The adverse health effects and harms related to marijuana use: An overview review

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Abstract

Background: Nine US jurisdictions have legalized marijuana and there is impending legislation in Canada. A broad understanding of the harms associated with marijuana is needed to inform the clinical community, public and to support evidence-informed public policy development. The purpose of the review was to synthesize the evidence on adverse health effects and harms of marijuana use.

Methods: MEDLINE, the Cochrane database of Systematic Reviews, EMBASE, PsycINFO, CINAHL, and the HTA database were searched from inception of each database up to June 2016. Given that systematic reviews evaluating one or other specific harm have been published, this is a synthesis of systematic reviews with their primary objective being to assess a health effect or harm. Data on author, country and year of publication, search strategy and results, and outcomes were extracted. Quality was assessed using the AMSTAR checklist.

Results: The final analysis included 68 reviews. Evidence of harm was reported in 62 reviews for several mental health disorders, brain changes, cognitive outcomes, pregnancy outcomes, and testicular cancer. Inconclusive evidence was found for 20 outcomes (some mental health outcomes, other types of cancers, all-cause mortality). No evidence of harm was reported for six outcomes.

Interpretation: Harm was associated with the majority of outcomes assessed. These results should be viewed with concern by physicians and policy makers given the prevalence of use, the persistent reporting of a lack of recognition of marijuana as a possibly harmful substance, and the emerging context of legalization for recreational use.

Introduction

Marijuana refers to the dried leaves of the *Cannabis sativa* plant [1]. Internationally, it is the most widely used illicit substance [2]. About 2.5% of the world's population uses marijuana and it accounts for half of all drug seizures worldwide [2]. In Canada, past-month marijuana use is approximately 10.5%[2].. Users report feelings of excitement, euphoria, sensory distortion, sedation, or drowsiness from using marijuana [4], which impel usage for similar reasons as alcohol, tobacco, or other illicit substances. However, there are negative health effects associated with marijuana use.

Currently, marijuana is legal in eight US states, Washington DC and Uruguay, with several other jurisdictions nationally and internationally actively developing legislation. Canada has legalization currently under consideration at the House of Commons having already being considered once by the Senate; legalization is likely to occur by Fall 2018. The individual health risks associated with marijuana use are widely reported in several focused systematic reviews [5-7]. Recently, there have been syntheses completed which report adverse events associated with medical use, the risks associated with use during pregnancy and the association of recreational use with driving safety [8-11]. A recent synthesis from the National Academy of Science, Engineering and Medicine (NASEM) included a variety of health effects associated with marijuana, but due to the heterogeneity of the literature, and time constraints, the report's breadth was limited to priorities [12]. To date, there has been no complete picture of harms and risks published in the peer-reviewed literature. The objective of this work is to synthesize comprehensively the evidence of the health effects and harms (e.g. mortality, mental health outcomes, respiratory illnesses, cardiovascular diseases) of non-medical marijuana use, providing clinicians with a broad and comprehensive overview of possible health impacts. Due to the board nature of this review, we build upon the robust existing synthesis literature thus we included systematic reviews and were intentionally broad on the outcomes included to ensure that we captured the breadth of knowledge available.

Method

Data Sources and Searches

A systematic review was conducted. Six databases were searched from inception until May

2018: MEDLINE, the Cochrane database of Systematic Reviews, EMBASE, PsycINFO, CINAHL, and the HTA database. The search strategy was developed by a library and information specialist. Key terms focused on marijuana and negative health outcomes. Terms for marijuana, such as cannabis, marihuana, pot, or weed were combined with terms for adverse health effects, such as adverse event, harm, reaction, change, and impairment; and, specific outcomes such as cancer, depression, and mortality. The search was limited to English or French, systematic reviews or other reviews, and meta-analyses. **No grey literature search was completed.** The MEDLINE search is included in Appendix 1 with full search strategy for all databases available from authors upon request.

Study Selection

All abstracts were screened by two independent reviewers. Inclusion criteria were systematic review design, publication in English or French, focus on human or animal populations, report on non-medical marijuana usage, and report an adverse health effect or harm. Abstracts were excluded if they failed to meet any of the inclusion criteria above. To ensure all relevant literature was captured, abstracts included by either reviewer proceeded to full-text review. All full texts were reviewed in duplicate by two independent reviewers. Any discrepancies between reviewers were resolved through discussion and consensus. All identified full-texts were hand searched for other articles that met the inclusion criteria.

Data Extraction and Quality Assessment

Data extracted from all studies included author, year and country of publication, search strategy, number of papers included, patient characteristics and key outcomes. When available, odds ratios, risk ratios and percentages were extracted. Quality was assessed using the AMSTAR checklist. Items covered by AMSTAR include presence of a priori design, duplicate selection and data extraction, listing of included and excluded studies, whether the status of publication was used as inclusion criteria, quality of included studies, likelihood of publication bias , and appropriate mode of combining the studies [13]. All studies were given a final quality score out of eleven, with a score of 0-4 considered low quality and scores of 9-11 considered high quality.

Data Synthesis and Analysis

Studies were categorized by clinical area and outcomes extracted included structural,

functional, or chemical brain changes, cognitive changes, cancer, changes in mental health, effects of prenatal exposure, death, and other health effects.

Results

Description of included reviews

Seven hundred and thirty-one unique abstracts were identified; 195 proceeded to full-text review. Sixty-eight systematic reviews were included in the final dataset. The most common reason for exclusion was lack of reporting of a health effect or harm (Figure 1). All were published from 1997 to 2017 and the most recent review was conducted in 2015. The most commonly searched databases were MEDLINE (53 reviews), EMBASE (39 reviews), PsycINFO (33 reviews), and PubMed (30 reviews) (Web Appendix Table 1). Twenty-two reviews examined mental health outcomes, 15 reported on functional and structural brain changes, 10 examined neurocognitive effects, four reported on cancer, five reported on prenatal exposure, and 12 examined overall health effects (Table 1; Box 1).

Quality of included reviews

Twenty-eight reviews were of low quality, 29 were moderate quality, and 11 were high quality. The lowest overall quality was in overall health effects and the highest was in cancer. Brain changes, prenatal exposure, and overall health effects had no high-quality reviews (9-11/11). There were two reviews with quality assessment of 1/11 [14, 15], one in brain changes and another in mental health effects. Many reviews reported multiple outcomes, and as such, some reviews concluded both harm and no harm for different outcomes. Overall, 62 of the assessed outcomes were associated with harm, for 20 there was insufficient evidence, and for six outcomes, there was no evidence of harm (Figure 2). In reviews that concluded harm, 20 [6, 14-32] were low quality and nine [7, 33-40] were high quality. In those that concluded no evidence of harm, five [21, 23, 31, 41, 42] were low quality and four [5, 34, 37, 43] were high quality. In those that reported inconsistent evidence, five[20, 44-47] were low quality and one [40] was high quality. Six reviews [20, 48-51] identified randomized trials.

Effect of interventions

Brain Changes

Of the fifteen included reviews, five assessed structural changes, three examined functional changes, four assessed both structural and functional changes, and three examined chemical changes. All papers reported either harm or insufficient evidence. Most (n=13) examined neuroimaging primary studies, including structural, functional, and volumetric magnetic resonance imaging [18, 44, 48, 49, 52-54], diffusion tensor imaging [41, 48, 52, 54, 55], positron emission tomography [49], single photon emission tomography [49], magnetic resonance spectroscopy [14], pneumoencephalography [18], and computed tomography [18].

In otherwise healthy users, changes were observed in amygdala [44, 48, 52], hippocampal [44, 48, 52], and white and grey matter volume [44, 48, 56] and blood flow [48, 49, 54, 56], but there were no changes to whole brain volume [41, 52], intracranial volume [52], or the corpus callosum [41]. Changes in learning [49], attention [48, 54], memory [48, 49, 54], and overall activity [18] were observed. Many of the structural changes can help explain the functional changes. In users with schizophrenia or psychosis, white matter deficits [55] and decreased global activity [57] were observed. Disruptions in glutamate [53], dopamine [50], N-acetyl-aspartate [14], myo-inositol [14], choline [14], and GABA [14] were observed in cannabis users.

Mental Health

Twenty-one reviews examined marijuana and mental health. Reviews assessed the association between marijuana use and psychosis or schizophrenia (n=15), anxiety (n=2), suicide or depression (n=2), mania (n=1), neurological soft signs (n=1), and marijuana dependence (n=1). Quality was variable with eight high quality, seven medium quality, and seven low quality reviews, with quality scores ranging from 1/11 to 10/11. None of the reviews included randomized trials. Most reviews compared marijuana users to non-users or the general population or those at high-risk of psychosis. Some reviews [33, 40] compared users to non-users among people with schizophrenia. One review compared users with first-episode psychosis with users with long-term chronic psychosis [58].

Psychosis and schizophrenia

There was an increased risk of schizophrenia and psychotic symptoms related to heavy (OR = 3.90, 95% CI: 2.84-5.34), average (OR = 1.97 (95% CI: 1.68-2.31)) [59], ever (OR = 1.41 (95% CI: 1.20-1.65)) [60], more frequent (OR = 2.09 (95% CI: 1.54-2.84)) [60], and early use (OR =

2.90 (95% CI: 2.40-3.60)) [61] compared to never or minimal use. Compared to no use, cannabis use was associated with an earlier onset of psychosis [38, 43, 47] (6.3 years (SMD = 1.56, 95% CI: 1.40-1.72)) [58]. Cannabis use or abuse was also associated with transition to psychosis in those at "ultra-high risk" for psychosis (OR = 1.75 (95% CI: 1.135-2.710)) [37] relative to never users. Lastly, cannabis use in those with psychosis was related to increased relapse, rehospitalization, and decreased treatment adherence [33, 40]. Cannabis use was higher in those with first-episode psychosis[47]. Any cannabis use was not associated with onset of psychosis in those at high risk or symptom severity compared to no use [37]. There was no association with neurological soft signs, or the neurological abnormalities in sensory and motor performance that have been associated with schizophrenia during neurodevelopment [62].

Mood, anxiety and suicide

Cannabis use, compared to no use, is associated with death by suicide (chronic users, OR = 2.56 (95% CI: 1.25-5.27)) [63], suicidal ideation (any use, OR = 1.43 (95% CI: 1.13-1.83); heavy use, OR = 2.53 (95% CI: 1.00-6.39)) [63], suicide attempt (any use, OR = 2.23 (95% CI: 1.24-4.00); heavy use, OR = 3.20 (95% CI: 1.72-5.94)) [63], and depression (any use, OR = 1.17 (95% CI: 1.05-1.30); heavy use, OR = 1.62 (95% CI: 1.21-2.16)) [39]. Increased severity and duration of manic phases (OR = 2.97 (95% CI: 1.80-4.90)) [7] and higher levels of anxiety are observed [21]. Those with anxiety are more likely to use cannabis (OR = 1.24 (95% CI: 1.06-1.45)) [36] and develop cannabis use disorder (OR = 1.68 (95% CI: 1.23-2.31)) [36].

Dependency

About 10% of users experience marijuana dependency; dependency increased with frequency of use [15]. This review, however, was limited to self-reported surveys rather than formal diagnoses of dependency [15].

Cognitive effects

Ten reviews assessed cognitive effects: five examined learning and memory, five examined executive function, five examined motor functioning, three examined reaction time, four examined attention, two examined forgetting/retrieval, one examined anhedonia (inability to experience pleasure), and one examined sleep. There is evidence of changes to functional and

structural integrity [34], memory and learning [20, 34], and increased anhedonia [22]. There is inconsistent evidence regarding learning [23, 64], attention [20, 23, 34, 64], forgetting/retrieval [23, 64], executive function [20, 23, 34, 64, 65], motor and perceptual motor function [20, 23, 34, 64, 65], and sleep [46]. There is no evidence of changes in reaction time [23, 64, 66], verbal/language skills [23, 64] or visual spatial function [34]. In people with psychosis, cannabis use was not associated with significant additional decline in general cognitive ability or intelligence [26], attention [26], executive abilities [26], working and learning memory [26, 28], retrieval and cognition [26], language [26] or visuospatial performance [26, 28].

Prenatal exposure

Five reviews examined marijuana use during pregnancy. Harms were reported for both the mother and the child. Pregnant women who used cannabis were more likely to experience anemia during pregnancy (OR = 1.36 (95% CI: 1.10-1.69)) [35]. Both reductions and increases in birthweight are reported (OR = 1.77 (95% CI: 1.04-3.01), adjusted OR = 1.16 (95% CI: 0.98-1.37)) [35, 67]. Compared to no use, there was a 48 gram reduction in birthweight for those with any use (95% CI: 14-83 g) [6], 131 gram reduction for those who used at least four times per week (95% CI: 52-209 g) [6], and a 62 gram increase for babies whose mothers used less than once a week (95% CI: 8 g reduction -132 g increase) [6]. However, women who smoked marijuana only were not at increased risk for preterm delivery compared to those who smoked both tobacco and marijuana (7.1% vs. 5.7%, RR = 1.25 (95% CI: 0.63-2.50)).Infants of users were more likely to be placed in the NICU than those of non-users (OR = 2.02 (95% CI: 1.27-3.21)) [35].

