Appendix 2 (as supplied by the authors). Detailed data extraction					
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	• No difference in the structural integrity of marijuana users compared to non-users • 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	*Number of citations identified in Search:* 142 *Number of studies included:* 43	*Structural* • In adults - reduced hippocampal volume and white matter integrity in chronic users, often persisting after abstinence • In adults - changes also described in amygdala, cerebellum, and frontal cortex of chronic users • Adolescent results inconclusive	6/11

		magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, 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	*Number of patients in all included studies:* 711	*Functional* • Lower resting blood flow globally, and in cerebellum, prefrontal cortex, and striatum • 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,	*Number of citations identified in Search:* 224 *Number of studies included:* 45 *Number of patients in all included studies:* 889	• Increased cerebral blood flow to prefrontal, insular, cerebellar, and anterior cingulate regions; associated with depersonalization and increase anxiety • THC influenced learning, memory, and affect; CBD seems to have the opposite effect	5/11

		microdialysis, electrophysiological, dopamine release, single photon emission tomography, 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	*Number of citations identified in Search:* 268 *Number of studies included:* 41 (5 human, 36 animal)	• Chronic cannabis use associated with decreased levels of glutamate in the cortical and subcortical areas, especially in females • Delta-9-tetrehydrocannabinol affects glutamate release and reuptake and reduces the inhibition of glutamate	7/11

		effects of cannabis use/administration or delta-9-tetrehydrocannabinol use/administration; studies measuring molecular markers related to glutamate 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	*Number of patients in all included studies:* 239 humans, 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	• Decreased white matter in early-phase schizophrenia without cannabis use • 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 *Outcome:* brain structure and function	*Databases searched:* EMBASE, Medline, PubMed, PsychLIT, LILACS *Years searched:* inception until December 2012 *Key words used:* marijuana, cannabis, delta-9-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	*Number of citations identified in Search:* 141 *Number of studies included:* 24 *Number of patients in all included studies:* 450	• Cannabis use associated with memory disruptions, loss of IQ, loss of inhibition, and more compensatory brain activity in adolescents • May be associated with adolescent-onset schizophrenia due to loss of grey and white matter, but minimal evidence exists	5/11
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	*Number of citations identified in Search:* 154 *Number of studies included:* 13 *Number of patients in all*	• Inconsistent findings, but abnormalities identified in the hippocampus, parahippocampus, and amygdala • Often related to high frequency and long-term use and more likely in adolescent users	3/11

		Exclusion criteria: samples with any major psychopathologies; not empirical studies (review articles, case studies)	*included studies:* 285		
Malchow, 2013, Germany	*Population:* schizophrenia patients *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain morphology	*Databases searched:* PubMed, We of Knowledge *Years searched:* inception until 2012 *Key words used:* schizophrenia, psychosis, sMRI, structural imaging, cannabis, marijuana, marihuana, tetrahydrocannabinol *Inclusion criteria:* humans; English language; neuroimaging studies examining brain structure *Exclusion criteria:* not reported	*Number of citations identified in Search:* 105 *Number of studies included:* 16 *Number of patients in all included studies:* 484	• Weak evidence that chronic cannabis use may affect brain morphology in patients with schizophrenia and those at high-risk • Inconclusive evidence that cannabis affects brain structure prior to schizophrenia or causes schizophrenia	4/11
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	*Number of citations identified in Search:* 66 *Number of studies included:* 41 *Number of patients in all included studies:* 665	• 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 • Impaired cognitive efficiency in cannabis users compared to controls • Changes in volume only related to chronic users	5/11

		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 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	• Smoked and infused cannabis increased global cortical activity, especially in chronic users • Acute and chronic exposure were associated with increased activity during exposure and decreased activity during abstinence in the frontal, limbic, and cerebellar regions • 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	*Databases searched:* ISI Web of Knowledge, PubMed	*Number of citations*	• Cannabis use associated with decreased activity globally and in the cingulum, dorsolateral	7/11

	Intervention: cannabis uses *Comparator:* healthy, non-users *Outcome:* brain structure	*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 *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	*identified in Search:* 33 *Number of studies included:* 19 *Number of patients in all included studies:* 350	prefrontal cortex, and cerebellum in users with or at high risk of psychosis compared to healthy non users • Post mortem results and studies examining white matter changes were inconclusive	
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	*Number of citations identified in Search:* not reported *Number of*	• No statistically significant differences in whole brain volume between users and non-users • Significantly decreased hippocampal volume in users • Inconsistent results on amygdala volume due to publication bias	8/11

