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Abstract

Objectives: *To provide an overview of the addiction potential; adverse effects (e.g., cardiovascular, immune dysfunction, respiratory system, mental health disorders); drug interactions; effects of accidental exposure; crime statistics; and pharmacist's considerations for the use of inhaled medical marijuana.* ***Methods:*** *A PubMed search was conducted from 1966 to March 2016 to identify articles in which the safety of inhaled medical marijuana was assessed. Key MeSH search terms included medical marijuana with a subheading for adverse effect. Only articles in adult patients were considered. In addition, medical marijuana or cannabis plus one of the following search terms were searched: drug interactions, herb-drug interactions, drug-related side effects and adverse drug reactions, substance-related disorders, addiction, and abuse. A free-text search was also conducted to identify articles not included in the MeSH term search. A bibliographic search was also conducted. Articles were included if they addressed adverse effects of medical marijuana for the treatment of a condition. Meta-analyses, randomized controlled clinical trials, and case reports were included in the review if the primary focus of the article related to the adverse effect profile of inhaled medical marijuana. Medical marijuana efficacy studies were not assessed. In the absence of this information, case reports or reports of inhaled recreational marijuana use was used. Studies were excluded if published in languages other than English. In addition, studies highlighting mechanisms of action, studies of pharmacodynamics or pharmacokinetic effects were excluded, unless these effects were due to drug-drug interactions. Prescription products containing marijuana or derivatives were excluded from evaluation. An Internet search was conducted to locate the most up-to-date information on the laws concerning medical marijuana.* ***Key findings:*** *A PubMed search revealed 58 articles and 28 of those studies were included in this review. Several studies were located that evaluated the safety of medical marijuana; however, much of the review focused on inhaled, recreational marijuana use due to the paucity of information on inhaled medical marijuana. Since marijuana is a Schedule1 product, few clinical studies have been conducted to determine the adverse event profile of the product. As a result, several articles that characterized recreational inhaled marijuana were included. Recreational inhaled marijuana use may be associated with an increase in cardiovascular (CV)/ cerebrovascular effects (CVA); however, conflicting information exists in the literature. Recreational marijuana use may also increase risky behaviors that increase the transmission of infectious diseases and respiratory diseases. Many of the studies were retrospective in nature; therefore, it was difficult to determine a cause and effect relationship between inhaled marijuana use and the development of adverse reactions or drug-drug interactions.* ***Conclusions:*** *There is a paucity of information related to the use of inhaled medical marijuana. Recreational marijuana use is associated with several adverse events including CV/CVA, respiratory, and transmission of infectious diseases. Theoretical literature indicates that medical marijuana may be associated with significant drug-drug interactions and adverse drug reactions. Legalization of medical marijuana may be associated with an increase in abuse/dependence and accidental exposures in children. Pharmacists need to be educated regarding the appropriate use of medical marijuana to avoid adverse reactions and potential drug-drug interactions between medical marijuana and other products.*

Key words: medical marijuana, cannabis, adverse effects, law

Introduction

Marijuana is the most commonly used illicit drug substance in the United States.[1] The Food and Drug Administration (FDA) currently classifies marijuana as a Schedule I drug under the Controlled Substances Act, declaring it to have no currently accepted medical use and a high potential for abuse.[2] The term "medical marijuana" has been coined to describe the use of the whole, unprocessed marijuana plant or its extracts to treat a disease or relieve symptoms.[3,4] The use of medical marijuana has gained significant momentum with the recent legalization of the product in many states. As of March 2016, 23 states and Washington, DC have legalized and approved the use of medical marijuana. In general, these state laws allow for the consumption of medical marijuana under the recommendation of a licensed medical professional and will allow patients to present a legal defense against marijuana possession charges if a medical need for the drug has been properly documented. Most states require that patients and physicians have an established relationship prior to the recommendation of medical marijuana use, and maintain a formal registry of its users. States require patients to register for an identification card and will permit caregivers to obtain

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the medicinal marijuana for patients. Of the 23 states, Arizona, Maine, Michigan, Nevada, New Hampshire, and Rhode Island will recognize other state registries through a reciprocity system.[5] Marijuana is being used therapeutically for various conditions. While all states have specific approved conditions for the use of cannabis, most also allow for the physician to determine "other debilitating illnesses" that may also be treated with marijuana.[5,6] Table 1 provides an overview of the legal marijuana states and their approved medical conditions for use.

The list of approved conditions for the use of medical marijuana varies from state to state. The most commonly approved disease states include Alzheimer's disease, amyotrophic lateral sclerosis (ALS), cachexia, cancer, Crohn's disease, epilepsy and seizure disorders, glaucoma, hepatitis C, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), multiple sclerosis and muscle spasticity disorders, severe and chronic pain, severe nausea, and post-traumatic stress disorder (PTSD).[5] Cannabis has been used to treat a number of disease states and associated symptoms. However, data is lacking in human models and with the use of actual "medicinal marijuana" in its unprocessed form, as most studies evaluated the effects of the tetrahydrocannabinol (THC) derivatives, dronabinol and nabilone. There is limited data to support the use of medicinal marijuana as a treatment option for Alzheimer's Disease and amyotrophic later sclerosis (ALS).[7] However, other investigators have found that smoked and vaporized cannabis was associated with a reduction in significant pain from HIV-associated sensory neuropathy and central neuropathic pain and HIV/AIDS associated cachexia.[4,8-12]

Over the past 30 years, substantial research in human and animal models has shown that prolonged use of marijuana may lead to physical dependence and a withdrawal syndrome upon discontinuation. Several mechanisms are thought to play a part in the drug reward system, and the resulting cannabis abuse or dependence. There are two types of cannabinoid receptors, cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2). The CB_1 receptors are expressed in the central nervous system and are found mainly in the brain, kidney, liver, and lungs.[13,14] The CB_2 receptors are most commonly associated with the immune system. In the brain, CB_1 receptors are most abundant in the cerebellum, basal ganglia, and hippocampus.[14] These locations explain many of the negative effects seen on short-term memory, impaired motor skills, and delayed reaction time when cannabinoids are inhaled and ingested.[15,16] Research shows that CB_1 receptors act as modulators of GABA release in the hippocampus.[17] The CB_1 receptors are also found on glutamate and GABA neuron axon terminals in the hippocampus and decrease the excitability of neurons. There they control the release of neurotransmitters, and it is thought that this is the primary means that cannabinoids inhibit hippocampal neuronal activity and disrupt memory. Activation of the CB_1 receptor affects the central nervous system in ways similar to those of other reward-enhancing drugs such as alcohol, cocaine, and opioids, and is the accepted mechanism for the addictive properties of cannabinoids.[14,16-18]

Chronic use of illicit and medicinal marijuana may lead to dependence or addiction. Chronic cannabis users develop tolerance to its effects and report being unable to control their use despite negative consequences.[15] Mental health surveys indicated that cannabis dependence is the most common type of drug dependence after alcohol and tobacco.[16] According to the National Institute on Drug Abuse, marijuana overstimulation of the endocannabinoid system can lead to addiction. Approximately 9 percent of marijuana users will become dependent (frequency of use undefined), and 20 to 50% of daily users will become dependent.[3,16]

Cannabis use disorder, defined as increased tolerance, compulsive use, craving, inability to cut down or control cannabis use, and withdrawal, is triggered by chronic marijuana use.[19] Patients with cannabis use disorders seeking discontinuation often report withdrawal symptoms including major mood changes, anxiety, appetite disturbance, depression, and personality changes.[1,15] Compton et al evaluated the prevalence of marijuana use disorders and found that marijuana abuse or dependence increased by 18% from 30.2% in 1991-1992 to 35.6% in 2001-2002. Current literature suggests that factors such as increased potency of marijuana may contribute to increased physical dependence.[1,15] States with legalized medicinal marijuana currently have no statutes governing the potency of marijuana products, and there is no normalization of product potency. As such, patients using medical marijuana may be at greater risk for addiction potential with chronic use.

