Review of the Scientific Evidence Regarding the Potential Benefits and Harms of Marijuana

David Galbis-Reig, M.D.
Medical Director of Addiction Services
Wheaton Franciscan Healthcare – All Saints

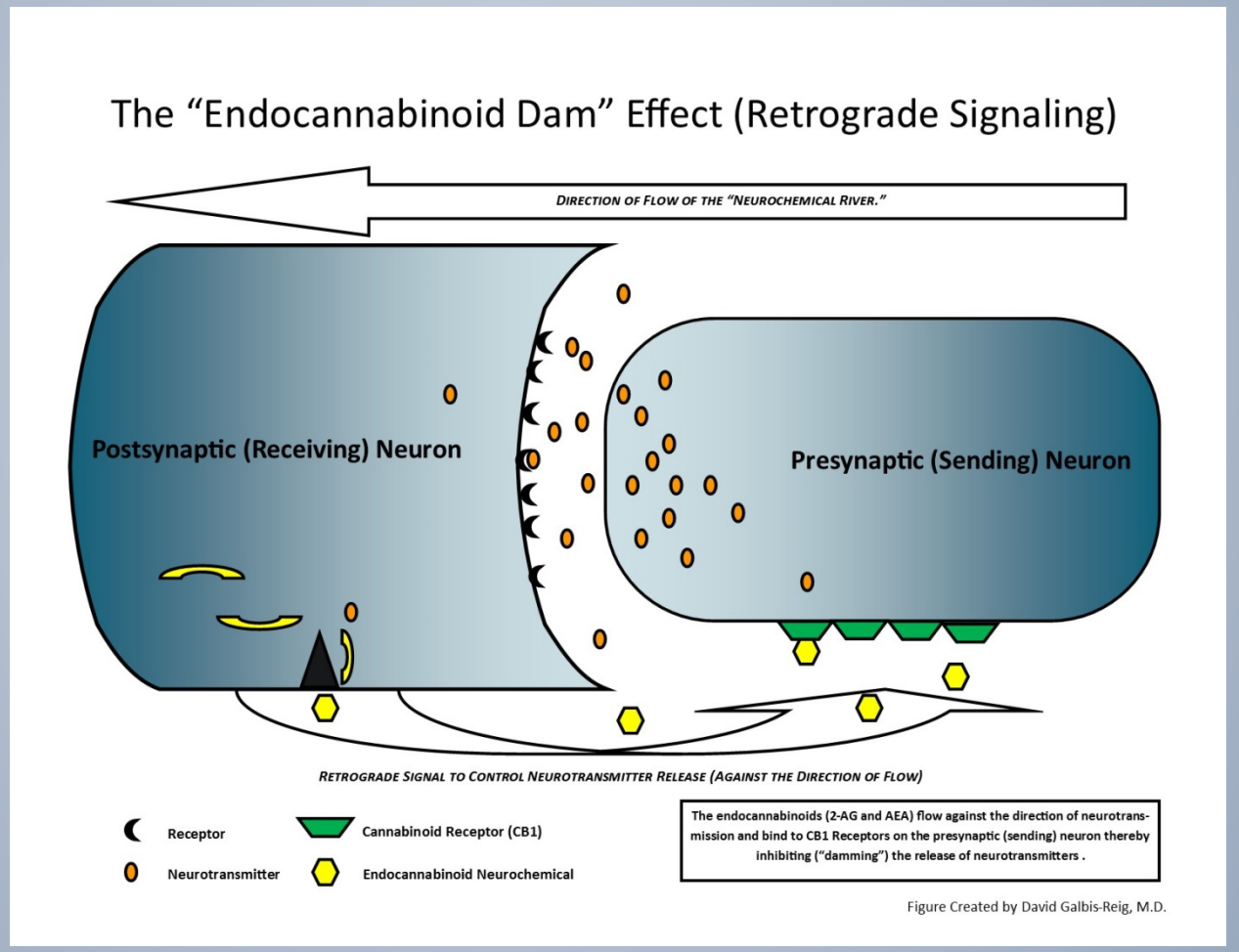
ASAM Disclosure of Relevant Financial Relationships Content of Activity: Review of the Scientific Evidence Regarding the Potential Benefits and Harms of Marijuana