		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	*studies included:* 14 *Number of patients in all included studies:* 362		
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	*Number of citations identified in Search:* 2796 *Number of studies included:* 25 *Number of patients in all included studies:* 244	• Minimal evidence, but acute cannabis use is weakly associated with increased peripheral and striatal dopamine and decreased neocortical dopamine • Similar results for chronic users • Larger effects in those at genetically predisposed to or at clinical high risk of psychosis	6/11

		Exclusion criteria: studies where cannabinoid administration was not the intervention or exposure of interest; or where neurochemical outcomes were not directly reported on			
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 patients in all included studies:* 140	• Cannabis use associated with lower levels of N-acetyl-aspartate, myo-inositol, and choline, which are associated with lower cognitive efficiency and impulse control • Associated with alterations in GABA levels in the frontal lobe	1/11
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	• Prefrontal blood flow was lower in chronic marijuana users • Studies found increased brain metabolism during marijuana use • Structural changes such as reduced prefrontal volume and white matter integrity differed between marijuana users in individuals who had not used marijuana • 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 *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	*Number of citations identified in Search:* 3558 *Number of studies included:* 6 *Number of patients in all included studies:* 907	• No association between lifetime marijuana use and risk of head and neck cancer (OR = 1.021, 95% CI = 0.912-1.143)	9/11
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*,	*Number of citations identified in Search:* 149 *Number of studies included:* 3	• Current cannabis use, using cannabis on a weekly basis, and chronic use associated with testicular germ cell tumors • Current cannabis use: OR = 1.62 (95% CI = 1.13-2.31) • Weekly use: OR = 1.92 (95% CI = 1.35-2.72)	8/11

		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 patients in all included studies:* 719	• Chronic use (more than 10 years): OR = 1.50 (95% CI = 1.08-2.09)	
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 estimates for marijuana exposure *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 34 *Number of patients in all included studies:* 21,138	• No association with head and neck, and lung cancer • Associated with testicular cancer • Insufficient evidence for bladder, prostate, penile, cervical and childhood cancer, but small associations exist for prostate and cervical cancer • Tends to be dose-dependent	5/11
Mehra, 2006, United States	*Population:* marijuana smokers *Intervention:* marijuana smoking *Comparator:* non-users, tobacco-only smokers	*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	*Number of citations identified in Search:* 186 *Number of studies included:* 19	• Cannabis smoking associated with more inhaled tar exposure than tobacco smoking • More pathological lung changes in cannabis smokers compared to tobacco smokers • No association with cannabis smoking and lung cancer, despite more tar and pathological changes	8/11

	Outcome: lung cancer, changes to the lung that could lead to cancer, inhaled tar exposure	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 patients in all included studies:* 66,349 (only the number of male participants reported)		
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 population *Outcome:* overall mortality	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* January 1990 until January 2008 *Key words used:* cannabis, mortality, cohort, drug use *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 citations identified in Search:* not reported *Number of studies included:* 19 *Number of patients in all included studies:* 387,635 (cannabis use not reported)	• Insufficient data to determine all-cause mortality is higher in users compared to the general population • Heavy cannabis use associated with increased risk of poor driving • Cannabis use associated with suicide, but minimal evidence	5/11
Blavos, 2017, United States	*Population:* college students *Intervention:* cannabis use	*Databases searched:* PubMed, Academic Search Complete, OhioLINK Electronic Journal Center, ProQuest Dissertations, and Google Scholar	*Number of citations identified in Search:* 70	• Marijuana users were more likely to suffer from schizotypy and experience difficulty coping with anxiety and stress	4/11

	Comparator: general population *Outcome:* college retention, academic performance, health outcomes, legal or conduct issues	*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 studies included:* 35 *Number of patients in all included studies:* 35,835	• 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	
Grotenhermen, 2010, Germany	*Population:* cannabis users *Intervention:* cannabis use *Comparator:* non-users *Outcome:* arteritis	*Databases searched:* PubMed, EMBASE, Web of Science *Years searched:* inception until February 2009 *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	*Number of citations identified in Search:* not reported *Number of studies included:* 17 *Number of patients in all included studies:* 94	• Most studies had concurrent tobacco and cannabis use, so little association was found for just cannabis and arteritis	4/11
Hackam, 2015, Canada	*Population:* cannabis users *Intervention:* cannabis exposure	*Databases searched:* Medline, EMBASE *Years searched:* inception until November 30th, 2014	*Number of citations identified in Search:* 989	• Cannabis exposure associated with increased risk of stroke	5/11