There is a perception that increased legalization may be associated with increased use because the public may consider that marijuana's adverse effect profile is benign. Cerdá et al evaluated the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence according to the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The investigators found that residents of states who had marijuana legalization laws had higher odds of marijuana use (OR, 1.92; 95% CI, 1.49 – 2.47) and marijuana abuse/dependence (OR, 1.81; 95% CI, 1.22 – 2.67) than residents of states without legalization status. However, abuse/dependence was not more prevalent among users in these states (OR, 1.03; 95% CI, 0.67 – 1.60). As a result, higher rates of abuse/dependence in the states with legalized

marijuana may be due to the higher rates of use in these states. [20,21]

Although an increasing number of states have passed laws and others have laws on the horizon, the long-term consequences of medical marijuana have not been fully elucidated. [5]

Recent changes in medical marijuana policies suggest greater acceptance of marijuana use in our society, and may cause users to feel it is a benign drug with a limited adverse side effect profile or potential for addiction.[21]The upsurge of dispensaries and patients growing their own medicinal supply of marijuana makes it imperative that the public and healthcare workers understand the possible therapeutic benefits of marijuana along with the known adverse health effects linked to marijuana.[3] In addition, the role of pharmacists in educating patients who may be taking medical marijuana needs to be identified. The purpose of this review is to provide an overview of the addiction potential; adverse effects (e.g., cardiovascular, immune dysfunction, respiratory system, mental health disorders); drug interactions; effects of accidental exposure; crime statistics; and pharmacist's considerations for the use of medical marijuana.

Methods

A PubMed search was conducted from 1966 to March 2016 to identify articles in which the safety of inhaled medical marijuana was assessed. Key MeSH search terms included medical marijuana with a subheading for adverse effect. Only articles in adult patients were included. In addition, medical marijuana or cannabis plus one of the following search terms were searched: drug interactions, herb-drug interactions, drug-related side effects and adverse drug reactions, substance-related disorders, addiction, and abuse. A free-text search was also conducted to identify articles not included in the MeSH term search. A bibliographic search was also conducted. An Internet search was conducted to locate the most up-to-date information on the laws concerning medical marijuana. Articles were included if they addressed adverse effects of medical marijuana for the treatment of a condition. Meta-analyses, randomized controlled clinical trials, and case reports were included in the review if the primary focus of the article related to the adverse effect profile of medical marijuana. Medical marijuana efficacy studies were not assessed. In the absence of this information, case reports or reports of recreational marijuana use was used. Studies were excluded if published in languages other than English. Studies focusing on mechanisms of action, studies of pharmacodynamics or pharmacokinetic effects, unless these effects were due to drug-drug interactions were also excluded. We excluded articles that did not evaluate adverse events of medical marijuana as the primary purpose. Prescription products containing marijuana or derivatives were excluded from evaluation.

Results

A PubMed search revealed 58 articles with medical marijuana and adverse effect as a subheading. A total of 11 articles were identified with a MeSH search for medical marijuana and adverse effect. A total of 28 articles were reviewed that related to marijuana addiction, adverse reactions, drug interactions, and accidental exposures. Of the articles identified by PubMed and bibliographic searches, one was a meta-analysis, 17 were clinical studies, and 10 were case reports/series. Table 2 provides a description of the clinical studies used in this review.

Cardiovascular / Cerebrovascular effects

Marijuana has well established effects on the cardiovascular system and may negatively impact patients with various disease states including cardiovascular disease, hypertension, and angina. Existing evidence supports the adverse cardiovascular effects of marijuana use. Cannabinoids have complex effects on blood pressure. The acute effects of recreational cannabis include an increase in blood pressure, and then decreased vascular resistance-induced orthostatic hypotension. [18,22,23] Smoked marijuana causes a dose-dependent increase in heart rate, increases myocardial oxygen demand, and decreases oxygen supply. Cannabis use may potentially cause tachycardia and transient hypertension and may increase the risk of myocardial infarction (MI).[23]

No reports of cardiovascular (CV)/cerebrovascular (CVA) complications associated with medical marijuana use were identified. As a result, CV/CVA adverse events with recreational cannabis use were explored. Several clinical studies evaluating CV/CVA effects of inhaled medical marijuana have been published. [23-26] Recreational marijuana use in the age group (20-92 years, mean age 44 years) most prone to coronary artery disease has increased. The risk of MI onset in the hour following marijuana use was almost five times greater than baseline. A rapid decline in risk occurred the second hour after smoking marijuana. [23,24] Marijuana may be a rare trigger of MI in patients with coronary artery disease.[23,25-26]

Several cases of myocardial infarction following recreational marijuana use have been reported, however, little is known about the actual association between marijuana and myocardial infarction (MI).[23,25,27-28] In one report, a 30-year-male with no family history of cardiovascular disease experienced a ST elevation MI caused by thrombosis of the descending artery. The patient had no prior medical history and denied taking any medications. He reported smoking

recreational marijuana two to three times weekly, with his last consumption being 2 hours prior to symptom onset.[29]

In another report, a 26-year-old male with no cardiovascular disease risk factors other than smoking, was admitted to the emergency department following recreational cannabis and cigarette smoking three hours prior to symptom onset.[25] Yurtdas et al also summarized 13 published cases of marijuana-induced MI. Of these cases, most patients (n = 12/13) presented with chest pain and MI, and the time from cannabis consumption to symptom onset ranged from one hour to five days.

Since marijuana is also an analgesic, chronic users may not experience the same pain syndrome associated with myocardial infarctions and may delay getting medical assistance.[30] In addition, there have been case reports of cerebral ischemic events in recreational marijuana users.[31-34] All of this information is limited by few case reports and several methodological flaws. Furthermore, long-term effects of medical marijuana use have not been evaluated and the majority of adverse events were associated with recreational use.[35]

Immune dysfunction / Cancer reports

Gordan et al systematically reviewed the literature to determine medical adverse effects/consequences associated with marijuana for recreational use.[35]Since marijuana has been associated with immune dysfunction, marijuana use may increase the risk of a variety of infectious diseases. Recreational marijuana use has been associated with outbreaks in tuberculosis (TB), *Neisseria meningitidis*, and sexually transmitted diseases.[36-40] There may also be a risk for marijuana users to develop severe steatosis (fatty degeneration) and fibrosis in the liver. This effect was observed in patients with chronic hepatitis C who had a liver biopsy and were daily marijuana users.[41] Marijuana use has also been associated with an increased risk of cancer; however, studies evaluating the potential carcinogenic activity of marijuana had several methodological flaws that limit the interpretation of the literature. There may be an increased risk of bladder cancer, head/neck, and lung cancer in habitual marijuana smokers.[42-44]

