

What the Latest Top Cannabis Research Tells Us

(A comparison to “Top 10 Old Cannabis Studies the Government Wished it had Never Funded”)

10. **The Claim You’ll Find Online:** Marijuana use has no effect on mortality. A massive study of California HMO members funded by the **National Institute on Drug Abuse (NIDA)** found marijuana use caused no significant increase in mortality. Tobacco use was associated with increased risk of death. Sidney, S et al. Marijuana Use and Mortality. American Journal of Public Health. Vol. 87 No. 4, April 1997. p. 585-590. Sept. 2002.

The More Recent Research: Marijuana Use Disorder IS associated with higher mortality.

A massive study was undertaken to understand the mortality rate of methamphetamine users, in relation to other drug users.

Methods: The current study identified cohorts of individuals hospitalized in California from 1990 to 2005 with ICD-9 diagnoses of methamphetamine- (n=74,139), alcohol- (n=582,771), opioid- (n=67,104), cannabis- (n=46,548), or cocaine-related disorders (n=48,927), and these groups were followed for up to 16 years. Age-, sex-, and race-adjusted standardized mortality rates (SMRs) were generated. [To be assigned to a drug cohort, an individual must have had:

- an ICD-9 diagnosis, in any of the diagnoses (up to 25) recorded in the patient’s medical record, indicating a condition within only one single drug category, at index admission;
- no indication in medical records of any alcohol- or drug-use diagnoses outside of their assigned drug cohort; and
- no ICD-9 indication of any other drug use disorders.

Thus, the algorithm excluded individuals from a drug group who had any ICD-9 diagnostic codes within a medical record or across records indicative of drug use other than that designated by their drug group membership.

Results: Those treated for addiction to cannabis (marijuana) had a higher mortality rate (3.85 times higher than controls), higher if compared to death rate risk of cocaine use disorder (2.96), alcohol use disorder (3.83), but lower than opioid use disorder (5.71) or methamphetamine use disorder (4.67).

The study demonstrates that individuals with cannabis (marijuana) use disorders have a higher mortality risk than those with diagnoses related to cocaine or alcohol, but lower mortality risk than persons with methamphetamine or opioid-related disorders.

Given the lack of long-term cohort studies of mortality risk among individuals with methamphetamine-related disorders, as well as among those with cocaine- or cannabis-related conditions, the current study provides important information for the assessment of the comparative drug-related burden associated with use and addiction. (Callaghan et al., All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study. Drug Alcohol Depend. 2012 Oct 1;125(3):290-4).

9. **The Claim You’ll Find Online:** Heavy marijuana use as a young adult won’t ruin your life. Veterans Affairs scientists looked at whether heavy marijuana use as a young adult caused long-term problems later, studying identical twins in which one twin had been a heavy marijuana user for a year or longer but had stopped at least one month before the study, while the second twin had used marijuana no more than five times ever. Marijuana use had no significant impact on physical or mental health care utilization, health-related quality of life, or current socio-demographic characteristics. Eisen SE et al. Does Marijuana Use Have Residual Adverse Effects

on Self-Reported Health Measures, Socio-Demographics or Quality of Life? A Monozygotic Co-Twin Control Study in Men. *Addiction*. Vol. 97 No. 9. p.1083-1086. Sept. 1997.

The More Recent Research: Heavy marijuana use as a young adult can adversely affect your life.

Background: Although cannabis is the most widely used illicit drug in the United States, few recent American studies have examined the attributes of long-term heavy cannabis users.

Method: Using a case-control design, we obtained psychological and demographic measures on 108 individuals, age 30-55, who had smoked cannabis a mean of 18,000 times and a minimum of 5,000 times in their lives. We compared these heavy users to 72 age-matched control subjects who had smoked at least once, but no more than 50 times in their lives.

Results: We found no significant differences between the two groups on reported levels of income and education in their families of origin. However, the heavy users themselves reported significantly lower educational attainment ($P < 0.001$) and income ($P = 0.003$) than the controls, even after adjustment for a large number of potentially confounding variables. When asked to rate the subjective effects of cannabis on their cognition, memory, career, social life, physical health and mental health, large majorities of heavy users (66-90%) reported a "negative effect." On several measures of quality of life, heavy users also reported significantly lower levels of satisfaction than controls.

Conclusion: Both objective and self-report measures suggest numerous negative features associated with long-term heavy cannabis use. Thus, it seems important to understand why heavy users continue to smoke regularly for years, despite acknowledging these negative effects. Such an understanding may guide the development of strategies to treat cannabis dependence. (Gruber et al., Attributes of long-term heavy cannabis users: a case-control study, *Psychol. Med* 33:1415-22. 2003)

And a very abbreviated list: Acute adverse effects of marijuana (short list): Anxiety and panic, especially in naive users; psychotic symptoms (at high doses); road crashes if a person drives while intoxicated

Chronic use of marijuana (short list): dependence syndrome (in around one in 10 users); chronic bronchitis and impaired respiratory function in regular smokers; psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders; impaired educational attainment in adolescents who are regular users; subtle cognitive impairment in those who are daily users for 10 years or more (Hall W. and Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*, 374: 1383-1391, 2009).