	Comparator: non-users *Outcome:* stroke	*Key words used:* cannabis, cerebrovascular disease *Inclusion criteria:* case studies; cases underwent parenchymal imaging; humans *Exclusion criteria:* not reported	*Number of studies included:* 34 *Number of patients in all included studies:* 64		
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 *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 6 *Number of patients in all included studies:* 6	• Marijuana smoking associated with atrial fibrillation, but minimal evidence exists	4/11
Lindsey, 2012, United States	*Population:* illicit drug users *Intervention:* illicit and prescription drug exposure *Comparator:* illicit drugs with no concurrent prescription drugs	*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*-	*Number of citations identified in Search:* not reported *Number of studies included:* not reported	• Cannabis may interact with tricyclic antidepressants, protease inhibitors, and warfarin therapy • Most common side effects of interactions related to cardiac functioning • May interact with other depressants (alcohol, barbiturates) but no clinical trials	4/11

	Outcome: cross-interactions of substances	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 patients in all included studies:* not reported		
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 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	*Number of citations identified in Search:* 281 *Number of studies included:* 48 *Number of patients in all included studies:* 207,908	• 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 hyperinflation, infectious disease transmission, and other pulmonary effects and respiratory symptoms also noted	5/11

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	• Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues • 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 cannabis and vision *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	• 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 • Many effects residual • Also associated with improvement in some visual functioning, but no experimental evidence	4/11
Tetrault, 2007, United States	*Population:* adult marijuana smokers	*Databases searched:* Medline, PsychInfo, EMBASE	*Number of citations*	• Acute marijuana inhalation associated with bronchodilation,	8/11

	Intervention: acute and chronic marijuana exposure *Comparator:* non-users *Outcome:* airway response, pulmonary function or respiratory complications	*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	*identified in Search:* 965 *Number of studies included:* 34 *Number of patients in all included studies:* 14,183	but not present in long-term smokers • Long-term smoking associated with increased respiratory complications such as cough, sputum production, and wheeze	
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 patients in all included studies:* not reported	• 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 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	3/11

				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	• Cannabis use was associated with psychosis in those with a vulnerability to psychosis • 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 *Inclusion criteria:* English language; original articles, critical review reports, public use data on cannabis use and suicidality *Exclusion criteria:* synthetic cannabinoids	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Minimal evidence for acute cannabis use and suicidality • Any and heavy cannabis use associated with suicidality, but heterogeneity and publication bias high • Chronic cannabis use and death by suicide: OR = 2.56 (95% CI = 1.25-5.27) • Any cannabis use and suicidal ideation: OR = 1.43 (95% CI = 1.13-1.83) • Heavy cannabis use and suicidal ideation: OR = 2.53 (95% CI = 1.00-6.39) • Any cannabis use and suicide attempt: OR = 2.23 (95% CI = 1.24-4.00)	5/11

				• 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	• Frequent cannabis use associated with higher levels of anxiety compared to non-users • Higher prevalence of anxiety disorders in chronic cannabis users than the general population; anxiety disorders may increase risk of using cannabis • Anxiety associated with cannabis withdrawal • 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 *Comparator:* non-users, those without bipolar *Outcome:* manic symptoms	*Databases searched:* PsychInfo, Cochrane, Scopus, EMBASE, Medline *Years searched:* 1980 until June 2014 *Key words used:* cannabis, marijuana, delta-9-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	*Number of citations identified in Search:* 781 *Number of studies included:* 6 *Number of patients in all included studies:* 2,391	• 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) • Cannabis use also associated with increased risk of hypomanic symptoms in those at high risk of developing bipolar disorder	9/11

		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			
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	• Those with anxiety are more likely to use cannabis or have cannabis use disorder • Anxiety and cannabis use: OR = 1.24 (95% CI = 1.06-1.45) • Anxiety and cannabis use disorder: OR = 1.68 (95% CI = 1.23-2.31) • 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 *Intervention:* cannabis use *Comparator:* non-users, general population *Outcome:* psychosis	*Databases searched:* EMBASE, Medline, PsychInfo *Years searched:* 1996 until August 2015 *Key words used:* clinical high risk, attenuated positive symptoms, brief limited intermittent psychotic symptoms, genetic risk and deterioration, basic symptoms, familial high risk,	*Number of citations identified in Search:* 5560 *Number of studies included:* 7	• No relationship between any cannabis use and transition to psychosis in ultra-high risk individuals (OR = 1.14, 95% CI = 0.856-1.524) • Cannabis abuse or dependence was significantly associated with transition to psychosis (OR = 1.75, 95% CI = 1.135-2.710)	10/11

