanus DE et al. Disease Month 2015;61:118-75;
Iseger TA, Bossong MG. Schizophr Res 2015;162:153-61.

THC vs. Cannabidiol: Different Binding Properties

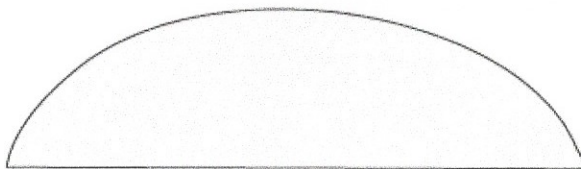
central and peripheral neuron terminals



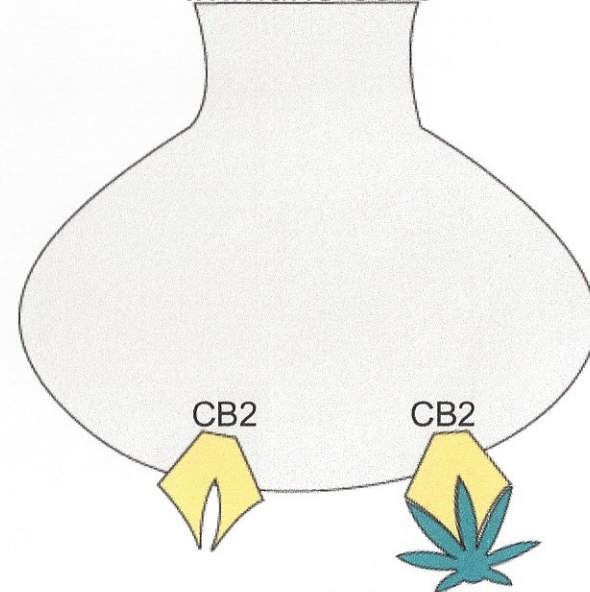
THC: partial agonist



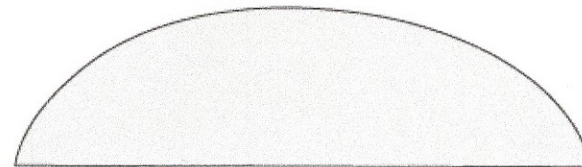
CBD: does not bind CB receptors;
may interact with 5HT receptors






immune cells



THC: partial agonist
(low affinity?)