Marijuana and driving. Risks for motor vehicle accidents are higher. Acute cannabis consumption is associated with an increased risk of a motor vehicle crash, especially for fatal collisions. Another study demonstrated a concentration-dependent crash risk for THC-positive drivers. Alcohol and alcohol-drug combinations are by far the most prevalent substances in drivers and subsequently pose the largest risk in traffic, both in terms of risk and scope. This information could be used as the basis for campaigns against drug impaired driving, developing regional or national policies to control acute drug use while driving, and raising public awareness. (Kuypers KP et al., A case-control study estimating accident risk for alcohol, medicines and illegal drugs. *PLoS One*. 2012;7(8):e43496. Epub 2012 Aug 28; Asbridge et al, Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*. 2012 Feb 9;344:e536. doi: 10.1136/bmj.e536. Gerberich et al.,

Marijuana use and injury events resulting in hospitalization. *Ann Epidemiol* 13: 230–37, 2003. Mura P et al., Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. *Forensic Sci Int* 133: 79–85, 2003. Drummer et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accid Anal Prev* 36: 239–48, 2004. Laumon et al., Cannabis intoxication and fatal road crashes in France: population based case-control study. *BMJ* 331: 1371, 2005.)

Marijuana and IQ Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were a prospective study of 1,037 individuals followed from birth (1972/1973) to age 38 years. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38. Neuropsychological testing was conducted at age 13 years, before initiation of cannabis use, and again at age 38 years, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents. (Meier et al., Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012 Oct 2;109(40):E2657-64.

Marijuana and depression High doses of cannabis in humans appear to increase the risk of depression, especially in the young (Ashton CH and Moore PB. Endocannabinoid system dysfunction in mood and related disorders. *Acta Psychiatr. Scand.*, 124: 250-261, 2011).

Marijuana and anxiety There is a strong pattern of cannabis relieving anxiety at low doses and promoting anxiety at higher doses. (Viveros et al., 2005; Moreira and Lutz, 2008; Akirav, 2011). Daily cannabis use was associated with anxiety disorder at 29 years (adjusted OR 2.5), as was cannabis dependence (adjusted OR 2.2). Among weekly+ adolescent cannabis users, those who continued to use cannabis use at 29 years remained at significantly increased odds of anxiety disorder (adjusted OR 3.2), (Degenhardt et al, The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction*. 2012 Jul 6. doi:10.1111/j.1360-0443.2012.04015.x. PubMed PMID: 22775447.)

Marijuana and brain function Cannabis produced dose-related impairments of immediate and delayed recall of information presented while under the influence of the drug. Learning, consolidation and retrieval of memory were all affected (Ranganathan M and D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology*, 188: 425-444, 2006).

Marijuana and executive function A broader spectrum of cognitive functions designated as executive functions were investigated (attention, concentration, decision-making, impulsivity, self-control of responses, reaction time, risk taking, verbal fluency and working memory) all were impaired acutely in a dose-dependent manner The authors concluded that some elements of executive function usually recover completely after stopping marijuana use, but deficits most

likely to persist for long periods of time are decision-making, concept formation and planning, especially in heavy users who started using at an early age (Crean et al., *J. Addict. Med.*, 5: 1-8. 2011)

Adverse health effects of marijuana In evidence-based review of acute and long-term effects of cannabis use on executive cognitive functions, there is generally good agreement between the conclusions based on these studies and the clinical impressions based on population studies (Hall W. and Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*, 374: 1383-1391, 2009).

Marijuana and psychosis

Context: A number of studies have found that the use of cannabis and other psychoactive substances is associated with an earlier onset of psychotic illness.

Objective: To establish the extent to which use of cannabis, alcohol, and other psychoactive substances affects the age at onset of psychosis by meta-analysis.

Data Sources: Peer-reviewed publications in English reporting age at onset of psychotic illness in substance-using and non-substance-using groups were located using searches of CINAHL, EMBASE, MEDLINE, PsycINFO, and ISI Web of Science.

Study Selection: Studies in English comparing the age at onset of psychosis in cohorts of patients who use substances with age at onset of psychosis in non-substance-using patients. The searches yielded 443 articles, from which 83 studies met the inclusion criteria.

Data Extraction: Information on study design, study population, and effect size were extracted independently by 2 of us.

Data Synthesis: Meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger than for nonusers; for those with broadly defined substance use, the age at onset of psychosis was 2.00 years younger (standardized mean difference = -0.315) than for nonusers. Alcohol use was not associated with a significantly earlier age at onset of psychosis. Differences in the proportion of cannabis users in the substance-using group made a significant contribution to the heterogeneity in the effect sizes between studies, confirming an association between cannabis use and earlier mean age at onset of psychotic illness.

Conclusions: The results of meta-analysis provide evidence for a relationship between cannabis use and earlier onset of psychotic illness, and they support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients. The results suggest the need for renewed warnings about the potentially harmful effects of cannabis. (Large M, et al., Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry*. 2011 Jun;68(6):555-61).

8. The Claim You'll See Online: "The 'Gateway Effect' may be a mirage."

"Marijuana is often called a 'gateway drug' by supporters of prohibition, who point to statistical 'associations' indicating that persons who use marijuana are more likely to eventually try hard drugs than those who never use marijuana – implying that marijuana use somehow causes hard drug use. But a model developed by RAND Corp. researcher Andrew Morral demonstrates that these associations can be explained 'without requiring a gateway effect.' More likely, this federally funded study suggests, some people simply have an underlying propensity to try drugs, and start with what's most readily available. Morral AR, McCaffrey D and Paddock S. Reassessing the Marijuana Gateway Effect. *Addiction*. December 2002. p. 1493-1504."

The More Recent Research: ‘Gateway,’ or by any other name, marijuana use increases probability of use of other drugs.

