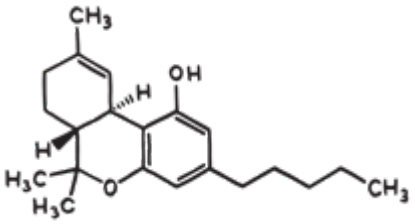
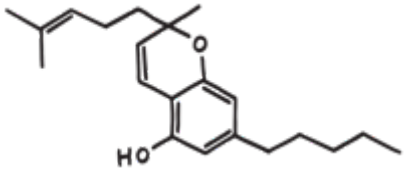
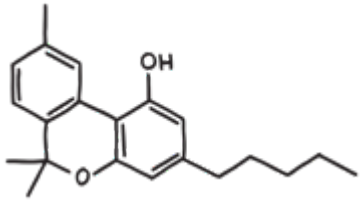


TETRAHYDROCANNABINOL (THC)



CANNABICHROMENE (CBC)



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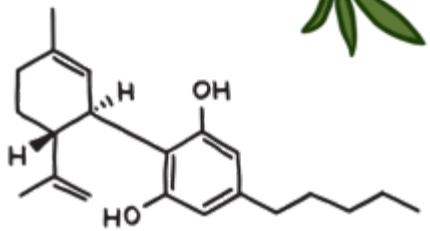
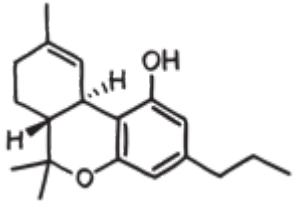


CANNABIDIOL (CBD)

Cannabis use risk analysis & an introduction to the Endocannabinoid System



(THCV)

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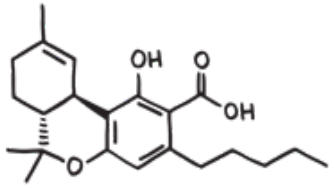
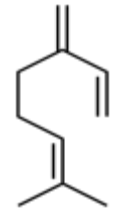
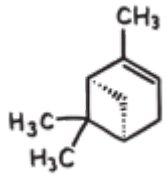


(THCA)



BETA-MYRCENE



ALPHA-PINENE

NICM

The science of integrative medicine

Key discussion points

- ✓ History of Use: How did we get here?
- ✓ Cannabis risk analysis: risks or myths?
- ✓ The Endocannabinoid System (ECS)
  - ✓ Cannabinoid Receptors
  - ✓ Endogenous ligands (endocannabinoids)
  - ✓ Enzymes (synthesis / degradation)
- ✓ Physiological Role of the ECS
- ✓ ECS Dysfunction

Cannabis History of Use

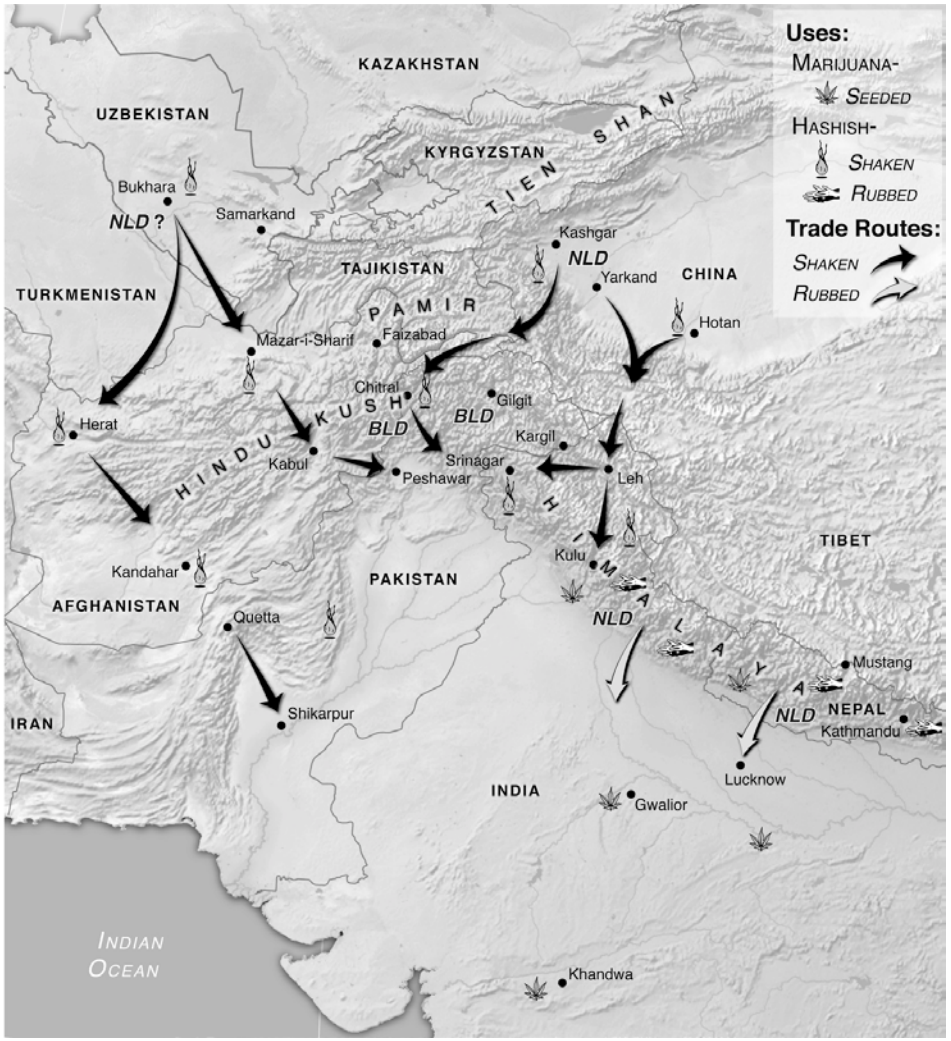


Figure 1: Trade routes of broad leaf drug variety throughout the Central Asian region. Photo courtesy of Robert Clarke.

- ✓ Cannabis use likely predates writing in human evolution (Ben-Amar 2006; Merlin 2003).
- ✓ Cannabis is believed to have originated in Central Asia. It has spread worldwide from this region.
- ✓ Cannabis use as both a medicine, fibre and food dates back over 10,000 years (Clarke & Merlin 2013).

Cannabis History of Use

- ✓ Archaeological evidence confirms Cannabis has been used since the Neolithic period; mainly as a medicine, food and as an entheogen (Li 1974; McKim 2000).
- ✓ Entheogen: “A substance used in shamanic, religious or spiritual ritual.”

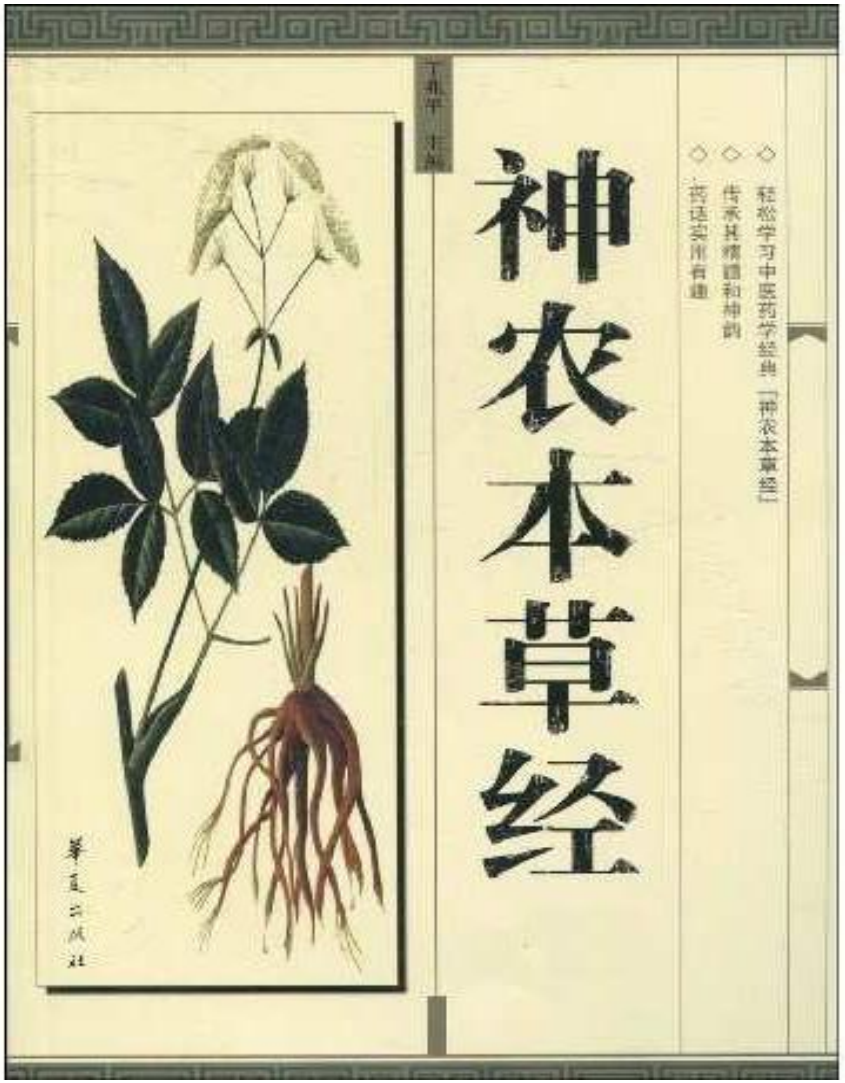


Figure 2: A page from the *Shen-nung Pen-Tsao Ching*, attributed to Shen Nung from around 2800-2700 BCE.

How did we get here?

How did we get here?

How did we get here?

Cannabis lowers your IQ?

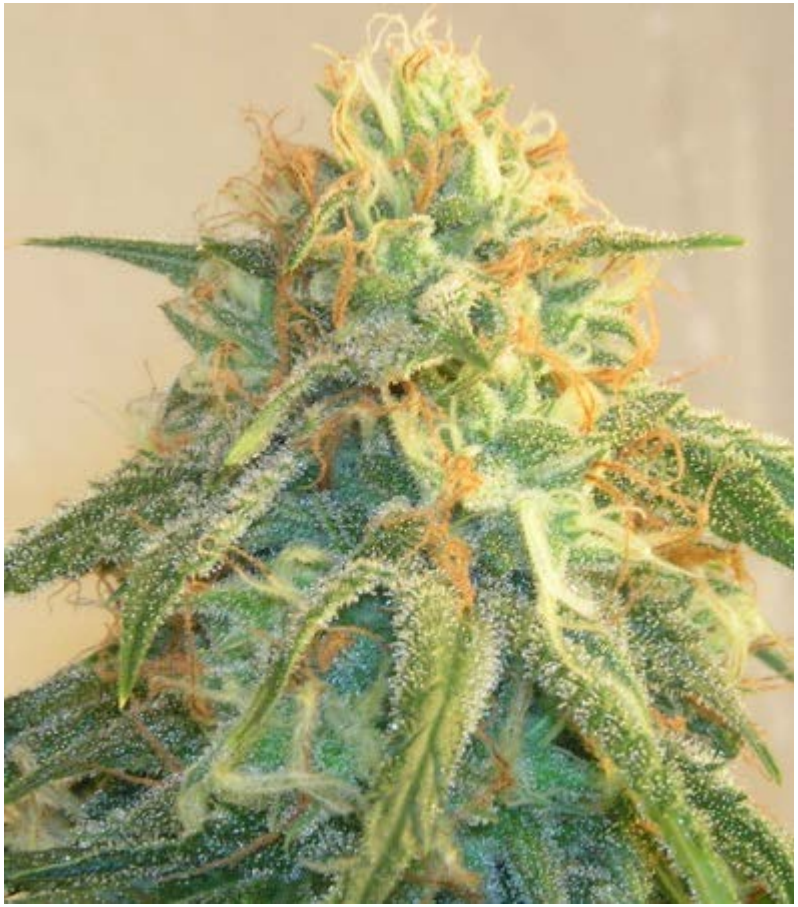


Figure 3: The female inflorescence (bud) of "*Super Silver Haze*", one of hundreds of different Cannabis strains.

- Cannabis may cause short term memory impairment whilst under the influence.
- This is considered reversible upon cessation...not permanent.
- Certain Cannabis phytochemicals such as Cannabidiol (CBD) actually exhibit neuroprotective activity.
- Animal studies are now showing the possibility of specific Cannabis phytochemistry assisting in:
  - Foetal hypoxia (Alvarez et al. 2008)
  - Multiple sclerosis
  - Hypoxic brain injury (Ischaemic stroke)
  - Alzheimer's Disease (Ramirez et al. 2005)

Cannabis lowers your IQ?