Children prenatally exposed to cannabis are more likely to experience inattention and impulsivity at 10 years. They also have lower IQ scores, increased errors of omission, academic underachievement (especially in spelling and reading), and increased rate of adolescent cannabis and cigarette use [31, 32]. There is no known association with congenital anomalies [31].

Overall health effects and harms

Twelve reviews examined overall health effects assessing several different outcomes. Five examined cardiovascular outcomes. There is an association with stroke [68], atrial fibrillation [69], bronchodilation [70], respiratory complications [70, 71], and COPD [71]. Some cases of increased lung

bullae were identified [71]. There is no association with arteritis [42]. Cannabis interacts with tricyclic antidepressants, protease inhibitors, and warfarin therapy and the most commonly reported side effects of these interactions related to cardiac functioning [25]. There are some residual effects on vision [29]. Cannabis use is associated with an increased risk of fatal motor vehicle collisions [11] (OR = 1.92 (95% CI: 1.35-2.73)) [16].

Five reviews examined cancer. Compared to never users, there is an increased risk of testicular cancer in current (OR = 1.62 (95% CI: 1.13-2.31)) [72], weekly (OR = 1.92 (95% CI: 1.35-2.72)) [72], and chronic users (OR = 1.50 (95% CI: 1.08-2.09)) [72, 73], but no increased risk of head and neck (OR = 1.02 (95% CI: 0.91-1.14)) [5] cancers. There was mixed evidence on lung cancer, with one review reporting a 2.1-4.1 fold increased risk in some marijuana users [71] and another reporting no increased risk [74]. One review noted increased pathological lung changes in non-tobacco-smoking marijuana smokers compared to non-smokers, but did not compare marijuana smokers and tobacco smokers [74]. There was insufficient evidence regarding bladder, prostate, penile, cervical, and childhood cancers to draw conclusions about the association between these outcomes and marijuana use [73].

Interpretation

Summary of main results

The 64 identified reviews reported harm for 61 outcomes, insufficient evidence of harm for 18 outcomes, and no evidence of harm for six outcomes. Most reviews were of low- to moderate-quality; however, this is not a comment on the quality of the primary studies included within these reviews but an assessment of how well the systematic reviews reported methods and results. Harm is reported for multiple mental health outcomes including psychosis, mania and suicide. There is evidence of structural, functional, and chemical brain changes that may underlie some of the associated risk for mental illness. There is also evidence for impaired driving, and changes to memory, learning and hedonic value.

This review provides important information regarding the need to consider adverse health effects of recreational or medical marijuana use. This information should be of use to policy makers and healthcare systems as jurisdictions prepare to address the health effects of increased accessibility of marijuana. Data regarding harms associated with marijuana, including those

related to mental health and brain changes should be considered when evaluating the potential impacts of legalizing marijuana, particularly related to the potential for increases in healthcare costs. As Canada prepares to legalize marijuana, there must be consideration of the impact on psychiatric and primary care practitioners who are are likely to encounter this within their practices. Although overall use if not expected to increase, as Canadians become more aware of the risks with marijuana, the healthcare system may observe an increase in patients presenting with the outcomes described.

Particular consideration should be given to special populations, namely pregnant women, adolescents, and those with risk for or established mental illness. Several reviews [24, 44, 51, 55, 61] suggest that effects are worse in adolescent users compared to adult users. All reviews examining prenatal exposure and several reviews examining those with several mental illnesses suggested poorer outcomes for those who use marijuana compared to the general population. Public health campaigns or initiatives to inform these populations about the potential risks of use are required. Policy makers may consider regulating marijuana from a public health perspective to reduce the harms among the most vulnerable groups. Physicians should also note this differential effect and advise youth, pregnant women, and those with mental illnesses against use.

However, none of the above evidence is causal; only associative evidence is available. The study designs available within humans are limited to observational cohorts as sufficiently-powered randomized control trials would not be feasible nor ethical. It is possible that the observed positive associations are due to systematic differences between marijuana users and non-users in underlying risks, social exposures or environmental factors. Nonetheless, clinicians should be aware that there are a variety of health harms associated with marijuana use and consider additional preventative measures for their patients such as additional behavioral counseling and more assertive diagnostic approaches if symptoms arise.

Only one review [15] examined dependency and was limited to examining only self-reported surveys; however, this review provides important information for physicians. This review reported that 10% of users meet criteria for marijuana dependency [15]. There were moderate effects of genetics on dependency, and those who also smoke cigarettes, begin smoking before the age of 17, and are weekly users were more likely to be dependent [15]. Other reviews noted that

those who are dependent on marijuana are more likely to develop psychosis, especially in those already at high-risk [37], and users with anxiety are more likely to develop marijuana dependency [38]. It is important for physicians to provide education to their patients that marijuana is not a harmless, recreational substance particularly in groups at risk due to personal or family history.

Potential biases in the overview process

This review is limited in the range of potential harms that could be examined, as only topics previously systematically reviewed were included. Some adverse effects may therefore have been missed in this review. One such topic is the toxicity of marijuana compared to other licit and illicit substances. Compared with alcohol and tobacco, two legal and often-used substances, marijuana is less toxic at the population-level [75]. Further, because of the nature of marijuana function on the brain, death due to overdose is not possible [76] and marijuana has therefore been classified as a relatively safe drug, which it is in the short term. The safety profile of marijuana in the short term may have overshadowed some of the longer term health risks that appear to be associated with even moderate use. This review was limited to English and French reviews, which may have excluded some important reviews. Additionally, this review protocol was not registered in PROPSERO.

Conclusions

Though there is inconsistent evidence of variable quality, the general conclusion is that marijuana is associated with negative effects on several aspects of mental and physical health. With legalization impending in Canada, it is important to understand the likely impact of increased accessibility on health and health services, particularly in youth, pregnant woman and people living with mental illness. Better understanding of both the short and long term health effects of marijuana use is essential to inform public and clinical policy, as well as to adapt clinical services to anticipate changing clinical need.

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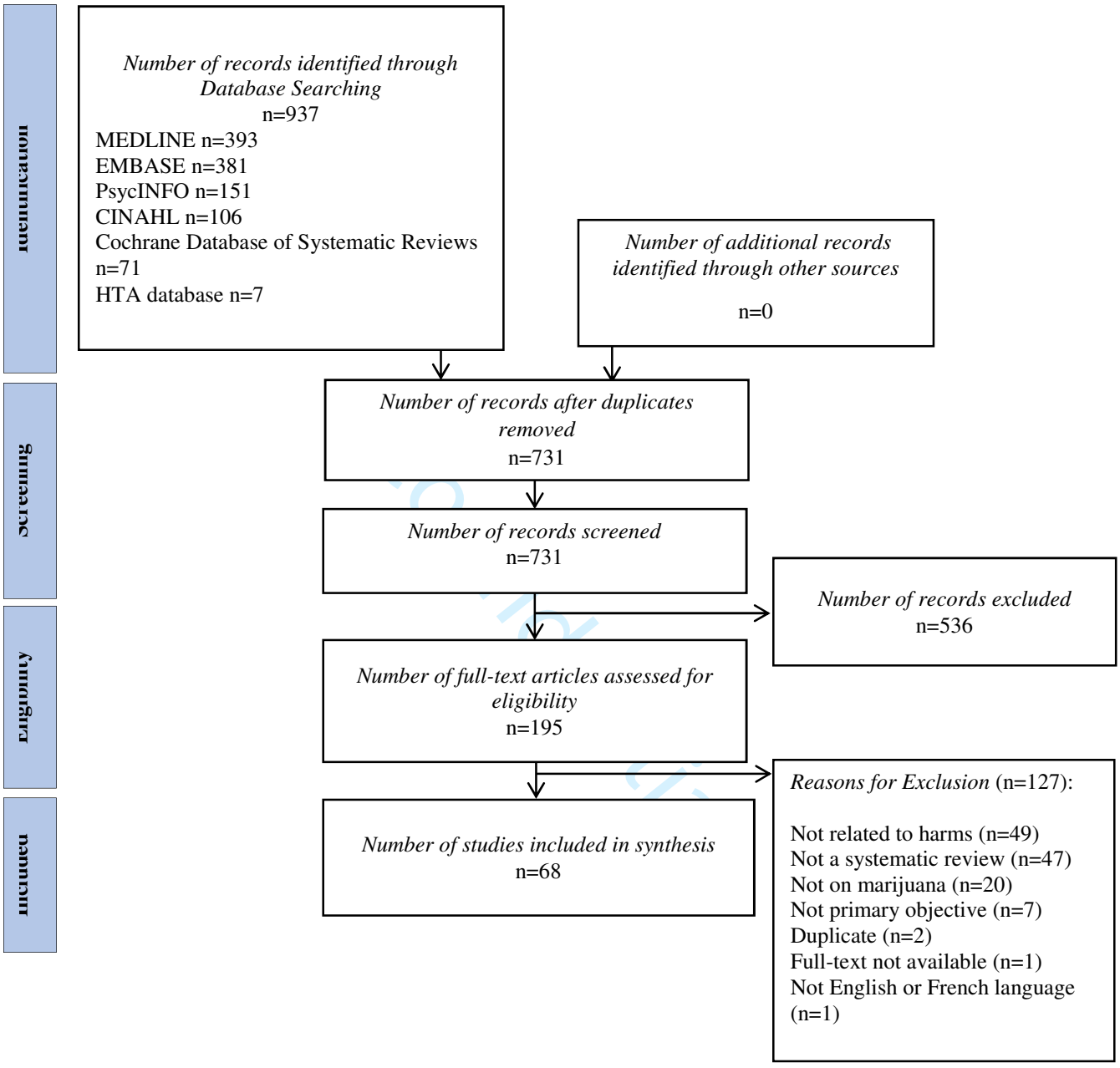
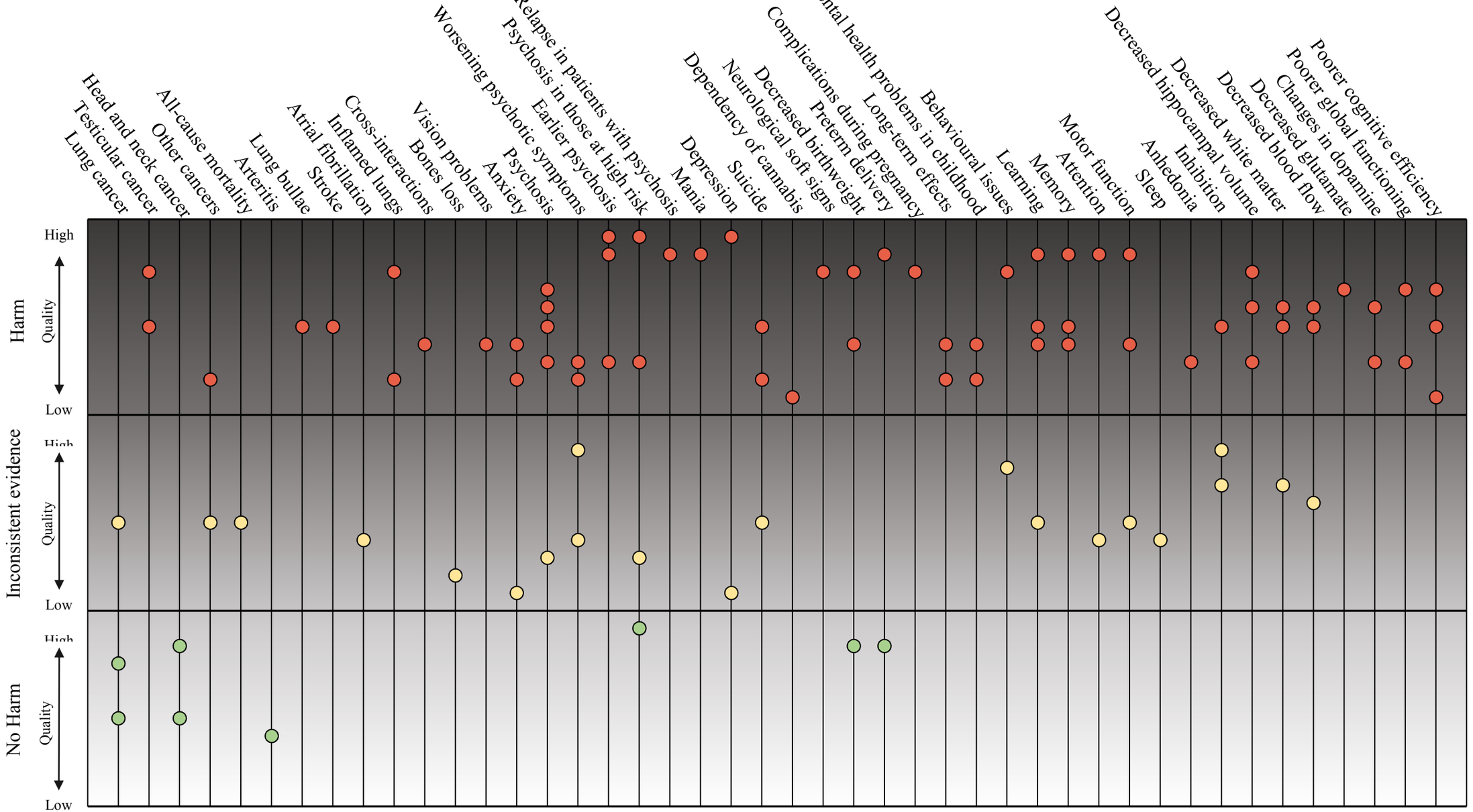
Table 1. Summary of findings