The aim of this study was to confirm the influence of cannabis use patterns on the probability of initiation with other illicit drugs (OID). A French nationwide retrospective cohort on drug use was reconstituted on 29,393 teenagers. Modelling was done of all possible pathways from initial abstinence to cannabis initiation, daily cannabis use and other illicit drug initiation. The model was adjusted for tobacco and alcohol use.

The risk for other illicit drug initiation appeared 21 times higher among cannabis experimenters and 124 times higher among daily cannabis users than among non-users.

Tobacco and alcohol use were associated with a greater risk of moving on to cannabis initiation (hazard ratio (HR)=1.2 for tobacco initiation, HR=2.6 for daily tobacco use and HR=2.8 for drunkenness initiation). The results of this study provide a confirmation of a stage process in drug use, mediated by cannabis and liable to lead to OID experiment. **This is compatible with the literature on the gateway theory, but goes further by modelling the entire sequence of use.** OID experiment could be a consequence of initial opportunity to use the more accessible illicit drug, cannabis. (Mayet A, Legleye S, Falissard B, Chau N. Cannabis use stages as predictors of subsequent initiation with other illicit drugs among French adolescents: use of a multi-state model. *Addict Behav.* 2012 Feb;37(2):160-6).

7. The Claim You’ll Find Online: “Prohibition doesn’t work” (Part 1):

“The White House had the National Research Council examine the data being gathered about drug use and the effects of U.S. drug policies. NRC concluded, ‘the nation possesses little information about the effectiveness of current drug policy, especially of drug law enforcement.’ And what data exist show ‘little apparent relationship between severity of sanctions prescribed for drug use and prevalence or frequency of use.’ In other words, there is no proof that prohibition – the cornerstone of U.S. drug policy for a century – reduces drug use. National Research Council. *Informing America’s Policy on Illegal Drugs: What We Don’t Know Keeps Hurting Us.* National Academy Press, 2001. p. 193.”

The Research: Why, Yes, Prohibition Has Worked:

- Abuse of opioids declined over 90% from early 1900’s-2,000’s as a result of prohibition (United Nations Office on Drugs and Crime or UNODC);
- Cocaine use has declined by 38% rapidly in the US since 2007. The annual number of cocaine initiates declined from 1.0 million in 2002 to 670,000 in 2011. The number of initiates of crack cocaine declined during this period from 337,000 to 76,000 (National Survey on Drug Use and Health, 2011).
- Among youth 12-17 years, current marijuana use (past month use) declined from 8.2 % in 2002 to 6.7 %, in 2008 (an 18% decrease) as a result of a concerted campaign to reduce use. With the rapid rise of medical marijuana outlets, marijuana use increased to 7.4 % in 2009 and 2010; the prevalence of current marijuana use in 2011 (7.9 percent) also was greater than that in 2008, but it was similar to the rates in 2009 and 2010 (National Survey on Drug use and Health, 2012).

According to Hans-Christian Raabe, general practitioner: “The recent report of the International Centre for Science in Drug Policy (ICS DP) claims that cannabis should be legalized because its use has increased in the past 20 years, despite increasing resources being spent on the criminal justice system.

However, it is very important to recognize:

- The ICSDP did not look at data before 1990: use of marijuana in the past month by US high school seniors peaked in 1978 at 37.1% and declined to its lowest level of 11.9% in 1992. Similar trends have been observed for all drug use.
- The prohibition that the ICSDP report claimed had not worked was associated with a two thirds reduction in cannabis use. The report has a cavalier attitude towards the harms of cannabis. However, since 2002 several key studies have shown the clear link between cannabis and serious mental health problems, including an increasing risk of developing schizophrenia.
- The report claims that selling cannabis through legal outlets would not result in increased cannabis use. However, in the Netherlands use increased sharply after quasi legalization: in those aged 18-20 use in the past year increased from 15% in 1984 to 44% in 1996. This contrasts with steady or declining use in cities such as Oslo, Stockholm, and Hamburg, and countries such as Denmark, Germany, and the U.S. over the same period.
- Empirical data therefore contradict the ICSDP claims. The report does not mention Sweden, whose drug policy aims at creating a drug-free society. Sweden now has among the lowest rates of drug misuse, including cannabis misuse, in Europe.
- The Swedish example shows that the most successful approach to drug policy is based on drug prevention, not legalization.

(Hans-Christian Raabe general practitioner, Partington Central Surgery, Manchester M31 4FY, UK; references: (1) Room R. Prohibition of cannabis. *BMJ* 2010;341:c5492. (6 October.) (2) Monitoring the Future. Survey data. [http:// monitoringthefuture.org/](http://monitoringthefuture.org/). (3) Fergusson DM, Poulton R, Smith PF, Boden JM. Cannabis and psychosis. *BMJ* 2006;332:172-6. (4) MacCoun R, Reuter P. Evaluating alternative cannabis regimes. *Br J Psychiatry* 2001;178:123-8. (5) EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. www.emcdda.europa.eu/stats10.) Benzylpiperazine (BZP) is the psychoactive ingredient in a range of 'legal highs' sold worldwide. BZP was prohibited in New Zealand in 2008.

The overall level of legal high use was lower following the prohibition of BZP. (Wilkins C, Sweetser P. The impact of the prohibition of benzylpiperazine (BZP) 'legal highs' on the prevalence of BZP, new legal highs and other drug use in New Zealand. *Drug Alcohol Depend.* 2012 Jul 19. [Epub ahead of print]). Similar reductions in use of "legal designer drugs" has been reported following their proscription by the Drug Enforcement Agency (Madras, in press, 2012).