Name	Commercial Interests	Relevant Financial Relationships: What Was Received	Relevant Financial Relationships: For What Role	No Relevant Financial Relationships with Any Commercial Interests
David Galbis-Reig	Pfizer, Inc.	Bond in IRA Rollover Account	Ownership Interest	
David Galbis-Reig	Cortex Pharmaceuticals	Stock in IRA Rollover Account	Ownership Interest	
David Galbis-Reig	GW Pharmaceuticals	Stock in IRA Rollover Account	Ownership Interest	
Spouse	Abbott Pharmaceuticals	Stock Options	Ownership Interest	
Spouse	AbbVie	Stock Options	Ownership Interest	
Spouse	Hospira	Stock Options	Ownership Interest	

Objectives

- Develop an Understanding of the Use of Marijuana as Medicine Throughout Human History.
- Be Able to Differentiate Marijuana (Cannabis) from Cannabinoid Pharmaceuticals.
- Be Able to Discuss the Evidence of the Potential Benefits of Cannabis and Cannabinoid Pharmaceuticals.
- Be Able to Discuss the Evidence of the Harms Associated with Use of Cannabis and Cannabinoid Pharmaceuticals.

Brief Review of the Endocannabinoid System



DEFINITIONS: CANNABIS VERSUS CANNABINOIDS

- **Cannabis** (i.e. **Marijuana**) is used to delineate products derived from the whole plant (flowers, stems, leaves) and is made up of a myriad of psychoactive and non-psychoactive compounds (including cannabinoids) in ratios that differ from plant to plant depending on growing conditions, plant subspecies, etc.
- **Cannabinoids** are distinct, purified, modern pharmaceuticals (whether synthetic or plant derived) with a known purity and an exact chemical composition.

Evidence for Potential Benefits of Cannabinoids

- Glaucoma
  - First study to demonstrate lowering of intraocular pressure with marijuana published in 1971[1]
  - Recent publications have demonstrated decreases in intraocular pressure in *animal models* using nabilone, THC, and Cannabinol.[2,3]
  - Problems:
    - Currently available topical agents are very effective for treatment of glaucoma with a very low side effect profile. Why introduce something new with addiction potential?
    - No adequate, long-term investigations in humans at this time.
  - Research Questions:
    - Are cannabinoids also neuroprotective (i.e. will they preserve retinal function) irrespective of ability to lower intraocular pressure?[4]
    - Are topical cannabinoids as effective as systemically administered options?

1 Hepler, R., & Frank, I. (1971). Marihuana smoking and intraocular pressures. Journal of the American Medical Association, 217, 1392.
2 Chen, J., Matias, I., Dinh, T., & al., e. (2005). Finding of endocannabinoids in human eye tissues: implications for glaucoma. Biochem Biophys Res Commun, 330, 1062-1067.
3 Volkow, N., Baler, R., Compton, W., & Weiss, S. (2014). Adverse Health Effects of Marijuana Use. (D. L. Longo, Ed.) New England Journal of Medicine, 370, 2219-2227.
4 Yazulla, S. (2008, September). Endocannabinoids in the retina: from marijuana to neuroprotection. Prog Retin Eye Res, 27(5), 501-526. doi:10.1016/j.preteyeres.2008.07.002.

Evidence for Potential Benefits of Cannabinoids

- Nausea
  - Dronabinol (synthetic THC) approved in 1985 for the treatment of Cancer Chemotherapy-Associated Nausea and Vomiting.
    - Received FDA approval for indication based on studies comparing with then-available anti-emetics (which are not as good as those currently available).
    - Not approved for treatment of other causes of nausea/vomiting.
  - Currently available anti-emetics much better than those available in 1985, when dronabinol approved.
    - Recent study comparing dronabinol alone, ondansetron alone, or a combination of the two demonstrated equal tolerability and efficacy of both medications for chemotherapy-associated nausea/ vomiting with no benefit of combined treatment.[1]
    - No addiction potential with ondansetron.
  - Cannabis has also been associated with a very well described Cannabis Hyperemesis Syndrome (CHS) with long-term, chronic cannabis use.

