DRUG FREE AUSTRALIA'S SUMMARY

OF THE US NATIONAL INSTITUTES OF HEALTH

2017 REVIEW

"THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS"

> **This summary is to facilitate the Australian public's understanding of the harms or benefits of cannabis, particularly in light of the spread of inaccurate information about the usefulness of medicinal cannabis, and in light of the push for cannabis legalisation.**

From page v & vi of the NIH report

COMMITTEE ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REVIEW AND RESEARCH AGENDA

MARIE C. McCORMICK (*Chair*), Sumner and Esther Feldberg Professor, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA

DONALD I. ABRAMS, Professor of Clinical Medicine, University of California, San Francisco, and Chief of Hematology–Oncology Division, Zuckerberg San Francisco General Hospital, San Francisco

MARGARITA ALEGRÍA, Professor, Departments of Medicine and Psychiatry, Harvard Medical School, and Chief, Disparities Research Unit, Massachusetts General Hospital, Boston

WILLIAM CHECKLEY, Associate Professor of Medicine, International Health, and Biostatistics, Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, MD

R. LORRAINE COLLINS, Associate Dean for Research, School of Public Health and Health Professions and Professor, Department of Community Health and Health Behavior, State University of New York at Buffalo–South Campus

ZIVA D. COOPER, Associate Professor of Clinical Neurobiology, Department of Psychiatry, Columbia University Medical Center, New York

ADRE J. dU PLESSIS, Director, Fetal Medicine Institute; Division Chief of Fetal and Transitional Medicine; and Director, Fetal Brain Program, Children's National Health System, Washington, DC

SARAH FELDSTEIN EWING, Professor, Department of Child and Adolescent Psychiatry, Oregon Health & Science University, Portland

SEAN HENNESSY, Professor of Epidemiology and Professor of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia

KENT HUTCHISON, Professor, Department of Psychology and Neuroscience and Director of Clinical Training, University of Colorado Boulder

NORBERT E. KAMINSKI, Professor, Pharmacology and Toxicology, and Director,

Institute for Integrative Toxicology, Michigan State University, East Lansing

SACHIN PATEL, Associate Professor of Psychiatry and Behavioral Sciences, and of Molecular Physiology and Biophysics, and Director of the Division of Addiction Psychiatry, Vanderbilt University Medical Center, Nashville, TN

DANIELE PIOMELLI, Professor, Anatomy and Neurobiology, School of Medicine and Louise Turner Arnold Chair in Neurosciences, Department of Anatomy and Neurobiology, University of California, Irvine

STEPHEN SIDNEY, Director of Research Clinics, Division of Research, Kaiser Permanente Northern California, Oakland

ROBERT B. WALLACE, Irene Ensminger Stecher Professor of Epidemiology and Internal Medicine, Department of Epidemiology, University of Iowa Colleges of Public Health and Medicine, Iowa City

JOHN WILEY WILLIAMS, Professor of Medicine, Duke University Medical Center, Durham, NC

Study Staff

LEIGH MILES JACKSON, Study Director
JENNIFER A. COHEN, Program Officer
KELSEY GEISER, Research Associate (*from July 2016*)
R. BRIAN WOODBURY, Research Associate
SARA THARAKAN, Research Associate (*until July 2016*)
MATTHEW MASIELLO, Research Assistant (*from June 2016*)
MARJORIE PICHON, Senior Program Assistant (*from August 2016*)
HOPE R. HARE, Administrative Assistant
DORIS ROMERO, Financial Officer
KATHLEEN STRATTON, Scholar (Advisor)
ROSE MARIE MARTINEZ, Senior Board Director, Board on Population Health and Public Health Practice

Norman F. Grant/American Board of Obstetrics and Gynecology Fellow

BROWNSYNE TUCKER EDMONDS, Assistant Professor of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis

Consultants

STEVEN DAVENPORT, BOTEC Analysis Corporation
TAMAR LASKY, MIE Resources, Maryland
LEANN LOCHER, LeAnn Locher and Associates
GUILLERMO MORENO-SANZ, University of California, Irvine
BRYCE PARDO, BOTEC Analysis Corporation
ROBERT POOL, Editor

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Eric Bass, Johns Hopkins University

Jonathan P. Caulkins, Carnegie Mellon University

Mary D'Alton, Columbia University Medical Center

Eden Evins, Massachusetts General Hospital

Frank F. Furstenberg, Jr., University of Pennsylvania

Raul Gonzalez, Florida International University

Igor Grant, University of California, San Diego, School of Medicine

Mark Helfand, Oregon Health & Science University

David A. Kessler, University of California, San Francisco

John H. Krystal, Yale University School of Medicine

Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

MEDICINAL CANNABIS – National Institutes of Health 2017 Conclusions

National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. The National Academies Press. Kindle Edition

There is conclusive or substantial evidence that cannabis or cannabinoids are effective for:

Condition	Research	Mode of administration	Limitations
Chronic pain (4-1)	5 reviews 2 additional studies	22 studies plant based cannabinoids (13 x nabiximols, 5 x plant flower, 3 x oramucosal spray, 1 x oral THC, 5 x synthetic THC nabilone	"It is worth noting that the conclusions across all the reviews were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain."
Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (4-3)	3 reviews	Nabilone Tetrahydrocannabinol Levantradol Dronabinol Nabiximols	Nabilone and dronabinol "were both found to be superior to placebo and equivalent to antiemetics at the time." (1980s) "Dronabinol equivalent to ondansetron . . . although no comparison to the currently more widely used neurokinin-1 inhibitors has been conducted."
multiple sclerosis spasticity symptoms (4-7a)	2 reviews, 1 additional study	Oral cannabis extract Nabiximols Orally administered THC	"The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale."

There is moderate evidence that cannabis or cannabinoids are effective

Condition	Research	Mode of administration	Limitations
Improving **short-term sleep outcomes** in individuals with sleep	1 review	Nabilone Dronabinol Nabiximols	There was only one comparison study against something other than placebo, amitriptyline, which is a second-line treatment when there is "availability of newer, more effective treatments

Condition		Mode of administration	Limitations
disturbance associated with **obstructive sleep apnea syndrome**, **fibromyalgia, chronic pain, and multiple sclerosis** (4-19)		THC/CBD capsules Smoked THC	that have fewer adverse effects."

There is moderate evidence of a statistical association between cannabis smoking

Condition	Research	Mode of administration	Limitations
Improved airway dynamics with acute use, but not with chronic use (7-1a)	1 review various additional studies	Smoked cannabis	"Overall, acute cannabis use was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly." "While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology."
Higher forced vital capacity (FVC) (7-1b)	1 review various additional studies	Smoked cannabis	"Overall, acute cannabis use was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly." "While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology."
Better cognitive performance among individuals **with psychotic disorders** and a history of cannabis use (12-2a)	3 reviews	Cannabis use	"Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients

			with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of memory, learning, and attention."

There is limited evidence that cannabis or cannabinoids are effective

Condition	Research	Mode of administration	Limitations
Increasing appetite and decreasing weight loss associated with HIV/AIDS (4-4a)	2 reviews	Dronabinol Inhaled cannabis	"There have not been any randomized controlled trials conducted studying the effect of plant-derived cannabis on appetite and weight with weight as the primary endpoint. This is, in part, due to existing obstacles to investigating the potential therapeutic benefit of the cannabis plant."
Improving clinician-measured **multiple sclerosis spasticity symptoms** (4-7a)	2 reviews 1 additional study	Nabiximols Nabilone Oral THC/CBD Oral cannabis extract	"The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices such as the modified Ashworth scale in patients with MS."
Improving symptoms of **Tourette syndrome** (4-8)	2 reviews 2 additional studies with 4 reports	THC capsules	"However, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect."
Improving **anxiety symptoms**, as assessed by a public speaking test, in individuals with social anxiety disorders (4-17)	1 review	CBD	"These positive findings are limited by weaknesses in the study design (e.g., an inadequate description of randomization and allocation concealment), a single dose of CBD, and uncertain applicability to patients with other anxiety disorders. Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms. In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety

			symptoms and heavy cannabis use is associated with social phobia disorder."
Improving symptoms of **posttraumatic stress disorder** (4-20)	1 study Extra studies in process	Nabilone	"Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period."

There is limited evidence of a statistical association between cannabinoids

Condition	Research	Mode of administration	Limitations
Better outcomes (i.e., mortality, disability) after a **traumatic brain injury or intracranial hemorrhage** (4-15)	2 studies	Cannabis use – not otherwise stated	". . . more conclusive observational studies or randomized controlled trials will be necessary before any conclusions can be drawn about the neuroprotective effect of cannabinoids in clinical populations."
A **decrease** in the production of several **inflammatory cytokines** in healthy individuals (8-1a) smoked cannabis	4 studies	Cannabis use Dronabinol	"The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence."

There is limited evidence that cannabis or cannabinoids are ineffective

Condition	Research	Mode of administration	Limitations
Improving symptoms associated with **dementia** (4-13)	2 reviews 1 additional study	Dronabinol Oral THC	

Improving intraocular pressure associated with **glaucoma** (4-14)	1 review	THC oromucosal spray CBD oromucosal spray	"The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma."
Reducing **depressive symptoms** in individuals with chronic pain or multiple sclerosis (4-18)	1 review	Nabiximols Dronabinal Nabilone	Although patients report using cannabinoids for depression, our search for a good-quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There are no trial data addressing the effects of cannabinoids for major depressive disorder."

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment

Condition	Research	Mode of administration	Limitations
Cancers, including glioma (4-2)	1 review	No extra studies beyond the one review	"The review focused exclusively on the anti-tumor effects of cannabinoids on gliomas." "The signal from the preclinical literature suggests that clinical research with cannabinoids needs to be conducted."
Cancer-associated **anorexia cachexia syndrome and anorbnexia nervosa** (4-4b)	3 studies	Cannabis extract THC	"Increased appetite was reported by 73 percent of the cannabis-extract, 58 percent of the THC group, and 69 percent of the placebo recipients." "Megestrol acetate was superior to dronabinol for the improvement of both appetite and weight, with the combination therapy conferring no additional benefit."

Symptoms of **irritable bowel syndrome** (4-5)	1 study	Dronabinol	"The quality of evidence for the finding of no effect for irritable bowel syndrome is insufficient based on the short treatment duration, small sample size, short-term follow-up, and lack of patient-reported outcomes."
Epilepsy (4-6)	2 reviews 2 case series	CBD CBD/THC	"Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence of efficacy."
Spasticity in patients with paralysis due to **spinal cord injury** (4-7b)	2 reviews 1 additional study	Nabiximols Nabilone Oral THC Oral THC/CBD	"Given the lack of published papers reporting the results of trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population."
Symptoms associated with **amyotrophic lateral sclerosis** (4-9)	1 study	Dronabinol	"Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated."
Chorea and certain neuropsychiatric symptoms associated with **Huntington's disease** (4-10)	1 review	Nabilone CBD	"Both studies were of short duration and likely underpowered because of their small sample sizes."
Motor system symptoms associated with **Parkinson's disease or the levodopa-induced**	1 review 2 studies	THC/CBD Nabilone CBD Smoked cannabis	"Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample

dyskinesia (4-11)			size limits the interpretation of the data. An observational study of inhaled cannabis demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations."
Dystonia (4-12)	1 review 1 additional study	Dronabinol Nabilone	"Two small trials of dronabinol and nabilone failed to demonstrate a significant benefit of the cannabinoids in improving dystonia compared with placebo. Cannabis has not been studied in the treatment of dystonia. Cannabis has not been studied in the treatment of dystonia."
Achieving **abstinence** in the use of addictive substances (4-16)	2 reviews	Dronabinol Nabiximols Inhaled CBD	"Based on the systematic reviews, neither of the two trials evaluating the efficacy of a cannabinoid in achieving or sustaining abstinence from cannabis showed a statistically significant effect. However, given the limited number of studies and their small size, their findings do not definitively rule out the existence of an effect."
Mental health outcomes in individuals with **schizophrenia or schizophreniform psychosis** (4-21)	2 reviews	CBD	"These studies provide only limited evidence due to the risk of bias, the short-term follow-up, and the evaluation of a single cannabinoid. Furthermore, the larger trial was designed to detect a moderate benefit of cannabidiol compared to the antipsychotic amisulpride, but it enrolled only 60 percent of the planned sample. Thus, it did not have the statistical power to detect small or moderate differences between CBD and amisulpride."

There is substantial evidence of a statistical association

Condition	Research	Mode of administration	Limitations
cannabis smoking and **worse respiratory**	1 review 5 additional studies	Cannabis smoking	"Cannabis smoking cessation was temporally associated with the resolution of chronic bronchitis symptoms, and a small

symptoms and more **frequent chronic bronchitis** episodes (7-3a)			feasibility study suggests that use of a vaporizer instead of smoking cannabis may lead to the resolution of respiratory symptoms."
Increased risk of **motor vehicle crashes** (9-3)	6 reviews	Cannabis use	"A missing component in this review (, Rogeberg and Elvik (2016)) is a better determination of the dose at which driving becomes sufficiently unsafe as to increase MVC risk."
Lower birth weight of the offspring – maternal smoking (10-2)	1 review 10 additional studies	Cannabis use	"The findings for birth weight are consistent with the effects of non-cannabinoid substances in smoked cannabis and cigarette smoking. It has been shown in several studies that the increases in carbon monoxide, with elevated carboxyhemoglobin blood levels, may be up to fivefold higher after marijuana than cigarettes.1'
The development of **schizophrenia** or other psychoses, with the highest risk among the most frequent users (12-1)	5 reviews 4 additional studies	Cannabis use	"The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors."
Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is **not a risk factor** for the development of problem cannabis use (13-2e)	1 review	Cannabis ever used Cannabis dependence	"One significant limitation of any conclusions drawn from the current literature is that the data on cannabis use, other drug use, and the symptoms of problem cannabis use are derived from self-reports."

Being male and smoking cigarettes are **risk factors** for the progression of cannabis use to problem cannabis use (13-2i)	Data from NLAES Data from NLSAH Data from NHSDA	Cannabis dependence	
Initiating **cannabis use at an earlier age** is a **risk factor** for the development of problem cannabis use (13-2j)	4 studies	Cannabis dependence	
Increases in cannabis use frequency and the progression to developing **problem cannabis use** (13-1)	5 studies	Cannabis dependence	"The limitations of these studies include the reliance on self-reported cannabis use, the fact that data were restricted to two time points of assessment separated by 3 years, and that the findings are based on epidemiological data obtained more than 10 years ago. A significant issue with relying on self-report methodologies to ascertain problem cannabis use is that this requires that the respondent have insight into the fact that cannabis is actually causing problems in order to meet criteria for cannabis abuse/dependence (as per the DSM-IV) or CUD (as per the DSM-V)."
Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)	4 studies	Cannabis dependence	