6. The Claim You'll Find Online: "Prohibition Does't Work" (Part II): Does Prohibition Cause the 'Gateway Effect?':

"U.S. and Dutch researchers, supported in part by NIDA, compared marijuana users in San Francisco, where non-medical use remains illegal, to Amsterdam, where adults may possess and purchase small amounts of marijuana from regulated businesses. Looking at such parameters as frequency and quantity of use and age at onset of use, they found no differences except one: lifetime use of hard drugs was significantly lower in Amsterdam, with its 'tolerant' marijuana policies. For example, lifetime crack cocaine use was 4.5 times higher in San Francisco than Amsterdam. Reinerman, C, Cohen, PDA, and Kaal, HL. The Limited Relevance of Drug Policy: Cannabis in Amsterdam and San Francisco. *American Journal of Public Health.* Vol. 94, No. 5. May 2004. p. 836-842."

The Recent Research: No, Prohibition does not cause the ‘Gateway Effect.’

The risk for other illicit drug initiation appeared 21 times higher among cannabis experimenters and **124 times higher among daily cannabis users than among non-users**. Tobacco and alcohol use were associated with a greater risk of moving on to cannabis initiation (hazard ratio (HR)=1.2 for tobacco initiation, HR=2.6 for daily tobacco use and HR=2.8 for drunkenness initiation). The results of this study provide a confirmation of a stage process in drug use, mediated by cannabis and liable to lead to other illicit drug experiments. This is compatible with the literature on the gateway theory, but goes further by modelling the entire sequence of use. Other illicit drug experimentation could be a consequence of initial opportunity to use the more accessible illicit drug, cannabis. (Mayet A, Legleye S, Falissard B, Chau N. Cannabis use stages as predictors of subsequent initiation with other illicit drugs among French adolescents: use of a multi-state model. *Addict Behav.* 2012 Feb;37(2):160-6).

5. The Claim You’ll Find Online: “Oops, marijuana may prevent cancer” (Part I):

Federal researchers implanted several types of cancer, including leukemia and lung cancers, in mice, then treated them with cannabinoids (unique, active components found in marijuana). THC and other cannabinoids shrank tumors and increased the mice’s lifespans. Munson, AE et al. Antineoplastic Activity of Cannabinoids. *Journal of the National Cancer Institute.* Sept. 1975. p. 597-602.”

4. The Claim You’ll Find Online: “Oops, marijuana may prevent cancer” (Part II): In a 1994 study the government tried to suppress, federal researchers gave mice and rats massive doses of THC, looking for cancers or other signs of toxicity. The rodents given THC lived longer and had fewer cancers, “in a dose-dependent manner” (i.e. the more THC they got, the fewer tumors). NTP Technical Report On The Toxicology And Carcinogenesis Studies Of 1-Trans- Delta-9-Tetrahydrocannabinol, CAS No. 1972-08-3, In F344/N Rats And B6C3F Mice, Gavage Studies. See also, “Medical Marijuana: Unpublished Federal Study Found THC-Treated Rats Lived Longer, Had Less Cancer,” *AIDS Treatment News* no. 263, Jan. 17, 1997.”

3. The Claim You’ll Find Online: “Oops, marijuana may prevent cancer” (Part III):

Researchers at the Kaiser-Permanente HMO, funded by NIDA, followed 65,000 patients for nearly a decade, comparing cancer rates among non-smokers, tobacco smokers, and marijuana smokers. Tobacco smokers had massively higher rates of lung cancer and other cancers. Marijuana smokers who didn’t also use tobacco had no increase in risk of tobacco-related cancers or of cancer risk overall. In fact their rates of lung and most other cancers were slightly lower than non-smokers, though the difference did not reach statistical significance. Sidney, S. et al. Marijuana Use and Cancer Incidence (California, United States). *Cancer Causes and Control.* Vol. 8. Sept. 1997, p. 722-728.”

2. The Claim You’ll Find Online: “Oops, marijuana may prevent cancer” (Part IV): Donald Tashkin, a UCLA researcher whose work is funded by NIDA, did a case-control study comparing 1,200 patients with lung, head and neck cancers to a matched group with no cancer. Even the heaviest marijuana smokers had no increased risk of cancer, and had somewhat lower cancer risk than non-smokers (tobacco smokers had a 20-fold increased lung cancer risk). Tashkin D. Marijuana Use and Lung Cancer: Results of a Case-Control Study. *American Thoracic Society International Conference.* May 23, 2006.

The Recent Research Addressing Nos. 5, 4, 3 and 2: OOPS, MARIJUANA IS NOT GOOD FOR CANCER.

Accumulating evidence from single studies and meta-analyses of multiple studies indicates that smoked marijuana is associated with, or a causative agent in specific cancers. Yet, a growing body of evidence, in very early stages, has introduced a potential role for cannabinoids (not smoked marijuana) in the treatment of various cancers. Can these two seemingly contradictory data sets be reconciled? Foremost, it is necessary to exclude marijuana, as there is no credible evidence that smoked marijuana is an anti-tumor agent – in fact data show the opposite.

Secondly, the promise of cannabinoids as anti-tumor agents are derived principally from preclinical research, using either cultured cells (cells growing in a petri dish) derived from human or rodent tumors or mouse tumor models. Both are insufficient to satisfy stringent criteria to approve use of cannabinoids in humans. Third, there are contradictory studies from cell cultures, showing that THC potentiates or inhibits tumor proliferation, as a function of tumor type and its pathology.