1 Meiri, E., Jhangiani, H., Vredenburgh, J., Barbato, L., Carter, F., Yang, H., & Baranowski, V. (2007, March). Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherpy-induced nausea and vomiting. Curr Med Res Opinion, 23(3), 533-543.

Evidence for Potential Benefits of Cannabinoids

- Spasticity in Multiple Sclerosis
  - Numerous studies demonstrate efficacy of nabiximols for intractable spasticity, neuropathic pain, and disturbed sleep in patients with Multiple Sclerosis[1-4]
  - Data for use of cannabinoid preparations in multiple sclerosis is robust enough that the *American Academy of Neurology* has provided specific recommendation regarding use of cannabinoid pharmaceuticals for multiple sclerosis in their 2014 evidence-based guidelines regarding complementary and alternative medicines for multiple sclerosis.[5]
    - Guidelines did not include recommendations for use of smoked cannabis.
    - Guidelines delineated strength of evidence for recommendation.

1 Arroyo, R., Vila, C., & Dechant, K. (2014). Impact of Sativex on quality of life and activities of daily living in patients with multiple sclerosis spasticity. *Journal of Comp Eff Res*, 3(4), 435-444.
2 Freidel, M., Tiel-Wilck, K., Schreiber, H., Prechtl, A., Essner, U., & Lang, M. (2015). Drug-resistant MS Spasticity treatment with Sativex ad-on and driving ability. *Acta Neurol Scand*, 131(1), 9-16. doi:10.1111/ane.12287.
3 Flachenecker, P., & Henze, T. Z. (2014). Long-term effectiveness and safety of nabiximols (tetrahydrocannabinol/ cannabidiol oromucosal spray) in clinical practice. *Eur Neurol*, 72, 95-102. doi:10.1159/000360285
4 Syed, Y., McKeage, K., & Scott, L. (2014). Delta-9-tetrahydrocannabinol/cannabidiol (Sativex): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis. *Drugs*, 74(5), 563-578. doi:10.1007/s40265-014-0197-5.
5 Yadav, V., Bever, C. j., Bowen, J., Bowling, A., Weinstock-Guttman, B., Cameron, M., . . . Narayanaswani, P. (2014, March 25). Summary of evidence-based guidelines: complementary and alternative medicine in multiple sclerosis: a report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*, 82(12), 1083-1092. doi:10.1212/WNL.0000000000000250

Evidence for Potential Benefits of Cannabinoids

	Level A Recommendation	Level B Recommendation	Level C Recommendation
Oral Cannabis Extract (Cannador®)	Physicians might offer agent for spasticity symptoms and pain (excluding central neuropathic pain).	Physicians should counsel patients that agent is probably ineffective for objective spasticity (short-term)/tremors.	Physicians should counsel patients that agent is possibly effective for spasticity and pain (long-term). Physicians might choose not to offer agent for tremors.
Tetrahydrocannabinol		Physicians might offer agent for spasticity symptoms and pain (excluding central neuropathic pain). Physicians should counsel patients that agent is probably ineffective for objective spasticity (short-term)/tremors.	Physicians should counsel patients that agent is possibly effective for spasticity and pain (long-term). Physicians might choose not to offer agent for tremors.
Nabiximols (Sativex®)		Physicians might offer agent for spasticity symptoms, pain, and urinary frequency. Physicians should counsel patient that agent is probably ineffective for objective spasticity/ urinary incontinence.	Physicians might choose not to offer agent for tremors.