Area	Outcomes assessed	Reviews included	Primary studies included	Reviews that included randomized studies	Average quality (range)	Summary of findings
Brain changes	• Structural changes • Functional changes • Chemical changes	15	359	3	4.9 (1-8)	Association • Amygdala, hippocampal, white and grey matter volume, blood flow • Learning, attention, memory, overall activity • Glutamate, dopamine, N-acetyl-aspartate, myo-inositol, choline GABA No association • Intracranial and whole brain volume, corpus callosum
Cancer	• Testicular • Head and neck • Lung • Other cancers	4	62	None	7.5 (5-9)	Association • Testicular cancer No association • Head and neck, lung, or other cancers
Mental health	• Psychosis and schizophrenia • Anxiety • Suicide and depression • Mania • Neurological soft signs	22	394	None	6.4 (1-10)	Association • Psychosis, earlier onset of psychosis, relapse and rehospitalization • Death by suicide, suicidal ideation, suicide attempt, depression, more severe mania, anxiety No association • Neurological soft signs
Neurocognitive effects	• Learning and memory • Executive function • Motor function • Reaction time • Attention • Forgetting/retrieval • Anhedonia	10	462	1	4.9 (3-9)	Association • Functional and structural integrity, memory and learning, anhedonia Inconsistent evidence • learning, attention, forgetting/retrieval, executive function, motor and perceptual motor function, sleep No association

	• Sleep					• Reaction time, verbal/language skills, visual spatial ability In those with psychosis • No changes to cognitive ability and intelligence, attention, executive abilities, working and learning memory, retrieval and cognition, learning abilities, visuospatial abilities
Prenatal exposure	• Harms to the mother • Harms to the child	5	69	None	5.4 (2-9)	Mother • Increased risk of anemia Child • Decreased birthweight • Increased NICU utilization • Effects in later life
Overall health effects and harms	• Stroke • Atrial fibrillation • Bronchodilation • Respiratory complication • Interactions with other drugs • Vision • Arteritis • Risk of a motor vehicle collision • Overall mortality	12	213	None	3.8 (2-8)	Association • Stroke, atrial fibrillation, bronchodilation, respiratory outcomes, lung bullae, COPD, emphysema, lung hyperinflation, infectious disease transmission, interactions with drugs, residual effects on vision • Fatal motor vehicle collisions No association • Arteritis, overall mortality

Figure 1. PRISMA Flow Chart




Lung cancer
Testicular cancer
Head and neck cancer
Other cancers
All-cause mortality
Arteritis
Lung bullae
Atrial fibrillation
Stroke
Inflamed lungs
Cross-interactions
Bones loss
Vision problems
Worsening psychotic symptoms
Anxiety
Psychosis
Earlier psychosis
Psychosis in those at high risk
Relapse in patients with psychosis
Mania
Depression
Suicide
Dependency of cannabis
Neurological soft signs
Decreased birthweight
Preterm delivery
Complications during pregnancy
Long-term effects
Mental health problems in childhood
Behavioural issues
Learning
Memory
Attention
Motor function
Sleep
Anhedonia
Inhibition
Decreased hippocampal volume
Decreased white matter
Decreased blood flow
Decreased glutamate
Changes in dopamine
Poorer global functioning
Poorer cognitive efficiency
Harm
Quality
High
Low
Inconsistent evidence
Quality
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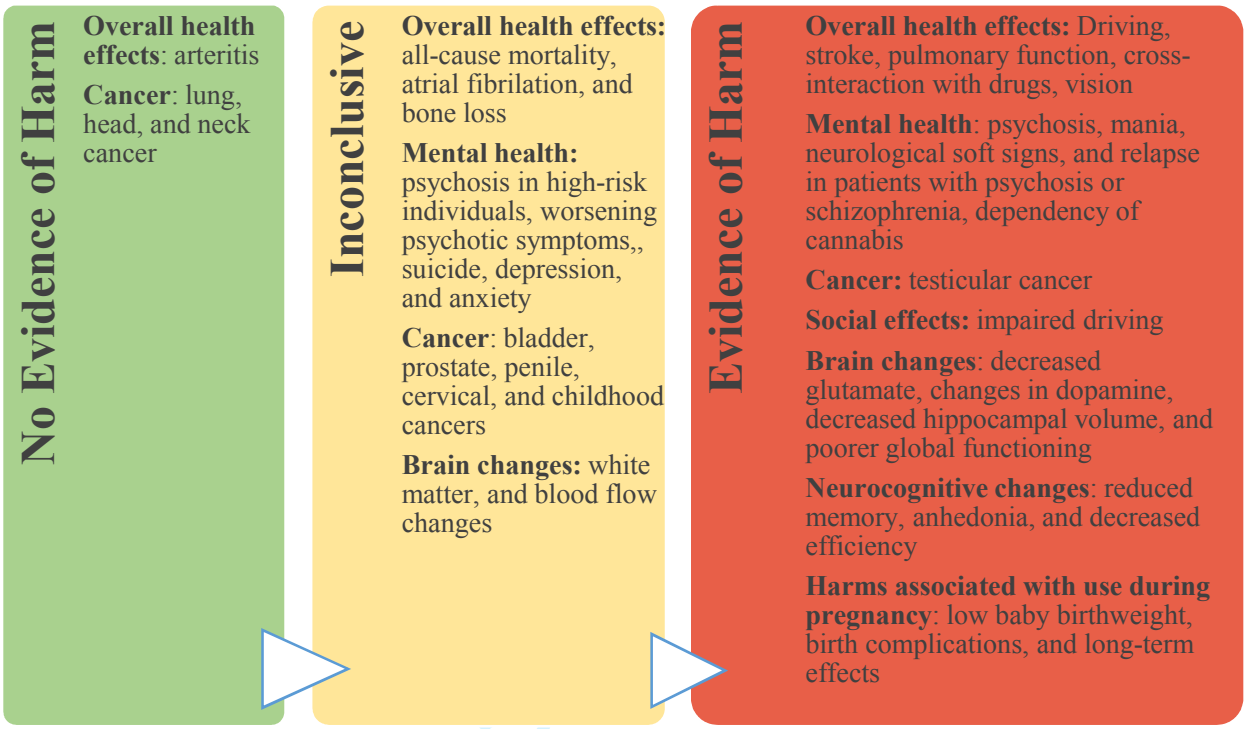

Box 1: An overview of the health effects and harms associated with marijuana use

Changes to the Brain					
Author, Year of Publication, Country	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Arnone, 2006, United Kingdom	*Population:* general population *Intervention:* illicit substance use *Comparator:* healthy, matched controls *Outcome:* mean diffusivity, fractional anisotropy, and intervoxel coherence changes in the corpus callosum (measures of structural damage)	*Databases searched:* BNI, CancerLit, Cochrane Library, EMBASE, Medline, PsychInfo, PubMed *Years searched:* introduction of DTI until July 2006 *Key words used:* diffusion tensor imaging, magnetic resonance imaging, DTI, RMI, alcoholism, marijuana, cannabis, cocaine, ecstasy, MDMA, methamphetamine, substance misuse *Inclusion criteria:* original data; studies that addressed the question "use of DTI in substance misuse" *Exclusion criteria:* studies that did not report significant results; studies that examine areas other than the corpus callosum	*Number of citations identified in Search:* not reported *Number of studies included:* 9 *Number of patients in all included studies:* 19	1. No difference in the structural integrity of marijuana users compared to non-users 2. Confounders not controlled for in either study	2/11
Batalla, 2013, Spain	*Population:* chronic adult and adolescent users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain structure and function	*Databases searched:* EMBASE, Medline, PubMed, LILACS *Years searched:* inception until August 2012 *Key words used:* cannabis, marijuana, marihuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI,	*Number of citations identified in Search:* 142 *Number of studies included:* 43 *Number of patients in all included studies:*	*Structural* 3. In adults - reduced hippocampal volume and white matter integrity in chronic users, often persisting after abstinence 4. In adults - changes also described in amygdala, cerebellum, and frontal cortex of chronic users 5. Adolescent results inconclusive *Functional*	6/11

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		spectroscopy, MRS *Inclusion criteria:* use of structural or functional neuroimaging techniques involving chronic cannabis users; inclusion of a control group of healthy volunteers matched by age, gender, and handedness; and users that were abstinent for at least 12 hours before brain scanning *Exclusion criteria:* non-neuroimaging studies of cannabis use; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals who met criteria for alcohol dependence or other substance use disorders; neuroimaging studies with recreational or naïve cannabis users	711	~~1.~~• Lower resting blood flow globally, and in cerebellum, prefrontal cortex, and striatum ~~2.~~• No significant difference in performance between controls and users	
Batalla, 2014, Spain	*Population:* naïve or occasional cannabis users; animals or human *Intervention:* cannabis use *Comparator:* non-users *Outcome:* acute effects of brain functioning	*Databases searched:* EMBASE, Medline, PubMed, LILACS *Years searched:* inception until June 2012 *Key words used: for humans:* cannabis, marijuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, cannabinoid, neuroimaging, brain imaging, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, spectroscopy, MRS; *for animals:* animal, rat, cannabis, marijuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, cannabinoid, cerebral blood flow, cerebral glucose utilization, microdialysis, electrophysiological, dopamine release, single photon emission tomography,	*Number of citations identified in Search:* 224 *Number of studies included:* 45 *Number of patients in all included studies:* 889	~~1.~~• Increased cerebral blood flow to prefrontal, insular, cerebellar, and anterior cingulate regions; associated with depersonalization and increase anxiety ~~2.~~• THC influenced learning, memory, and affect; CBD seems to have the opposite effect	5/11

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		SPECT, positron emission tomography, PET *Inclusion criteria:* use of functional neuroimaging techniques involving animals naïve to cannabinoids or naïve/occasional users; acute experimental administration of cannabinoids; same gender, age, handedness in all subjects; in vivo studies involving cannabinoid effects on blood flow, cerebral metabolism, or dopamine release *Exclusion criteria:* non-neuroimaging studies of experimental administration of cannabinoids; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals with substance abuse disorders; neuroimaging studies with chronic cannabis users; in vitro experiments; chronic or combined drug administration; anesthetized animals during the experimental procedure			
Colizzi, 2016, United Kingdom	*Population:* general human population and animals *Intervention:* cannabis and delta-9-tetrehydrocannabinol exposure *Comparator:* non-users *Outcome:* glutamate functioning	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* inception until October 29th, 2015 *Key words used:* cannabis, delta-9-tetrehydrocannabinol, marijuana, marihuana, tetrahydrocannabinol, dronabinol, glu*, glutamate(s), glutamine, glutamic acid *Inclusion criteria:* human or animal studies; studies investigating the acute and/or long-term effects of cannabis use/administration or delta-9-tetrehydrocannabinol use/administration; studies measuring molecular markers related to glutamate	*Number of citations identified in Search:* 268 *Number of studies included:* 41 (5 human, 36 animal) *Number of patients in all included studies:* 239 humans,	1. Chronic cannabis use associated with decreased levels of glutamate in the cortical and subcortical areas, especially in females 2. Delta-9-tetrehydrocannabinol affects glutamate release and reuptake and reduces the inhibition of glutamate	7/11