Finally, after all the prolific preclinical research, there is but one small Phase I trial of nine patients with brain cancer, treated with direct infusions of THC (2006). No follow-up, no replications. Surprisingly, this study was a highlight of a glowing report of cannabinoids as anti-tumor agents by Martin E. Lee of the *Daily Beast* (Sept 6, 2012).

I begin with the Guzman study (2006) and contrast it with the report from the *Daily Beast*. In viewing the association of smoked marijuana and cancer risk, it should be pointed out, that this is not the only or most important risk of marijuana to health and well-being. Guzmán M, Duarte MJ, Blázquez C, Ravina J, Rosa MC, Galve-Roperh I, Sánchez C, Velasco G, González-Feria L. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer*. 2006 Jul 17;95(2):197-203.

Guzman study In this pilot Phase I safety study, nine male and female patients with aggressive glioblastomas has two surgeries and then were treated with 1 or more infusions into the tumor site with Delta(9)-Tetrahydrocannabinol (THC). The mean life span of the patients was 24 weeks after initiation of the THC, with the shortest life span 9 weeks and the longest 53 weeks. Apparently THC did not extend the life span of these patients, although a placebo control group was not used for comparison. In only 2 patients, THC decreased tumour-cell staining. The authors conclude that THC “is not the most appropriate cannabinoid agonist for future antitumoral strategies owing to its high hydrophobicity, relatively weak agonistic potency and ability to elicit CB1-mediated psychoactivity”. “Owing to the characteristics of this study the effect of THC on patient survival was unclear, and an evaluation of survival would require a larger trial with a different design”. “a few studies have shown that THC may induce proliferation of tumour cells in vitro and in vivo”. The most parsimonious conclusion of the study was that THC did not facilitate tumor growth (but there was no comparative group to confirm this assertion) and that THC did not decrease patient survival, at least in the cohort of brain tumor patients expressing cannabinoid receptors.

***Daily Beast* (Sept 6, 2012), Martin E. Lee:** “A team of Spanish scientists led by Manuel Guzman conducted the first clinical trial assessing the antitumoral action of THC on human beings. Guzman administered pure THC via a catheter into the tumors of nine hospitalized patients with glioblastoma, who had failed to respond to standard brain-cancer therapies. The

results were published in 2006 in the British Journal of Pharmacology: (Actually, British Journal of Cancer). THC treatment was associated with significantly reduced tumor cell proliferation in *every test subject.*” (Actually, all patients died, average duration 24 weeks, and only two showed any signs of improvement – 1 with one episode of the treatment, the other with six episodes of treatment).

Conclusions

- Intervention with THC in 9 patients harboring this aggressive brain tumor was a failure.
- **The *Daily Beast* misrepresented the findings of the study.**
- Guzman et al, stated they would follow up with “our next goal is to evaluate the efficacy of THC in patients with newly diagnosed glioblastoma multiforme”, but 6 years later there is no follow up.
- No other investigator has rushed in to confirm, to extend the number of patients, to convert this trial in a placebo-controlled trial.

Is smoked marijuana associated with increased risk of cancer?

1. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer*. 2012 Sep 10. doi: 10.1002/cncr.27554. [Epub ahead of print] Testicular germ cell tumor (TGCT) incidence increased steadily in recent decades, but causes remain elusive. Germ cell function may be influenced by cannabinoids, and 2 prior epidemiologic studies reported that the use of marijuana may be associated with nonseminomatous TGCT.

Methods: 163 patients who were diagnosed with TGCT in Los Angeles County from December 1986 to April 1991 were enrolled, and 292 controls were matched on age, race/ethnicity, and neighborhood.

Results: Compared with never use, ever use of marijuana had a 2-fold increased risk, whereas ever use of cocaine had a negative association with TGCT. A specific association of marijuana use with nonseminoma and mixed histology tumors increased risk 2.42 fold or 240%).

Conclusions: The current results warrant mechanistic studies of marijuana’s effect on the endocannabinoid system and TGCT risk and caution that recreational and therapeutic use of cannabinoids by young men may confer malignant potential to testicular germ cells. *Cancer* 2012. © 2012 American Cancer Society.

2. Daniel W. Bowles, Cindy L. O’Bryant, D. Ross Camidge, Antonio Jimeno. The intersection between cannabis and cancer in the United States. *Critical Reviews in Oncology/Hematology*, Vol 83, Issue 1, July 2012, Pages 1–10

One of the principle concerns of the use of cannabinoids, particularly inhaled marijuana, is carcinogenic potential. Cannabis smoke is carcinogenic in rodents and mutagenic in the Ames test (a cancer test routinely performed for candidate medications in rodents, before drug testing in humans). Cannabis smoke contains several of the same carcinogens as tobacco smoke, at up to 50% higher concentrations and with three times the tar per cigarette. Respiratory mucosa exposed to chronic cannabis smoke shows pre-neoplastic histological and molecular changes. Despite this in vitro and in vivo evidence, however, it has been difficult to strongly correlate cannabis use and the development of human cancers.

Head and neck squamous cell carcinoma (HNSCC) risk and cannabis are inconsistent.

Three studies have found a statistically significant increased risk of HNSCC in cannabis users – 2.6-fold increased risk of HNSCC compared with blood-bank controls when adjusted for cannabis dose, duration of use, and confounding variables such as alcohol or tobacco use.