There is moderate evidence of/ or there is a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations/Other
Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)	10 studies	Cannabis use including edible	"Collectively, these findings indicate that state-based legalization of cannabis is associated with a subsequent increase in pediatric cannabis exposures in those states." "Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may over-represent serious cases or cases from states where cannabis is legal."
The **impairment in the cognitive domains of learning, memory, and attention** (11-1a)	Learning - 3 reviews memory - 3 reviews cognition - 4 reviews	Cannabis use	
Increased symptoms of **mania and hypomania** in individuals diagnosed with bipolar disorders (12-4)	1 review 2 additional studies	Cannabis use	"Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem."
A small increased risk for the development of **depressive disorders** (12-5)	2 reviews, 7 additional studies	Cannabis use	"Although the supplemental studies from the primary literature reported mixed findings, the committee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran et al., 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62;"
Increased incidence of **suicidal ideation** and suicide attempts with a	2 reviews one additional study	Cannabis use	"The studies presented demonstrate evidence of a dose–response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts."

higher incidence among heavier users (12-7a)			"Several limitations should be noted, including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose–response analyses, and problems of small sample size."
Increased incidence of suicide completion (12-7b)	2 reviews 1 additional study	Cannabis use	"However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicide attempts without these symptoms."
Increased incidence of social anxiety disorder (12-8b)	1 review 8 additional studies	Cannabis use	"Some of the limitations of these studies are that cannabis use was ascertained by self-report; that causality cannot be established because of the possibility of residual confounding; that the follow-up period was limited to 3 years; and that there was a high loss in the follow-up and limited power to detect small effects.
Anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use (13-2b)	Anxiety - 1 review Psychopathology – 5 studies	Cannabis use	"It is important to highlight that the studies reviewed above vary in their age grouping and generally include populations that cross from late adolescence into young adulthood." "Another concern is that the structured interviews used to assess baseline dependent variables (i.e., mental health) and outcomes (i.e., problem cannabis use) vary between studies, and even for some longer longitudinal studies, within individual studies."
Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)	Psychopathology – 5 studies	Cannabis use	

Adolescent ADHD is not a risk factor for the development of problem cannabis use (13-2d)	1 review	Cannabis use	"Some suggestion of publication bias was noted, and heterogeneity was noted in the group of nine studies with data about marijuana abuse or dependence."
Being male is a risk factor for the development of **problem cannabis use** (13-2f)	4 studies	Cannabis use	"However, it is not known if differences between men and women would have emerged if a shorter time frame from cannabis use onset had been explored."
Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)	2 studies	Cannabis use	"The rate of developing cannabis dependence within 24 months of first cannabis use was doubled among respondents who had experience with three or more other drugs (tobacco, alcohol, and other drugs) prior to cannabis use (adjusted risk ratio [aRR] = 2.2; 95% CI = 1.1–4.3; p = 0.03)"
Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)	2 studies	Cannabis use	
During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental	9 studies	Cannabis use	

substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are **risk factors** for the development of problem cannabis use (13-2k)			
A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)	3 studies	Cannabis use	"In addition to the limitations cited for the first two sections such as issues with self-reported cannabis use, the respondents' reporting of symptoms of problem cannabis use, and data restricted to trends of cannabis use and cannabis strength that do not accurately reflect current trends, the current findings are additionally restricted to limited followup with participants and to only a few of the risk factors highlighted in the second section, including biological sex."
Problem cannabis use and **increased severity of posttraumatic stress disorder symptoms** (13-3c)	3 studies	Cannabis use	"It should be noted, however, that these are cross-sectional data and that the directionality and causality of these associations cannot be determined."
The **development of substance dependence** and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)	Alcohol – 2 studies Opioids – 1 study Tobacco – 1 study Mixed drug use – 3 studies		"With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions 1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the

			potential for self-report bias."

There is moderate evidence of no statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Incidence of **lung cancer** (5-1)	1 review 1 additional study	Cannabis use	"Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking; the study did not adjust or account for tobacco or cannabis during the 40-year follow-up period; the authors were unaware whether study participants mixed tobacco and cannabis; and the self-reporting process was not anonymized."
Incidence of **head and neck cancers** (5-2)	1 review	Cannabis use	"First, although a nonsignificant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers."

Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)	3 studies	Cannabis use	"With regard to negative symptoms, the data reviewed were generally more homogenous, with most studies reporting either an absence of association between cannabis use and negative symptoms or else reduced negative symptoms in cannabis users."

There is limited evidence that/ or there is a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Non-seminoma-type **testicular germ cell tumors** (5-3)	2 reviews	Cannabis use	"First, each of the three case-control studies informing the review relied on self-report without biological validation," "bias. Second, two of the studies reported response rates that were both low and unequal:" "Third, the high and growing prevalence of cannabis use in the general population may render the category "ever-smoker" uninformative," "A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders:"
The triggering of **acute myocardial infarction** (cannabis smoking) (6-1a)	3 reviews provided descriptive background 2 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use."
Ischemic stroke or subarachnoid hemorrhage (6-2)	5 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g., smoked, edible, etc.); the absence of information on dose, including accounting for the

			content of THC and other cannabinoids and potential additives or contaminants; and the lack of information on the total lifetime duration/dose of cannabis use."
Decreased risk of metabolic syndrome and **diabetes** (6-3a)	Metabolic syndrome -3 studies Diabetes – 3 studies	Cannabis use	"As noted earlier, these are counterintuitive findings because THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis."
Increased risk of prediabetes (6-3b)	1 study	Cannabis use	
An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (7-2a)	6 studies	Cannabis smoking	"Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users."
Pregnancy complications for the mother (10-1)	1 review 3 additional studies	Cannabis use	"Despite identifying one good- to fair-quality systematic review addressing pregnancy complications for the mother, the findings of the review must be interpreted with caution. The review relied on a primary literature that is limited in the number, quality, and rigor of the studies that have been carried out to date."
Admission of the infant to the **neonatal intensive care unit** (NICU) (10-3)	1 review 1 study	Cannabis use	"Findings related to health care use, such as the increase in NICU admissions, need to be treated with caution. This pattern may reflect protocols requiring admission of all infants whose mothers have a history of substance use in pregnancy or failed toxicological screens during labor, rather than the health of the infant per se, particularly as there appears to be no increase in length of neonatal stay.

Impaired academic achievement and education outcomes (11-2)	1 review 8 studies	Cannabis use	The NIH listed 9 limitations – too many to list here but available on p 280 of the report
Increased rates of **unemployment and/or low income** (11-3)	8 studies	Cannabis use	"Because employment status is not static, it is possible that the relationships may be cyclical (e.g., depending on context, unemployment could contribute to the use of cannabis and other substances [Lee et al., 2015a] and cannabis/substance use could contribute to unemployment)."
Impaired social functioning or engagement in developmentally appropriate social roles (11-4)	1 review 4 studies	Cannabis use	"This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce selection bias; see Chassin et al., 2010). The use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative social outcomes."
An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)	2 reviews 7 additional studies	Cannabis use	"The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity; issues with study design (observational); a reliance on self-reports; and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime)."
The likelihood of developing **bipolar disorder**, particularly among regular or daily users (12-3)	1 review 3 additional studies	Cannabis use	"Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine.

The development of any type of **anxiety disorder**, except social anxiety disorder (12-8a)	1 review 8 additional studies	Cannabis use	"Further work needs to be done to examine why the outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder."
Increased symptoms of **anxiety** (12-9)	1 study	Cannabis use	"In addition, although this study uses a prospective design in which cannabis use and temperament are evalutated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site."
Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)	5 studies	Cannabis use	"Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies; that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn."
Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use **(13-2a)**	Anxiety – 1 review 2 studies Depression – 3 studies	Cannabis use	
The **initiation of tobacco use** (14-1)	3 studies	Cannabis use	"Two studies had relatively large samples. The data do not provide compelling evidence that cannabis is associated with the initiation of other drugs of abuse, although this is one possibility."
Changes in the rates and **use patterns of other licit and illicit**	Alcohol – 1 study Opioids – 1 study Tobacco – 1 study	Cannabis use	"With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions

substances (14-2)	Mixed drug use – 4 studies		1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the potential for self-report bias. "