		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	*Number of patients in all included studies:* 330		
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	• Significantly earlier age of onset of psychosis in cannabis users compared to non-users (2.70 years earlier, $p<0.001$) • General substance use also associated with earlier age of onset • Alcohol not associated with earlier onset	9/11
Le Bec, 2009, France	*Population:* adolescents or young adults without psychosis *Intervention:* cannabis use	*Databases searched:* MEDLINE *Years searched:* 1966 until June 2005	*Number of citations identified in Search:* 60	• Statistically significant associations between cannabis use and psychosis or psychotic symptoms	3/11

	Comparator: non-users *Outcome:* chronic psychotic disorders	*Inclusion criteria:* human studies; prospective and longitudinal studies; objective of studies to examine causal link between cannabis use and psychosis *Exclusion criteria:* literature reviews	*Number of studies included:* 7 *Number of patients in all included studies:* 50,275	• Those initially with pre-psychotic symptoms had stronger associations between cannabis and psychosis • 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	• Cannabis use associated with risk of developing depression compared to non-users • Any cannabis use and depression: OR = 1.17 (96% CI = 1.05-1.30) • 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 *Outcome:* psychosis or psychotic symptoms	*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,	*Number of citations identified in Search:* 571 *Number of studies included:* 16; 10	• 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) • Average cannabis use also significantly associated with schizophrenia and psychotic	7/11

		schizophrenia, 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	for meta-analysis *Number of patients in all included studies:* 66,816	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	• Consistent, significant associations between cannabis use and onset of psychotic symptoms • 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*	• Increased incidence of psychosis-related outcomes in those who had ever used cannabis (OR=1.41, 95% CI: 1.20-1.65) • Heavy and earlier use increased risk	7/11

	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	• 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	• 33.7% (95% CI = 29-38%) of subjects used cannabis prior to psychosis • Pooled interval between first cannabis use and age of psychosis onset was 6.3 years (SMD = 1.56, 95% CI = 1.40-1.72) • 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	*Databases searched:* EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until September 2011	*Number of citations identified in Search: 589*	• Tobacco not significantly associated with earlier ago of onset of psychosis • Cannabis significantly associated with earlier age of onset of	10/11

	Comparator: tobacco users compared to cannabis users *Outcome:* age of onset of psychosis	*Key words used:* cannabis, marijuana, tobacco, 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	*Number of studies included:* 38 for cannabis; 40 for tobacco *Number of patients in all included studies:* 3199 for cannabis; 5562 for tobacco	schizophrenia spectrum psychosis and broad psychosis • 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	• Marijuana has a low non-continuation rate • About 10% of users have cannabis dependence; more common in those who start use young • Data on cannabis as a gateway drug is inconclusive • 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	*Databases searched:* BIOSIS Citation Index SM, BIOSIS Previews, the Cochrane Library, EMBASE, Inspec, ISI Proceedings, Journal	*Number of citations*	• Smoking cannabis was associated with fewer	8/11

	Intervention: cannabis use *Comparator:* non-users *Outcome:* neurological soft signs focused on sensory integration, motor coordination, motor sequencing, and primitive reflexes (ex. audio-visual integration, finger-nose test, gaze)	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* 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	*identified in Search:* 1225 *Number of studies included:* 5, 2 for meta-analysis *Number of patients in all included studies:* 172	neurological soft signs in psychotic patients than non-users	
Schoeler, 2016, United Kingdom	*Population:* patients with psychosis *Intervention:* continued cannabis use	*Databases searched:* Medline *Years searched:* inception until April 2015	*Number of citations identified in Search:* 1903	• Patients who continued using cannabis had higher relapse rates than patients who discontinued use and non-users	9/11

	Comparator: non-users, patients who discontinue use *Outcome:* relapse	*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 cannabis use could not be determined	*Number of studies included:* 24 *Number of patients in all included studies:* 16565	• Patients who discontinued cannabis did not differ in relapse rate from non-users	
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	• Early use of cannabis was associated with an increased risk of psychosis (OR = 2.9, 95% CI = 2.4-3.6) • 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	*Number of citations identified in Search:* 63 *Number of studies included:* 29	• Life-time cannabis use and current cannabis use were both associated with higher schizotypy scores	3/11