Similarly, heavy cannabis smokers in Northern Africa had a 2.62 increased risk for nasopharyngeal carcinomas. A recent study found that human papilloma virus HNSCC was associated with increased cannabis smoking intensity, and cumulative joint-years, due to cannabis-induced immune suppression through CB2? Seven studies, 4 small, others larger found no association. At this point the majority of studies do not support the hypothesis that smoked cannabis is strongly associated with an increased risk of HNSCC, once tobacco and alcohol intake are controlled, though smoked cannabis may raise the risk of HPV-16-associated HNSCC.

Lung cancer A systematic review evaluating 19 studies from 1966 to 2006 found no significant tobacco-adjusted association between cannabis smoking and lung cancer development despite evidence of precancerous histopathologic changes of the respiratory mucosa. However, a pooled analysis of three studies of male cannabis smokers in North Africa found that the risk for developing lung cancer was increased 2.4 times, for ever cannabis smokers. A case control study of patients with lung cancer under 55 years of age in New Zealand found an 8% increased risk for each joint-year (one joint/day/year) of cannabis use. This effect persisted only in the highest tertile of cannabis use (>10.5 joint-years of exposure) when adjusted for tobacco use (risk 5.7 fold).

A study of 65,855 members of a U.S. health management organization (HMO) that classified member as experimenters (six or fewer lifetime usages), former users, or current users found no increased risk of HNSCC, **lung, colorectal, melanoma, or breast cancers** in current or former cannabis smokers versus never smokers or experimenters when controlled for tobacco use, alcohol intake, and socioeconomic status.

Prostate and cervical cancer There was a trend towards increased prostate cancer (3-fold risk), and cervical cancer (1.4 fold risk).

Glioma A U.S. study of 105,005 HMO members found an increased risk of malignant primary gliomas (2.8 fold or 280% increased risk), in people who smoked cannabis once per month or more.

Bladder cancer and testicular germ cell cancer Smaller studies have implicated cannabis use in the development of bladder cancer and testicular germ cell tumors. The reasons for the great heterogeneity in epidemiologic studies correlating cannabis use and cancer may be related to difficulties in quantifying cannabis use, unmeasured confounders in the cases or controls, and variable expression of cannabinoid receptors in target tissues.

Conclusions

- Smoked marijuana is associated with an elevated risk for certain cancers.
- There is no future in smoked marijuana as an anti-tumor therapy.
- How do cannabinoids act biologically, and can these mechanisms portend safe and effective anti-tumor agents?

Some background tips on understanding why CB1 and CB2 are so important

The brain and body have a cannabinoid signaling system. What does this mean? Cells communicate with each other by releasing chemical messages, with the brain the master communication system. Each signal has three main components: a chemical message, an interpreter (receptor) that receives the message and interprets it, and a transport system that “deletes” the message once sent and processed. The brain and body produce their own chemical messages (such as dopamine or serotonin). Drugs (such as THC or LSD or amphetamine or morphine) resemble these messages (imposters) and can bind to the receptor. When a message binds to the receptor, it undergoes a change in shape and triggers a cascade of changes in cells in the brain activity, or immune system, or blood vessels and other tissues. Incidentally, the

signaling process involves more than a hundred other components that orchestrate this exquisite process.

The CB2 receptor, which does not produce psychoactive effects, is the critical mediator of anti-tumor activity. The body produces two types of cannabinoid targets or receptors, the CB1 and CB2 receptors (and quite a few others) that become active in the presence of cannabinoids (THC, cannabidiol, 2-AG, anandamide, etc). Whether the cannabinoids arise from the body itself (endocannabinoids), are made by plants (phyto-cannabinoids from marijuana) or made in a medicinal chemistry laboratory (synthetic cannabinoids), cannabinoids have different effects at these receptors. THC binds equally well to CB1 and CB2, while others do not. Interestingly, the majority of cannabinoids that display anti-tumor activity in cell culture act through the CB2 receptor. This is a critical discovery, because the CB2 receptor does not trigger psychoactive effects, memory cognitive, impairment, etc.

Some tips on assessing the research studies: There is some evidence from in cell culture (cells growing on a petri dish) and from whole body experiments, that cannabinoids promote cancer and evidence that they protect cells from cancer. A few critical questions should be asked when evaluating the validity of these reports:

Is the anti-tumor effect seen only if cells are exposed to concentrations of THC or other cannabinoids that are unrealistically high compared to levels reached with ingested or inhaled marijuana? Why is this a problem? In certain experiments in this field, the concentrations of THC or other cannabinoids are much higher than levels found in blood after smoking marijuana or cannabinoids. For example, a 6.8% THC marijuana cigarette generates a plasma blood level of 0.24 uM in humans (MW of THC is 314.45). Yet some researchers strongly advocating for the anti-tumor effect of THC used THC at 5 uM concentration in cell cultures to detect an anti-tumor effect. This concentration is 20 times higher than the tumor would be exposed to in a living human who smoked a high dose (6.8%) marijuana cigarette.

Is the anti-tumor effect observed in whole animals – not only in cultured cells? Many factors, including metabolism are among the “absent elephants” in petri dishes. The body can convert THC and the other 60+ cannabinoids in marijuana smoke to a myriad of metabolites which may work in the opposite direction of THC or other cannabinoids. You would not be able to observe this in cell culture.