Proc Natl Acad Sci U S A. 2016 Feb 2;113(5):E500-8. doi: 10.1073/pnas.1516648113. Epub 2016 Jan 19.

Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies.

Jackson NJ[1], Isen JD[2], Khoddam R[3], Irons D[4], Tuvblad C[5], Iacono WG[4], McGue M[4], Raine A[6], Baker LA[3].

Author information

Abstract

Marijuana is one of the most commonly used drugs in the United States, and use during adolescence--when the brain is still developing--has been proposed as a cause of poorer neurocognitive outcome. Nonetheless, research on this topic is scarce and often shows conflicting results, with some studies showing detrimental effects of marijuana use on cognitive functioning and others showing no significant long-term effects. The purpose of the present study was to examine the associations of marijuana use with changes in intellectual performance in two longitudinal studies of adolescent twins (n = 789 and n = 2,277). We used a quasiexperimental approach to adjust for participants' family background characteristics and genetic propensities, helping us to assess the causal nature of any potential associations. Standardized measures of intelligence were administered at ages 9-12 y, before marijuana involvement, and again at ages 17-20 y. Marijuana use was self-reported at the time of each cognitive assessment as well as during the intervening period. Marijuana users had lower test scores relative to nonusers and showed a significant decline in crystallized intelligence between preadolescence and late adolescence. However, there was no evidence of a dose-response relationship between frequency of use and intelligence quotient (IQ) change. Furthermore, marijuana-using twins failed to show significantly greater IQ decline relative to their abstinent siblings. Evidence from these two samples suggests that observed declines in measured IQ may not be a direct result of marijuana exposure but rather attributable to familial factors that underlie both marijuana initiation and low intellectual attainment.

KEYWORDS: adolescence; intelligence; longitudinal; marijuana use; twins

All Cannabis gets you “high”?

- The psychoactivity of cannabis is largely dependent on the phytochemistry exhibited in the specific strain of the plant.
- There exist numerous strains of Cannabis that have been selectively bred to be low in THC, but higher in other phytochemicals such as CBD.
- Individual dosing (titration) and appropriate Cannabis strain selection is key to reducing psychoactive effects.

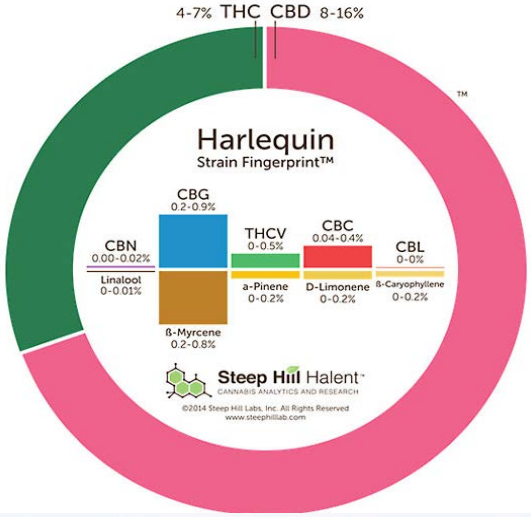


Figure 4: Harlequin, is rich in CBD and has much lower levels of THC (the main psychoactive cannabinoid) than most recreationally used varieties. Phytochemical profile produced with permission from Steep Hill (Halent) Laboratories (USA).

Cannabis causes Lung cancer

Cancer Epidemiol Biomarkers Prev. 2006 Oct;15(10):1829-34.

Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study.

Hashibe M[1], Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, Mack TM, Greenland S.

Author information

Abstract

BACKGROUND: Despite several lines of evidence suggesting the biological plausibility of marijuana being carcinogenic, epidemiologic findings are inconsistent. We conducted a population-based case-control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers in Los Angeles.

METHODS: Our study included 1,212 incident cancer cases and 1,040 cancer-free controls matched to cases on age, gender, and neighborhood. Subjects were interviewed with a standardized questionnaire. The cumulative use of marijuana was expressed in joint-years, where 1 joint-year is equivalent to smoking one joint per day for 1 year.

RESULTS: Although using marijuana for > or =30 joint-years was positively associated in the crude analyses with each cancer type (except pharyngeal cancer), no positive associations were observed when adjusting for several confounders including cigarette smoking. The adjusted odds ratio estimate (and 95% confidence limits) for > or =60 versus 0 joint-years was 1.1 (0.56, 2.1) for oral cancer, 0.84 (0.28, 2.5) for laryngeal cancer, and 0.62 (0.32, 1.2) for lung cancer; the adjusted odds ratio estimate for > or =30 versus 0 joint-years was 0.57 (0.20, 1.6) for pharyngeal cancer, and 0.53 (0.22, 1.3) for esophageal cancer. No association was consistently monotonic across exposure categories, and restriction to subjects who never smoked cigarettes yielded similar findings.

CONCLUSIONS: Our results may have been affected by selection bias or error in measuring lifetime exposure and confounder histories; but they suggest that the association of these cancers with marijuana, even long-term or heavy use, is not strong and may be below practically detectable limits.

PMID: 17035389 DOI: 10.1158/1055-9965.EPI-06-0330

[PubMed - indexed for MEDLINE] Free full text

Cannabis causes Lung cancer

J Natl Cancer Inst. 1975 Sep;55(3):597-602.

Antineoplastic activity of cannabinoids.

Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA.

Abstract

Lewis lung adenocarcinoma growth was retarded by the oral administration of delta9-tetrahydrocannabinol (delta9-THC), delta8-tetrahydrocannabinol (delta8-THC), and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. Mice treated for 20 consecutive days with delta8-THC and CBN had reduced primary tumor size. CBD showed no inhibitory effect on tumor growth at 14, 21, or 28 days. Delta9-THC, delta8-THC, and CBN increased the mean survival time (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg, respectively), whereas CBD did not. Delta9-THC administered orally daily until death in doses of 50, 100, or 200 mg/kg did not increase the life-spans of (C57BL/6 times DBA/2)F1 (BDF1) mice hosting the L1210 murine leukemia. However, delta9-THC administered daily for 10 days significantly inhibited Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta9-THC and delta8-THC showed a dose-dependent (10(-4)-10(-7)) inhibition (80-20%, respectively) of tritiated thymidine and 14C-uridine uptake into these cells. CBD was active only in high concentrations (10(-4)).

PMID: 1159836

[PubMed - indexed for MEDLINE]

Cannabis causes Lung cancer

Ann Am Thorac Soc. 2013 Jun;10(3):239-47. doi: 10.1513/AnnalsATS.201212-127FR.

Effects of marijuana smoking on the lung.

Tashkin DP[1].

Author information

Abstract

Regular smoking of marijuana by itself causes visible and microscopic injury to the large airways that is consistently associated with an increased likelihood of symptoms of chronic bronchitis that subside after cessation of use. On the other hand, habitual use of marijuana alone does not appear to lead to significant abnormalities in lung function when assessed either cross-sectionally or longitudinally, except for possible increases in lung volumes and modest increases in airway resistance of unclear clinical significance. Therefore, no clear link to chronic obstructive pulmonary disease has been established. Although marijuana smoke contains a number of carcinogens and cocarcinogens, findings from a limited number of well-designed epidemiological studies do not suggest an increased risk for the development of either lung or upper airway cancer from light or moderate use, although evidence is mixed concerning possible carcinogenic risks of heavy, long-term use. Although regular marijuana smoking leads to bronchial epithelial ciliary loss and impairs the microbicidal function of alveolar macrophages, evidence is inconclusive regarding possible associated risks for lower respiratory tract infection. Several case reports have implicated marijuana smoking as an etiologic factor in pneumothorax/pneumomediastinum and bullous lung disease, although evidence of a possible causal link from epidemiologic studies is lacking. In summary, the accumulated weight of evidence implies far lower risks for pulmonary complications of even regular heavy use of marijuana compared with the grave pulmonary consequences of tobacco.

Comment in

Cannabis and the lung: no more smoking gun? [Ann Am Thorac Soc. 2013]

PMID: 23802821 DOI: 10.1513/AnnalsATS.201212-127FR

[PubMed - indexed for MEDLINE]

Cannabis as a drug of dependence?

Experimental and Clinical Psychopharmacology
1994, Vol. 2, No. 3, 244–268

Comparative Epidemiology of Dependence on Tobacco, Alcohol, Controlled Substances, and Inhalants: Basic Findings From the National Comorbidity Survey

James C. Anthony, Lynn A. Warner, and Ronald C. Kessler

Studying prevalence of *Diagnostic and Statistical Manual* (3rd ed., rev., American Psychiatric Association, 1987) drug dependence among Americans 15–54 years old, we found about 1 in 4 (24%) had a history of tobacco dependence; about 1 in 7 (14%) had a history of alcohol dependence; and about 1 in 13 (7.5%) had a history of dependence on an inhalant or controlled drug. About one third of tobacco smokers had developed tobacco dependence and about 15% of drinkers had become alcohol dependent. Among users of the other drugs, about 15% had become dependent. Many more Americans age 15–54 have been affected by dependence on psychoactive substances than by other psychiatric disturbances now accorded a higher priority in mental health service delivery systems, prevention, and sponsored research programs.

The aim of this article is to report basic descriptive findings from new research on the epidemiology of drug dependence syndromes, conducted as part of the National Comorbidity Survey (NCS). In this study, our research team secured a nationally representative sample and applied standardized diagnostic assessments in a way that allows direct comparisons across prevalence estimates and correlates of tobacco dependence, alcohol dependence, and dependence on other psychoactive drugs (Kessler et al., 1994).

For this overview of the survey's findings, a primary goal has been to answer two basic epidemiologic questions about drug dependence involving tobacco, alcohol, controlled drugs such as cocaine, and inhalants: First, in the population under study, what proportion of persons now qualifies as a currently active or former case of drug dependence? Second, where are the affected cases more likely to be found within the sociodemographic structure of the study population?

In addition, population estimates presented in this article shed light on the epidemiology of dependence on tobacco, alcohol, and the following individual drugs and drug groups: cannabis; heroin; cocaine; psychostimulants other than cocaine; analgesic drugs; a drug group consisting of anxiolytic, sedative, and hypnotic drugs; psychedelic drugs; and inhalant drugs. The following population estimates are presented for each of these listed drugs, including tobacco and alcohol: (a) lifetime prevalence of drug dependence, evaluated in relation to criteria published in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (DSM–III–R; American Psychiatric Association, 1987); (b) lifetime prevalence of extramedical drug use, defined to encompass illicit drug use as well as patients taking prescribed medicines to get

James C. Anthony, Etiology Branch, Addiction Research Center, National Institute on Drug Abuse and Johns Hopkins University; Lynn A. Warner and Ronald C. Kessler, Institute for Social Research and Department of Sociology, University of Michigan.

The National Comorbidity Survey (NCS) is a collaborative epidemiologic investigation of the prevalence, causes, and consequences of psychiatric morbidity and comorbidity in the United States. The NCS is supported by U.S. Public Health Service Grants MH 46376 and MH 49098 with supplemental support from the National Institute on Drug Abuse and W. T. Grant Foundation Grant 90135190.

Preparation of this article was supported by the National Institute on Drug Abuse Addiction Research Center. We acknowledge H. Chilcoat for valuable research assistance.

Correspondence concerning this article may be addressed to James C. Anthony, P. O. Box 5180, Addiction Research Center, National Institute on Drug Abuse, Baltimore, Maryland 21224. Electronic mail may be sent to anthony@jhuhyg.sph.jhu.edu.

(Anthony, Warner & Kessler 1994).

Cannabis as a drug of dependence?