Respiratory Disorders

Cannabis smoke contains many of the same carcinogens found in cigarette smoke; however, the effects of cannabis smoking on the respiratory system remain unclear. Marijuana smokers may have an increased risk of respiratory dysfunction (e.g., chronic bronchitis, increased mucus production, wheezing, increased hyperinflation, Forced Vital Capacity [FVC], and residual volume in respiratory function tests).[45-48] Inhaled marijuana may increase the risk of lung cancer, emphysema, bronchitis, reduced lung density, wheeze, phlegm, and cough. [15,49]Studies over the past two decades have shown that regular recreational marijuana smokers report more chronic bronchitis than non-smokers and also have higher rates of respiratory infections and pneumonia. [15,18] In a study assessing cannabis-related adverse events leading to hospitalization, respiratory system disorders were observed among 31.0% of patients (n=62/200) and consisted of dyspnea (n=16), hemoptysis (n=10), and spontaneous pneumothorax (n=7). The corresponding incidence was 1.6 per 1000 (95% CI 1.2, 2.0) among recent cannabis users.[24]Respiratory disorders associated with cannabis may be exacerbated in patients with underlying asthma and chronic obstructive pulmonary disease (COPD).[49]

Cannabis smokers inhale more deeply than tobacco smokers, hold their smoke longer, and thereby retain more carcinogens, tar and particulate matter. Chronic cannabis smokers show pathological changes in lung cells that precede the development of cancer.[15] There is conflicting evidence as to whether smoking marijuana causes lung and other types of cancers, suggesting the need for further study in this area.

Marijuana has also been identified as a risk factor for developing bullous disease and pneumothorax. The incidence of bullae was higher in marijuana smokers in a retrospective evaluation of habitual marijuana smokers referred for treatment of spontaneous pneumothorax. Incidence of bullae was higher in marijuana smokers compared to non-marijuana smokers (7/10 vs. 3/10 patients, respectively, $p<0.05$). In another retrospective case series of 17 patients less than 40 years of age presenting with spontaneous pneumothoraxes, 16 patients reported smoking marijuana daily for a mean of 8.8 years and tobacco for 11.8 years. These findings have led to the terms “marijuana lung” and “bong lung” to describe patients developing large peripheral paraseptal lung bullae.[49]

There is conflicting information regarding the adverse effects of medical marijuana on respiratory disorders (specifically cancers); however, asthma and COPD symptoms may be exacerbated with inhaled medical marijuana.

Mental Health Disorders

Repeated cannabis use causes behavioral alterations, and increased risk of mental illness including increased rates of psychosis, depression, and anxiety.[3,13,18] Studies report that chronic cannabis use results in at least a twofold increase in schizophrenia and psychotic symptoms, and those with schizophrenia are more likely to use marijuana.[15,18] According to the National Institute on Drug Abuse, ingesting large doses of cannabis may cause an acute psychosis presenting with hallucinations, delusions, and a loss of the sense of self.[3]

Chronic users with cannabis use disorders have been found to be six times more likely to have mood or anxiety disorders; and exacerbation of psychiatric disorders has been associated with repeated cannabis use.[50]Cannabis withdrawal also causes a variety of psychological withdrawal symptoms including anger, irritability, aggression, anxiety, and sleep difficulties.[13] Cannabis intoxication presents with a plethora of psychological manifestations including euphoria, relaxation, impaired memory and concentration, anxiety, panic attack, and psychosis.[50]

There appears to be mixed reports about posttraumatic stress disorder (PTSD) symptomatology following marijuana use. Wilkinson et al evaluated marijuana use in symptom severity and violent behavior in patients with posttraumatic stress disorder. [21] Patients in the study were drawn from the national evaluation of specialized intensive PTSD programs implemented by the Northeast Program Evaluation Center of the Veterans Health Administration from 1992 to 2011. A sample of 47,130 patients with PTSD were included. Patients were excluded if they had problematic alcohol use (more than two drinks on one occasion), those with any drug use (other than marijuana) within 30 days of admission, and those who entered treatment on transfer from an inpatient or residential program that restricted their access to alcohol and drugs. A total of 12,770 patients met the inclusion criteria and were classified into the following groups: no marijuana use ("never users", n=11,344), those reporting marijuana use at admission, but not at four months after discharge ("stoppers", n=299), those reporting use at admission and four months after discharge ("continuing users", n=296), and those reporting no use at admission but reporting use four months after discharge (starters, n=831). A total of 850 subjects were randomly selected from the never-user group, yielding a total sample of 2,276 veterans. Patients were evaluated at four months to assess PTSD symptom severity, employment status, violent behavior and composite measures of alcohol and drug use from the Addiction Severity Index (ASI). Marijuana use after treatment was associated with higher PTSD symptoms, more violent behavior, and alcohol use. [21]

Pierre et al reports psychosis associated with cannabis use in a 24-year-old man who was hospitalized for insomnia, irritability and aggressiveness two years after military service. He was given quetiapine 100 mg/day and had a rapid resolution of symptoms. Six months later, the patient was rehospitalized with psychotic symptoms after converting to medical marijuana with an increased frequency of twice daily use. After a course of aripiprazole and substance abuse treatment, the patient discontinued cannabis use and remained psychotic free.[52]

Greer et al evaluated PTSD symptoms collected during 80 psychiatric evaluations of patients applying to the New Mexico Medical Cannabis Program from 2009 to 2011. Results indicated that a greater than 75% reduction in symptoms, as measured by the Clinician Administered Posttraumatic Scale for DSM-IV (CAPS), was observed in patients using cannabis compared when they were not users of cannabis.[53]

Increased psychotic symptoms in patients with PTSD receiving marijuana were identified by Bonn-Miller et al.[54] Patients (n=432, male) in the study participated in a residential PTSD treatment at a Department of Veterans Affairs (VA) Medical Center between 1994 and 2000.The average length of stay in the program was 69.86 days. Approximately 56.9% of the patients were white and the remaining patients were identified as Hispanic/Latino American (14.1%), African American (13.9%), mixed ethnicity (6.9%), Native American (5.3%), Asian/Pacific Islander (1.6%), and "Other" (1.2%). Patients were excluded from the residential program if that had current psychotic symptoms, had substance use within 15 days of the start of treatment, or had medical conditions with a high probability of interfering with or preventing psychological treatment. Patients were evaluated at treatment intake, discharge and 4-month follow up. Approximately 23.1% of patients reported alcohol use, 8.1% reported cannabis use, 3% reported opiate use, 2.1% reported cocaine use and 1.9% reported amphetamine use. The frequency of cannabis use was correlated with follow up cannabis use. Change in PTSD Checklist-Military (PCL-M) scores between treatment intake and discharge were significantly predictive of greater frequency of cannabis use during the 30 days before the 4-month follow up (P<0.05).[54]

Approximately 20-30% of patients who smoke marijuana for recreational use report anxiety and panic attacks. Low dose marijuana appears to be sedating, whereas, larger doses appear to induce anxiety. It has not been determined if marijuana is associated with an increased risk of developing bipolar disorder. The data regarding an increased risk of depression associated with marijuana use is conflicting. In addition, marijuana worsens psychotic symptoms and outcomes in patients with schizophrenia or other psychotic disorders. [55]