Is the effect observed with a single cannabinoid, or with smoked marijuana that has more than 60 cannabinoids? No biomedical scientist would attempt to promote a treatment for cancer that contains >400 compounds, 60 of which are cannabinoids.

Is a selective CB2 cannabinoid as effective or exclusively effective compared with a CB1 cannabinoid? This is important because some evidence suggests the anti-tumor effects are mediated largely by the CB2 receptor – **THE ONE THAT PRODUCES NO PSYCHOACTIVE EFFECTS**. So theoretically, it is possible to design a CB2 agent without the psychoactive properties of THC.

The key question: Has the effect been observed only in mice, or also in men? Unless effectiveness is shown in Phase I, II, III randomized controlled multi-center clinical trials (in

patients without a history of marijuana use) and approved by FDA, there is no meaningful evidence to support patient use of cannabinoids for this purpose.

Conclusions

- It is critical to view the details of manuscripts that purport anti-tumor activity: cells, mice, or men? Appropriate concentrations, controls, outcomes?
- It is necessary to exercise caution in promoting anti-cancer drugs, for they can influence patient choices.

Do cannabinoids, not smoked marijuana, have potential for treating cancer?

Daniel J. Hermanson & Lawrence J. Marnett. Cannabinoids, endocannabinoids and cancer
Published online: Cancer Metastasis Rev (2011) 30:599–612. Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. Nat Rev Cancer. 2012 May 4;12(6):436-44.

Paraphrased below from manuscripts cited above

Breast cancer cells, expressing low levels of cannabinoid receptors, showed growth enhancement when exposed to cannabinoids, possibly due to altered immune response. Some studies suggest that abnormal regulation of the endocannabinoid system may promote cancer by fostering conditions that allow cancer cells to divide and migrate to other locations. For this reason, the endocannabinoid is a new target for pharmacological intervention in the treatment of cancer. Cannabinoids and the endocannabinoid system are implicated in inhibiting cancer cell proliferation and angiogenesis (growth of blood supply for the cancer), reducing tumor growth and metastases, and inducing apoptosis (programmed cell death) in these cells. Laboratories have observed that cannabinoids and endocannabinoids inhibit growth of several types of cancers in test tubes and in animal tumor models (glioma, glioblastoma, breast cancer, prostate cancer, thyroid cancer, colon carcinoma, leukemia, and lymphoid tumors). These have been inhibited by natural (plant derived) or synthetic cannabinoids or endocannabinoids (made by the body), or cannabinoids that block natural processing of endocannabinoids.

Non-psychoactive cannabinoids – not smoked marijuana – that target the CB2 receptor have potential as anti-tumor agents. The CB2 receptor is non-psychoactive.

Modulation of the endocannabinoid system to treat cancer. Modulation of the body's own cannabinoids has been shown in some studies to affect tumor cells while not affecting normal cells (many anti-cancer agents have more robust effects on tumor cells).

CB2 may be more important than CB1 in mediating cannabinoids' anti-cancer activity.

Recall that the CB2 has no psychoactive effects. High concentrations of anandamide or methanandamide, made by the body, killed prostate cancer cells, but tumor growth was inhibited exclusively through CB2.

CB2 may be more important than CB1 in mediating cannabinoids' anti-cancer activity.

JWH-133, by selective activity at CB2, produced programmed cell death in a brain tumor model (glioblastoma).

CB2 may be more important than CB1 in mediating cannabinoids' anti-cancer activity.

In a mouse model of human positive breast cancer, THC and JHW-133 decreased tumor size and lung metastasis via CB2.

The anti-cancer effects of cannabidiol may occur completely independently of cannabinoid receptor activation. Cannabidiol (non psychoactive) is effective in tumor models.

Cannabidiol together with temozolomide produces a striking reduction in the growth of glioma even when low doses of THC are used.

Cannabidiol has also been shown to alleviate some of the undesired effects of THC administration, such as convulsions, discoordination and psychotic events, and, therefore, improves the tolerability of cannabis-based medicines.

Some other cannabinoids in marijuana might attenuate the psychoactive side effects of THC or might even produce other therapeutic benefits.

Although there is accumulating data from test tube studies (cell culture), and some in living mice, there is scant, insufficient, inadequate clinical data on cannabinoid effects on cancer treatment in living humans. This is puzzling, as many cannabinoids have been tested in non-human model systems. In one clinical phase I study, the safety and efficacy of THC in patients with refractory glioblastoma was assessed. A total of **nine patients** underwent tumor surgery to remove the bulk tumor, then had a catheter perfuse THC into the cavity daily for 10–64 days for total doses ranging from 0.80 to 3.29 mg. One patient had mild psychotropic effects but it was otherwise well-tolerated. No significant conclusions can be extracted from nine patients, but some patients responded, at least partially, to THC treatment in terms of decreased tumor growth rate.

Further preclinical and clinical studies are required to fully define cannabinoids' potential as anti-cancer agents.

Conclusions

- Smoked marijuana is associated with increased risk for cancer, and not with potential as an anti-tumor agent.
- Preclinical research demonstrates that some cannabinoids have anti-tumor activity.
- The activity is mainly at the CB2 receptor, which has no psychoactive effects. Drugs selective for this receptor (and for other non- CB targets) may have a therapeutic role in tumor regression.
- More preclinical research is needed, to define with precision, which class of cannabinoids will function and how genotypes may affect therapeutic benefit.
- It is premature to surmise that cannabinoids will succeed as anti-tumor agents, until rigorous Phase III clinical trials in human subjects display therapeutic potential.