COMPARATIVE EPIDEMIOLOGY OF DRUGS

Table 2
Estimated Prevalence of Extramedical Use and Dependence in Total Study Population and Lifetime Dependence Among Users

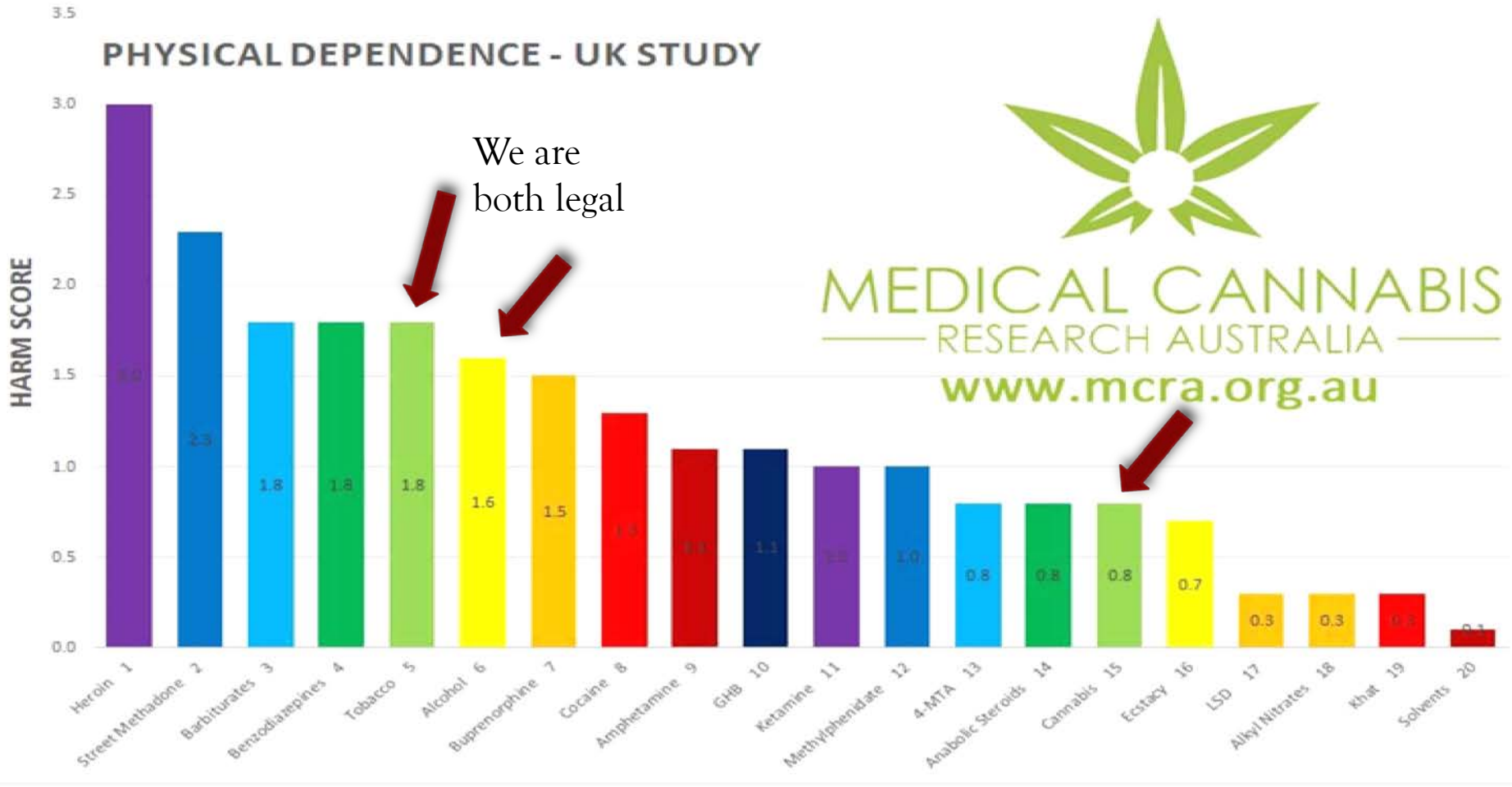
Drug categories	Proportion with a history of dependence		Proportion with a history of extramedical use		Dependence among extramedical users	
	P	*SE*	*P*	*SE*	*P*	*SE*
Tobacco[a]	24.1	1.0	75.6	0.6	31.9	–
Alcohol	14.1	0.7	91.5	0.5	15.4	0.7
Other drugs	7.5	0.4	51.0	1.0	14.7	0.7
Cannabis	4.2	0.3	46.3	1.1	9.1	0.7
Cocaine	2.7	0.2	16.2	0.6	16.7	1.5
Stimulant	1.7	0.3	15.3	0.7	11.2	1.6
Anxiolytics, etc.[b]	1.2	0.2	12.7	0.5	9.2	1.1
Analgesics	0.7	0.1	9.7	0.5	7.5	1.0
Psychedelics	0.5	0.1	10.6	0.6	4.9	0.7
Heroin	0.4	0.1	1.5	0.2	23.1	5.6
Inhalants	0.3	0.1	6.8	0.4	3.7	1.4

Note. Weighted estimates from the National Comorbidity Survey data gathered in 1990–1992 for persons 15–54 years old (n = 8,098). Dash indicates data not estimated. P = Estimated prevalence proportion.
[a] n = 4,414. [b] Anxiolytics, sedatives, and hypnotic drugs, grouped.

(Anthony, Warner & Kessler 1994).

- Cannabis dependency does exist but is also dependent on the individual.
- Factors such as individual polymorphic expression, individual variability, the strain of Cannabis being utilised and the dosage taken are also important contributing factors.

Cannabis as a drug of dependence?



Cannabis as a gateway drug?

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Cannabis as a substitute for alcohol and other drugs

Amanda Reiman

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Email: Amanda Reiman - areiman@berkeley.edu

Published: 3 December 2009

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Accepted: 3 December 2009

This article is available from: http://www.harmreductionjournal.com/content/6/1/35

Abstract

Background: Substitution can be operationalized as the conscious choice to use one drug (legal or illicit) instead of, or in conjunction with, another due to issues such as: perceived safety; level of addiction potential; effectiveness in relieving symptoms; access and level of acceptance. This practice of substitution has been observed among individuals using cannabis for medical purposes. This study examined drug and alcohol use, and the occurrence of substitution among medical cannabis patients.

Methods: Anonymous survey data were collected at the Berkeley Patient's Group (BPG), a medical cannabis dispensary in Berkeley, CA. (N = 350) The sample was 68% male, 54% single, 66% White, mean age was 39; 74% have health insurance (including MediCal), 41% work full time, 81% have completed at least some college, 55% make less than $40,000 a year. Seventy one percent report having a chronic medical condition, 52% use cannabis for a pain related condition, 75% use cannabis for a mental health issue.

Results: Fifty three percent of the sample currently drinks alcohol, 2.6 was the average number of drinking days per week, 2.9 was the average number of drinks on a drinking occasion. One quarter currently uses tobacco, 9.5 is the average number of cigarettes smoked daily. Eleven percent have used a non-prescribed, non OTC drug in the past 30 days with cocaine, MDMA and Vicodin reported most frequently. Twenty five percent reported growing up in an abusive or addictive household. Sixteen percent reported previous alcohol and/or drug treatment, and 2% are currently in a 12-step or other recovery program. Forty percent have used cannabis as a substitute for alcohol, 26% as a substitute for illicit drugs and 66% as a substitute for prescription drugs. The most common reasons given for substituting were: less adverse side effects (65%), better symptom management (57%), and less withdrawal potential (34%) with cannabis.

Conclusion: The substitution of one psychoactive substance for another with the goal of reducing negative outcomes can be included within the framework of harm reduction. Medical cannabis patients have been engaging in substitution by using cannabis as an alternative to alcohol, prescription and illicit drugs.

Background

It has been observed that those who use large amounts of cannabis frequently use other drugs as well, especially alcohol. This can create a potential synergistic effect, resulting in increased harms [1-4]. Economic research has looked at the substitution and complimentarity of particular substances by modelling the effects of price fluctuation on use, although the limits of such research have

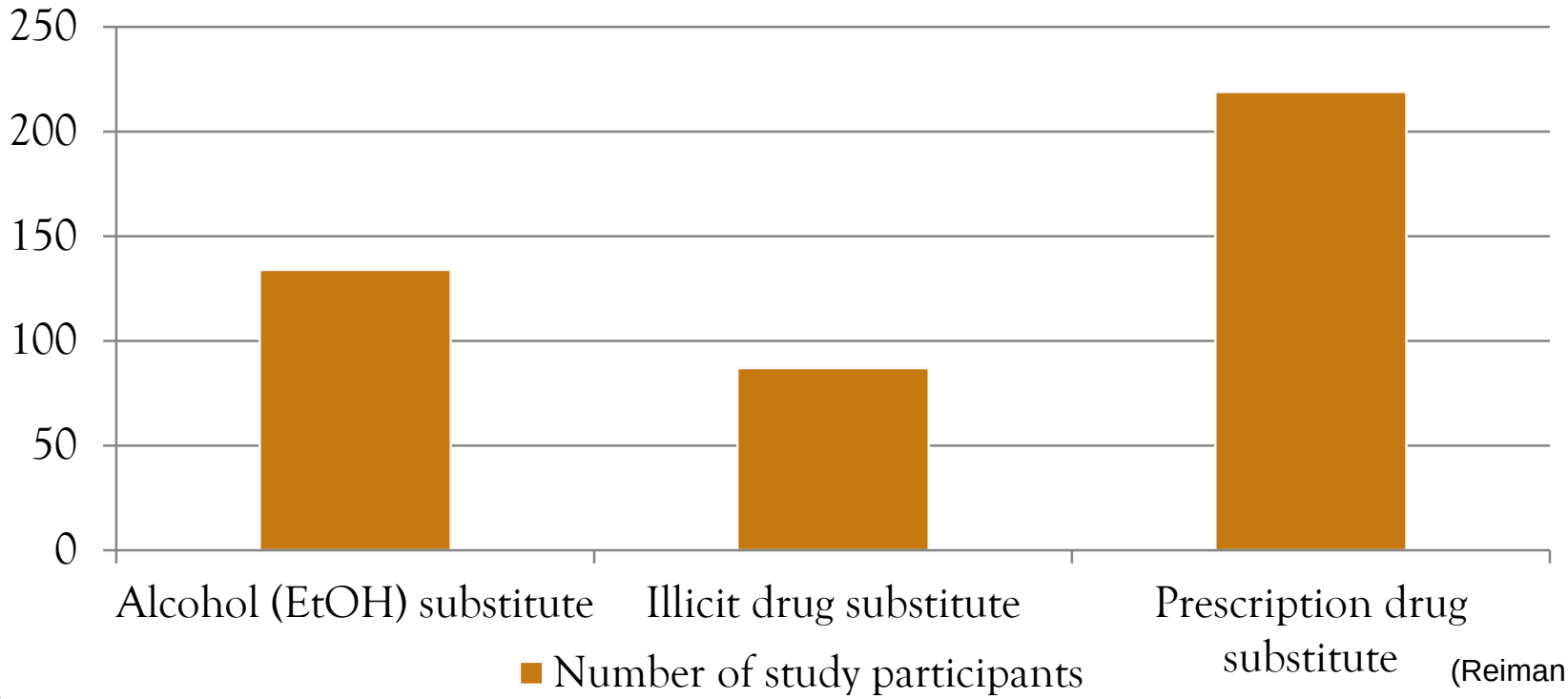
(Reiman 2009)

- A Gateway drug is defined as "*one that apparently can lead to the use of harder, more addictive or dangerous drugs".*
- Examples of hard drugs may include:
  - Heroine
  - Methamphetamine
  - Cocaine

Cannabis is a gateway drug?

Table 1: Percent of sample reporting using cannabis as a substitute.

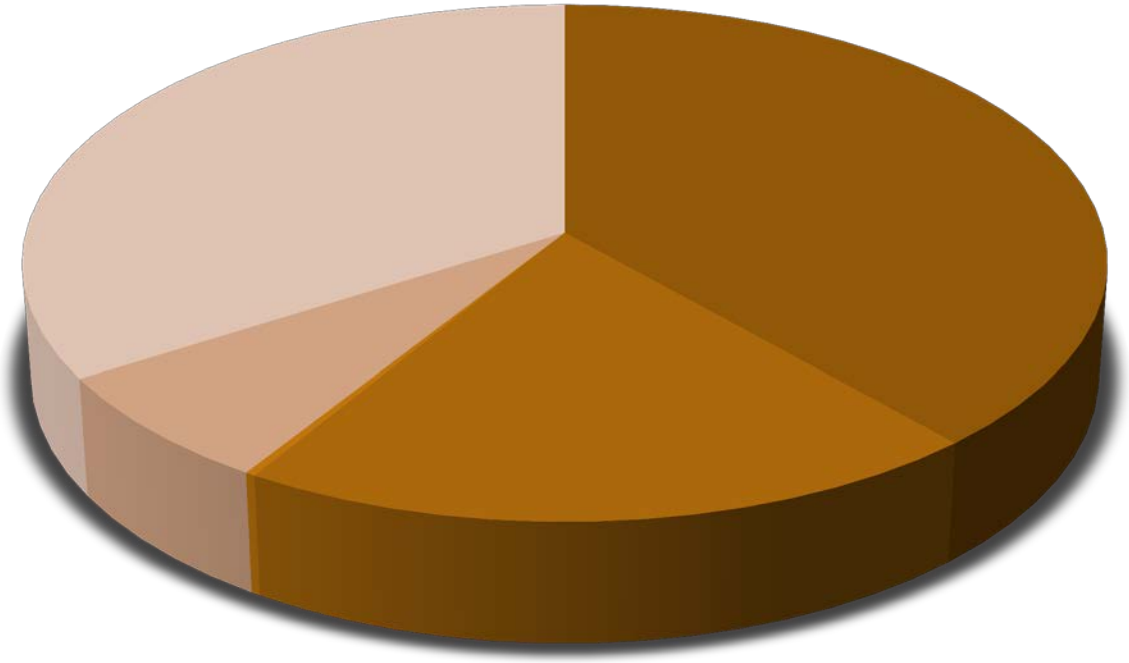
Type of substitution	# of Participants	% of Participants
EtOH substitute	n = 134	40%
Illicit drug substitute	n= 87	26%
Prescription drug substitute	n= 219	65.8%



(Reiman 2009)

Cannabis is a gateway drug?