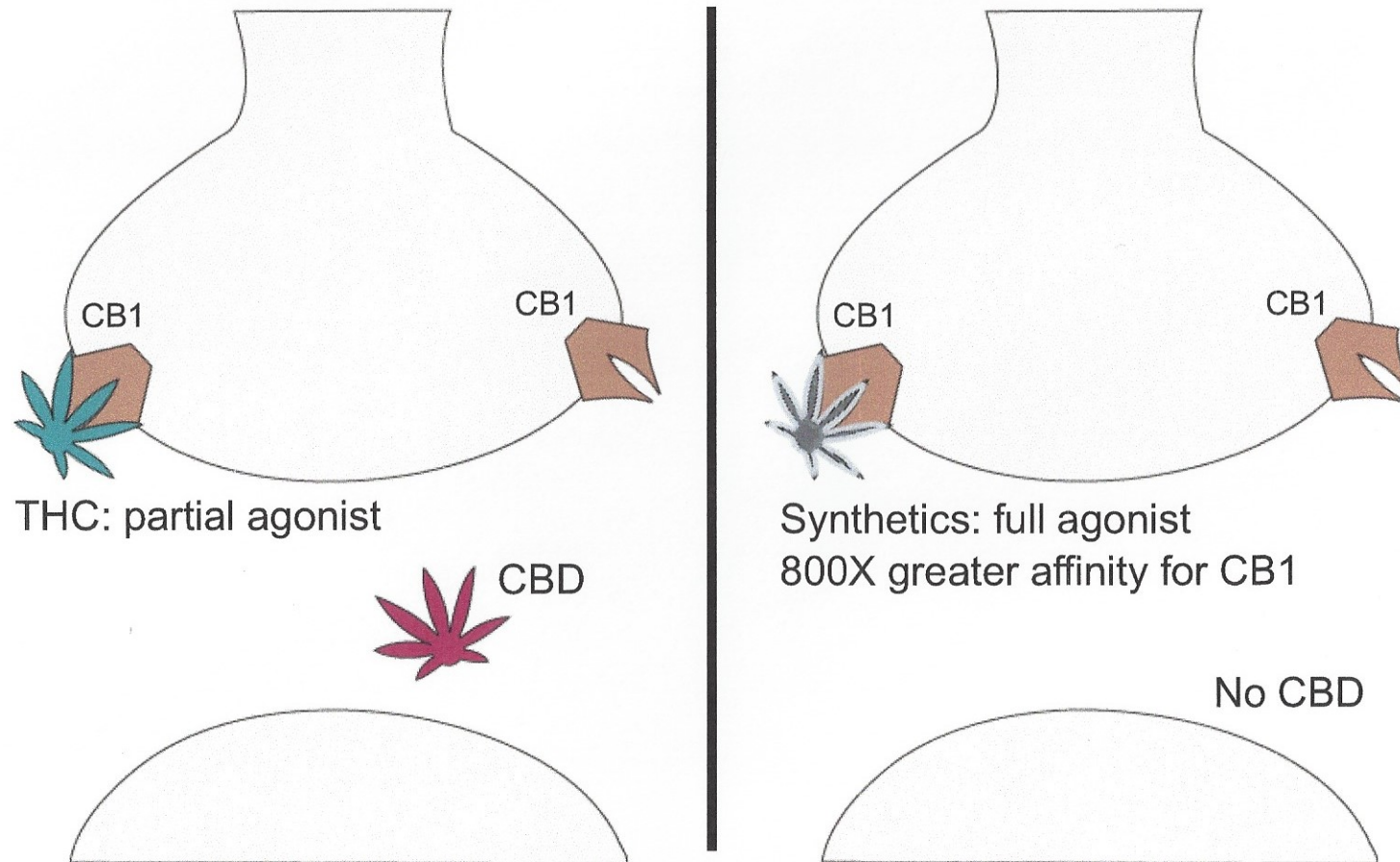


THC vs. CBD: Psychiatric Effects

	 Cannabis w/ Low CBD Content	 Cannabis w/ High CBD Content	 CBD alone
Psychosis symptoms	Higher risk of hallucinations and delusions	Lower risk of hallucinations and delusions	Possible antipsychotic effects
Psychotic disorder	Earlier age of onset	Later age of onset	
Cognition	Higher risk of acute memory impairment	Lower risk of acute memory impairment	
Anxiety	Anxiogenic; Increased amygdalar activity		Anxiolytic; Reduced amygdalar activity

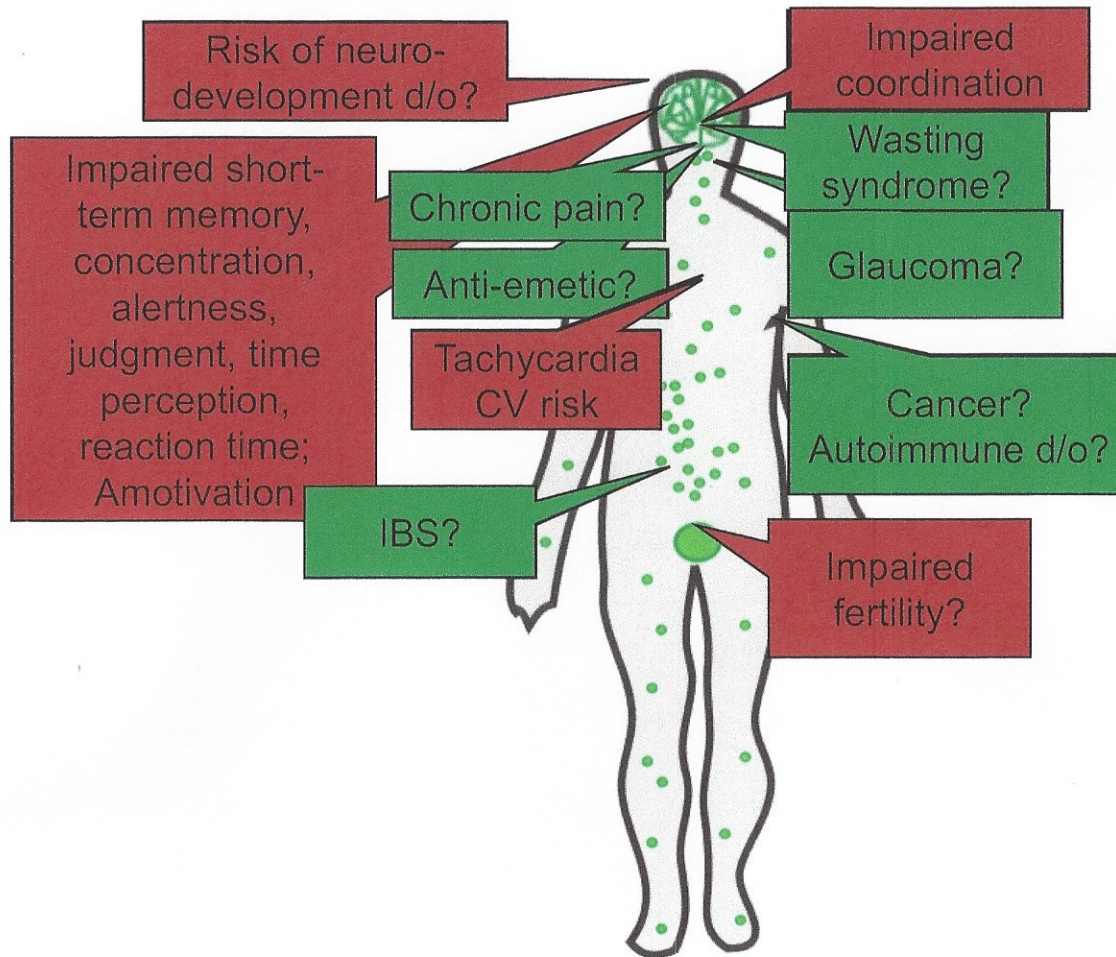
Iseger TA, Bossong MG. Schizophr Res 2016;162:153-61.