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		neurotransmission including glutamate metabolites, synaptic transmission, enzyme activity, neurotransmitter release and uptake, transporters, receptors, brain neurotransmitter levels *Exclusion criteria:* studies where cannabis or delta-9-tetrehydrocannabinol were not the intervention or exposure of interest; studies in which the neurochemical outcomes were not directly reported upon	animal not reported		
Cookey, 2014, Canada	*Population:* cannabis users and non-users *Intervention:* cannabis use *Comparator:* early-phase schizophrenia without cannabis use vs. cannabis use without schizophrenia vs. concurrent cannabis use and schizophrenia *Outcome:* white matter tissue	*Databases searched:* Medline, EMBASE, Cochrane, PsychInfo *Years searched:* 1994 until November 2013 *Key words used:* schizophrenia, diffusion tensor imaging, humans, cannabis or marijuana smoking, diffusion, tensor, imaging, diffusion tensor imaging, early onset, first episode, cannabis, marijuana *Inclusion criteria:* English language; assess early phase schizophrenia relative to healthy controls; report diffusion tensor imaging, fractional anisotropy values *Exclusion criteria:* multiple illicit drug use or heavy alcohol use; sample sizes smaller than 20	*Number of citations identified in Search:* 65 *Number of studies included:* 18 *Number of patients in all included studies:* 725	~~1.~~• Decreased white matter in early-phase schizophrenia without cannabis use ~~2.~~• Cannabis use caused additional white matter disruption, especially in adolescence	5/11
James, 2013, United Kingdom	*Population:* adolescent cannabis users *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* EMBASE, Medline, PubMed, PsychLIT, LILACS *Years searched:* inception until December 2012 *Key words used:* marijuana, cannabis, delta-9-	*Number of citations identified in Search:* 141 *Number of*	~~1.~~• Cannabis use associated with memory disruptions, loss of IQ, loss of inhibition, and more compensatory brain activity in adolescents ~~2.~~• May be associated with	5/11

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	Outcome: brain structure and function	tetrahydro- cannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI- MRI, spectroscopy, MRS. *Inclusion criteria:* case-control design; healthy controls; participants under 19 *Exclusion criteria:* non-neuroimaging studies of cannabis use; participants older than 19; subjects with other neurological or psychiatric disorders or other substance abuse disorders	*studies included:* 24 *Number of patients in all included studies:* 450	adolescent-onset schizophrenia due to loss of grey and white matter, but minimal evidence exists	
Lorenzetti, 2010, Australia	*Population:* chronic cannabis users *Intervention:* chronic cannabis use *Comparator:* non-users *Outcome:* brain changes and psychopathological symptoms	*Databases searched:* PubMed *Years searched:* not reported *Key words used:* cannabis or marijuana, MRI, computed tomography, or neuroimaging *Inclusion criteria:* use of structural neuroimaging techniques; cannabis as the principal drug of abuse *Exclusion criteria:* samples with any major psychopathologies; not empirical studies (review articles, case studies)	*Number of citations identified in Search:* 154 *Number of studies included:* 13 *Number of patients in all included studies:* 285	~~3.~~ Inconsistent findings, but abnormalities identified in the hippocampus, parahippocampus, and amygdala ~~4.~~ Often related to high frequency and long-term use and more likely in adolescent users	3/11
Malchow, 2013, Germany	*Population:* schizophrenia patients *Intervention:* cannabis use	*Databases searched:* PubMed, We of Knowledge *Years searched:* inception until 2012 *Key words used:* schizophrenia, psychosis, sMRI,	*Number of citations identified in Search:* 105	~~5.~~ Weak evidence that chronic cannabis use may affect brain morphology in patients with schizophrenia and those at high-risk	4/11

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	Comparator: non-users *Outcome:* brain morphology	structural imaging, cannabis, marijuana, marihuana, tetrahydrocannabinol *Inclusion criteria:* humans; English language; neuroimaging studies examining brain structure *Exclusion criteria:* not reported	*Number of studies included:* 16 *Number of patients in all included studies:* 484	~~6.~~ • Inconclusive evidence that cannabis affects brain structure prior to schizophrenia or causes schizophrenia	
Martin-Santos, 2010, United Kingdom	*Population:* adult cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain structure and functioning	*Databases searched:* EMBASE, Medline, PubMed, LILACS, PsychLIT, books on substance abuse neuroimaging *Years searched:* inception until January 2009 *Key words used:* marijuana, cannabis, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS *Inclusion criteria: for case-control studies:* inclusion of a control group of healthy volunteers matched for age, sex, and handedness; users were abstinent for 12 hours before brain scanning; *for experimental administration of cannabinoids:* parallel or cross-over design; participants were abstinent for at least 1 week *Exclusion criteria:* non-neuroimaging studies of	*Number of citations identified in Search:* 66 *Number of studies included:* 41 *Number of patients in all included studies:* 665	~~7.~~ • Lower resting global, prefrontal, and anterior cingulate cortex blood flow in cannabis users, related to impairments in time estimation, attention, working memory, cognitive flexibility, decision making and psychomotor speed ~~8.~~ • Impaired cognitive efficiency in cannabis users compared to controls ~~9.~~ • Changes in volume only related to chronic users	5/11

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		cannabis use; neuroimaging studies involving those under 18 years of age; subjects who had other neurological or psychiatric disorders or who tested positive for drugs other than cannabis			
Quickfall, 2006, Canada	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain structure and functioning	*Databases searched:* Medline *Years searched:* 1966 until February 2005 *Key words used:* cannabis, marijuana, or tetrahydrocannabinol, and computed tomography, MRI, functional MRI, single photon emission computed tomography, positron emission tomography, cerebral blood flow, or neuroimaging *Inclusion criteria:* published in peer-reviewed journals; focus on users who were directly exposed to cannabis; employed anatomical structural or functional neuroimaging techniques *Exclusion criteria:* animal studies; single case reports	*Number of citations identified in Search:* 112 *Number of studies included:* 30 *Number of patients in all included studies:* 655	~~1.~~ Smoked and infused cannabis increased global cortical activity, especially in chronic users ~~2.~~ Acute and chronic exposure were associated with increased activity during exposure and decreased activity during abstinence in the frontal, limbic, and cerebellar regions ~~3.~~ Conflicting results of the effect on the temporal lobe	3/11
Rapp, 2012, Switzerland	*Population:* cannabis users with psychosis or at high-risk or genetic risk of psychosis *Intervention:* cannabis uses *Comparator:* healthy, non-users *Outcome:* brain structure	*Databases searched:* ISI Web of Knowledge, PubMed *Years searched:* inception until November 2011 *Key words used:* psychosis, schizophrenia, first episode, at-risk mental state, high risk, and cannabis, marijuana, delta-9-tetrahydrocannabinol, and brain structure, neuroimaging, brain imaging, brain abnormalities, magnetic resonance, diffusion sensor MRI, post mortem, quantitative autoradiography, radiology and binding, in situ hybridization	*Number of citations identified in Search:* 33 *Number of studies included:* 19 *Number of patients in all included studies:*	~~4.~~ Cannabis use associated with decreased activity globally and in the cingulum, dorsolateral prefrontal cortex, and cerebellum in users with or at high risk of psychosis compared to healthy non users ~~5.~~ Post mortem results and studies examining white matter changes were inconclusive	7/11

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		Inclusion criteria: original publication in a peer reviewed journal; studying the brain of psychosis patients or individuals at risk for psychosis or individuals at genetic risk for psychosis in relation to cannabis use applying in vivo structural neuroimaging or post mortem autoradiography or in situ hybridization techniques; included both cannabis smokers and non-smokers; described specific effects of cannabis on brain if subjects had a general substance abuse or substance dependence disorder diagnosis *Exclusion criteria:* functional brain imaging studies	350		
Rocchetti, 2013, United Kingdom	*Population:* non-psychotic cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain structure	*Databases searched:* Web of Knowledge (Medline, Web of Science) *Years searched:* inception to February 2013 *Key words used:* MRI, DTI, VBM, cannabis, neuroimaging, structural, grey matter, white matter *Inclusion criteria:* original paper or short communication in a peer-reviewed journal; recruited cannabis-user subjects without a diagnosis of psychosis and matched controls; employed structural imaging techniques; reported sufficient data to allow meta-analytical computations *Exclusion criteria:* subjects with a diagnosis of a psychotic disorder; overlapping samples; systematic or critical reviews; did not report enough data to be included in the meta-analysis	*Number of citations identified in Search:* not reported *Number of studies included:* 14 *Number of patients in all included studies:* 362	6. No statistically significant differences in whole brain volume between users and non-users 7. Significantly decreased hippocampal volume in users 8. Inconsistent results on amygdala volume due to publication bias	8/11

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Sami, 2015, United Kingdom	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* dopamine functioning	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* inception until July 2014 *Key words used:* cannabidiol, cannabinoid, cannabis, CBD, THC, hashish, marijuana, tetrahydrocannabinol, endocannabinoid, dopa*, dopamine, PHNO, raclopride, fallypride, iodobenzamide, IBZM, FMT, PE21, CIT, NNC112, SCH23390, D1, D2, D3, DAT, AADC, MAO *Inclusion criteria:* human studies; investigating acute and long-term effects of cannabinoid administration; measuring molecular markers related to dopaminergic neurotransmission including biomarkers in peripheral blood, in vivo imaging, or post mortem brain tissue *Exclusion criteria:* studies where cannabinoid administration was not the intervention or exposure of interest; or where neurochemical outcomes were not directly reported on	*Number of citations identified in Search:* 2796 *Number of studies included:* 25 *Number of patients in all included studies:* 244	~~9.~~• Minimal evidence, but acute cannabis use is weakly associated with increased peripheral and striatal dopamine and decreased neocortical dopamine ~~10.~~• Similar results for chronic users ~~11.~~• Larger effects in those at genetically predisposed to or at clinical high risk of psychosis	6/11
Sneider, 2014, United States	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* changes in brain chemistry	*Databases searched:* PubMed, EMBASE *Years searched:* not reported *Key words used:* marijuana, cannabis, MRS, MRSI, proton MRS *Inclusion criteria:* not reported *Exclusion criteria:* neuroimaging other than MRS (MRI, CT, PET, DTI, fMRI, CBF, CBV)	*Number of citations identified in Search:* not reported *Number of studies included:* 8 *Number of*	~~12.~~• Cannabis use associated with lower levels of N-acetyl-aspartate, myo-inositol, and choline, which are associated with lower cognitive efficiency and impulse control ~~13.~~• Associated with alterations in GABA levels in the frontal lobe	1/11

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			patients in all included studies: 140		
Wrege, 2014, Switzerland	*Population:* general population *Intervention:* acute or chronic marijuana use *Comparator:* no marijuana use *Outcome:* impulsivity and neuroimaging	*Databases searched:* PubMed *Years searched:* inception until 2012 *Key words used:* cannabis, cannabinoid, THC, marihuana, marijuana, impulsivity, motor control, motor inhibition, disinhibition *Inclusion criteria:* English German or Spanish; parallel, crossover or case-control design with control group; include impulsivity measure *Exclusion criteria:* psychiatric or neurological disorder	*Number of citations identified in Search:* 774 *Number of studies included:* 13 *Number of patients in all included studies:* 223	~~1.~~ Prefrontal blood flow was lower in chronic marijuana users ~~2.~~ Studies found increased brain metabolism during marijuana use ~~3.~~ Structural changes such as reduced prefrontal volume and white matter integrity differed between marijuana users in individuals who had not used marijuana ~~4.~~ Brain structure alterations were stronger in those who used marijuana before 16 years old	6/11
Cancer					
Author, Year of Publication, Country	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
De Carvalho, 2015, Brazil	*Population:* adult cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* head and neck cancer	*Databases searched:* the Cochrane library, PubMed, LILACS, EMBASE, BBO, Bireme SciELO *Years searched:* inception to July 2015 *Key words used:* hashish, marijuana, bhang, ganja, hemp, C. *sativa,* oral, oropharyngeal, nasopharyngeal, head and neck neoplasms, neoplasm neck, cancer of the head and neck, head and neck cancer, head cancer, neck cancer, aerodigestive tract neoplasms upper, upper aerodigestive tract neoplasms	*Number of citations identified in Search:* 3558 *Number of studies included:* 6 *Number of patients in all included studies:*	~~5.~~ No association between lifetime marijuana use and risk of head and neck cancer (OR = 1.021, 95% CI = 0.912-1.143)	9/11