Reasons for using cannabis as a substitute



- Less adverse side effects (n=197)
- Less withdrawal potential (n=103)
- Ability to obtain Cannabis (n=54)
- Greater social acceptance (n=36)
- Better symptom management (n=174)

(Reiman 2009)

Cannabis is a gateway drug?

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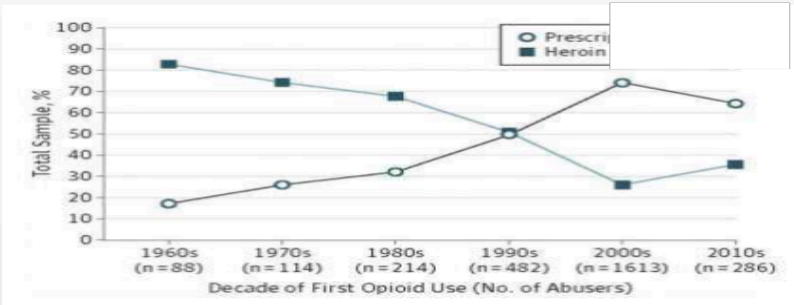
NIDA DRUGPUBS

Prescription opioid use is a risk factor for heroin use

Pooling data from 2002 to 2012, the incidence of heroin initiation was 19 times higher among those who reported prior nonmedical pain reliever use than among those who did not (0.39 vs. 0.02 percent) (Muhuri et al., 2013). A study of young, urban injection drug users interviewed in 2008 and 2009 found that 86 percent had used opioid pain relievers nonmedically prior to using heroin, and their initiation into nonmedical use was characterized by three main sources of opioids: family, friends, or personal prescriptions (Lankenau et al., 2012). This rate represents a shift from historical trends. Of people entering treatment for heroin addiction who began abusing opioids in the 1960s, more than 80 percent started with heroin. Of those who began abusing opioids in the 2000s, 75 percent reported that their first opioid was a prescription drug (Cicero et al., 2014). Examining national-level general population heroin data (including those in and not in treatment), nearly 80 percent of heroin users reported using prescription opioids prior to heroin (Jones, 2013; Muhuri et al., 2013).



Percentage of the total heroin-dependent sample that used heroin or a prescription opioid as their first opioid of abuse. Data are plotted as a function of the decade in which respondents initiated their opioid abuse. *Source: Cicero et al., 2014*

Cannabis is a gateway drug?

Drug types	2009	2010	2011	2012	2013	2014	2015
All overdose deaths	379	342	362	367	380	387	453
Pharmaceutical	295	266	275	306	313	316	358
Illegal	147	149	153	133	166	164	227
Alcohol	94	85	88	80	94	94	106

Table 2. Overdose deaths by individual contributing drugs 2009–15, opioids and benzodiazepines[8]

Drug types	2009	2010	2011	2012	2013	2014	2015
All overdose deaths	379	342	362	367	380	387	453
Contributing drug: benzodiazepines	**160**	**169**	**180**	**199**	**212**	**215**	**238**
Diazepam	104	109	124	133	164	169	192
Oxazepam	18	19	44	41	17	19	34
Alprazolam	62	56	43	57	45	28	23
Clonazepam	7	9	14	18	19	25	33
Contributing drug: opioids	**177**	**145**	**183**	**212**	**192**	**186**	**199**
Oxycodone	41	39	46	46	61	46	58
Codeine	76	57	66	93	71	54	64
Morphine	22	11	10	13	7	12	8
Methadone	50	55	72	75	70	67	67
Buprenorphine	3	4	14	4	3	7	4

Reproduced from Coroners Court of Victoria. Findings Case 408012, Attachment C. Coroners Prevention Unit, Coroners Prevention Unit Data Summary, Re: Victorian Overdose Death 2009–2015. Last revised 30th August 2016. Available at www.coronerscourt.vic.gov.au/home/coroners+written+findings [Accessed 6 November 2016].

Cannabis is a gateway drug?

JAMA Intern Med. 2014 Oct;174(10):1668-73. doi: 10.1001/jamainternmed.2014.4005.

Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010.

Bachhuber MA[1], Saloner B[2], Cunningham CO[3], Barry CL[4].

⊕ **Author information**

Erratum in
JAMA Intern Med. 2014 Nov;174(11):1875.

Abstract

IMPORTANCE: Opioid analgesic overdose mortality continues to rise in the United States, driven by increases in prescribing for chronic pain. Because chronic pain is a major indication for medical cannabis, laws that establish access to medical cannabis may change overdose mortality related to opioid analgesics in states that have enacted them.

OBJECTIVE: To determine the association between the presence of state medical cannabis laws and opioid analgesic overdose mortality.

DESIGN, SETTING, AND PARTICIPANTS: A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.

EXPOSURES: Presence of a law establishing a medical cannabis program in the state.

MAIN OUTCOMES AND MEASURES: Age-adjusted opioid analgesic overdose death rate per 100 000 population in each state. Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.

RESULTS: Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, -37.5% to -9.5%; P = .003) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (-19.9%; 95% CI, -30.6% to -7.7%; P = .002), year 2 (-25.2%; 95% CI, -40.6% to -5.9%; P = .01), year 3 (-23.6%; 95% CI, -41.1% to -1.0%; P = .04), year 4 (-20.2%; 95% CI, -33.6% to -4.0%; P = .02), year 5 (-33.7%; 95% CI, -50.9% to -10.4%; P = .008), and year 6 (-33.3%; 95% CI, -44.7% to -19.6%; P < .001). In secondary analyses, the findings remained similar.

CONCLUSIONS AND RELEVANCE: Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.

Comment in
What ecologic analyses cannot tell us about medical marijuana legalization and opioid pain medication mortality. [JAMA Intern Med. 2015]
What ecologic analyses cannot tell us about medical marijuana legalization and opioid pain medication mortality--reply. [JAMA Intern Med. 2015]
Legalization of medical marijuana and incidence of opioid mortality. [JAMA Intern Med. 2014]

PMID: 25154332 PMCID: PMC4392651 DOI: 10.1001/jamainternmed.2014.4005

[PubMed - indexed for MEDLINE] **Free PMC Article**

Cannabis is a gateway drug?

Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661.

Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D.

Bradford AC[1], Bradford WD[2].

Author information

Abstract

Legalization of medical marijuana has been one of the most controversial areas of state policy change over the past twenty years. However, little is known about whether medical marijuana is being used clinically to any significant degree. Using data on all prescriptions filled by Medicare Part D enrollees from 2010 to 2013, we found that the use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented. National overall reductions in Medicare program and enrollee spending when states implemented medical marijuana laws were estimated to be $165.2 million per year in 2013. The availability of medical marijuana has a significant effect on prescribing patterns and spending in Medicare Part D.

Project HOPE—The People-to-People Health Foundation, Inc.

KEYWORDS: Medicare Part D; medical marijuana; state policy

PMID: 27385238 DOI: 10.1377/hlthaff.2015.1661

[PubMed - in process]

Journal of Psychopharmacology

Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep

Brian J Piper, Rebecca M DeKeuster, Monica L Beals, ...

Show all authors

First Published April 4, 2017 | Research Article

Abstract

A prior epidemiological study identified a reduction in opioid overdose deaths in US states that legalized medical cannabis (MC). One theory to explain this phenomenon is a potential substitution effect of MC for opioids. This study evaluated whether this substitution effect of MC for opioids also applies to other psychoactive medications. New England dispensary members (n = 1,513) completed an online survey about their medical history and MC experiences. Among respondents that regularly used opioids, over three-quarters (76.7%) indicated that they reduced their use since they started MC. This was significantly ($p < 0.0001$) greater than the patients that reduced their use of antidepressants (37.6%) or alcohol (42.0%). Approximately two-thirds of patients decreased their use of anti-anxiety (71.8%), migraine (66.7%), and sleep (65.2%) medications following MC which significantly ($p < 0.0001$) exceeded the reduction in antidepressants or alcohol use. The patient's spouse, family, and other friends were more likely to know about their MC use than was their primary care provider. In conclusion, a majority of patients reported using less opioids as well as fewer medications to treat anxiety, migraines, and sleep after initiating MC. A smaller portion used less antidepressants or alcohol. Additional research is needed to corroborate these self-reported, retrospective, cross-sectional findings using other data sources.

Cannabis can cause psychosis?

PubMed

Abstract

Full text links

SpringerLink FULL-TEXT ARTICLE

Curr Psychiatry Rep. 2016 Feb;18(2):12. doi: 10.1007/s11920-015-0657-y.

Cannabis and Psychosis: a Critical Overview of the Relationship.

Ksir C[1], Hart CL[2,3,4,5].

Author information

Abstract

Interest in the relationship between cannabis use and psychosis has increased dramatically in recent years, in part because of concerns related to the growing availability of cannabis and potential risks to health and human functioning. There now exists a plethora of scientific articles addressing this issue, but few provide a clear verdict about the causal nature of the cannabis-psychosis association. Here, we review recent research reports on cannabis and psychosis, giving particular attention to how each report provides evidence relating to two hypotheses: (1) cannabis as a contributing cause and (2) shared vulnerability. Two primary kinds of data are brought to bear on this issue: studies done with schizophrenic patients and studies of first-episode psychosis. Evidence reviewed here suggests that cannabis does not in itself cause a psychosis disorder. Rather, the evidence leads us to conclude that both early use and heavy use of cannabis are more likely in individuals with a vulnerability to psychosis. The role of early and heavy cannabis use as a prodromal sign merits further examination, along with a variety of other problem behaviors (e.g., early or heavy use of cigarettes or alcohol and poor school performance). Future research studies that focus exclusively on the cannabis-psychosis association will therefore be of little value in our quest to better understand psychosis and how and why it occurs.

KEYWORDS: Cognition; Marijuana; Mental illness; Psychotic disorder; Schizophrenia; THC

PMID: 26781550 [PubMed - in process]

(Ksir & Hart 2016)

- Psychosis is an inability to distinguish what is real and can include delusions and hallucinations.
- Psychosis can be a brief episode or longer term as seen in psychiatric conditions such as schizophrenia.
- The exact cause of psychosis is unknown but likely involves a complex interplay of physical, genetic, psychological and environmental factors.

Cannabis can cause psychosis?

Abstract Send to:

Addiction. 2009 Nov;104(11):1856-61. doi: 10.1111/j.1360-0443.2009.02736.x.

If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations.

Hickman M[1], Vickerman P, Macleod J, Lewis G, Zammit S, Kirkbride J, Jones P.

Author information

Abstract

BACKGROUND: We consider how many cannabis users may need to be prevented in order to prevent one case of schizophrenia or psychosis [defined as number needed to prevent (NNP)].