[1] Note: Oral Cannabis Extract is not FDA approved in the United States.
[2] Note: Nabiximols (Sativex®) is not FDA approved in the United States. Phase 3 Trials to gain approval for at least two indications are currently underway. (GW Pharmaceuticals, 2014) (GW Pharmaceuticals, 2012)

1 Yadav, V., Bever, C. j., Bowen, J., Bowling, A., Weinstock-Guttman, B., Cameron, M., Narayanaswani, P. (2014, March 25). Summary of evidence-based guidelines: complementary and alternative medicine in multiple sclerosis: a report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*, 82(12), 1083-1092. doi:10.1212/WNL.0000000000000250

Evidence for Potential Benefits of Cannabinoids

- Epilepsy
  - Preclinical trials documented anti-epileptic effects of cannabinoids in animal models as early as the 1970's[1-3]
  - First trial in humans (n=15) published in 1980 when patients with temporal lobe epilepsy refractory to other treatments were given a cannabidiol (CBD) rich extract and demonstrated some improvement. Data were promising.[4]
  - Not until Sanjay Gupta's Special aired on CNN in 2013 did widespread support and interest in CBD for Seizures re-emerge.[5]
    - Documentary described use of Charlotte's Web (CBD-Rich strain of Cannabis) in a child with Dravet's Syndrome (syndrome associated with severe, frequent, refractory seizures).
    - Charlotte's Web (named after the little girl) appeared to completely eradicate her seizures (despite failure of currently available anti-seizure medications to do so).

1 Carlini, E., Leite, E., Tannhauser, M., & Berardi, A. (1973). Letter: Cannabidiol and Cannabis Sativa Extract Protect mice and rats against convulsive agents. *The Journal of Pharmacy and Pharmacology*, 25(8), 664-665.
2 Izquierdo, I., Orsingher, O., & Berardi, A. (1973). Effect of Cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. *Psychopharmacology*, 28(1), 95-102.
3 Karler, R., Cely, W., & Turkanis, S. (1973). The anticonvulsant activity of cannabidiol and cannabinol. *Life Sciences*, 13(11), 1527-1531.
4 Cunha, J., Carlini, E., Pereira, A., Ramos, O., Pimentel, C., Gagliardi, R., & al, e. (1980). Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*, 21(3), 175-185.
5 Young, S. (2013, August 7). Marijuana Stops Child's Severe Seizures. Retrieved April 4, 2015, from CNN.com: http://www.cnn.com/2013/08/07/health/charlotte-child-medical-marijuana/index.html

Evidence for Potential Benefits of Cannabinoids

- Epilepsy
  - As a result of this documentary, and growing public opinion favoring legalization, despite a lack of studies meeting the rigorous criteria required for drug approval by the Food and Drug Administration (FDA), a number of states, including Wisconsin, have legalized use of CBD Oil for seizures.
  - Popular media touts CBD Oil as a miracle “treatment” for seizure disorders.
    - No discussion of long-term risks or side effects
    - Evidence-base is weak BUT growing for CBD in human trials

Evidence for Potential Benefits of Cannabinoids

- Epilepsy
  - What does current medical literature say about efficacy and safety for epilepsy?
    - Recent Open-Label study presented at the American Epilepsy Society's 68th Annual Meeting that utilized 98% pure CBD Oil (Epidiolex®) demonstrated a greater than 50% reduction in 39% of patients.[1]
    - A second study using oral cannabis extract from different strains of cannabis demonstrated similar results with approximately 1/3 of patients reporting seizure reductions of 50%.[2]
    - Purified CBD Oil (Epidiolex®) granted orphan drug status by FDA and is currently in Phase 3 Clinical Trials for treatment of refractory seizures in childhood epilepsy, specifically in patients with difficult to treat seizure syndromes.

1 Devinsky, O., Sullivan, J., Friedman, D., Thiele, E., Marsh, E., Laux, L., . . . Cilio, M. (2014, December 6-9). Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistent epilepsy: initial data from an expanded access program. Retrieved April 4, 2015, from *American Epilepsy Society (aesnet.org)*: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868751.

2 Press, C., Knupp, K., & Chapman, K. (2014, December 6-9). *American Epilepsy Society (aesnet.org)*. Retrieved from Parental reporting of response to oral cannabis extracts as adjuvant treatment for medically refractory epilepsy.: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868031.

Evidence for Potential Benefits of Cannabinoids

- Epilepsy
  - What does current medical literature say about efficacy and safety for epilepsy?
    - Side Effects in these trials noted to be Mild to Moderate and included:[1]
      - Somnolence
      - Fatigue
      - Weight Changes
      - Diarrhea
      - Changes in Appetite
    - Separate study looked at interactions of purified CBD Oil extract with other Anti-Epileptic Drugs (AED's) and found that CBD did not affect levels of most other AED's with the exception of clobazam which mean levels were significantly increased.[2]
    - CBD is a non-psychoactive cannabinoid of the cannabis plant.