		Exclusion criteria: not reported	*Number of patients in all included studies:* 21,736		
Van der Meer, 2012, The Netherlands	*Population:* those at clinical high risk for psychosis *Intervention:* cannabis use *Comparator:* non-users *Outcome:* first episode psychosis	*Databases searched:* Medline, PsychInfo, PubMed, EMBASE *Years searched:* 1995 until October 31st 2011 *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 citations identified in Search:* 729 *Number of studies included:* 11 *Number of patients in all included studies:* 742	• Inconclusive results about cannabis use and severity of symptoms at baseline, pre-psychotic symptoms, and early onset of psychosis • Weak evidence suggesting cannabis may worsen symptoms in younger users	4/11
Zammit, 2008, United Kingdom	*Population:* patients with psychosis	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Knowledge, ISI	*Number of citations*	• Cannabis use was associated with increased relapse and	9/11

	Intervention: cannabis use *Comparator:* patients with psychosis without cannabis use *Outcome:* severity of symptoms, adherence to treatment, other adverse outcomes	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 *Exclusion criteria:* comorbid psychosis and cannabis misuse or dependence	*identified in Search:* 15,303 *Number of studies included:* 13 *Number of patients in all included studies:* not specified	rehospitalization and decreased treatment adherence • Inconsistent results about cannabis use and severity of symptoms	
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	*Number of citations identified in Search:* 6441 *Number of studies included:* 105 *Number of patients in all included studies:* not reported	• Impaired verbal learning and memory and psychomotor functioning in chronic and occasional users • Inconsistent evidence regarding working memory, attention, and executive functioning, but some evidence suggests impairment • Many impairments exist after abstinence	4/11

		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			
Ganzer, 2016, Germany	*Population:* abstinent cannabis users *Intervention:* cannabis use *Comparator:* current users, non-users *Outcome:* neurocognitive functioning	*Databases searched:* EMBASE, Ovid MEDLINER, PsychInfo, PSYNDEXplus Literature *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	*Number of citations identified in Search:* 1038 *Number of studies included:* 38 *Number of patients in all included studies:* 2025	• Poorer attention, motor function, and memory and learning in abstinent users than non-users • Impairments in inhibition, impulsivity, and decision making in abstinent users, but inconsistent evidence • Highly inconsistent evidence with regards to visual spatial functioning • Differences in activation patterns and structural differences in the brain of abstinent users compared to controls	9/11
Garfield, 2013, Australia	*Population:* illicit substance users *Intervention:* substance use	*Databases searched:* PubMed, PsychInfo, Medline *Years searched:* not reported	*Number of citations identified in Search:* 245	• Those with baseline cannabis abuse reported higher levels of anhedonia than those with no baseline cannabis abuse	3/11

	Comparator: non-users *Outcome:* anhedonia	*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 studies included:* 32, 3 on cannabis *Number of patients in all included studies:* not reported	• Baseline anhedonia did not predict cannabis use • Abstinence from cannabis was associated with a decrease in anhedonia	
Gates, 2014, Australia	*Population:* adult cannabis users *Intervention:* measured cannabis *Comparator:* non-users *Outcome:* sleep	*Databases searched:* EMBASE, CINAHL, Cochrane Library/EBM Reviews, Medline, PsycEXTRA *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 citations identified in Search:* 2215 *Number of studies included:* 39 *Number of patients in all included studies:* 203 recreational users	• No consistent effect of cannabis on sleep time • Increased time spent in stage 2 and decreased time in slow wave sleep • Overall results inconsistent	4/11
Gonzalez, 2002, United States	*Population:* abstinent cannabis users *Intervention:* cannabis use	*Databases searched:* not reported *Years searched:* not reported	*Number of citations identified in Search:* 1014	• Poorer motor performance, executive function, reaction time, learning, and verbal domains	5/11

	Comparator: non-users, current users *Outcome:* neurocognitive effects	*Key words used:* not reported *Inclusion criteria:* non-acute neuropsychological effects of cannabis; humans; adults; English language *Exclusion criteria:* not reported	*Number of studies included:* 40 *Number of patients in all included studies:* 741	• However, results highly inconsistent and generally poor quality	
Grant, 2003, United States	*Population:* adult, long-term cannabis users *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* neurocognitive performance	*Databases searched:* Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts international, Article First, Science Citation Index Expanded, Social Science Citation Index *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	*Number of citations identified in Search:* 1014 *Number of studies included:* 11 for meta-analysis *Number of patients in all included studies:* 1032; 632 users	• Inconsistent results on all measures except learning and forgetting, both of which were small • Learning: -0.21 (99% CI = -0.39- -0.022 • Forgetting: -0.27 (99% CI = -0.49- -0.044)	4/11
Rabin, 2011, Canada	*Population:* patients with schizophrenia *Intervention:* cannabis use	*Databases searched:* PsychInfo, Medline, PubMed *Years searched:* not reported	*Number of citations identified in Search:* not reported	• Higher neurocognitive functioning in cannabis users compared to non-users	4/11