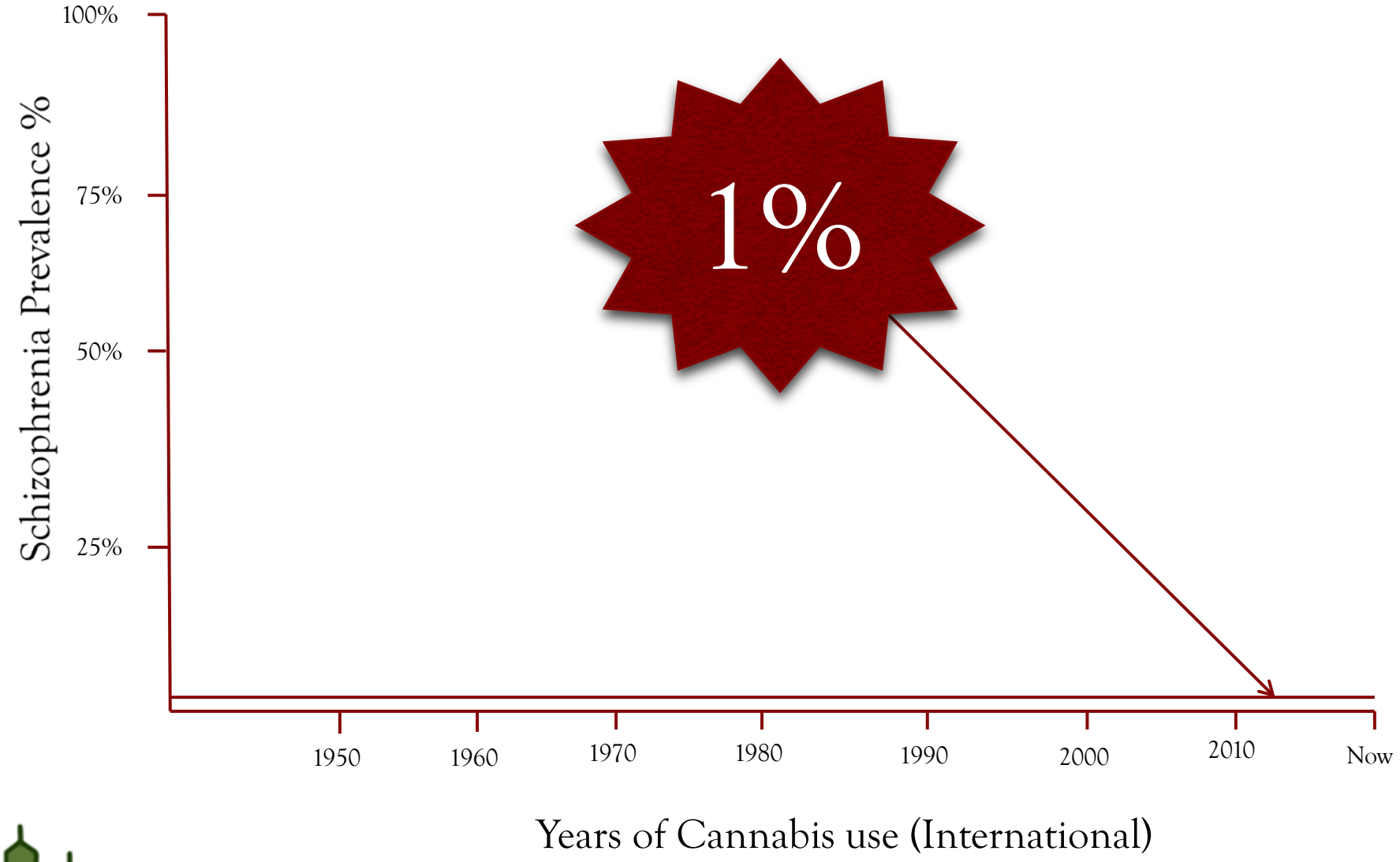
METHOD: Calculation for England and Wales using best available estimates of: incidence of schizophrenia; rates of heavy and light cannabis use; and risk that cannabis causes schizophrenia.

RESULTS: In men the annual mean NNP for heavy cannabis and schizophrenia ranged from 2800 [90% confidence interval (CI) 2018-4530] in those aged 20-24 years to 4700 (90% CI 3114-8416) in those aged 35-39. In women, mean NNP for heavy cannabis use and schizophrenia ranged from 5470 (90% CI 3640-9839) in those aged 25-29 to 10 870 (90% CI 6786-22 732) in 35-39-year-olds. Equivalent mean NNP for heavy cannabis use and psychosis were lower, from 1360 (90% CI 1007-2124) in men aged 20-24 and 2480 (90% CI 1408-3518) in women aged 16-19. The mean and median number of light cannabis users that would need to be prevented in order to prevent one case of schizophrenia or psychosis per year are four to five times greater than among heavy users.

CONCLUSIONS: The number of young people who need to be exposed to an intervention to generate NNP and prevent one case of schizophrenia will be even larger. The public health importance of preventing cannabis to reduce schizophrenia or psychosis remains uncertain. More attention should be given to testing the hypothesis that cannabis is related causally to psychotic outcomes, and to considering what strategies will be the most effective in reducing heavy cannabis use among young people.

- In this UK study, it was estimated that to prevent one case of psychosis approximately 2000 young men would need to stop using Cannabis.

Cannabis can cause psychosis?



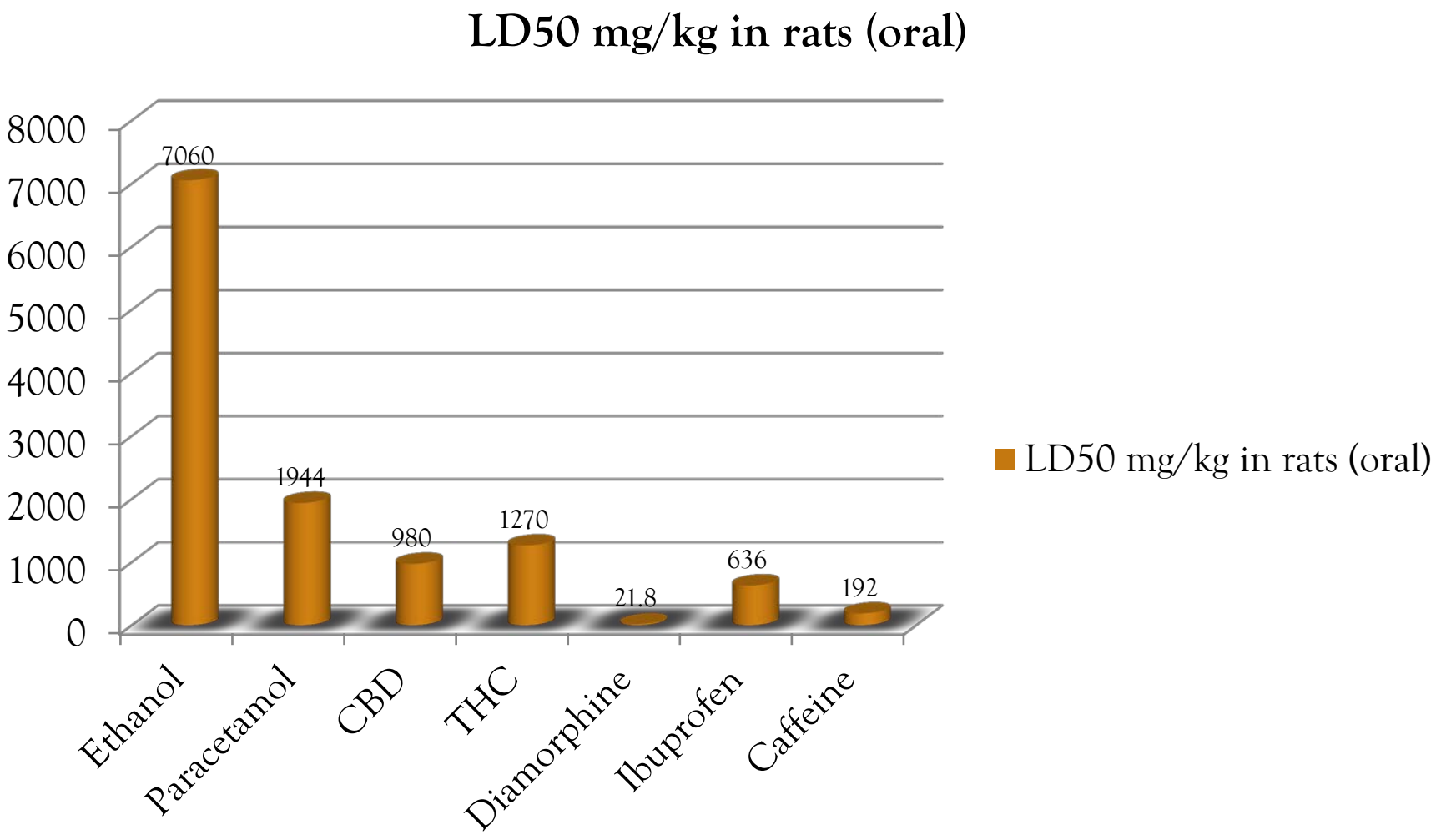
Justin Sinclair, M.HerbMed (USyd) BHSc (UNE) ND

Cannabis use is harmful?

Figure 5: An example of an old United States Pharmacopoeia Fluid extract of Cannabis.

- Statistics regarding Cannabis causing harm are skewed as they often involve multiple other drugs such as alcohol.
- Data specifically relating to Cannabis overdose or toxicity is difficult to find.
- Cannabis related harm is more likely, such as operating motor vehicles or predisposing to mental illness or accident.

Cannabis use is harmful?



How much MC to cause death?

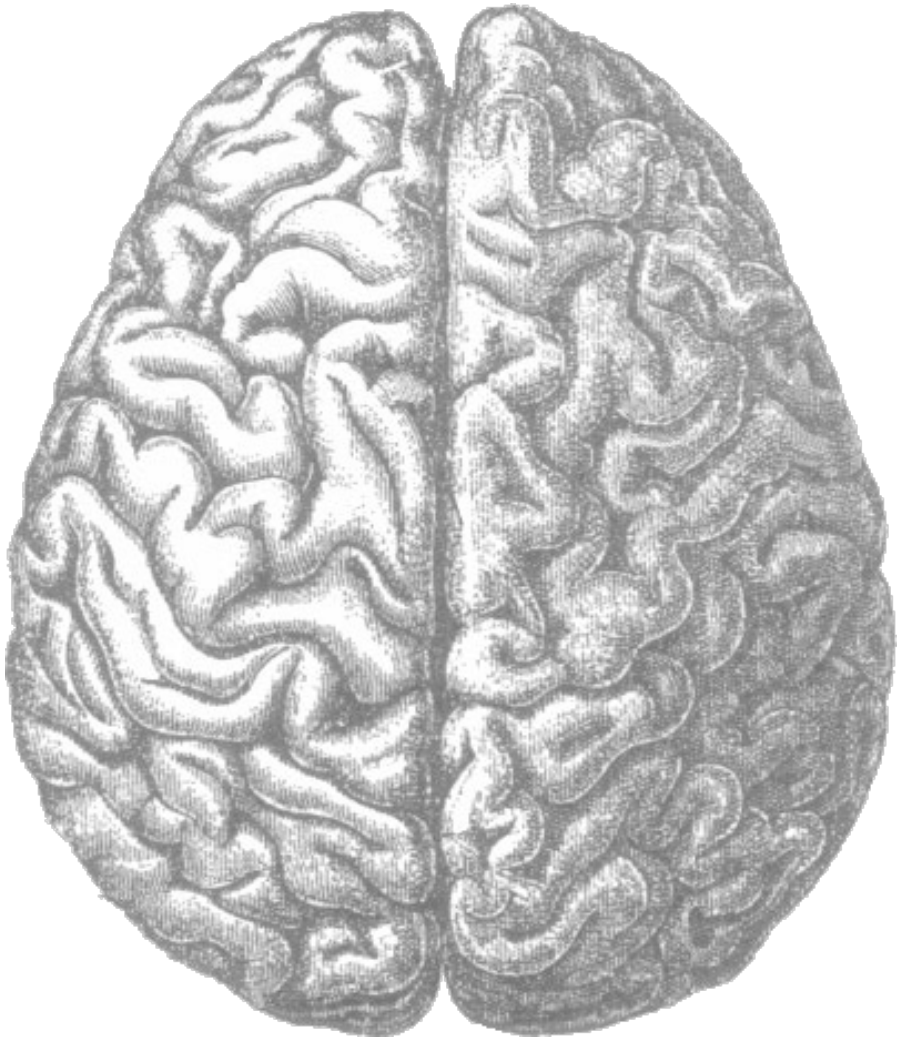
How about some Audience participation

With a show of hands...how many of you support the use of Cannabis for medical conditions?

How many of you support the legalisation of Cannabis for social / recreational / spiritual use by adults?

Lastly – how many of you have cannabinoids in your system right now?

The Endocannabinoid System (ECS)



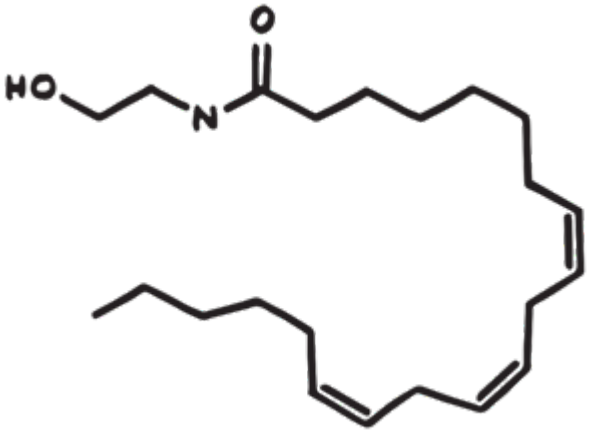
- The ECS has evolved over 500 million years in mammals, birds & fish (McGeeney 2013; Grotenhermen 2006).
- It is a major neuromodulatory system involved in the regulation of homeostasis.
- The ECS was originally found by researchers investigating how Cannabis interacted with human physiology (Herkenham et al. 1990; Pertwee 1997; Devane et al. 1992; Galiegue et al. 1995).
- It is not a main focus of teaching in current medical or Allied healthcare curriculums.