Hospitalizations

A cross sectional study in an urban academic hospital in Aurora, Colorado was conducted to determine if the rates of emergency department (ED) visits possibly related to cannabis use have increased disproportionately among out-of-state residents, as compared with Colorado residents. The study was conducted between 2012 – 2014. Residency of patients was determined by zip codes given by the patients

upon registering in the ED. Patient files with ICD-9 codes for cannabis used within the designated time period were evaluated. The visits were due to psychiatric (26%), gastrointestinal symptoms (27%), and cardiopulmonary (16%) symptoms. The majority of patients were male (65%) and white (46%). Other races identified were black (38%) and other (16%). The rates of ED visits possibly related to cannabis use among out-of-state residents doubled from 85 per 10,000 visits in 2013 to 168 per 10,000 visits in 2014 (*P* = 0.001). No change was observed in ED visits possibly related to cannabis between 2012 and 2013 among out-of-state residents or Colorado residents. In addition, data from the Colorado Hospital Association did not indicate a significant change from 2011 to 2012 in the ED visits among out-of-state residents; however, from 2012 to 2014, the statewide rate among out-of-state residents increased from 78 per 10,000 visits in 2012 to 112 per 10,000 visits in 2013 to 163 per 10,000 visits in 2014 (rate ratios, 1.44 (2012 to 2013) and 1.46 (2013 to 2013); *P* <0.001 for both comparisons). Rates of ED use increased for Colorado residents from 2011 to 2014, the rate of ED visits possibly related to cannabis use increased from 61 to 70 to 86 to 101, respectively, per 10,000 visits (rate ratios, 1.14 [2011 to 2012], 1.24 [2012 to 2013], and 1.17 [2013 to 2014]; P<0.001 for all comparisons). [56] This study is limited by its small sample size and it only reflects cannabis use in one state.

Miscellaneous adverse drug reactions

Several investigators have evaluated adverse drug reactions associated with medical marijuana. Wang et al evaluated the adverse effects associated with medical cannabinoid use (oral Δ-9-tetrahydrocannabinol or Δ-9 tetrahydrocannabinol-cannabidiol and oromucosal Δ-9-tetrahydrocannabinol-cannabidiol were evaluated) in a systematic review and meta analysis.[57] No studies involving the smoking of marijuana were included. A total of 31 studies (n = 1932 patients) was reviewed. In these studies, the median duration of cannabis exposure was two weeks (range, 8 hours to 12 months) and patients received cannabis for chronic conditions (e.g., cancer, multiple sclerosis). A total of 164 serious adverse events occurred in patients taking cannabinoid therapy compared to 60 among the control group (either placebo or standard care). The most common adverse events were relapse of multiple sclerosis, vomiting, and urinary tract infection. Among the randomized controlled studies, no statistically significant differences between serious adverse events were observed between groups (RR, 1.04; 95% CI, 0.78 – 1.39). Adverse events were reported as respiratory (16.5%), gastrointestinal disorders (16.5%), nervous system disorders (15.2%), general disorders and administration-site conditions (12.85%), renal/urinary disorders (9.8%); neoplasm (benign and malignant) (8.5%), and psychiatric disorders (6.7%) The incidence for nonserious adverse events was significantly higher in patients taking cannabinoids than among patients assigned to the control group; (RR, 1.86; 95% CI, 1.57-2.21; *P*<0.001). Central nervous system (23.1%) and psychiatric disorders (10.3%) were the most common serious adverse events reported in the observational studies with no control group. However, this study was limited because it did not include reports of adverse events due to inhaled cannabis and only short-term use was evaluated (up to 12 months).[57,58]

Drug Interactions

The major active ingredient in marijuana is delta-9-tetrahydrocannabinol (THC). This agent exerts its effects by binding to cannabinoid receptors that are present mainly in the central nervous system (CNS). Binding of THC to these receptors causes several therapeutic and psychoactive effects. [59] Effects are also associated with modulatory effects in neurotransmitters (e.g., acetylcholine, norepinephrine, dopamine, serotonin, gamma aminobutyric acid, glutamate, and D-aspartate).[59-61] The metabolism of THC has not been completely elucidated. Several enzymes appear to play a role in metabolism including CYP2C9 and CYP3A4. As a result, medications that are metabolized by either of these pathways are subjected to an increased risk of interactions.[62]

There is a paucity of information related to drug-drug interactions with marijuana. Several interactions exist between dronabinol (marinol) and commercially available agents. In addition, major interactions exist between dronabinol and cocaine, ethanol, and droperidol. Other interactions include anxiolytics, barbiturates, disulfiram, monoamine oxidase inhibitors (MAOIs), protease inhibitors, selective serotonin reuptake inhibitors (SSRIs), sildenafil, sedatives, theophylline, tricyclic antidepressants, and warfarin.[59,63] Most of the interactions cited in drug interaction monographs are theoretical in nature based on the proposed mechanism of action of dronabinol and the potential offending agent; however, case reports/clinical studies indicating a potential interaction have occurred with anticholinergics, barbiturates, disulfiram, lithium, protease inhibitors (e.g., indinavir, nelfinavir), SSRIs (e.g., fluoxetine), sildenafil, theophylline, tricyclic antidepressants, opioid analgesics, and warfarin.[59,61,62,64-66]

Kleinloog et al evaluated the effects of THC in a placebo-controlled, cross-over study in 49 healthy male patients who were mild cannabis users. Subjects received a single dose of olanzapine (10 mg) or two oral doses of diphenhydramine (15 mg, used as a positive control for sedation) on intrapulmonary THC administration (2, 4, and 6 mg with 90 minute intervals). Psychomimetic symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS), were observed after THC administration (20.6% increase on positive subscale *P*<0.001) and the visual analogue scale for

psychedelic effects (+10.7 mm on feeling high). After THC and olanzapine administration, the positive subscale increased by only 13.7% and feeling high by 8.7 mm (*P*=0.066). Only one-third of patients did not show an increase in psychomimetic symptoms after THC alone. Of the responders, olanzapine significantly reduced the effects of THC (*P* = 0.005).[64]

Accidental exposures

According to the American Association of Poison Control Centers' National Poison Data System (NDPS) annual report from 2013, marijuana was mentioned a total of 5,033 times for exposures and THC analogs were mentioned 2,666 times. The largest number of exposures were in patients aged >20 years (n=614) and the smallest in children < 5 years (n=256). Unintentional exposures were cited in 398 cases involving marijuana and 86 cases with THC homologs. No major deaths were reported associated with marijuana use; however, three deaths were reported with the use of THC homologs.[67]

Wang et al evaluated the number of calls to Poison Control Centers as a function of medical marijuana legalization in a retrospective review of the American Association of Poison Control Centers National Poison Data System between January 1, 2005 and December 31, 2011.[68] State laws regarding marijuana use was classified as nonlegal if they had not passed legislation, transitional if legislation was in effect between 2005 and 2011, and decriminalized if laws were in effect before 2005. A total of 985 unintentional marijuana exposures were reported during that time period in children less than 9 years. Of the 985 exposures, 496 were in nonlegal states, 93 in transitional states, and 396 in decriminalized states. The majority of exposures were in males between 1.5 to 2 years. A variety of clinical events were reported; however, neurological effects were reported most frequently. Exposures in decriminalized states were associated with increased healthcare utilization, as measured by call rates (difference, +28.3%; 95% CI, 19-38%), more moderate to major clinical effects (OR, 2.1; 95% CI, 1.4 to 3.1) and more critical care admissions (OR, 3.4; 95% CI, 1.8 to 6.5) compared with exposures from nonlegal states. The most common symptom associated with medical marijuana was drowsiness/lethargy in patients in nonlegal (20%), transitional (30%), and decriminalized (37%) states. No changes in call rate in nonlegal states were observed; however, the call rate in decriminalized states increased by 30.3% calls per year. Similarly, call rates in transitional states increased to 11.5% per year.[68]