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		Inclusion criteria: case-control studies, cohort, or systematic reviews; allocation criteria defined for cases and controls; cases with definitive diagnosis of head and neck cancer; matched controls by at least gender *Exclusion criteria:* technical articles; reports or case reports; opinion articles; review articles	907		
Gurney, 2015, New Zealand	*Population:* adult cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* testicular cancer	*Databases searched:* CINAHL, Cochrane library, EMBASE, Medline, ProQuest Central, ProQuest Dissertations and Theses, Scopus, Web of Science *Years searched:* January 1980 until May 2015 *Key words used:* cannabi*, marijuana, marihuana, THC, tetrahydrocannabinol, cancer of the testi*, seminoma*, testi* cancer, testi* carcinoma, testi* germ cell tumo(u)r, testi* neoplasm, testi* tumo(u)r *Inclusion criteria:* reported association between cannabis and testicular cancer; data provided were summary associations *Exclusion criteria:* not reported	*Number of citations identified in Search:* 149 *Number of studies included:* 3 *Number of patients in all included studies:* 719	~~6.~~• Current cannabis use, using cannabis on a weekly basis, and chronic use associated with testicular germ cell tumors ~~7.~~• Current cannabis use: OR = 1.62 (95% CI = 1.13-2.31) ~~8.~~• Weekly use: OR = 1.92 (95% CI = 1.35-2.72) ~~9.~~• Chronic use (more than 10 years): OR = 1.50 (95% CI = 1.08-2.09)	8/11
Huang, 2015, United States	*Population:* marijuana users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* any cancer	*Databases searched:* PubMed, Medline *Years searched:* inception until August 2014 *Key words used:* marijuana, cannabis, cancer *Inclusion criteria:* epidemiologic studies investigating marijuana use that provided risk	*Number of citations identified in Search:* not reported *Number of studies included:*	~~10.~~• No association with head and neck, and lung cancer ~~11.~~• Associated with testicular cancer ~~12.~~• Insufficient evidence for bladder, prostate, penile, cervical and childhood cancer, but small associations exist for	5/11

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		estimates for marijuana exposure *Exclusion criteria:* not reported	34 *Number of patients in all included studies:* 21,138	prostate and cervical cancer ~~13.~~ Tends to be dose-dependent	
Mehra, 2006, United States	*Population:* marijuana smokers *Intervention:* marijuana smoking *Comparator:* non-users, tobacco-only smokers *Outcome:* lung cancer, changes to the lung that could lead to cancer, inhaled tar exposure	*Databases searched:* Medline, EMBASE, Psychlit *Years searched:* 1966 until October 2005 *Key words used:* cannabis, cannabinoids, marijuana abuse, marijuana smoking, marijuana usage, neoplasms, carcinoma, pathology, smoking/pathology, tars/respiratory tract diseases, respiratory physiology, lung, respiratory tract tumor, respiratory tract infections, respiratory system *Inclusion criteria:* adults (18+); humans *Exclusion criteria:* letters, reviews, case series involving fewer than 10 patients; studies not involving humans or intentional smoking or lung conditions	*Number of citations identified in Search:* 186 *Number of studies included:* 19 *Number of patients in all included studies:* 66,349 (only the number of male participants reported)	~~14.~~ Cannabis smoking associated with more inhaled tar exposure than tobacco smoking ~~15.~~ More pathological lung changes in cannabis smokers compared to tobacco smokers ~~16.~~ No association with cannabis smoking and lung cancer, despite more tar and pathological changes	8/11

Health Effects

Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Calabria, 2010, Australia	*Population:* cannabis users *Intervention:* cannabis exposure *Comparator:* general	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* January 1990 until January 2008 *Key words used:* cannabis, mortality, cohort, drug use	*Number of citations identified in Search:* not reported	~~1.~~ Insufficient data to determine all-cause mortality is higher in users compared to the general population ~~2.~~ Heavy cannabis use	5/11

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	population *Outcome:* overall mortality	*Inclusion criteria:* human studies; mortality associated with cannabis use or dependence *Exclusion criteria:* not focused on cannabis or mortality; review articles and case series	*Number of studies included:* 19 *Number of patients in all included studies:* 387,635 (cannabis use not reported)	associated with increased risk of poor driving 3. Cannabis use associated with suicide, but minimal evidence	
Blavos, 2017, United States	*Population:* college students *Intervention:* cannabis use *Comparator:* general population *Outcome:* college retention, academic performance, health outcomes, legal or conduct issues	*Databases searched:* PubMed, Academic Search Complete, OhioLINK Electronic Journal Center, ProQuest Dissertations, and Google Scholar *Years searched:* searched in December 2014 *Key words used:* marijuana, cannabis; college students, college; academics; law, legal, conduct, judicial; cognition; negative outcomes, consequences; perceived norms *Inclusion criteria:* published after 2000; focused on undergraduate students aged 17-24 who used marijuana; and reported on associated effects of marijuana use *Exclusion criteria:* did not include U.S. college students exclusively; article published before 2000; if the research was intervention-based	*Number of citations identified in Search:* 70 *Number of studies included:* 35 *Number of patients in all included studies:* 35,835	• Marijuana users were more likely to suffer from schizotypy and experience difficulty coping with anxiety and stress • Users visited the doctor for physical or mental health reasons, were sick more often, and experienced higher levels of emotional impairment and physical injury • Marijuana use was associated with discontinued enrollment among college students	4/11
Grotenhermen, 2010, Germany	*Population:* cannabis users *Intervention:* cannabis use	*Databases searched:* PubMed, EMBASE, Web of Science *Years searched:* inception until February 2009	*Number of citations identified in Search:* not	4. Most studies had concurrent tobacco and cannabis use, so little association was found for just cannabis and arteritis	4/11

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	Comparator: non-users *Outcome:* arteritis	*Key words used:* cannabi*, marijuana, THC, arteritis, thromboangiitis obliterans, Buerger's disease *Inclusion criteria:* case reports, reviews, commentaries; cannabis arteritis; TAO mentioning cannabis, marijuana, cannabinoids, or THC *Exclusion criteria:* not reported	reported *Number of studies included:* 17 *Number of patients in all included studies:* 94		
Hackam, 2015, Canada	*Population:* cannabis users *Intervention:* cannabis exposure *Comparator:* non-users *Outcome:* stroke	*Databases searched:* Medline, EMBASE *Years searched:* inception until November 30th, 2014 *Key words used:* cannabis, cerebrovascular disease *Inclusion criteria:* case studies; cases underwent parenchymal imaging; humans *Exclusion criteria:* not reported	*Number of citations identified in Search:* 989 *Number of studies included:* 34 *Number of patients in all included studies:* 64	~~5.~~ Cannabis exposure associated with increased risk of stroke	5/11
Koranztopolous, 2008, Greece	*Population:* marijuana smokers *Intervention:* marijuana smoking *Comparator:* non-smokers *Outcome:* atrial fibrillation	*Databases searched:* Medline, EMBASE *Years searched:* inception until January 2007 *Key words used:* marijuana, hashish, cannabis, atrial fibrillation, arrhythmias, tachycardia, palpitations, heart, cardiovascular *Inclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 6	~~6.~~ Marijuana smoking associated with atrial fibrillation, but minimal evidence exists	4/11

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		Exclusion criteria: not reported	*Number of patients in all included studies:* 6		
Lindsey, 2012, United States	*Population:* illicit drug users *Intervention:* illicit and prescription drug exposure *Comparator:* illicit drugs with no concurrent prescription drugs *Outcome:* cross-interactions of substances	*Databases searched:* Medline, Iowa Drug Information Service, Google Scholar, International Pharmaceutical Abstracts, EBSCO Academic Search Premier *Years searched:* inception to March 2011 *Key words used:* cocaine, marijuana, cannabis, methamphetamine, amphetamine, ecstasy, *N*-methyl-3,4-methylenedioxymethamphetamine, methylenedioxymethamphetamine, heroin, gamma-hydroxybutyrate, sodium oxybate, interaction(s), drug interactions, drug-drug interactions *Inclusion criteria:* human clinical trials, case reports/reviews *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	~~7.~~• Cannabis may interact with tricyclic antidepressants, protease inhibitors, and warfarin therapy ~~8.~~• Most common side effects of interactions related to cardiac functioning ~~9.~~• May interact with other depressants (alcohol, barbiturates) but no clinical trials	4/11
Martinasek, 2016, United States	*Population:* cannabis users *Intervention:* cannabis inhalation *Comparator:* general population *Outcome:* respiratory effects	*Databases searched:* PubMed, OVID, Web of Science *Years searched:* *Key words used:* marijuana; marijuana smoking and respiratory system; cannabis: adverse effects; marijuana smoking: epidemiology; marijuana smoking/epidemiology; cannabis/adverse effects*; marijuana smoking/physiopathology; lung	*Number of citations identified in Search:* 281 *Number of studies included:* 48 *Number of*	• 12 studies examined the risk of lung cancer, eight of which indicated increased risk of lung cancer (ranged from 2.1 to 4.1-fold increased risk); the other four reported no or deceased risk of lung cancer • Lung bullae identified in five cases • COPD, emphysema, lung	5/11

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		disease/chemically induced; marijuana smoking/adverse effects*; respiratory system/drug effects*; marijuana abuse/respiratory complications *Inclusion criteria:* inhalation marijuana; respiratory health effects *Exclusion criteria:* systematic reviews; editorials; commentaries; non-English language articles; animal studies; unattainable full text articles; not inclusive of respiratory health	*patients in all included studies:* 207,908	hyperinflation, infectious disease transmission, and other pulmonary effects and respiratory symptoms also noted	
Reece, 2009, Australia	*Population:* chronic cannabis users *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* psychiatric, respiratory, cardiovascular, bone, neurodevelopment, genotoxic, mutagenic, and oncogenic effects	*Databases searched:* Medline, PubMed, PsychInfo, Google Scholar, Scopus, ProQuest, Web of Knowledge, EbscoHost *Years searched:* not reported *Key words used:* cannabis, marijuana, marihuana, toxicity, complications, mechanisms *Inclusion criteria:* original data; describe mechanisms; published in "recent years" *Exclusion criteria:* not reported	*Number of citations identified in Search:* 5198 *Number of studies included:* not reported *Number of patients in all included studies:* not reported	~~10.~~• Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues ~~11.~~• Heavy chronic use may be associated with bone loss and certain cancers	2/11
Schwitzer, 2015, France	*Population:* cannabis users *Intervention:* cannabis exposure *Comparator:* non-users *Outcome:* visual processing	*Databases searched:* PubMed, Google Scholar *Years searched:* inception until February 2014 *Key words used:* cannabis, cannabinoid, marijuana, THC, vision, visual processing, visual system, visual cortex, retinal processing, retina, thalamus *Inclusion criteria:* English language only; related to	*Number of citations identified in Search:* not reported *Number of studies included:* not reported	~~12.~~• Acute and regular cannabis use associated with increased visual disturbances, increased foveal glare, decreased retinal processing, reduction of visual symptoms, decreased activation in the secondary visual cortex, and decreased thalamic volume ~~13.~~• Many effects residual	4/11

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		cannabis and vision *Exclusion criteria:* not reported	*Number of patients in all included studies:* not reported	~~14.~~• Also associated with improvement in some visual functioning, but no experimental evidence	
Tetrault, 2007, United States	*Population:* adult marijuana smokers *Intervention:* acute and chronic marijuana exposure *Comparator:* non-users *Outcome:* airway response, pulmonary function or respiratory complications	*Databases searched:* Medline, PsychInfo, EMBASE *Years searched:* January 1966 until October 2005 *Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not humans; did not report results of respiratory complications or pulmonary functioning; case series with fewer than 10 subjects	*Number of citations identified in Search:* 965 *Number of studies included:* 34 *Number of patients in all included studies:* 14,183	~~15.~~• Acute marijuana inhalation associated with bronchodilation, but not present in long-term smokers ~~16.~~• Long-term smoking associated with increased respiratory complications such as cough, sputum production, and wheeze	8/11
Mental Illness					
Author, Year of Publication, Country	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Alharbi, 2016, Saudi Arabia	*Population:* those with psychosis *Intervention:* cannabis or amphetamine-type stimulant use *Comparator:* *Outcome:* psychosis	*Databases searched:* MEDLINE, PsycInfo, PubMed *Years searched:* 1980 to 2015 *Key words used:* methamphetamine, amphetamine, stimulants; schizophrenia, psychosis; cannabis, marijuana, hash, hashish *Inclusion criteria:* English *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of*	• Mixed evidence for cannabis use preceding psychosis, though may be higher for those who are at higher risk • Cannabis use higher in those with first-episode psychosis • Cannabis use may be related to earlier onset of psychosis, especially if cannabis is used early in youth • Cannabis use is neither	3/11