The scientific evolution of the ECS

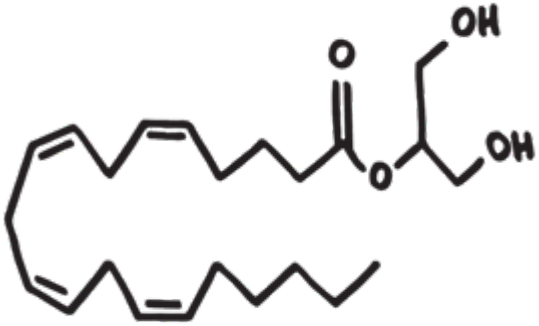
- ✓ **1964** Δ^9-tetrahydrocannabinol (THC) was elucidated
  (Gaoni & Mechoulam 1964)
- ✓ **1967** THC was chemically synthesised in 1967
  (Mechoulam, Braun & Gaoni 1967)
- ✓ **1988** Research identified that THC was stereospecific
  (Mechoulam *et al*. 1988)
- ✓ **1988** First cannabinoid receptor (CB_1) was identified
  (Devane *et al.* 1999; Matsuda *et al.* 1990)
- ✓ **1992** The endocannabinoid Anandamide was identified
  (Devane *et al*. 1992)
- ✓ **1993** Second cannabinoid receptor (CB_2) was identified
  (Munro, Thomas & Abu-Shaar 1993)
- ✓ **1995** The endocannabinoid 2-AG was identified
  (Mechoulam *et al.* 1995; Sugiura *et al.* 1995)

The Endocannabinoid System (ECS)

2. Endogenous ligands

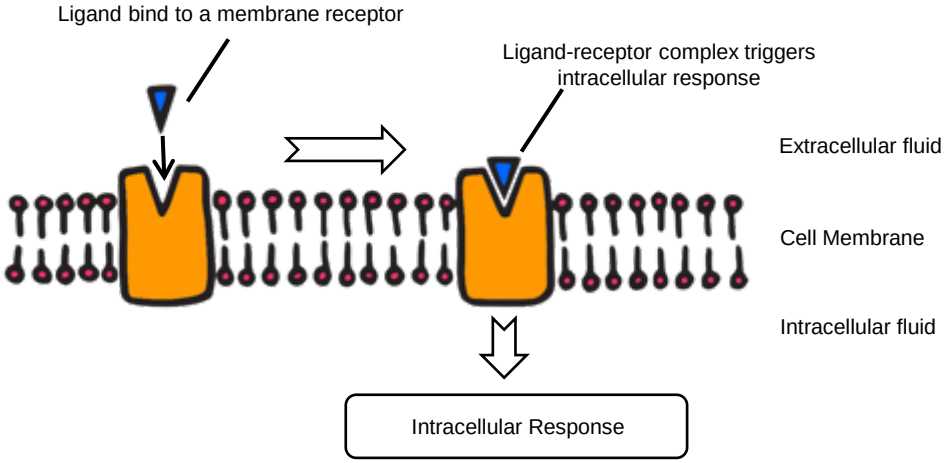


Anandamide
(N-arachidonoylethanolamine).

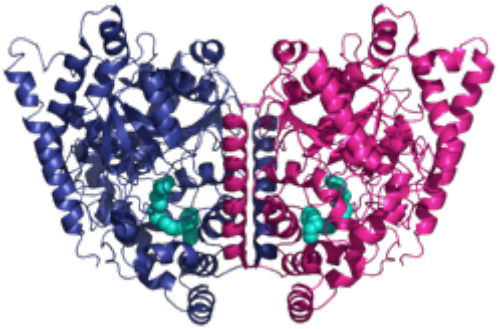


2-AG (2-arachidonoyl glycerol).

1. Cannabinoid Receptors *



3. Enzymes



Fatty Acid Amide Hydrolase (FAAH)

* for educational purposes only. Not an accurate reflection of cannabinoid receptor activity.

1. Cannabinoid receptors

- ✓ CB_1 and CB_2 cannabinoid receptors belong to the family of 7-transmembrane (comprised of α-helices, a glycosylated amino-terminus and an intracellular carboxyl-terminus) Gi/o protein–coupled receptors (GPCRs) (Sanchez & Garcia-Merino 2012)
- ✓ Expressed in abundance in the CNS (Russo 2016)
- ✓ G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 119 (GPR119) are being postulated as new members of the cannabinoid receptor family (Ross 2009; Sanchez & Garcia-Merino 2012; Baker *et al.* 2006)
- ✓ Further research suggests the transient receptor potential vanilloid 1 (TRPV1) receptor and peroxisome proliferator-activated receptor (PPAR) α and γ subtypes are also a target for endocannabinoid binding (Di Marzo & De Petrocellis 2010; Pistis & Melis 2010)

1. Cannabinoid receptors

- ✓ CB_1 and CB_2 cannabinoid receptors exhibit physiological effects by:
  1. Inhibiting adenylate cyclases (Pistis & Melis 2010; Grotenhermen 2006)
  2. Stimulating mitogen-activated protein kinases (MAPK)
  2. Modulating the activity of K^+ and Ca^{2+} ion channels assisting in transducing the binding of agonists

(Kano 2014; Mackie et al. 1995)

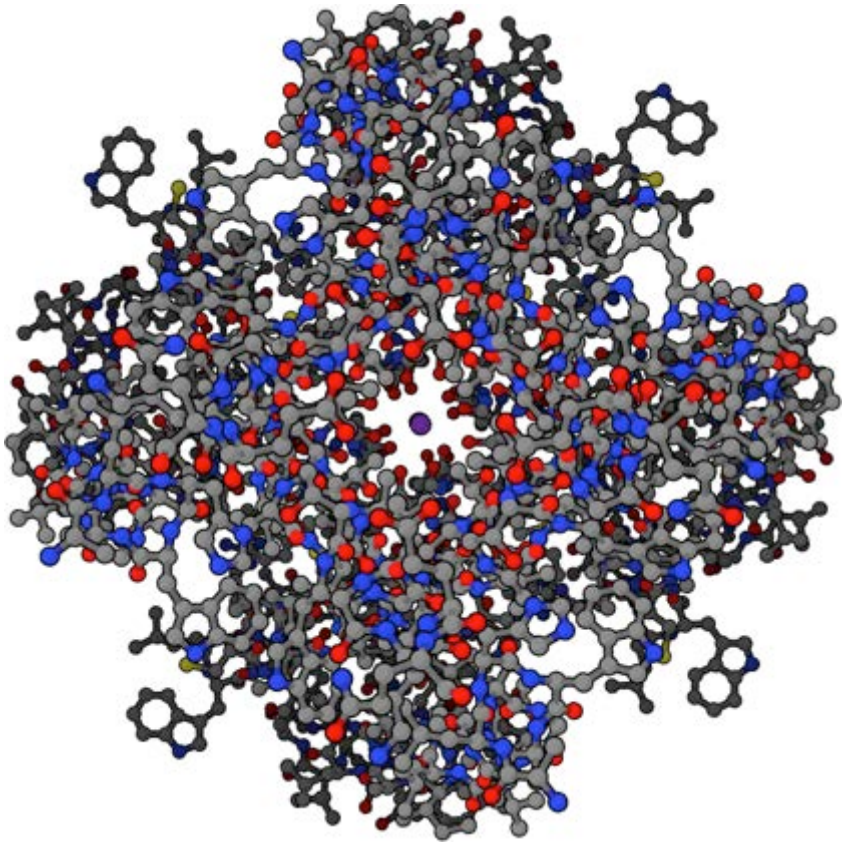


Figure 6: Potassium ions (in purple) moving through a Potassium channel

1. Cannabinoid receptors

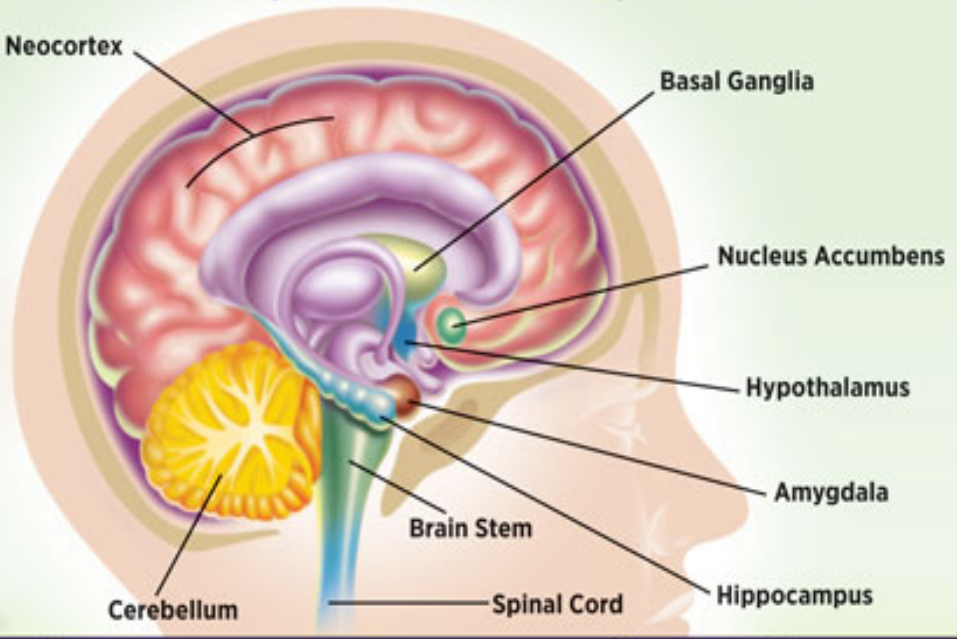
Cannabinoid 1 receptors (CB_1)

- ✓ First receptor to be isolated.
- ✓ Major cannabinoid receptor located in the CNS.
- ✓ Polymorphisms have been characterised for the human CB_1 receptor gene (CNR1), located at chromosome 6q14-15.
- ✓ There are multiple single-nucleotide polymorphisms (SNPs) associated with CNR1.

Cerebral cortex *	Basal ganglia *
➢ Frontal lobe	Amygdala
➢ Olfactory cortex	Cerebellum *
➢ Entorhinal cortex	Hippocampus *
➢ Somatosensory cortex	Periaqueductal gray matter
Rostroventrolateral medulla (RVM)	Spinal interneurons
Substantia nigra	Globus pallidus
* Highest receptor concentration	Substantia gelatinosa (spinal cord)

CB1 receptors and THC

How does THC affect behavior? ***It depends on where the CB receptors are in the brain.***



Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

Figure 7: Figure obtained from Scholastic Inc 2011.

1. Cannabinoid receptors

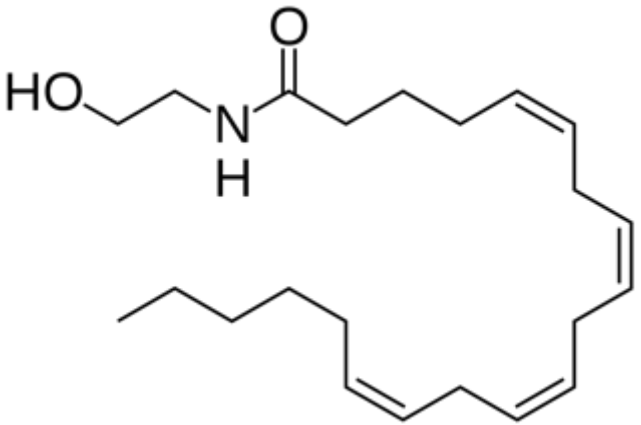
Cannabinoid 2 receptors (CB_2)

- ✓ CB_2 receptors are expressed in the immune tissues, such as the marginal zone of the spleen, thymus, tonsils and gastrointestinal tract, as well as specific immune cells such as CD4+ and CD8+ T-cells, B-cells, macrophages, monocytes, natural killer cells and neutrophils.
- ✓ CB_2 receptors are also expressed on primary sensory neurons, microglial cells and throughout the central nervous system.
- ✓ Researchers believe CB_2 receptors are involved in the well-described pharmacological effects of cannabinoids on inflammation and immunological function.
- ✓ CB_2 receptors are involved in the endogenous response to injury (Anand *et al.* 2009).