There is no or insufficient evidence to support or refute a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Incidence of **esophageal cancer** (5-4)	1 study	Cannabis use	"In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants."
Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)	1 review 9 studies	Cannabis use	
Subsequent risk of developing acute myeloid leukemia/ acute non-	1 review	Cannabis use	

lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (5-6)			
Hospital admissions for COPD (7-2b)	1 study	Cannabis smoking	"Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users."
Asthma development or asthma exacerbation (7-4)	3 studies	Cannabis smoking	"The evidence linking cannabis use with asthma risk or exacerbation is limited by the scope and sample size of available studies and by the use of more standardized approaches to measure asthma prevalence or exacerbations of asthma."
Other **adverse immune cell responses** in healthy individuals (8-1b)	5 studies	Cannabis smoking	"The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence."
Adverse effects on immune status in individuals with HIV (8-2)	4 studies	Cannabis use	"However, each of the four studies possessed major shortcomings in experimental design which could have contributed to the absence of adverse effects being observed in HIV patients who used cannabis or cannabinoids; these shortcomings include study durations that where insufficient to observe adverse effects in the endpoints being measured, small numbers of study participants, and poorly defined and variable levels of cannabinoid exposure."
Increased incidence of oral human papilloma	2 studies	Cannabis use	

virus **(HPV)** (8-4)			
All-cause mortality (9-1)	3 reviews 2 additional studies	Cannabis use	"There is an overall dearth of cohort studies empirically assessing general population cannabis use and all-cause mortality. Although the available evidence suggests that cannabis use is not associated with an increased risk of all-cause mortality, the limited nature of that evidence makes it impossible to have confidence in these findings."
Occupational accidents or injuries (9-2)	9 studies	Cannabis use	"In light of the diversity among and limitations of these studies, it was not possible to determine whether general, nonmedical cannabis use is associated with a clearly increased risk of occupational accidents and injuries across a broad range of occupational and industrial settings in the absence of other important risk factors."
Death due to **cannabis overdose** (9-4a)	10 studies	Cannabis use	". . . Onders et al. (2016) observed that cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures do not necessarily allow for an estimation of trends in cannabis overdose or poisoning."
Later outcomes in the offspring (e.g., **sudden infant death syndrome, cognition/academic achievement, and later substance use**) (10-4)	SIDS – 1 study Cognition/Academic Achievement - 6 studies Substance use – 5 studies	Cannabis smoking	"While the studies attempted to control for the child's environment using standard measures of socioeconomic status as well as a direct assessment of the home environment, these approaches may be insufficient to detect potentially subtle differences in the family and neighborhood environments of women who smoke cannabis during pregnancy and those who do not." "In addition, these studies did not address heritable or epigenetic vulnerability."
Changes in the course or symptoms of **depressive disorders**	No studies	Cannabis use	

(12-6)			
The **development of posttraumatic stress disorder** (12-10)	No studies	Cannabis use	

There is no evidence to support or refute a statistical association

Condition	Research	Mode of administration	Limitations
chronic effects of cannabis use and: The **increased risk of acute myocardial infarction** (6-1b)	3 reviews provided descriptive background 2 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use."

There is limited evidence of no statistical association between cannabis use and:

Condition	Research	Mode of administration	Limitations/Other
The progression of **liver fibrosis or hepatic disease** in individuals with viral hepatitis C (HCV) (8-3)	3 studies	Cannabis use	"Overall, the available evidence that cannabis use is not associated with the progression of liver fibrosis and hepatic disease in individuals with HCV is stronger than the available evidence that cannabis use is associated with the progression of liver fibrosis and hepatic disease in individuals with HCV."