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			patients in all included studies: not reported	sufficient nor necessary for psychosis • THC exposure influences dopamine function in the prefrontal cortex • Overstimulation of the CB1 receptor on GABAergic and glutamatergic terminals may play an important role in producing THC-induced psychosis	
Ben Amar, 2007, Canada	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychosis	*Databases searched:* PubMed, PsychInfo *Years searched:* January 1962 until June 2005 *Key words used:* cannabis or marijuana, schizophrenia or psychosis *Inclusion criteria:* longitudinal studies, reviews; addresses the causal nature of the cannabis/psychosis relationship *Exclusion criteria:* not reported	*Number of citations identified in Search:* 622 *Number of studies included:* 15 *Number of patients in all included studies:* 107,691	~~17.~~• Cannabis use was associated with psychosis in those with a vulnerability to psychosis ~~18.~~• Cannabis use associated with worsening of psychotic symptoms	3/11
Borges, 2016, Mexico	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* suicidality	*Databases searched:* Medline, PsychInfo, Google Scholar, public-use databases *Years searched:* 1990(1995 for acute use) until February 2015 *Key words used:* cannabis, marijuana, marihuana, suicide, suicide attempt, suicide ideation, suicidal, suicidality	*Number of citations identified in Search:* not reported *Number of studies included:* not reported	~~19.~~• Minimal evidence for acute cannabis use and suicidality ~~20.~~• Any and heavy cannabis use associated with suicidality, but heterogeneity and publication bias high ~~21.~~• Chronic cannabis use and death by suicide: OR = 2.56 (95% CI = 1.25-5.27)	5/11

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		Inclusion criteria: English language; original articles, critical review reports, public use data on cannabis use and suicidality *Exclusion criteria:* synthetic cannabinoids	*Number of patients in all included studies:* not reported	~~22.~~• Any cannabis use and suicidal ideation: OR = 1.43 (95% CI = 1.13-1.83) ~~23.~~• Heavy cannabis use and suicidal ideation: OR = 2.53 (95% CI = 1.00-6.39) ~~24.~~• Any cannabis use and suicide attempt: OR = 2.23 (95% CI = 1.24-4.00) ~~25.~~• Heavy cannabis use and suicide attempt: OR = 3.20 (95% CI = 1.72–5.94)	
Crippa, 2009, United Kingdom	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* anxiety	*Databases searched:* Medline, PsychLIT, EMBASE *Years searched:* inception until August 2008 *Key words used:* cannabis, marijuana, THC, tetrahydrocannabinol, delta-9-tetrahydrocannabinol, cannabinoids, anxiety, panic, phobia, stress *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	~~26.~~• Frequent cannabis use associated with higher levels of anxiety compared to non-users ~~27.~~• Higher prevalence of anxiety disorders in chronic cannabis users than the general population; anxiety disorders may increase risk of using cannabis ~~28.~~• Anxiety associated with cannabis withdrawal ~~29.~~• No association between cannabis use and an increased risk in developing anxiety disorders	4/11
Gibbs, 2015, United Kingdom	*Population:* cannabis users, those with bipolar *Intervention:* cannabis exposure	*Databases searched:* PsychInfo, Cochrane, Scopus, EMBASE, Medline *Years searched:* 1980 until June 2014 *Key words used:* cannabis, marijuana, delta-9-	*Number of citations identified in Search:* 781 *Number of*	~~30.~~• Cannabis use increases the likelihood, severity or duration of manic phases in those with bipolar disorder (OR = 2.97, 95% CI = 1.80-4.90) ~~31.~~• Cannabis use also associated	9/11

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	Comparator: non-users, those without bipolar *Outcome:* manic symptoms	tetrahydrocannabinol, cannabinoids, cannabidiol, cannabinol, tetrehydrocannabivarin, bipolar disorder, manic depressive disorder, mania, hypomania, manic depression, dipolar spectrum, onset, trigger, induce*, course *Inclusion criteria:* prospective primary experimental, prospective, cohort, longitudinal designs; participants had bipolar I or II or described as experiencing mania; clinical and subclinical mania symptoms and episodes; English language *Exclusion criteria:* participants primarily diagnosed with a psychotic disorder; non-English	*studies included:* 6 *Number of patients in all included studies:* 2,391	with increased risk of hypomanic symptoms in those at high risk of developing bipolar disorder	
Kedzoir, 2014, Germany	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* anxiety	*Databases searched:* PsychInfo, Medline *Years searched:* inception until March 2013 *Key words used:* cannabis, marijuana, marihuana, affective disorder, anxiety disorder, anxiety, misus*, abus*, depend*, harmful use, harmful usage *Inclusion criteria:* general population; anxiety diagnosis with or without cannabis use; odds ratios; cannabis use with or without anxiety *Exclusion criteria:* no data from healthy non-users; data from people seeking treatment for cannabis use disorder or other psychiatric disorders other than anxiety or depression; inadequate data	*Number of citations identified in Search:* 267 *Number of studies included:* 31 *Number of patients in all included studies:* 173,577	~~32.~~• Those with anxiety are more likely to use cannabis or have cannabis use disorder ~~33.~~• Anxiety and cannabis use: OR = 1.24 (95% CI = 1.06-1.45) ~~34.~~• Anxiety and cannabis use disorder: OR = 1.68 (95% CI = 1.23-2.31) ~~35.~~• Comorbid anxiety and cannabis use disorder may require more treatment than cannabis use disorder alone	9/11
Kraan, 2016, The Netherlands	*Population:* those at ultra-high risk of psychosis	*Databases searched:* EMBASE, Medline, PsychInfo *Years searched:* 1996 until August 2015	*Number of citations identified in*	~~36.~~• No relationship between any cannabis use and transition to psychosis in ultra-high risk	10/11

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	Intervention: cannabis use *Comparator:* non-users, general population *Outcome:* psychosis	*Key words used:* clinical high risk, attenuated positive symptoms, brief limited intermittent psychotic symptoms, genetic risk and deterioration, basic symptoms, familial high risk, prodrom*, at risk mental state, ultra high risk, attenuated psychotic symptoms, high risk, substance use, substance abuse, substance use disorder, cannabis, marijuana, tobacco, hallucinogens, cannabis misuse, risk factors, psychosis, schizophrenia, schizo*, psychoti* *Inclusion criteria:* individuals meeting ultra-high risk criteria; reported the effect of cannabis use on transition to psychosis; prospective design; English language *Exclusion criteria:* cannabis use not assessed separately	*Search:* 5560 *Number of studies included:* 7 *Number of patients in all included studies:* 330	individuals (OR = 1.14, 95% CI = 0.856-1.524) ~~37.~~• Cannabis abuse or dependence was significantly associated with transition to psychosis (OR = 1.75, 95% CI = 1.135-2.710)	
Large, 2011, Australia	*Population:* substance users *Intervention:* cannabis, alcohol, other psychoactive drugs *Comparator:* patients with psychosis but no drug use *Outcome:* age of onset of psychosis	*Databases searched:* CINAHL, EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until June 2010 *Key words used:* schizophrenia, psychosis, substance, dual diagnosis, drug abuse, cannabis, alcohol, amphetamine, cocaine, age *Inclusion criteria:* English language; reported the use of a psychoactive drug other than tobacco; compared age of onset with a control group *Exclusion criteria:* not reported	*Number of citations identified in Search:* 1293 *Number of studies included:* 83 *Number of patients in all included studies:* 8167	~~38.~~• Significantly earlier age of onset of psychosis in cannabis users compared to non-users (2.70 years earlier, p<0.001) ~~39.~~• General substance use also associated with earlier age of onset ~~40.~~• Alcohol not associated with earlier onset	9/11
Le Bec, 2009,	*Population:* adolescents or	*Databases searched:* MEDLINE	*Number of*	~~1.~~• Statistically significant	3/11

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France	young adults without psychosis *Intervention:* cannabis use *Comparator:* non-users *Outcome:* chronic psychotic disorders	*Years searched:* 1966 until June 2005 *Inclusion criteria:* human studies; prospective and longitudinal studies; objective of studies to examine causal link between cannabis use and psychosis *Exclusion criteria:* literature reviews	*citations identified in Search:* 60 *Number of studies included:* 7 *Number of patients in all included studies:* 50,275	associations between cannabis use and psychosis or psychotic symptoms 2. Those initially with pre-psychotic symptoms had stronger associations between cannabis and psychosis 3. Many studies observed dose-response associations and cannabis use occurring before emergence of psychotic symptoms	
Lev-Ran, 2014, Canada	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* depression	*Databases searched:* EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until December 2012 *Key words used:* cannabis, marijuana, marihuana, depression, depressed, depressive disorder, mood, mood disorder, affective disorder, dysthymia *Inclusion criteria:* original paper in a peer-review journal; population-based data collected longitudinally and prospectively; cannabis use; depression was controlled at baseline; odds ratio *Exclusion criteria:* not reported	*Number of citations identified in Search:* 4764 *Number of studies included:* 14 *Number of patients in all included studies:* 76,058	4. Cannabis use associated with risk of developing depression compared to non-users 5. Any cannabis use and depression: OR = 1.17 (96% CI = 1.05-1.30) 6. Heavy cannabis use and depression compared to no or light use: OR = 1.62 (95% CI = 1.21-2.16)	10/11
Marconi, 2016, United Kingdom	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* PubMed, EMBASE, PsychInfo *Years searched:* inception until December 31st 2013 *Key words used:* dose-response, daily use, duration, high frequency, heavy use, psychosis, schizophrenia,	*Number of citations identified in Search:* 571 *Number of*	1. Heavy cannabis use associated with a significant increase in risk of schizophrenia and other psychotic outcomes compared to non-users (OR = 3.90, 95% CI = 2.84-5.34)	7/11

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	Outcome: psychosis or psychotic symptoms	schizophreni*, cannab*, cannabis, marijuana, marihuana *Inclusion criteria:* peer-reviewed; any language; cohort, cross-sectional; assessed cannabis with a dose criterion before onset of psychosis; psychosis-related outcomes *Exclusion criteria:* subjects who had a mental illness before cannabis use; subjects at ultra-high risk; studies examining comorbidity; studies examining age of onset of psychosis; neuropsychological measures or schizoid personality traits; cannabis not measured by dose	*studies included:* 16; 10 for meta-analysis *Number of patients in all included studies:* 66,816	~~2.~~ Average cannabis use also significantly associated with schizophrenia and psychotic outcomes (OR = 1.97, 95% CI = 1.68-2.31)	
Minozzi, 2010, Italy	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychosis	*Databases searched:* Medline, EMBASE, CINAHL *Years searched:* 2000 until August 2007 *Key words used:* substance-related disorders, cannabis, marihuana, marijuana, psychosis, psychotic disorders, schizophrenia, psychotic* *Inclusion criteria:* systematic reviews that assess cannabis and psychosis *Exclusion criteria:* not reported	*Number of citations identified in Search:* 41 *Number of studies included:* 5 *Number of patients in all included studies:* 265,403	~~3.~~ Consistent, significant associations between cannabis use and onset of psychotic symptoms ~~4.~~ Quality and methodological concerns limit the results	7/11
Moore, 2007, United Kingdom	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Wed of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib *Years searched:* inception until September 2006	*Number of citations identified in Search:* 4804 *Number of*	~~5.~~ Increased incidence of psychosis-related outcomes in those who had ever used cannabis (OR=1.41, 95% CI: 1.20-1.65) ~~6.~~ Heavy and earlier use increased	7/11

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	Outcome: psychotic or affective mental health outcomes	*Key words used:* psychosis, schizophrenia, affective disorder, depression, cannabis (all with synonyms not reported) *Inclusion criteria:* population-based longitudinal or case-control nested studies; humans *Exclusion criteria:* patients with mental illness or substance-related problems; prison populations; RCTs of medical cannabis	*studies included:* 11 *Number of patients in all included studies:* not reported	risk ~~7.~~ More frequent cannabis use increased the incidence of any psychotic outcome (OR = 2.09, 95% CI = 1.54-2.84)	
Myles, 2016, Australia	*Population:* patients with first episode psychosis *Intervention:* inhaled cannabis *Comparator:* patients with first episode psychosis who do not use cannabis, patients with chronic psychosis *Outcome:* length of time from cannabis use to psychosis	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Science *Years searched:* October 2014 to "current" *Key words used:* psychosis, schizophrenia, cannabis, marijuana *Inclusion criteria:* English language; cohorts that reported on first episode psychosis; inhaled organic cannabis; could be included in a meta-analysis *Exclusion criteria:* not first episode; subjects suffering from drug-induced or organic psychoses; subjects recruited for a clinical trial or RCT; synthetic or oral cannabinoids; cohorts that were part of a larger cohort	*Number of citations identified in Search:* 2113 *Number of studies included:* 61 *Number of patients in all included studies:* 10,762	~~8.~~ 33.7% (95% CI = 29-38%) of subjects used cannabis prior to psychosis ~~9.~~ Pooled interval between first cannabis use and age of psychosis onset was 6.3 years (SMD = 1.56, 95% CI = 1.40-1.72) ~~10.~~ Cannabis use higher in patients with first episode psychosis compared to patients with chronic, long-term psychosis	6/11
Myles, 2012, Australia	*Population:* smokers *Intervention:* cannabis or tobacco use *Comparator:* tobacco users	*Databases searched:* EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until September 2011 *Key words used:* cannabis, marijuana, tobacco,	*Number of citations identified in Search: 589* *Number of*	~~11.~~ Tobacco not significantly associated with earlier ago of onset of psychosis ~~12.~~ Cannabis significantly associated with earlier age of onset of schizophrenia spectrum	10/11