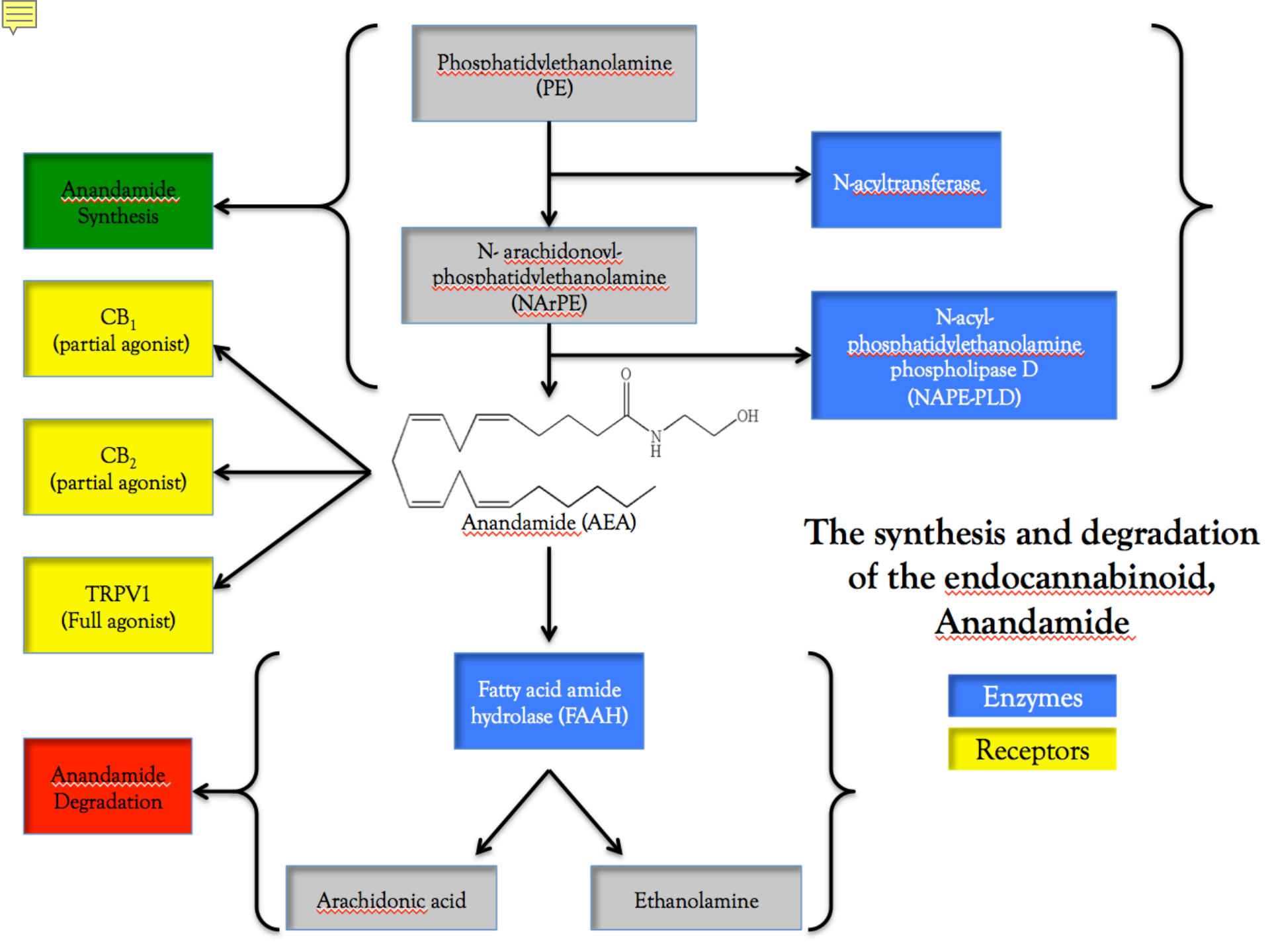
2. Endocannabinoids (Ligands)

Anandamide (AEA) N-arachidonoylethanolamine

- ✓ Anandamide (AEA), named after the Sanskrit word *ananda* meaning “supreme joy” or “bliss”
- ✓ Exhibits partial agonistic activity at both CB receptors but binds with modestly higher affinity at CB_1 receptors in comparison to CB_2
- ✓ Other endocannabinoid like compounds have been identified including O-arachidonoyl ethanolamine (virodhamine), 2-arachidonoyl glycerol ether (noladin ether), *N*-palmitoylethanolamine (PEA), *N*-oleoylethanolamine (OEA) and *N*-stearoylethanolamine (SEA)
- ✓ Anandamide is a partial agonist for CB_1 and CB_2 receptors and a full agonist for TRPV1.



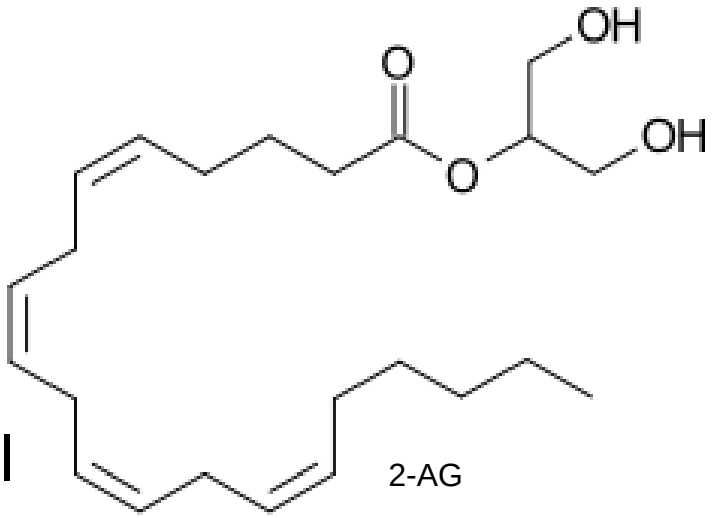
Anandamide (AEA)


Phosphatidylethanolamine (PE)
N-acyltransferase
N- arachidonoyl-phosphatidylethanolamine (NArPE)
N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD)
Anandamide Synthesis
CB1 (partial agonist)
CB2 (partial agonist)
TRPV1 (Full agonist)
O
N
H
OH
Anandamide (AEA)
Fatty acid amide hydrolase (FAAH)
Anandamide Degradation
Arachidonic acid
Ethanolamine
The synthesis and degradation of the endocannabinoid, Anandamide
Enzymes
Receptors

2. Endocannabinoids (Ligands)

2-AG (2-arachidonoyl glycerol)

- ✓ Fast retrograde synaptic messenger
- ✓ Both anandamide and 2-AG are arachidonic acid derivatives of polyunsaturated fatty acids
- ✓ 2-AG can be produced by several different pathways, highlighting its importance
- ✓ 2-AG appears to be the true ligand for cannabinoid receptors and is key in retrograde signaling within the brain



2-AG

Phosphatidylinositol

Membrane phospholipids

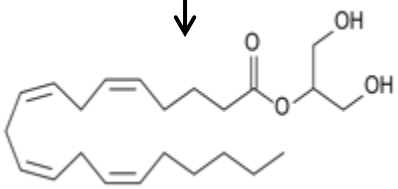
2-AG Synthesis

Phospholipase C (PLC)

Diacylglycerol

CB_1 (full agonist)

Diacylglycerol lipase (DGL)



2-AG (2-arachidonoyl glycerol).

CB_2 (full agonist)

The synthesis and degradation of the endocannabinoid, 2-AG

Monoacylglycerol lipase (MAGL)