1 Devinsky, O., Sullivan, J., Friedman, D., Thiele, E., Marsh, E., Laux, L., Cilio, M. (2014, December 6-9). Efficacy and safety of Epidiolex (cannabidiol) in children and young adults with treatment-resistent epilepsy: initial data from an expanded access program. Retrieved April 4, 2015, from *American Epilepsy Society (aesnet.org)*: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868751.

2 Friedman, D., Cilio, M., Tilton, N., Sullivan, J., Hedlund, J., Rosenburg, E., Devinsky, O. (2014, December 6-9). The effect of Epidiolex (cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults in treatment resistent epilepsy in an expanded access program. Retrieved from *American Epilepsy Society (aesnet.org)*: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/1868391.

Evidence for Potential Benefits of Cannabinoids

As Dr. Chapman, the primary investigator of the second study using marijuana, states eloquently in an interview with Medscape, “I would say be cautious. Don’t expect miracles. Families have been led to believe that marijuana products are more effective than anything else but our data do not suggest that this is necessarily true.”[1]

1 Hughes, S. (2014, October 23). Initial Data on 'Pharma Grade' Cannabidiol in Epilepsy. Retrieved January 30, 2015, from *Medscape.com*: http://www.medscape.com/viewarticle/833770_print.

Evidence for Potential Benefits of Cannabinoids

- Chronic Pain
  - Studies demonstrate benefits of cannabinoid pharmaceuticals in alleviating cancer pain and non-malignant neuropathic pain.
  - Even very low levels of vaporized THC (1.29%) provide analgesic benefit[1], indicating that currently available cannabis preparations containing higher level THC content (often in the double digits) may not be necessary and have been associated with greater neuropsychiatric side effects.
  - In one study comparing oral dronabinol (synthetic THC that is currently already available by prescription in all states) to smoked marijuana in daily marijuana smokers, decreases in pain sensitivity and pain tolerance were equivalent in both groups, but the effect lasted longer in the dronabinol group with less abuse-related subjective effects (drug likability/ subjective high) than with smoked marijuana.[2]
  - This latter study begs the question: why legalize herbal marijuana if a prescription alternative is already available?

1 Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., & Donaghe, H. (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*, 14, 136-148.
2 Cooper, Z., Comer, S., & Haney, M. (2013, May 15). Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. *Neuropsychopharmacology*, 38, 1984-1992. doi:10.1038/npp.2013.97.

Evidence for Potential Benefits of Cannabinoids

- Aids-Associated Anorexia and Wasting Syndrome
  - Cannabis thought to increase appetite and weight when ingested or smoked on a regular basis in patients with AIDS-associated anorexia and wasting syndrome.[1]
    - Dronabinol is the only FDA approved cannabinoid for AIDs-associated anorexia and wasting syndrome.
    - Smoked marijuana has not been rigorously studied for this indication despite widespread use.
  - Recent studies have failed to demonstrate clear benefits of cannabinoids on morbidity or mortality in patients with AIDS-associated anorexia and wasting syndrome who are receiving adequate anti-retroviral therapy.[2]

1 D'Souza, G., Matson, P., Grady, C., & al., e. (2012). Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. *Journal of Acquired Immunodeficiency Syndrome*, 61, 618-626.
2 Lutge, E., Gary, A., & Siegfried, N. (2013). The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Systematic Review*, 4:CD005175.

Evidence for Potential Benefits of Cannabinoids

- Post-Traumatic Stress Disorder (PTSD)
  - Endocannabinoid system plays a crucial role in allowing the brain to adapt to stressful situations by promoting extinction of the fear response.[1]
    - In one study, levels of the endocannabinoid anandamide where significantly suppressed in patients with PTSD.[2]
    - In a pre-clinical open label study, add-on oral dronabinol demonstrated statistically significant improvements in global symptoms of severity, sleep quality, frequency of nightmares, and hyper-arousal symptoms with only mild side effects[3]

1 Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., & Ressler, K. (2015). Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety, and trauma-related disorders. *Pharmacology and Therapeutics*, 149, 150-190.