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	compared to cannabis users *Outcome:* age of onset of psychosis	nicotine, smoking, schizophrenia, psychosis *Inclusion criteria:* separately reported substance and non-using groups; report age of onset of psychosis; be suitable for meta-analysis *Exclusion criteria:* bipolar, psychotic depression, substance-induced psychosis	*studies included:* 38 for cannabis; 40 for tobacco *Number of patients in all included studies:* 3199 for cannabis; 5562 for tobacco	psychosis and broad psychosis 13. Age of psychosis was 32 months earlier (SMD = 0.399, 95% CI = -0.493- -0.306) for cannabis users compared to non-users	
Rey, 2004, Australia	*Population:* young cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* behavioural problems, mental disorders	*Databases searched:* Medline, Pre-Medline, PsychInfo, EMBASE, Web of Science *Years searched:* 1994 until 2004 *Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not English; adults	*Number of citations identified in Search:* Not reported *Number of studies included:* Not reported *Number of patients in all included studies:* Not reported	14. Marijuana has a low non-continuation rate 15. About 10% of users have cannabis dependence; more common in those who start use young 16. Data on cannabis as a gateway drug is inconclusive 17. Symptoms of anxiety and depression higher in females, but results are inconclusive	1/11
Ruiz-Veguilla, 2012, Spain	*Population:* patients with schizophrenia and first-episode psychosis *Intervention:* cannabis use *Comparator:* non-users *Outcome:* neurological soft	*Databases searched:* BIOSIS Citation Index SM, BIOSIS Previews, the Cochrane Library, EMBASE, Inspec, ISI Proceedings, Journal Citation Reports, Medline, PsychInfo, PubMed, Web of Science *Years searched:* inception until November 2011 *Key words used:* psycho, schizophreni*, first episode, neurolog* soft signs, neurolog*	*Number of citations identified in Search:* 1225 *Number of studies included:* 5, 2 for meta-analysis	18. Smoking cannabis was associated with fewer neurological soft signs in psychotic patients than non-users	8/11

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	signs focused on sensory integration, motor coordination, motor sequencing, and primitive reflexes (ex. audio-visual integration, finger-nose test, gaze)	soft signs, movement* disorder*, NSS, sensory integrati*, motor coordinati*, motor sequenc*, primitive reflex*, audio-visual integrat*, stereognos*, graphaestes*, extinction, right-left confusion, tandem walk*, rapid alternat* movement*, finger-thumb opposition, finger-nose test, rhythm tapping, fist-ring test, rhythm tapping, fist-ring test, fist-edge-palm test, Oszeretski test, gaz*, palmo-mental, snout, grasp*, cannab*, tetrahydrocannab*, THC, marihuana, marijuana, endocannabinoid*, CBD *Inclusion criteria:* Subjects met the clinical definition of psychosis or schizophrenia; any cannabis use; any age and gender; studies were not excluded due to any medications or comorbidities of subjects; all the studies were included irrespective of other design quality issues, and case report studies were also initially considered *Exclusion criteria:* not reported	*Number of patients in all included studies:* 172		
Schoeler, 2016, United Kingdom	*Population:* patients with psychosis *Intervention:* continued cannabis use *Comparator:* non-users, patients who discontinue use *Outcome:* relapse	*Databases searched:* Medline *Years searched:* inception until April 2015 *Key words used:* marijuana, marihuana, cannabis, illicit substance, outcome, hospital*, relapse, readmission, psycho*, bipolar, schizophrenia *Inclusion criteria:* patients with pre-existing psychotic disorders; follow-up of at least 6 months *Exclusion criteria:* continued or discontinues	*Number of citations identified in Search:* 1903 *Number of studies included:* 24 *Number of patients in all included studies:*	~~19.~~• Patients who continued using cannabis had higher relapse rates than patients who discontinued use and non-users ~~20.~~• Patients who discontinued cannabis did not differ in relapse rate from non-users	9/11

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		cannabis use could not be determined	16565		
Semple, 2005, United Kingdom	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* schizophrenia or schizophrenia-like psychosis	*Databases searched:* EMBASE, PsychInfo, Medline *Years searched:* 1966 until January 2004 *Key words used:* cannabis, schizophrenia, other key words not reported *Inclusion criteria:* original data; case-control studies; exposure to cannabis preceded schizophrenia or schizophrenia-like psychosis *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 11, 7 in meta-analysis *Number of patients in all included studies:* 113,802	21. Early use of cannabis was associated with an increased risk of psychosis (OR = 2.9, 95% CI = 2.4-3.6) 22. Dose-related effect seen in individuals who used cannabis during adolescence, those who previously experience psychosis, and those at genetic high risk	5/11
Szoke, 2014, France	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychometric schizotypy	*Databases searched:* PubMed, PsychInfo *Years searched:* inception until 2013 *Key words used:* schizot*, psychotic-like, psychosis-proneness, cannabi*, THC, marijuana *Inclusion criteria:* humans; English-language *Exclusion criteria:* not reported	*Number of citations identified in Search:* 63 *Number of studies included:* 29 *Number of patients in all included studies:* 21,736	23. Life-time cannabis use and current cannabis use were both associated with higher schizotypy scores	3/11
Van der Meer, 2012, The Netherlands	*Population:* those at clinical high risk for psychosis *Intervention:* cannabis use	*Databases searched:* Medline, PsychInfo, PubMed, EMBASE *Years searched:* 1995 until October 31st 2011	*Number of citations identified in Search:* 729	24. Inconclusive results about cannabis use and severity of symptoms at baseline, pre-psychotic symptoms, and early	4/11

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	Comparator: non-users *Outcome:* first episode psychosis	*Key words used:* at risk population*, high risk, UHR, risk factor*, prodromal, prodrome, at * risk, early * symptom*, clinical* * risk, high risk population, psychosis, psychoses, psychotic, psychotic disorder*, prepsychosis, prepsychotic, schizophrenia, schizophrenic, paranoi*, delusion*, hallucination*, hallucinogen*, psychedelic?, psychodelic?, cannabis, cannabinoid*, tetrahydrocannabinol, THC, hashish, marijuana, marijuana, marijuana usage, marijuana smoking, hallucinogenic drugs, psychoactive drug, psychedelic agent* *Inclusion criteria:* English language; contained data on the relation between cannabis use and clinical high risk status or symptomatology; first episode *Exclusion criteria:* papers where cannabis was only analyzed as a confounder or was not analyzed separately	*Number of studies included:* 11 *Number of patients in all included studies:* 742	onset of psychosis ~~25.~~ Weak evidence suggesting cannabis may worsen symptoms in younger users	
Zammit, 2008, United Kingdom	*Population:* patients with psychosis *Intervention:* cannabis use *Comparator:* patients with psychosis without cannabis use *Outcome:* severity of symptoms, adherence to treatment, other adverse	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib *Years searched:* inception until November 2006 *Key words used:* psychosis, schizophrenia, hallucinations, delusions, substance abuse, and unspecified synonyms *Inclusion criteria:* longitudinal studies of people with psychosis; case-control nested studies	*Number of citations identified in Search:* 15,303 *Number of studies included:* 13 *Number of patients in all included studies:*	~~26.~~ Cannabis use was associated with increased relapse and rehospitalization and decreased treatment adherence ~~27.~~ Inconsistent results about cannabis use and severity of symptoms	9/11

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	outcomes	*Exclusion criteria:* comorbid psychosis and cannabis misuse or dependence	not specified		
Neurocognitive Effects					
Author, Year of Publication, Country	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Broyd, 2016, Australia	*Population:* cannabis users *Intervention:* cannabis exposures *Comparator:* non-users *Outcome:* cognitive outcomes	*Databases searched:* PubMed, Scopus *Years searched:* January 2004 until February 2015 *Key words used:* cannabi*, marijuana, cognit*, memory, attention*, learning, inhibit*, impuls*, reward, decision making, executive function*, information process*, performance, functional brain imaging, fMRI, event related potential, electroencephalogram, not rats or mice or review or MDMA or ecstasy or amphetamine *Inclusion criteria:* neuropsychological or cognitive experimental tasks; regular or former cannabis users or following acute administration of cannabis; human participants *Exclusion criteria:* cannabis is not the primary drug; trait measures of cognition; major psychopathology or neurological conditions; animals; neuroimaging, electrophysiological, or autonomic measures as the primary outcome; treatment; "real world" tasks; case studies	*Number of citations identified in Search:* 6441 *Number of studies included:* 105 *Number of patients in all included studies:* not reported	~~28.~~• Impaired verbal learning and memory and psychomotor functioning in chronic and occasional users ~~29.~~• Inconsistent evidence regarding working memory, attention, and executive functioning, but some evidence suggests impairment ~~30.~~• Many impairments exist after abstinence	4/11
Ganzer, 2016, Germany	*Population:* abstinent cannabis users	*Databases searched:* EMBASE, Ovid MEDLINER, PsychInfo, PSYNDEXplus Literature	*Number of citations identified in*	~~31.~~• Poorer attention, motor function, and memory and learning in abstinent users than	9/11

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	Intervention: cannabis use *Comparator:* current users, non-users *Outcome:* neurocognitive functioning	*Years searched:* 2004 until 2015 *Key words used:* cannabi*, THC, marijuana, marihuana, neuro*, cognit*, assess*, abilit*, affect*, process*, function*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, non-intox*, persist* *Inclusion criteria:* clinical trials; humans *Exclusion criteria:* subjects with a history of chronic medical and neurological illness or severe psychiatric disorder, or substance use disorder; animal studies; case reports, expertises, commentaries, books	*Search:* 1038 *Number of studies included:* 38 *Number of patients in all included studies:* 2025	non-users ~~32.~~ Impairments in inhibition, impulsivity, and decision making in abstinent users, but inconsistent evidence ~~33.~~ Highly inconsistent evidence with regards to visual spatial functioning ~~34.~~ Differences in activation patterns and structural differences in the brain of abstinent users compared to controls	
Garfield, 2013, Australia	*Population:* illicit substance users *Intervention:* substance use *Comparator:* non-users *Outcome:* anhedonia	*Databases searched:* PubMed, PsychInfo, Medline *Years searched:* not reported *Key words used:* anhedonia, drug, substance, alcohol, nicotine, dependence, addiction, abuse *Inclusion criteria:* human samples; lifetime history of a defined substance use disorder or long-term daily use; measured anhedonia *Exclusion criteria:* reviews; non-substance related psychiatric disorders	*Number of citations identified in Search:* 245 *Number of studies included:* 32, 3 on cannabis *Number of patients in all included studies:* not reported	~~35.~~ Those with baseline cannabis abuse reported higher levels of anhedonia than those with no baseline cannabis abuse ~~36.~~ Baseline anhedonia did not predict cannabis use ~~37.~~ Abstinence from cannabis was associated with a decrease in anhedonia	3/11
Gates, 2014, Australia	*Population:* adult cannabis users *Intervention:* measured	*Databases searched:* EMBASE, CINAHL, Cochrane Library/EBM Reviews, Medline, PsycEXTRA	*Number of citations identified in Search:* 2215	~~38.~~ No consistent effect of cannabis on sleep time ~~39.~~ Increased time spent in stage 2 and decreased time in slow	4/11

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	cannabis *Comparator:* non-users *Outcome:* sleep	*Years searched:* inception until 2012 *Key words used:* cannabinoid/s, tetrahydrocannabinol, THC, cannabis/marijuana, sleep, sleep onset, sleep apnea, sleep treatment, sleep wake cycle, sleep deprivation, rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep, sleep disorder, insomnia *Inclusion criteria:* not reported *Exclusion criteria:* review papers, posters, qualitative articles, opinion pieces, letter, editorials, case reports (n<7), published abstracts	*Number of studies included:* 39 *Number of patients in all included studies:* 203 recreational users	wave sleep 40. Overall results inconsistent	
Gonzalez, 2002, United States	*Population:* abstinent cannabis users *Intervention:* cannabis use *Comparator:* non-users, current users *Outcome:* neurocognitive effects	*Databases searched:* not reported *Years searched:* not reported *Key words used:* not reported *Inclusion criteria:* non-acute neuropsychological effects of cannabis; humans; adults; English language *Exclusion criteria:* not reported	*Number of citations identified in Search:* 1014 *Number of studies included:* 40 *Number of patients in all included studies:* 741	41. Poorer motor performance, executive function, reaction time, learning, and verbal domains 42. However, results highly inconsistent and generally poor quality	5/11
Grant, 2003, United States	*Population:* adult, long-term cannabis users *Intervention:* cannabis use *Comparator:* non-users,	*Databases searched:* Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts international, Article First, Science Citation Index Expanded, Social Science Citation Index	*Number of citations identified in Search:* 1014 *Number of*	43. Inconsistent results on all measures except learning and forgetting, both of which were small 44. Learning: -0.21 (99% CI = -0.39- -0.022	4/11