Does Marijuana have any role in cancer treatment?

Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. J Natl Compr Canc Netw. 2012 Apr;10(4):487-92.

Chemotherapy-induced nausea Before the introduction of the serotonin receptor antagonists (5-HT₃ receptor antagonists) in the early 1990s, limited effective options were available to prevent and treat chemotherapy-induced nausea and vomiting (CINV). In 1985, the FDA approved 2 cannabinoid derivatives, dronabinol and nabilone, for the treatment of CINV not effectively treated by other agents. Today, the standard of care for prevention of CINV for highly and moderately emetogenic chemotherapy is a 5-HT₃ receptor antagonist, dexamethasone, with or without aprepitant or fosaprepitant. With the approval of safer and more effective agents, cannabinoids are not recommended as first-line treatment for the prevention of CINV and are reserved for patients with breakthrough nausea and vomiting. Because of medical and legal concerns, the use of marijuana is not recommended for management of CINV and is not part of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis. Although patients may like to pursue this treatment option in states that have approved the use of marijuana for medical purposes, its use remains legally and therapeutically controversial.

Pain suppression There are little data regarding inhaled cannabis or cannabis extract in comparison to conventional pain medications for cancer related or chronic non-neuropathic pain. A systematic review of single dose studies of dronabinol, nabilone, and levonandradol found them to be as effective as 50–120 mg of oral codeine. One study found nabilone to be less effective than modest doses of dihydrocodeine in patients with neuropathic pain and has less desirable side effects. No studies comparing inhaled or ingested cannabis to conventional analgesics could be identified. Therefore, it appears that inhaled cannabis and pharmaceutical cannabinoids are more effective than placebo in treating neuropathic pain, but their effectiveness compared to conventional pain medications is uncertain.

Appetite enhancement A recent double-blinded, randomized, 46 patient study suggested that cancer patients with altered chemosensory had increased pre-meal appetite and improved taste when given dronabinol (THC) compared to placebo. However, large randomized studies have been discouraging. In a randomized trial of patients with cancer-associated anorexia, low dose dronabinol as a single agent or in combination with high dose megestrol, a synthetic progestin, was less effective at generating weight gain and improving quality of life than megestrol alone. A subsequent randomized, double blinded trial from Europe for patients with cancer-associated anorexia found no difference in weight gain or quality of life at 6 weeks for patients treated with cannabis extract or THC compared to patients given placebo. Patients given cannabinoids had increased side effects. The data for cannabinoids in cancer-associated anorexia based on these three randomized studies are weak and the data for inhaled cannabis for cancer-associated cachexia are lacking.

Nausea and vomiting Since the CINV systematic review the use of 5-hydroxytryptamine 3 receptor and proachykinin antagonists have been major advances in the treatment of acute and chronic CINV. The current American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines do not recommend cannabinoids as first-line therapies.

1. The Claim You'll Find Online: Marijuana does have medical value.

“In response to passage of California’s medical marijuana law, the White House had the Institute of Medicine (IOM) review the data on marijuana’s medical benefits and risks. The IOM concluded, “Nausea, appetite loss, pain and anxiety are all afflictions of wasting, and all can be mitigated by marijuana.” While noting potential risks of smoking, the report acknowledged there is no clear alternative for people suffering from chronic conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. The government’s refusal to acknowledge this finding caused co-author John A. Benson to tell the New York Times that the government loves to ignore our report; they would rather it never happened. (Joy, JE, Watson, SJ, and Benson, JA. Marijuana and Medicine: Assessing the Science Base. National Academy Press. 1999. p. 159. See also, Harris, G. FDA Dismisses Medical Benefit From Marijuana. New York Times. Apr. 21, 2006)”

The Research: OOPS, SMOKED MARIJUANA DOES NOT HAVE A FUTURE AS MEDICINE.

Here is a review of the IOM report and more recent statements.

That same IOM report also said the following: “Smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.” Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.” “Chronic marijuana

smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cell lining the bronchial passageways, some of which may be premalignant. These respiratory symptoms are similar to those of tobacco smokers, and the combination of marijuana and tobacco smoking augments these effects.”

The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma.” Their recommendations were:

- 1. Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.
- 2. Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: Trial should involve only short-term marijuana use (less than six months), Should be conducted in patients with conditions for which there is reasonable expectation of efficacy, Should be approved by institutional review boards., Should collect data about efficacy.

Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (e.g., intractable pain or vomiting) **must meet the following conditions:**

- Failure of all approved medications to provide relief has been documented
- The symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs
- Such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness
- Involves an oversight strategy comparable to an institutional review board that could provide guidance within 24 hours of submission by a physician to provide marijuana to a patient for specified use.

Crude marijuana is considered a Schedule 1 drug, the most restrictive designation given by the Controlled Substances Act (CSA) that places all drugs regulated by federal law into one of five schedules. What this means is that marijuana has a high potential for abuse; it has no currently accepted medical use in treatment in the U.S.; it lacks the accepted safety for use of the drug under medical supervision; it cannot be prescribed by a doctor; it is not sold in a pharmacy; and is in the same category as heroin, LSD and Ecstasy (MDMA).

Crude marijuana has been rejected for medicinal use by many prominent national health organizations, including the American Medical Association, National Multiple Sclerosis Society, American Glaucoma Society, American Academy of Ophthalmology, American Cancer Society, National Eye Institute, National Institute for Neurological Disorders and Stroke and most importantly the Federal Food and Drug Administration (FDA).

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