2 Neumeister, A., Normandin, M., Pietrzak, R., Piomelli, D., Zheng, M., Gujarro-Anton, A., & al, e. (2013). Elevated brian cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emmision tomography study. *Molecular Psychiatry*, 18, 1034-1040.

3 Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014, June 17). Preliminary, open-label, pilot study of add-on oral delta-9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation*, 34(8), 587-591.

Evidence for Potential Benefits of Cannabinoids

- Post-Traumatic Stress Disorder (PTSD)
  - Problem:
    - It is important to note that chronic use of recreational marijuana, which typically has high levels of THC, is linked with poorer affective functioning, including altered amygdala response to emotion[1], abnormal amygdala structure[2], and reduced fronto-limbic white matter quality[3] – these brain abnormalities are associated with increased depressive symptoms and apathy in young adults.
    - As a result, if found to be effective, treatment for chronic PTSD must use low dose THC that will not result in long-term down-regulation of the endogenous cannabinoid system.

1 Gruber SA, R. J.-T. (2009, November 1). Altered affective response in marijuana smokers: an FMRI study. *Drug Alcohol Depend*, 105(1-2), 139-153.
2 McQueeny TM, P. C. (2011). Gender effects on amygdala morphometry in adolescent marijuana users. *Behavioural Brain Research*, 224(1), 128-134.
3 Shollenbarger S, P. J. (2015). Poorer frontolimbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults. *Neuroimaging: Clinical*, 8, 117-125.

Evidence for Potential Harms of Cannabinoids

- Motor Vehicle Accidents (Drugged Driving)[1,2]
- Psychiatric Adverse Effects[3]
  - Depression
  - Anxiety
  - Psychosis
- Neuropsychological Decline
  - More prominent with use at a younger age.
  - Marijuana interferes with synaptic pruning and myelination.
  - One recent longitudinal study following youth from age 13 to 38 found that use of cannabis on a regular basis before the age of 18 predicted significant long-term cognitive deficits that do not appear to completely reverse even when use stops in adulthood.[4]

1 Lenne, M., Dietze, P., Triggs, T., Walmsley, S., Murphy, B., & Redman, J. (2010). The effects of cannabis and alcohol on simulated arterial driving: influences of driving experience and task demand. *Accid Anal Prev*, 42, 859-866.
2 Hartman, R., & Huestis, M. (2013). Cannabis effects on driving skills. *Clin Chem*, 59, 478-492.
3 Volkow, N., Baler, R., Compton, W., & Weiss, S. (2014). Adverse Health Effects of Marijuana Use. (D. L. Longo, Ed.) *New England Journal of Medicine*, 370, 2219-2227.
4 Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. Moffitt, T. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *PNAS*, E2657-E2664.

Evidence for Potential Harms of Cannabinoids

- Addiction Potential
  - 9% of the general population will develop addiction to cannabis.[1]
  - The risk of addiction is greatest for individuals who first use cannabis as teenagers (up to 16%) and for those individuals who use marijuana on a daily basis (as high as 50%).[2]
- Cannabis Withdrawal Syndrome
- Cannabis Hyperemesis Syndrome
- Chronic Bronchitis (smoked cannabis)

1 Volkow, N., Baler, R., Compton, W., & Weiss, S. (2014). Adverse Health Effects of Marijuana Use. (D. L. Longo, Ed.) *New England Journal of Medicine*, 370, 2219-2227.
2 Hall, W., & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *Lancet*, 374, 1383-1391.

Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use
Impaired short-term memory, making it difficult to learn and to retain information
Impaired motor coordination, interfering with driving skills and increasing the risk of injuries
Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases
In high doses, paranoia and psychosis
Effects of long-term or heavy use
Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*
Altered brain development*
Poor educational outcome, with increased likelihood of dropping out of school*
Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*
Symptoms of chronic bronchitis
Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

Volkow ND et al. N Engl J Med 2014;370:2219-2227

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Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

Volkow ND et al. N Engl J Med 2014;370:2219-2227

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Questions?