Crime / Car Accident Fatalities

Medical marijuana dispensaries are perceived to be associated with increased criminal activity in proximity to dispensary location; however, few investigators have evaluated whether or not the dispensaries are associated with increased criminal activity. Although medical marijuana dispensaries produce conditions associated with an increased crime rate (e.g., burglary, robbery, assault, etc), the typical patient population (e.g., older White men) is not believed to be a high risk population for perpetrating crimes.[69] Kepple et al evaluated the crime rates associated with medical marijuana dispensaries in Sacramento, CA in an ecological, cross-section study. Results indicated that violent crime rates were not significantly related to the presence of a medical marijuana dispensary. However, a significant increase in crime rates were observed when there was a high population of individuals in the community between the ages of 15-24 years, high percentage of one-person households, high unemployment rate and high percentage of commercial zoning locations.[69] In another study, ease of access to medical marijuana was not a significant risk factor for fatal car crashes.[70]

Pharmacists' consideration

Pharmacists may be asked to provide counseling to patients who are using medical marijuana. As a result, pharmacists need to know potential adverse effects, drug-drug interactions, and policies / procedures associated with dispensing medical marijuana. Several states have proposed that pharmacists be responsible for dispensing medical marijuana and although state laws may sanction this activity, federal laws will be violated.[71] In most states, pharmacists are not allowed to recommend a source or provide instructions on how to obtain medical marijuana. Furthermore, Pharmacy and Therapeutics committees may be asked for guidance and or policy considerations regarding the dispensing of medical marijuana.[72,73] The American Society of Health System Pharmacists (ASHP) "oppose(s) state legislation that authorizes the use of medical marijuana until there is sufficient evidence to support its safety and effectiveness and a standardized product that would be subject to the same regulations as a prescription drug product." ASHP encourages research into the effectiveness, safety and clinical use of medical marijuana and will advocate for development processes that would ensure standardization of the products. In addition to encouraging the DEA to eliminate barriers to medical research of medical marijuana (e.g., potentially reclassifying the product to something other than a Schedule 1 controlled substance), they oppose storage, procurement, and distribution of the product by licensed pharmacies/health facilities for uses other than research.[74] A general Internet search yielded several resources that may assist practitioners in learning more about medical marijuana. One school of pharmacy, St. John Fisher College offered a day-long medical marijuana training session.[75] Several continuing education classes have been dedicated to the topic as well. The Cannabis Training

Institute provides a Cannabis Industry Certification for individuals completing the course. This program is a training and certification resource for cannabis businesses, entrepreneurs, clinicians, and policymakers.[76]

Clinical questions are still unanswered related to the use of medical marijuana including which method of delivery is best to product therapeutic effect without producing untoward adverse effects. The most efficacious method of delivery has not been established. In addition, the content of THC in cannabis may vary according to geographic origin, the part of the plant used, methods for storage, and cultivation techniques. [77] Cultivation can also be associated with contaminants in the cannabis. Biological contaminants of cannabis plants include fungus and bacteria.

At least two states with legalized medical marijuana prohibit the use of smoked marijuana.[5] In addition, the appropriate dosage of medical marijuana needs to be determined. If dispensed, pharmacists need to be able to ensure the potency of the products and ensure that the products are not contaminated with harmful substances.

Conclusion

The legalization of marijuana has led to the misconception that it is a safe, natural product with few side effects and no serious drug or disease state interactions. [21] Although a limited amount of information was located for medical marijuana, this information is based on the assumption that medical and recreational marijuana adverse effects are similar. The efficacy of medical marijuana in several disease states has not been elucidated; however, use may be associated with significant drug-drug interactions and adverse drug reactions. In addition, legalization has been associated with increased marijuana abuse/dependence and accidental exposures in children. Increased case reports of cardiovascular events following recreational marijuana use, its potential to exacerbate respiratory disorders, and the potential for psychiatric changes establishes the need for extensive study and education to minimize these events. In order to appropriately counsel patients, pharmacists need to be informed about the use of marijuana. Additional training is necessary and essential for pharmacists to understand and recognize the potential interactions with chronic medications, especially those used for marijuana approved disease states. Extensive investigation is needed to fully understand the pharmacologic effects of marijuana for treating disease states and to minimize the detrimental effects experienced by chronic users. Pharmacists play a key role in medication management, and the legalization of medical marijuana complicates this role with little guidance. Additional studies need to be performed to determine long-term adverse effects of medical marijuana in various populations.

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Table 1: Summary chart of States with Legal Medical Marijuana[5]

State	Year Passed	Approved Conditions
1. Alaska	1998	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV or AIDS, multiple sclerosis and other disorders characterized by muscle spasticity, and nausea. Other conditions are subject to approval by the Alaska Department of Health and Social Services.
2. Arizona	2010	Cancer, glaucoma, HIV/AIDS, Hepatitis C, ALS, Crohn's disease, Alzheimer's disease, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms (including multiple sclerosis). Starting Jan.1, 2015, PTSD was added to the list.
3. California	1996	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms, including spasms associated with multiple sclerosis, seizures, including seizures associated with epilepsy, severe nausea; Other chronic or persistent medical symptoms.
4. Colorado	2000	Cancer, glaucoma, HIV/AIDS positive, cachexia; severe pain; severe nausea; seizures, including those that are characteristic of epilepsy; or persistent muscle spasms, including those that are characteristic of multiple sclerosis. Other conditions are subject to approval by the Colorado Board of Health.
5. Connecticut	2012	"Cancer, glaucoma, positive status for human immunodeficiency virus or acquired immune deficiency syndrome [HIV/AIDS], Parkinson's disease, multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, wasting syndrome, Crohn's disease, posttraumatic stress disorder, or... any medical condition, medical treatment or disease approved by the Department of Consumer Protection..." On Mar. 14, 2016, the Connecticut Department of Consumer Protection announced six new qualifying conditions: sickle cell disease, post laminectomy syndrome with chronic radiculopathy, severe psoriasis and psoriatic arthritis, amyotrophic lateral sclerosis, ulcerative colitis, and complex regional pain syndrome.
6. District of Columbia	2010	Azidothymidine/Protease inhibitor therapy, Cancer, Chemotherapy/Radiotherapy, Glaucoma, HIV/AIDS, Multiple sclerosis/Severe and persistent muscle spasms
7. Delaware	2011	ALS, Alzheimer's disease, Cachexia or wasting syndrome, Cancer, Decompensated cirrhosis (Hepatitis C), HIV/AIDS, Intractable nausea, Multiple sclerosis/Severe and persistent muscle spasms, Severe/Debilitating pain unresponsive to previously prescribed medication or surgical measures for more than 3 months or for which other treatment options produced serious side effects, PTSD
8. Hawaii	2000	Cachexia or wasting syndrome, Cancer, Epilepsy/Seizure disorder, Glaucoma, HIV/AIDS, Multiple sclerosis/Severe and persistent muscle spasms, Severe nausea, Severe pain, PTSD
9. Illinois	2013	Includes about 40 chronic diseases. Alzheimer's disease agitation, Amyotrophic lateral sclerosis, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Cachexia/wasting syndrome, Cancer, Causalgia, Chronic inflammatory Demyelinating Polyneuropathy, Crohn's disease, Dystonia, Fibrous dysplasia, Glaucoma, Hepatitis C, HIV/AIDS, Hydrocephalus, Hydromyelia syringomyelia, Interstitial Cystitis, Lupus, Multiple Sclerosis, Muscular dystrophy, Myasthenia Gravis, Myoclonus, Nail-patella syndrome or residual limb pain, Neurofibromatosis, Parkinson's Disease, Reflex Sympathetic Dystrophy, Rheumatoid arthritis, Severe fibromyalgia, Sjogren's Syndrome, Spinal cord disease, Spinal cord injury, Tarlov cysts, Tourette's Syndrome, Traumatic brain injury and post-concussion syndrome