Cannabis vs. “The Synthetics”



Cameron K et al. Psychopharmacology 2013;227(3):493-9;
Loeffler G et al. Milit Med 2012;177(9):1041-8.

Potential Effects of Cannabis



Does cannabis use affect cognitive capacity?

- Short-term: YES
- Long-term: mixed data
 - Meta-analysis: non-intoxicated users do worse than non-users, BUT
 - In studies with at least 1 month abstinence, difference not seen
- Neuroimaging data: inconsistent, don't seem to correlate with neuropsychological test performance
- Genetic factors that increase risk of impairment (COMT, AKT1)?
- Magnitude and persistence of impairment may depend on:
 - Frequency and duration of use
 - Age of onset of use
 - Length of abstinence

COMT: catechol-O-methyltransferase
AKT1: serine/threonine kinase 1

Volkow ND et al. JAMA Psychiatry 2016;73(3):292-7.
Meta-analysis: Schreiner AM et al. Psychopharmacology 2012;20(5):420-9.

Health Effects of Cannabis: National Academies of Science, Engineering, and Medicine

			Associated with benefits to:	Associated with risk of:
Substantial Evidence			<ul style="list-style-type: none"> Chronic pain Chemotherapy-induced nausea Spasticity in multiple sclerosis (patient-reported) 	<ul style="list-style-type: none"> Respiratory symptoms Motor vehicle crashes Lower birth weight Psychosis
Moderate Evidence			<ul style="list-style-type: none"> Sleep in obstructive sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis Airway dynamics Forced vital capacity Cognition in psychosis 	<ul style="list-style-type: none"> Overdose injuries in pediatric population Impaired learning, memory, and attention Increased (hypo)mania in bipolar disorder Depressive disorders Suicidality and suicide completion Social anxiety disorder Development of substance use disorder for other substances

National Academies of Sciences, Engineering, and Medicine. 2017. <https://doi.org/10.17226/24625>.

Health Effects of Cannabis: National Academies of Science, Engineering, and Medicine

	Associated with benefits to:	Associated with risk of:
Limited Evidence	<ul style="list-style-type: none"> • Increasing appetite/decreasing weight loss in HIV/AIDS • Spasticity in multiple sclerosis (clinician-reported) • Tourette syndrome • Anxiety • PTSD 	<ul style="list-style-type: none"> • Testicular cancer • Acute myocardial infarction • Ischemic stroke of subarachnoid hemorrhage • Prediabetes • Chronic obstructive pulmonary disease • Pregnancy complications • Infant admission to neonatal intensive care • Impaired academic achievement • Increased unemployment • Impaired social functioning • Increased positive symptoms in schizophrenia • Bipolar disorder • Anxiety disorders (other than social anxiety disorder) • Increased severity of PTSD symptoms

National Academies of Sciences, Engineering, and Medicine. 2017. <https://doi.org/10.17226/24625>.