2-AG Degradation

Arachidonic acid

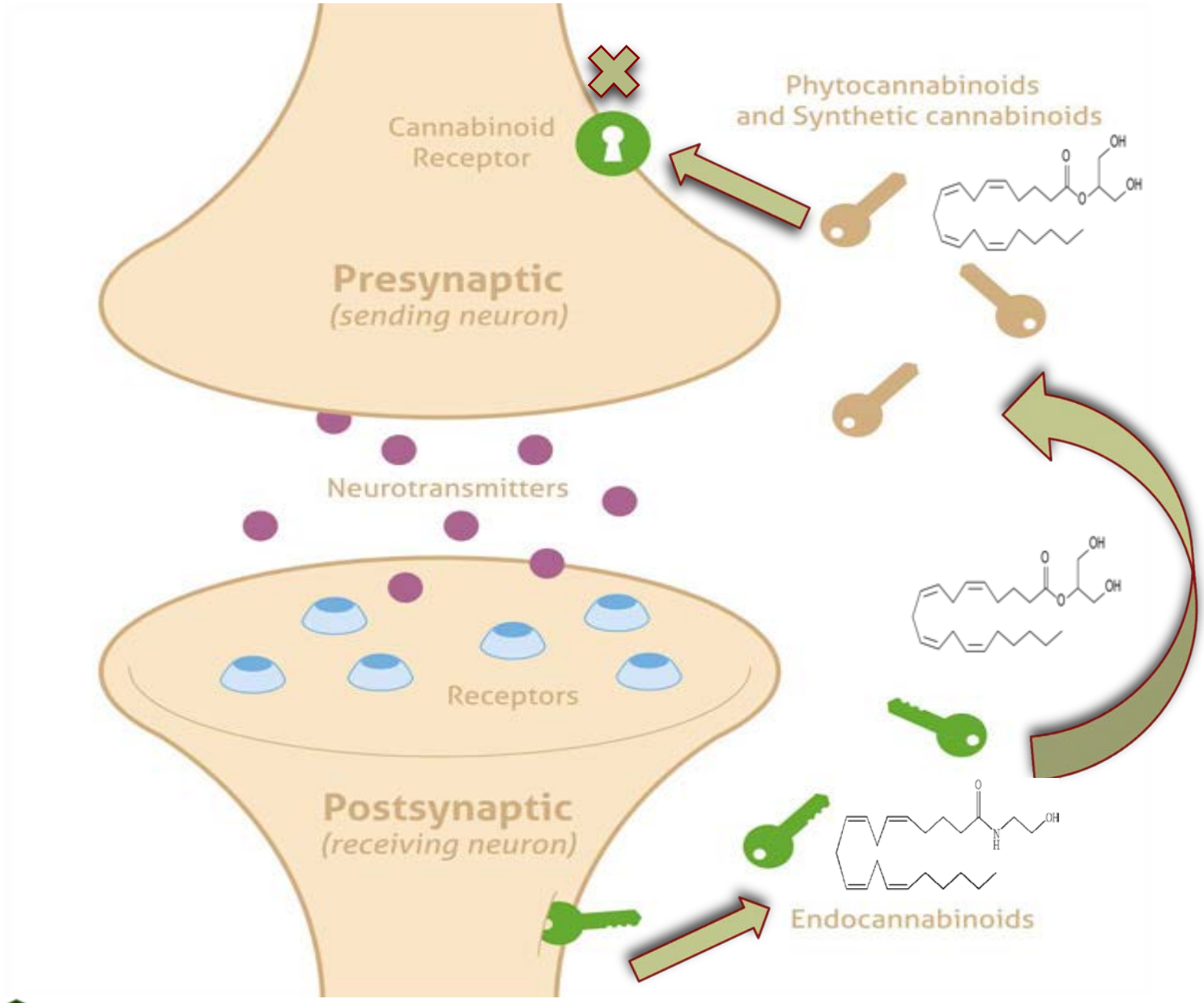
Glycerol

Enzymes

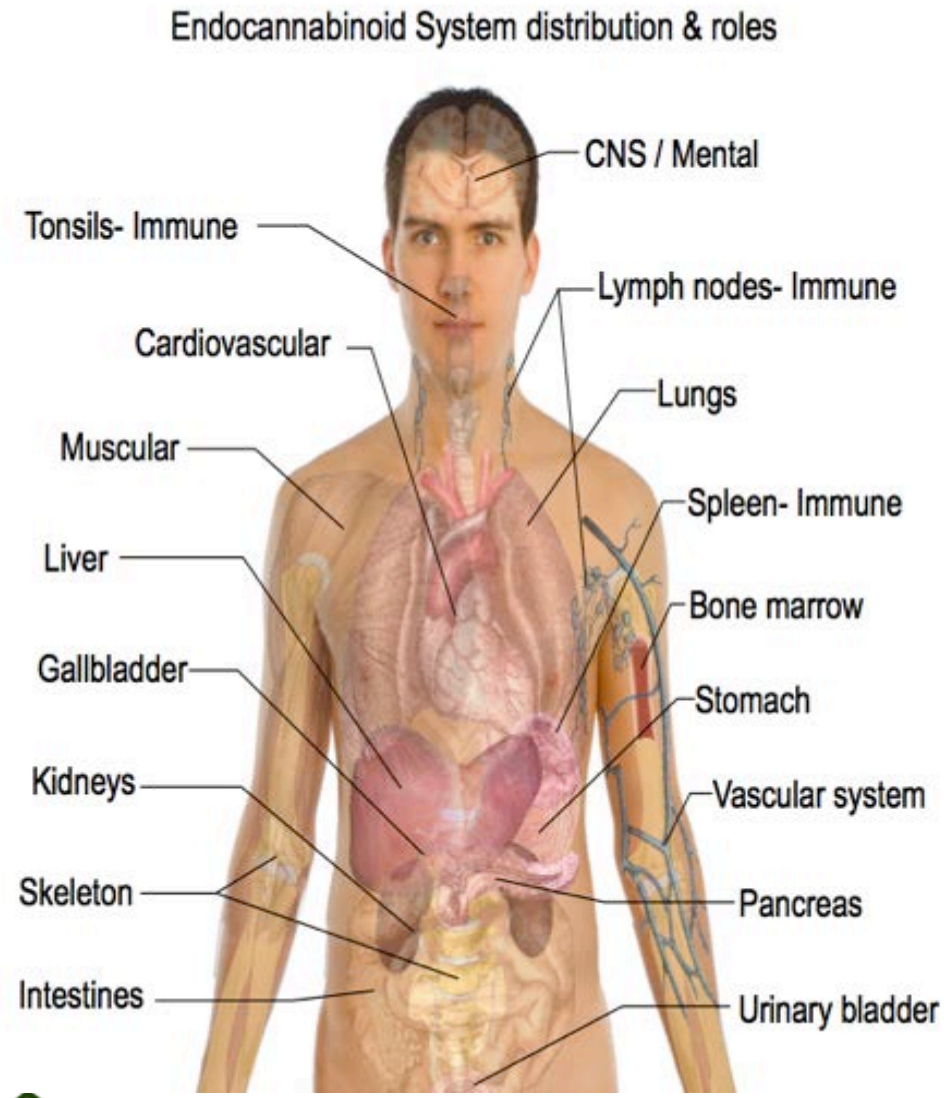
Receptors

Justin Sinclair, M.HerbMed (USyd) BHSc (UNE) ND

Endocannabinoid Retrograde transmission



The Endocannabinoid System (ECS)



ECS and homeostasis

- ✓ the regulation of stress and emotions, digestion, pain, cardiovascular function, immune function, neural development, synaptic plasticity and learning, memory, bodily movement, metabolism, energy expenditure, inflammation, appetite regulation, sleep / wake cycles and even temperature regulation.

Physiology of the ECS: Neurological

- ✓ Abnormal physiology has been shown in research for the ECS and epilepsy
- ✓ Patients with newly diagnosed temporal lobe epilepsy exhibited significantly lower levels of anandamide in their CSF then healthy controls (Friedman 2015; Romigi *et al.* 2010)
- ✓ Resected tissue following surgery for epilepsy demonstrated lower levels of CB_1 receptor mRNA expression in the glutamatergic terminals of the dentate gyrus (Friedman 2015)
- ✓ Reduced levels of DAGL-α has also been identified in epilepsy patients, which is the enzyme responsible for the manufacture of 2-AG on the post-synaptic membrane (Ludanyi *et al*. 2008)

Physiology of the ECS: Neurological

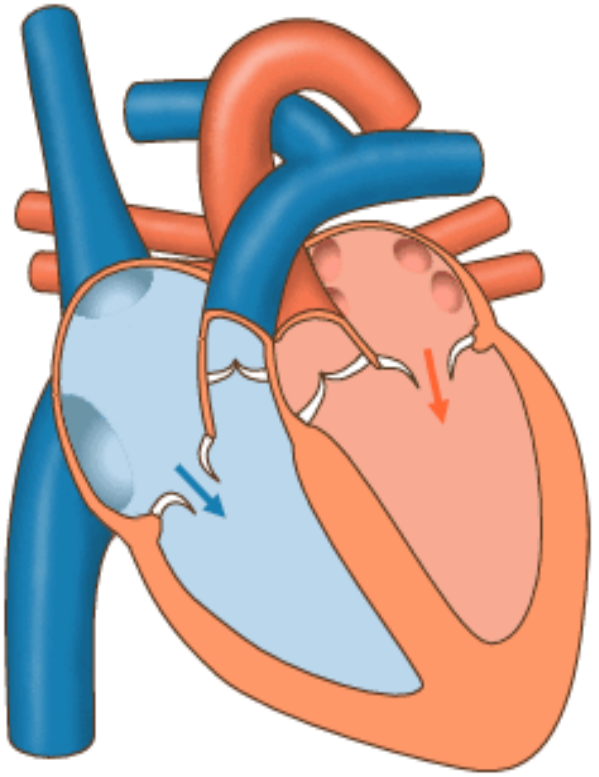
- ✓ Reduced anandamide levels have been observed in patients with chronic migraine (CSF) (Sarchielli *et al.* 2007; Russo 2004)
- ✓ CNR1 gene is linked with a chromosomal region posited as being related to migraine (Nyholt *et al.* 2005)
- ✓ Variations in CNR1 gene expression exhibits predisposition to higher risk of migraine development (Juhasz *et al.* 2009)

Physiology of the ECS: Neurological

- ✓ Elevated anandamide levels have been observed in both normal and abnormal ECS function.
- ✓ Increased anandamide plasma levels have been observed during and after moderate intensity aerobic workouts in healthy individuals (Sparling *et al.* 2003; Raichlen *et al.* 2012)
- ✓ Markedly increased levels of anandamide has been found in both plasma and CSF of schizophrenic patients in contrast to healthy controls (Desfosses *et al.* 2010; De Marchi *et al.* 2003)
- ✓ The CNR1 gene may be a susceptibility locus for schizophrenia (Cao *et al.* 1997)
- ✓ Susceptibility for schizophrenia may be increased by a genetically predetermined decrease in CB_2 receptor functioning. (Desfosses *et al.* 2010; Ishiguru *et al*. 2010)

Physiology of the ECS: Cardiovascular

- ✓ Heart failure: activated monocytes produce endocannabinoids which can lead to hypotension and negative inotropism (Pacher, Batkai & Kunos 2006)
- ✓ Cardiac myocytes and vascular smooth muscle produce endocannabinoids which can interact with CB1 receptors, causing ROS and AGE product accumulation (Rajesh *et al.* 2012; Pacher & Kunos 2013)
- ✓ The pro-inflammatory role of CB_1 receptors in the CVS has been confirmed in knockout mice (FAAH) in models of atherosclerosis and cardiomyopathy (Pacher & Kunos 2013)



Physiology of the ECS: Cardiovascular

- ✓ CB_2 receptors appear to be protective within the CVS
- ✓ Activation of CB_2 decreases pro-inflammatory and fibrotic responses and initiates protective mechanisms in cardiac myocytes (Steffens & Pacher 2012)
- ✓ CB_2 activation reduces immune cell chemotaxis, cellular activation and inflammatory cell adhesion (Steffens & Pacher 2012)
- ✓ These actions appear to be the reason for the protective effects shown in preclinical models of MI, restenosis, stroke and atherosclerosis
- ✓ CB_1 antagonists and CB_2 agonists are of particular clinical interest pharmacologically for specific CVS disorders (Maccarrone et al. 2015)

Physiology of the ECS: Immunity

- ✓ CB2 expression predominates in immune cells, particularly CD4+ and CD8+ T-cells, B-cells, macrophages, monocytes, natural killer cells and neutrophils (Maccarrone *et al.* 2015)
- ✓ Anandamide may inhibit immune function by reducing proinflammatory cytokine production
- ✓ 2-AG may inhibit the migratory activities of certain immune cells via CB2 receptor modulation (Liu et al. 2013)
- ✓ Anandamide reduces IL-6 and IL-8 in human monocytes and suppresses the release of TNF-α and IFN-γ (Berdyshev *et al.* 1997; Cencioni *et al*. 2010)
- ✓ Cannabinoid based therapies may be of benefit in numerous autoimmune, neurodegenerative and neuroinflammatory disorders.

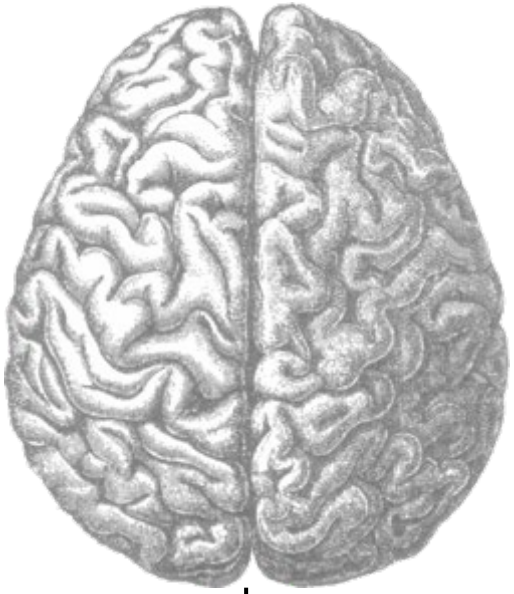
Physiology of the ECS: Gastrointestinal

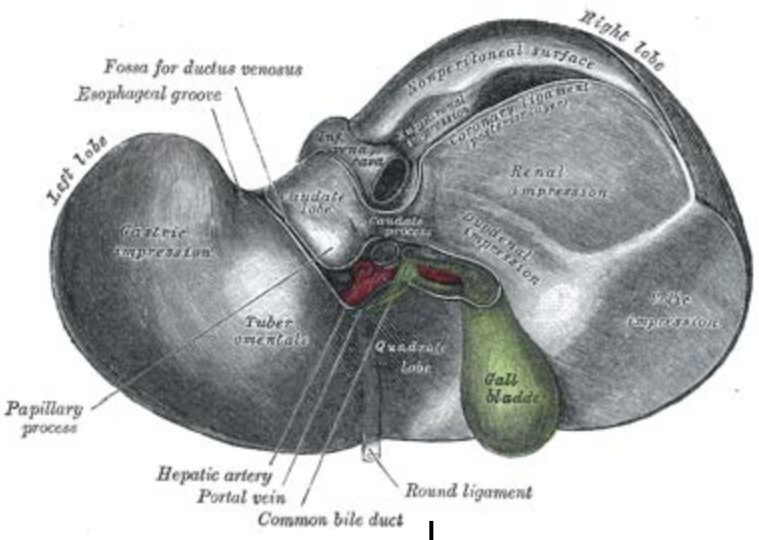
- ✓ CB_1 receptors are found on enteroendocrine cells, immune cells and enterocytes (Maccarrone *et al.* 2015)
- ✓ CB_2 expression is based mainly on enterocytes and immune cells (Maccarrone *et al.* 2015)
- ✓ Within the GIT, the ECS is involved in:
  - ✓ Hunger (Sykaras *et al.* 2012)
  - ✓ Regulation of food intake and energy (Piomelli 2013)
  - ✓ Nausea and emesis
  - ✓ Gastric secretions / gastro-protection (Wright, Duncan & Sharkey 2008)
  - ✓ GI motility (Duncan *et al.* 2008)
  - ✓ Visceral sensation and ion transport
  - ✓ Intestinal inflammation and intestinal barrier protection (Fichna *et al.* 2014; Muccioli *et al.* 2010)
  - ✓ Normal cellular proliferation in the GIT (Izzo & Sharkey 2010)

Physiology of the ECS: Gastrointestinal

- ✓ The liver is sparsely populated with CB_1 and CB_2 receptors
- ✓ CB_1 are found in hepatocytes, vascular endothelial cells and stellate cells whereas CB_2 receptors are found on immune cells, myofibroblasts and kupffer cells (Maccarrone 2015)
- ✓ Activation of the CB_1 receptor in the liver can cause:
  - ✓ Vasodilation, (ascites)
  - ✓ increase in fat accumulation,
  - ✓ insulin resistance and fibrosis.
- ✓ CB_2 activation is anti-inflammatory and reduces cytokine production and has been shown to minimise reperfusion injury, reduce fatty deposition injury and is antifibrotic (Batkai *et al.* 2007; Guillot *et al.* 2014; Julien *et al.* 2005)

Genetic/variability impacting the ECS





- ✓ CB_1/CB_2 receptor expression (high or low);
- ✓ Deficiency of endocannabinoids;
- ✓ Deficiency or abundance of enzymes involved in synthesis / degradation;
- ✓ Genetic polymorphisms

- ✓ Changes in pharmacokinetics (Absorption, Distribution, Metabolism & Excretion);
- ✓ Age related change to organ function;
- ✓ Genetic polymorphisms of CYP450 enzymes

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