10. Maine	1999	Epilepsy/Seizure disorders, Glaucoma, Multiple sclerosis/Muscle spasticity disorders, Nausea or vomiting as a result of AIDS or cancer chemotherapy
11. Maryland	2014	Anorexia or Wasting syndrome, Cachexia, Seizures, Severe nausea, Severe or chronic pain, Severe or persistent muscle spasms or other conditions approved by the Commission.
12. Massachusetts	2012	ALS, Cancer, Crohn's disease, Glaucoma, Hepatitis C, HIV/AIDS, Multiple sclerosis, Parkinson's disease
13. Michigan	2008	ALS, Alzheimer's disease agitation, Cachexia or wasting syndrome, Cancer, Crohn's disease, Epilepsy/Seizure disorders, Glaucoma, Hepatitis C, HIV/AIDS, Multiple sclerosis/Other muscle spasm disorders, Nail patella, PTSD, Severe and chronic pain, Severe nausea
14. Minnesota	2014	ALS, Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea or severe vomiting, or cachexia or severe wasting), Crohn's disease, Epilepsy/Seizure disorders, Glaucoma, HIV/AIDS, Multiple sclerosis/Severe & persistent muscle spasms, Terminal illness with a life expectancy of under one year, Tourette's syndrome> Patients with intractable pain may become eligible to receive medical marijuana August 2016.
15. Montana	2004	Cachexia or wasting syndrome, Cancer, Crohn's disease, Epilepsy/Seizure disorders, Glaucoma, HIV/AIDS, Multiple sclerosis/Muscle spasticity, Severe nausea, Severe or chronic pain
16. Nevada	2000	AIDS, Cachexia, Cancer, Glaucoma, Persistent muscle spasms, PTSD, Seizures, Severe nausea or pain
17. New Hampshire	2013	ALS, Alzheimer's disease agitation, Cancer, Chronic pancreatitis, Crohn's disease, Glaucoma, Hepatitis C, HIV/AIDS, Injuries that significantly interferes with daily activities as documented by the patient's provider, Multiple sclerosis, Muscular dystrophy, Severely debilitating or terminal medical condition or its treatment that has produced at least one of the following: elevated intraocular pressure, cachexia, chemotherapy induced anorexia, wasting syndrome, severe pain that has not responded to previously prescribed medication or surgical measures or for which other treatment options produced serious side effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms; Spinal cord injury or disease, Traumatic brain injury
18. New Jersey	2010	Epilepsy/Seizure disorder, Multiple sclerosis, Intractable skeletal muscular spasticity, Glaucoma, Severe or chronic pain, Severe nausea/vomiting, cachexia, or wasting syndrome resulting from HIV/AIDS or cancer, ALS, Terminal cancer, Muscular dystrophy, Inflammatory bowel disease including Crohn's disease, Terminal illness if prognosis < 12 months of life
19. New Mexico	2007	ALS, Cancer, Cervical dystonia, Crohn's disease, Damage to the nervous tissue of the spinal cord with intractable spasticity, Epilepsy, Glaucoma, Hepatitis C infection, HIV/AIDS, Hospice patients, Huntington's disease, Inflammatory Autoimmune-mediated Arthritis, Intractable nausea/vomiting, Multiple sclerosis, Painful peripheral neuropathy, Parkinson's disease, PTSD, Severe anorexia/cachexia, Severe chronic pain, ulcerative colitis, spasmodic torticollis
20. New York	2014	ALS, Cancer, Epilepsy, HIV/AIDS, Huntington's disease, Inflammatory bowel disease, Multiple sclerosis, Neuropathies, Parkinson's disease, Spinal cord damage causing spasticity. The Department of Health commissioner has the discretion to add or delete conditions and must decide whether to add Alzheimer's, muscular dystrophy, dystonia, PTSD, and rheumatoid arthritis within 18 months of the law becoming effective.
21. Oregon	1998	Cancer, Cachexia, Epilepsy/Seizure disorder, Glaucoma, HIV/AIDS, Multiple sclerosis/Persistent muscle spasms, Severe nausea, Severe pain

22. Rhode Island	2006	Alzheimer's Disease agitation, Cachexia/Wasting syndrome, Cancer, Crohn's disease, Epilepsy/Seizure disorder, Glaucoma, Hepatitis C, HIV/AIDS, Multiple sclerosis/Severe & persistent muscle spasms, Severe debilitating chronic pain, Severe nausea
23. Vermont	2004	Cachexia/Wasting syndrome, Cancer, Chronic, debilitating disease treatment which produces severe, persistent symptoms, HIV/AIDS, Multiple sclerosis, Seizures, Severe nausea, Severe pain
24. Washington	1998	Anorexia, Cachexia, Cancer, Chronic renal failure, Crohn's disease, Diseases which result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity, when those conditions are unrelieved by standard treatments or medications, Epilepsy, Glaucoma, Hepatitis C with debilitating nausea or intractable pain, HIV/AIDS, Intractable pain (defined as pain unrelieved by standard treatment or medications), Multiple sclerosis

*ALS = Amyotrophic lateral sclerosis
+PTSD = Posttraumatic Distress Disorder
HIV = Human Immunodeficiency Virus

Table 2: Summary of clinical data assessing adverse drug reactions with medical marijuana

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
CV/CVA effects					
Mittleman et al.[23]	Case-cross over Recreational marijuana use	3,882 patients Female: 1258 with an acute MI average of 4 days after infarction onset	Compared the reported use of marijuana in the hour preceeding symptoms of MI onset to its expected frequency using self-matched controlled data	124 (3.2%) reported smoking marijuana in the prior year, 37 within 24 hours and 9 within 1 hour of MI symptoms. Marijuana users were more likely to be men (94% vs. 67%, *P*<0.001), current cigarette smokers (68% vs. 32%, *P*<0.001), and obese (43% vs. 32%; *P*=0.008. These patients were less like to have a history of angina (12% vs, 25%, *P*<0.001) or hypertension (30% vs. 44%; *P* =0.002). The risk of MI was elevated 4.8 times over baseline (95% CI, 2.4 to 9.5) in the 60 minutes following marijuana use.	Marijuana smoking may rarely trigger AMI.
Jouanjus et al.[24]	Retrospective, observational database evaluation Recreational marijuana use	Patients admitted to public hospitals (n=6) in the Toulouse area (France) between January 2004 and December 2007 in relation to the use of cannabis. Of the 200 patients, 153 (76.5%) were men; mean age was 28 years	Cannabis use was identified through ICD-10 codes and systematic review of medical charts. Cannabis use was validated in 41.9% (294/701) of previously selected hospitalizations, which correlated to 43.6% (232/532) of selected patients. The final sample included 224 hospitalizations (n=200 patients).	619 adverse events occurred, one led to death. Cannabis use was associated with psychiatric disorders (n=119/619, 19.2% of total) and involved 57.5% of patients. Incidence of psychiatric disorders was 2.9 per 1000 among recent users, and 5 per 1000 among regular users.	Cannabis use is associated with serious complications that can lead to hospitalizations.