	Comparator: non-users *Outcome:* neurocognition	*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 studies included:* 8 *Number of patients in all included studies:* 942; 356 cannabis users		
Schoeler, 2016, United Kingdom	*Population:* patients with or without a psychotic disorder *Intervention:* long-term cannabis use *Comparator:* non-users *Outcome:* memory function	*Databases searched:* Medline *Years searched:* inception until June 2014 *Key words used:* neuropsych*, cognit*, memory, learning, recall, marijuana, marihuana, cannabis, THC, cannabinol, cannabidiol *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 88 *Number of patients in all included studies:* 3261 subjects with a psychotic disorder	• Cannabis use significantly impaired global memory in healthy users compared to non-users • Cannabis use in patients with psychosis improved memory compared to non-users	4/11
Schreiner, 2012, United States	*Population:* chronic cannabis users, abstinent or current *Intervention:* cannabis use	*Databases searched:* PsychInfo, PsycARTICLES, PubMed, Medline *Years searched:* not reported	*Number of citations identified in Search:* not reported (~800)	• Cannabis use was associated with significant effects on global neurocognition	5/11

	Comparator: non- or minimal-users *Outcome:* neurocognitive performance	*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 imaging; not humans or chronic users	*Number of studies included:* 33 *Number of patients in all included studies:* 1010 current or former users	• No significant residual effects seen on abstinent users compared to non-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	*Number of citations identified in Search:* 265 *Number of studies included:* 97 *Number of patients in all included studies:* 6,542	• No statistically significant evidence of inhibitory deficit was observed for cannabis • Small to medium non-statistically significant effects were observed	7/11

		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			
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 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 citations identified in Search:* 2,693 *Number of studies included:* 31 *Number of patients in all included studies:* 7,851 who used marijuana; 124,867 control	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 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	9/11

				• 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 *Intervention:* cannabis use during pregnancy *Comparator:* no cannabis use during pregnancy *Outcome:* birth weight	*Databases searched:* Medline *Years searched:* 1966-November 1995 *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	*Number of citations identified in Search:* Not reported *Number of studies included:* 10 *Number of patients in all included studies:* 32,843	• Women who used cannabis at least four times per week had a 131g reduction in birth weight (95% CI = 52-109g) • Birth weight increase by 62 g (95% CI = 8g-132g) among women who were infrequent users • The pooled odds of low birthweight for any use was 1.09 (95% CI 0.94-1.27)	4/11

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	• Women who use marijuana during pregnancy have increased odds of anemia (OR = 1.36. 95% CI = 1.10-1.69) • Infants whose mothers used marijuana during pregnancy had decreased birthweight (OR = 1.77, 95% CI = 1.04-3.01) • 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 pregnancy *Comparator:* no maternal marijuana use during pregnancy *Outcome:* congenital anomalies, long-term implications	*Databases searched:* PubMed *Years searched:* not reported *Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 128 (number included on marijuana not reported) *Number of patients in all*	• Inconsistent association between teratogenicity (congenital anomalies) and marijuana. Most studies suggest a lack of teratogenicity or a small affect • 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	2/11

			included studies: not reported		
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 following mental disorders: organic disorder, schizophrenia, manic episode bipolar disorder, sexual dysfunction, and disorders of adult personality and behavior	*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	• Marijuana use during pregnancy impacted child's ability to maintain attention • Children exposed to marijuana were found to have increased depressive symptoms from ages 10-12	4/11

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	• Cannabis significantly increase the risk of collisions with an odds ratio of 1.92 (95% CI = 1.35-2.73) • 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, psychological health,	*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 *Number of patients in all*	• Cannabis use was consistently associated with reduced educational attainment, and use of other drugs • Cannabis use was inconsistently associated with psychological problems (some found no association, others found increased use was associated with increase problems), and anti-social or other problematic behavior • Cannabis used at a younger age was consistently associated with greater psychological and social problems	8/11

	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	*included studies:* not reported		