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	occasional users *Outcome:* neurocognitive performance	*Years searched:* not reported *Key words used:* marijuana, marijuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognitive, assessment, ability, effects, processes, impairment, cognition, drug effects *Inclusion criteria:* includes a cannabis only group and control group; can calculate effect size; measures neuropsychological tests; reports length of abstinence *Exclusion criteria:* not humans or adults	*studies included:* 11 for meta-analysis *Number of patients in all included studies:* 1032; 632 users	45.• Forgetting: -0.27 (99% CI = -0.49- -0.044)	
Rabin, 2011, Canada	*Population:* patients with schizophrenia *Intervention:* cannabis use *Comparator:* non-users *Outcome:* neurocognition	*Databases searched:* PsychInfo, Medline, PubMed *Years searched:* not reported *Key words used:* schizophrenia, psychosis, cannabis, tetrahydrocannabinol, THC, marijuana, neuropsych*, neurocog*, cognitive impairment *Inclusion criteria:* English language; humans; compare schizophrenia cannabis-users to a control group; could be used for meta-analysis; participants have no other concurrent drug or alcohol use disorders *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 8 *Number of patients in all included studies:* 942; 356 cannabis users	46.• Higher neurocognitive functioning in cannabis users compared to non-users	4/11
Schoeler, 2016, United Kingdom	*Population:* patients with or without a psychotic disorder *Intervention:* long-term cannabis use	*Databases searched:* Medline *Years searched:* inception until June 2014 *Key words used:* neuropsych*, cognit*, memory,	*Number of citations identified in Search:* not reported	47.• Cannabis use significantly impaired global memory in healthy users compared to non-users 48.• Cannabis use in patients	4/11

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	Comparator: non-users *Outcome:* memory function	learning, recall, marijuana, marihuana, cannabis, THC, cannabinol, cannabidiol *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of studies included:* 88 *Number of patients in all included studies:* 3261 subjects with a psychotic disorder	with psychosis improved memory compared to non-users	
Schreiner, 2012, United States	*Population:* chronic cannabis users, abstinent or current *Intervention:* cannabis use *Comparator:* non- or minimal-users *Outcome:* neurocognitive performance	*Databases searched:* PsychInfo, PsycARTICLES, PubMed, Medline *Years searched:* not reported *Key words used:* marijuana, marihuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognit*, assess*, ability*, effect*, process*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, persist* *Inclusion criteria:* human subjects; cannabis only users; control group of nonusers or with very limited drug experience; could be included in meta-analysis; behavioral measure of neuropsychological functioning; participants not under the influence of any substances during testing; history of other substance use or psychiatric illness addressed; the period of abstinence from cannabis before testing is reported *Exclusion criteria:* reviews; acute effects only; brain	*Number of citations identified in Search:* not reported (~800) *Number of studies included:* 33 *Number of patients in all included studies:* 1010 current or former users	~~49.~~• Cannabis use was associated with significant effects on global neurocognition ~~50.~~• No significant residual effects seen on abstinent users compared to non-users	5/11

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		imaging; not humans or chronic users			
Smith, 2014, Australia	*Population:* chronic heavy users or drug dependent *Intervention:* chronic drug use or dependence *Comparator:* healthy non-dependent individuals *Outcome:* behavioral inhibition	*Databases searched:* PubMed, PsychInfo, Project Cork, DRUG, Medline, Medline in process, EMBASE, CINAHL *Years searched:* not reported *Key words used:* Go-NoGo, SSRT, stop-signal, response inhibition, inhibit, disinhibit, neurocognitive function, executive function, executive dysfunction, cognitive control, cognition disorders, reaction time *Inclusion criteria:* English, compare drug dependent or chronic heavy-user group to control, report outcome on behavioural inhibition *Exclusion criteria:* studies that delivered stop-signals at only one delay; within-subject acute effects of drugs; studies on family members of substance dependent individuals	*Number of citations identified in Search:* 265 *Number of studies included:* 97 *Number of patients in all included studies:* 6,542	1. No statistically significant evidence of inhibitory deficit was observed for cannabis 1. Small to medium non-statistically significant effects were observed	7/11

Prenatal Effects

Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Conner, 2016, United States	*Population:* pregnant women *Intervention:* marijuana use *Comparator:* pregnant women with no marijuana use *Outcome:* neonatal outcomes	*Databases searched:* PubMed/MEDLINE, EMBASE, Scopus, Cochrane Library, ClinicalTrials.gov, Cumulative Index to Nursing and Allied Health *Years searched:* inception to August 2015 *Key words used:* neonatal outcomes, pregnancy	*Number of citations identified in Search:* 2,693 *Number of studies included:* 31	Unadjusted analysis • Low birth weight: 15.4% vs. 10.4%, RR 1.43, 95% CI: 1.27-1.62 • Preterm delivery: 15.3% vs. 9.6%, RR 1.32, 95% CI: 1.14-1.54 • Evidence of statistical	9/11

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		complications, marijuana use *Inclusion criteria:* English language; human studies; observational studies *Exclusion criteria:* studies with marijuana users in the control group; did not report on the prespecified outcomes; studies with unusable data; case series; case reports; abstracts; unpublished data; expert opinions; review articles; animal studies; non-English publications	*Number of patients in all included studies:* 7,851 who used marijuana; 124,867 control	heterogeneity among studies (P = .03, I^2 = 47.6% for low birth weight; P = .01, I^2 = 65.7% for preterm delivery) Stratification by amount of marijuana • Low birth weight: 8.8% vs. 6.7%, RR 1.22, 95% CI: 0.91-1.64 • Preterm delivery: 6.8% vs. 5.7%, RR 1.09, 95% CI: 0.91-1.32 Women who used marijuana weekly • Low birth weight: 11.2% vs. 6.7%, RR 1.90, 95% CI: 1.44-2.45 • Preterm delivery: 10.4% vs. 5.7%, RR 2.04, 95% CI: 1.32–3.17 Stratification by tobacco use • Women who smoked marijuana only were not at increased risk for preterm delivery (7.1% vs. 5.7%, RR 1.25, 95% CI: 0.63-2.50) Pooled adjusted analysis • Low birth weight: adjusted OR 1.16, 95% CI: 0.98-1.37 • Preterm delivery: adjusted OR 1.08, 95% CI: 0.82-1.43	
English, 1997, Australia	*Population:* babies born to mothers using cannabis during pregnancy	*Databases searched:* Medline *Years searched:* 1966-November 1995	*Number of citations identified in*	~~1.~~• Women who used cannabis at least four times per week had a 131g reduction in birth weight	4/11

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	Intervention: cannabis use during pregnancy *Comparator:* no cannabis use during pregnancy *Outcome:* birth weight	*Key words used:* cannabis, substance abuse, fetal-development, pregnancy complications, neonatal diseases and abnormalities, infant-newborn, birth weight *Inclusion criteria:* cannabis use during pregnancy and birth weight *Exclusion criteria:* commentaries, letters and abstracts	*Search:* Not reported *Number of studies included:* 10 *Number of patients in all included studies:* 32,843	(95% CI = 52-109g) 2. Birth weight increase by 62 g (95% CI = 8g-132g) among women who were infrequent users 3. The pooled odds of low birthweight for any use was 1.09 (95% CI 0.94-1.27)	
Gunn, 2016, United States	*Population:* children of women who used marijuana during pregnancy, and women who used marijuana during pregnancy *Intervention:* marijuana use during pregnancy *Comparator:* No marijuana use during pregnancy *Outcome:* Maternal, fetal, perinatal and neonatal outcomes	*Databases searched:* PubMed, Medline, EMBASE, CINAHL, PsychInfo, Web of Science and Sociological Abstracts *Years searched:* inception to April 2014 *Key words used:* cannabis, and maternal, fetal, perinatal, and neonatal outcomes; details not reported *Inclusion criteria:* randomized controlled trials, case-control, cross sectional, and cohort studies, investigate effects of prenatal use of cannabis on maternal, fetal, perinatal and neonatal outcomes *Exclusion criteria:* inclusion of women using other illicit drugs in addition to cannabis	*Number of citations identified in Search:* 6854 *Number of studies included:* 24 *Number of patients in all included studies:* not reported	1. Women who use marijuana during pregnancy have increased odds of anemia (OR = 1.36. 95% CI = 1.10-1.69) 2. Infants whose mothers used marijuana during pregnancy had decreased birthweight (OR = 1.77, 95% CI = 1.04-3.01) 3. Infants whose mothers used marijuana during pregnancy were more likely to be placed in the ICU (OR = 2.02, 95% CI = 1.27-3.21)	8/11
Viteri, 2015, United States	*Population:* illicit drug users *Intervention:* maternal marijuana use during	*Databases searched:* PubMed *Years searched:* not reported	*Number of citations identified in Search:* not	1. Inconsistent association between teratogenicity (congenital anomalies) and marijuana. Most studies suggest a lack of	2/11

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	pregnancy *Comparator:* no maternal marijuana use during pregnancy *Outcome:* congenital anomalies, long-term implications	*Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not reported	reported *Number of studies included:* 128 (number included on marijuana not reported) *Number of patients in all included studies:* not reported	teratogenicity or a small affect 2. Marijuana use associated with inattention and impulsivity at 10 years old, lower IQ scores, increased errors of omission, academic underachievement (especially in spelling and reading), and increased rate of adolescent marijuana and cigarette use	
Williams, 2007, Scotland	*Population:* children ages 0-18 followed from birth *Intervention:* maternal exposure to pregnancy *Comparator:* no maternal exposure to toxins during pregnancy *Outcome:* childhood mental health disorders	*Databases searched:* EMBASE, Medline, PsychInfo, SSCI *Years searched:* Inception until 2005 *Key words used:* key words related to longitudinal studies, risk period, measurements, risks, children, substances, and childhood mental health; details not reported *Inclusion criteria:* birth cohort, prospective, longitudinal, twin or prospective epidemiological studies; examine prenatal, prostnatal and/or early childhood risk factors and association with childhood mental health disorders; children 0-18 years old followed from birth *Exclusion criteria:* risk factors not identified as being associated with the prenatal period; the	*Number of citations identified in Search:* 2,968 *Number of studies included:* 100 (6 on marijuana use) *Number of patients in all included studies:* not reported	3. Marijuana use during pregnancy impacted child's ability to maintain attention 4. Children exposed to marijuana were found to have increased depressive symptoms from ages 10-12	4/11

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		following mental disorders: organic disorder, schizophrenia, manic episode bipolar disorder, sexual dysfunction, and disorders of adult personality and behavior			
Social Harms					
Author, Year of Publication, Country	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Ashbridge, 2012, Canada	*Population:* general population *Intervention:* Marijuana use *Comparator:* no marijuana use *Outcome:* motor vehicle collisions	*Databases searched:* 19 databases (detailed not reported) *Years searched:* not reported *Key words used:* not reported *Inclusion criteria:* controlled observational epidemiology studies focused on motor vehicle collisions *Exclusion criteria:* experimental studies or simulations	*Number of citations identified in Search:* not reported *Number of studies included:* 9 *Number of patients in all included studies:* not reported	~~1.~~• Cannabis significantly increase the risk of collisions with an odds ratio of 1.92 (95% CI = 1.35-2.73) ~~2.~~• Estimates were higher in case-control studies and studies of fatal collisions	4/11
Macleod, 2004, United Kingdom	*Population:* general population aged 25 and under *Intervention:* marijuana use *Comparator:* no marijuana use *Outcome:* educational attainment, use of other drugs,	*Databases searched:* Medline, EMBASE, CINAHL, PsychLIT, Web of Science, Lindesmith Center, DrugScopt, US National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration, and Addiction Abstracts *Years searched:* inception until June 2003 *Key words used:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 32	~~1.~~• Cannabis use was consistently associated with reduced educational attainment, and use of other drugs ~~2.~~• Cannabis use was inconsistently associated with psychological problems (some found no association, others found increased use was associated	8/11

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	psychological health, antisocial behavior, other social problems	*Inclusion criteria:* prospective studies. General population, measured use of any illicit drug by individuals aged 25 or younger and looked at psychological or social harm *Exclusion criteria:* not reported	*Number of patients in all included studies:* not reported	with increase problems), and anti-social or other problematic behavior ~~3.~~ • Cannabis used at a younger age was consistently associated with greater psychological and social problems	