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
				CNS disorders were the second most identified organ system (15.8% of toal adverse reactions that affected 44% of the patients. Respiratory disorders (11%) were observed among 31% of patients and included dyspnea, hemoptysis, and spontaneous pneumothorax. CV disorders occurred for 9.5% of the total AEs and involved 29% of patients. The incidence of CV events was 1.5 per 1000 among recent users and 2.6 per 1000 among regular users. A total of 17 extracardiac vascular disorders were reported and 4 of these were CVA.	
Yurtdas et al.[25]	Case report Recreational marijuana use	28-year old man who presented to ED with marijuana use.	Smoking cannabis twice weekly for the prior 8 years (last consumption 3 hours before onset of symptoms). Also a cigarette smoker.	The patient was discharged without complications after 8 days.	Recreational marijuana use may be associated MI symptoms.
Nawrot et al.[26]	Meta-regression analysis to determine triggers of MI at an individual and population level.	Mean age of patients ranged from 44 years to 72 years. Most studies had a time window before onset of	A total of 36 studies were investigated; 13 types of triggers for acute MI, 28 case-crossover studies, 7 time-series, and one case-control study.	The prevalence of marijuana exposure was 0.2%; OR 4.8 (95% CI, 2.9-9.5%). Population attributable factors (PAF): 0.75% (95% CI, 0.38% to 1.67%)	The investigators found that participation in traffic and exposure to particulate matter air pollution were contributors to air pollution.

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
		MI ranging from less than 2 hours to 1 day (except respiratory infections which ranged from 1 to 10 days).			
Frost et al.[27]	Cohort, multicentered Recreational marijuana use	MI patients enrolled in 1989 to 1996 and followed up for mortality using the National Death Index. A total of 3,886 patients hospitalized in 64 centers nationwide were interviewed for a median of 4 days. All marijuana users were <63 years, so patients in this age range were included. The final sample size was 2,097.	The average age of patients reporting marijuana use was 43.7 years, 6% were female, 78% were white and 35% had some college. Most of these patients were current smokers (67%).	After 12.7 years, 519 patients died as a result of their MI including 22 of the 109 patients reporting marijuana use died at the time of their MI.	Chronic marijuana use increased mortality; however, no statistically significant differences were observed between groups.

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
Rodondi et al.[28]	Multicentered, cohort longitudinal study (CARDIA)	Cohort enrolled 5,115 black and white adults between 18-30 years in age in 1985 to 1986. A total of 3,672 patients completed the year 15 examination. A detailed, self-administered questionnaire was given to assess current and ever use of illicit drugs.	Most marijuana users (89%) reported using marijuana for <1,800 days over 15 years (average 10 days/month). A total of 37 participants (1%) used marijuana for >3600 days (20 days/month).	Higher marijuana use was associated with being male, tobacco use, use of other ilicit drug, less education, lower income. Higher use was also associated with higher physical activity and fitness, but these differences were not significant. Marijuana use was associated with higher triglyceride levels (*P* <0.001). Marijuana use was associated with systolic blood pressure levels (*P*<.001); however, the changes are unlikely to be clinically significant. Marijuana use was also associated with higher triglyceride use.	Marijuana use was not independently associated with BMI and cardiovascular risk factors in young, healthy adults; however, these results are confounded by higher alcohol use in these patients.
Cappelli et al.[29]	Case report Recreational marijuana use	30-year-old male reported to the ED with chest pain radiating from neck to jaw.	Patient had no family history of coronary artery disease. BMI=28 15-pack cigarette smoking history. Reported using cannabis 2-3 times a week since his adolescent years; last consumption was 2 hours before symptom onset.	Patient had clot in left anterior descending artery. The patient recovered and was discharged 7 days after admission.	Cannabis use may be associated with MI in patients with established CAD.
Zachariah et al.[31]	Case report Recreational marijuana use	34-year-old, white man Tobacco smoking history of 1 pack and up to seven marijuana	No significant differences were observed in platelet function after smoking marijuana.	Patient experienced a left basal ganglia infarct.	After 3 months of physician and occupational therapy, the patient experienced marked improvement of his

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
		cigarettes per day			neurological deficits.
Geller et al.[32]	Retrospective case and chart review Recreational marijuana use	Inpatient and intensive care hospitalization units managing children and adolescents.	Male adolescent patients (n=3) with ischemic cerebellar stroke after use of marijuana.	All patients had similar presentations including headache, fluctuating level of consciousness or lethargy, visual disturbance, and variable ataxia after self-administration of marijuana.	Occasional marijuana use may be a risk factor for stroke in childhood.
Finsterer et al.[33]	Case report Recreational marijuana use	37-year-old Albanese man Smoked cigarette containing marijuana 250 mg	Patient also smoked up to 20 cigarettes per day. Patient smoked marijuana cigarette 2 hours before hospitalization.	Patient experienced a stroke in the right occipital area subcortically.	Patient was dismissed after 3 days.
Herning et al.[34]	Case controlled study Recreational marijuana use	Marijuana male abusers (n=16) Control male subjects (n=19)	Blood flow velocity from cerebral arteries using transcranial Doppler sonography was evaluated for a month of monitored abstinence to determine if perfusion changes in early abstinence were a part of marijuana withdrawal syndrome or permanent cerebrovascular deficit.	Marijuana users had a significantly higher pulsatility idex (PI) than control subjects on both cerebral arteries ($p<0.01$). No changes were observed for PI for middle and anterior cerebral arteries.	Chronic marijuana use may be a risk factor for stroke.
Munchkhof et al.[36]	Case series (n=5) Cluster investigation Recreational marijuana use	45 contacts had a marijuana water pipe	5 cases of pulmonary TB were identified. All cases were Australian-born Caucasian male (median age 20 years).	Transmission of TB occurred with sharing a marijuana water pipe (OR, 2.22; 95% CI, 0.96-5.17). All 5 cases were culture positive, and 4 were sputum AFB smear positive.	All cases received directly observed therapy (DOT) and completed treatment.