Health Effects of Cannabis: National Academies of Science, Engineering, and Medicine

	Associated with benefits to:	Associated with risk of:
Insufficient Evidence	<ul style="list-style-type: none"> • Dementia • Intraocular pressure associated with glaucoma • Depression in chronic pain or multiple sclerosis • Cancer • Anorexia nervosa • Irritable bowel syndrome • Epilepsy • Spasticity in spinal cord injury • Amyotrophic lateral sclerosis • Huntington’s disease • Parkinson’s disease • Dystonia • Addiction • Psychosis 	<ul style="list-style-type: none"> • Lung, head and neck cancers • Esophageal cancer • Prostate and cervical cancer • Certain leukemias • Asthma • Liver fibrosis or hepatic disease in individuals with Hepatitis C • Adverse immune cell response • Adverse effects on immune status in HIV • Oral human papilloma virus • All-cause mortality • Occupational accidents/injuries • Death from overdose • Later outcomes to offspring (eg, sudden infant death syndrome, academic achievement, later substance abuse) • Worsening of negative symptoms in schizophrenia

National Academies of Sciences, Engineering, and Medicine. 2017. <https://doi.org/10.17226/24625>.

Psychosis Risk in Adolescent Cannabis Users

- 4-year prospective study using novel model to test causal relationship with multiple follow-up periods
- 3720 adolescents age 13-16 years
- Cannabis use predicted an increase in psychosis symptoms a year later

Does cannabis improve symptoms of PTSD, bipolar disorder, and depression?

- Subjective **ACUTE** improvements in PTSD (reduced nightmares), bipolar disorder (stabilized mood), and depression (increased motivation)
- Recent review reveals **negative long-term outcomes** of frequent cannabis use in PTSD (three studies), bipolar disorder (five studies), and depression (two studies)
 - Greater symptom severity over time compared to baseline
 - Less remission
 - Reduced improvements associated with recommended treatments
 - Cannabis use may interfere with treatment, including cognitive behavioral therapy
 - Stopping cannabis use associated with improved symptom severity

Cannabis Efficacy for Chronic Pain

- Systematic reviews have suggested that cannabinoids demonstrate a modest effect on pain
- “The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research”
 - *Conclusion 4-1* There is substantial evidence that cannabis is an effective treatment for chronic pain in adults

Whiting PF et al. JAMA. 2015;313(24):2456-73; Andrae MH, et al. J Pain. 2015;16(12):1221-32; Health Effects of Cannabis and Cannabinoids. Natl Academy Pr; 2017; doi:<https://doi.org/10.17226/24625>;

American Society of Addiction Medicine (ASAM) Recommendations

- Cannabis-related products **should not** be distributed unless/until they have FDA approval
- Smoking is not an appropriate drug delivery mechanism
- Need for federal regulatory standards for approval and distribution
- State should not enact regulatory standards more permissive than federal ones
- Clinicians who choose to discuss medical use of cannabis must:
 - Adhere to established professional tenets of proper patient care
 - Have a preexisting and ongoing relationship with the patient
 - Not recommend cannabis as a disproportionately large portion of practice
 - Not issue recommendation without adequate information regarding composition and dose
 - Have adequate training in identifying substance abuse and addiction

College of Family Physicians of Canada (CFPC) Recommendations

- Pain: only for patients with neuropathic pain that has failed to respond to standard treatment (including adequate trial of pharmaceutical cannabinoids)
- Anxiety: not appropriate therapy
- Insomnia: not appropriate therapy
- Not appropriate for:
 - <25 years of age
 - Personal/family history of psychosis
 - Current or past cannabis use disorder
 - Cardiovascular or respiratory disease
 - Pregnant, planning pregnancy, or breastfeeding

College of Family Physicians of Canada. Authorizing Dried Cannabis for Chronic Pain or Anxiety: Preliminary Guidance from the College of Family Physicians of Canada. Mississauga, ON: College of Family Physicians of Canada; 2014.

Cautions About Cannabis Use: Time to Peak Concentration

Inhalation

- Fast brain uptake
- Higher risk of addiction
- Risk of impairment greatest immediately and within first 2 hours

Oral

- Delayed brain uptake
- Lower risk of addiction
- Risk of impairment delayed and may be greatest between 2–6 hours after consumption