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Oeltmann et al.[37]	Case series (n=4) Recreational marijuana use	Cluster of TB cases in Seattle from February to April 2004	East-African immigrants with histories of incarceration and illicit drug use.	A total of 11 patients were found from February to October 2004. Four patients had confirmed TB. All patients were unemployed and had histories of incarceration and illicit drug use.	"Hotboxing" (smoking marijuana inside a closed car with friends) appeared to fuel transmission of TB.
Krause et al.[38]	Case series (n=9) Recreational marijuana use	Investigators interviewed all patients with suspected meningococcal disease by using questionnaires. They evaluated demographics and social networks and close contacts of the infected people.	7 of the 9 cases had culture-confirmed serogroup C meningococcal disease.	Case-patients and close contacts shared a variety of social activities.	Social networks and marijuana exposure may help locate close contacts of patients with meningococcal disease and help prevent other infections.
Finn et al.[39]	Case series (n=3) Recreational marijuana use	Cases were 18-21 years of age had a diagnosis of N meningitides of the same strain.	All transmissions appeared to have occurred at a May 14th party at a college.	A large number of people reported marijuana and alcohol use at the party.	Transmission may have occurred due to binge drinking and smoking.
Liau et al. [40]	Self-administered survey and face to face interview Recreational marijuana use	African American female adolescents (n=522)	Average patient age was 16 years (SD, 1.2 years); majority were full-time students (81.2%). Approximately 20% reported having a paying job and 28% tested positive for at least one of the three STDs tested.	Of the study patients, 5.4% tested positive for marijuana. These adolescents were more likely to test positive for Neisseria gonorrhea (adjusted OR, 3.4) and Chlamydia trachomatis (AOR, 3.9). They were more likely to avoid condoms in the previous 30 days (AOR, 2.9) and to have not used condoms consistently in the	Marijuana use may increase risky sexual behavior in adolescents.

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				previous 6 months (AOR, 3.6).	
Hezode et al.[41]	Cohort study Recreational marijuana use	315 consecutive patients with untreated chronic hepatitis C (CHC) undergoing liver biopsy were included.	Patients were categorized as cannabis nonusers (63.5%), occasional cannabis smokers (12.4%), or daily cannabis smokers (24.1%). Approximately 71% were male, route of transmission was IV drug use (44.1%) or blood transfusion (30.2%). The majority of patients had HCV genotype 1 (62.5%). Median cannabis consumption was 4 cigarettes/month and 24.1% of patients were daily cannabis users and smoked a median of 82 cannabis cigarettes/month (p<0.001).	Marked steatosis was significantly more frequent with daily cannabis use compared with occasional users and nonusers (32.9%, 7.7%, and 16%, respectively; p<0.001). Marked steatosis was associated with daily use of cannabis (OR, 2.1; 95% CI, 1.01-1.45).	Marijuana use may be a novel independent predictor of steatosis severity during CHC.
Nieder et al.[42]	Case report Recreational marijuana use	45-year-old man History of heavy marijuana use (up to 5 cigarettes for more than 30 years).	Patient presented with gross hematuria over the course of 2 months.	After a confirmed large papillary lesion was observed on the right lateral wall on cytology and therapy was provided, the cytology findings were normal after a 3-month surveillance. The patient stopped smoking marijuana.	The patient's only risk factor for transitional cell carcinoma was inhalation of marijuana.
Berthiller et al.[43]	Pooled analysis of case controlled studies.	A total of 4,029 head and neck cancer (HNC) and 5,015 cases from 5 case-control studies were included.	Patients ranged in age from 15-79 years. Approximately 10.1% of cases and 14.8% of controls were marijuana smokers. Sources of information was random digit dialing, cancer screening clinics, neighborhood, hospital	The risk of HNC was not increased with ever marijuana smoking (OR, 0.88; 95% CI, 0.67 – 1.16).	Infrequent marijuana use does not increase the risk of HNC.

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			visitors, and hospital patients.		
Respiratory effects					
Taylor et al. [44]	Retrospective chart review Recreational marijuana use	Surgical pathology reports over 4 years were assessed in patients under 40 years with a diagnosis of respiratory tract carcinoma to determine if marijuana use was associated with respiratory tract carcinoma.	A total of 887 patients were screened. A total of 10 patients were included. Six patients were male. The age range of the patients was between 28-39 years. Patients were categorized as heavy (daily use), regular (Frequent, but less than daily use), possible, and infrequent. Sites of carcinoma included oropharynx (n=4), larynx (n=4), and lung (n=2). A total of 9 lesions were squamous cell carcinoma and one was small cell anaplastic carcinoma.	Five patients had a documented history of heavy marijuana smoking. Two patients were described as regular users. One patient was a possible marijuana smoker. Two patients had no documentation of marijuana use.	Regular use of marijuana may be a risk factor for hastening the development of respiratory tract carcinomas.
Friedman et al.[45]	Retrospective chart review Recreational marijuana use	Members of the Kaiser Permanente Medical Care program who had at least one health check up between July 1979 and December 1985. The purpose was to determine the healthcare usage between the two groups.	A total of 14,600 respondents to the tobacco-marijuana survey responded smoking marijuana more than 6 times in their lifetime. Marijuana smokers (n=746) and nonmarijuana smokers (n=709) were evaluated. A total of 486 pairs had medical charts reviewed. A total of 70 were excluded which left a total of 452 marijuana smokers and 450 nonsmokers.	Approximately 66% of subjects were male and the majority were between ages 25-34 years. Approximately 60% were white. Marijuana smokers had a lower educational level and less likely to be married than nonsmokers. Marijuana smokers reported more days ill with a cold, flu,	Marijuana smokers were associated with small, but significant increases in outpatient visits.

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
				or sore throat in the past year compared to nonsmokers. A total of 6,088 visits were recorded including 3,206 among the marijuana smoking group and 2,882 among the nonsmoking group. At least one outpatient visit for respiratory problems was made by 36% of the marijuana smokers vs. 33% of nonsmokers.	
Taylor et al.[46]	Cohort study Recreational marijuana use	943 adults born in Dunedin, New Zealand in 1972/73 were evaluated at 21 years of age.	Tobacco and marijuana history was obtained from a self-administered questionnaire. Subjects also completed a questionnaire for lung function.FEV1 and FVC was also assessed.	A total of 588 non-smokers, 264 tobacco-only smokers, and 28 cannabis-dependent non-tobacco smokers, and 63 who smoked tobacco and cannabis were included. A total of 91 subjects were cannabis-dependent. The mean cannabis use was 230 times (95% CI, 193.6, 266.4) during the previous 12 months, compared to 40 (95% CI, 31.3, 48.7) among users who were not dependent.	Cannabis-dependent subjects (after controlling for tobacco use) had a significant increase in wheezing apart from colds (61%; $p<0.05$), exercise-related shortness of breath (65%; $p<0.05$), nocturnal wakening with chest tightness (72%; $p<.05$) and morning sputum production (144%; $p<0.001$).
Taylor et al.[47]	Cohort study Recreational marijuana use	Out of a cohort of 1037 subjects, a group of 900 young adults served as the	Cannabis and tobacco use was documented at each age with a standard interview. Lung function was also evaluated.	Subjects who used cannabis on 900 or more occasions had a mean FEV1/VC value that was	A dose-dependent relationship between cannabis use and decline in FEV/VC was

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
		cohort. Subjects were born in Dunedin, New Zealand in 1972/3 were studied at ages 18, 21, and 26 years.	Results were available for 930 subjects.	7.2%, 2.6%, and 5% less than non users at ages 18, 21, and 26, respectively.	observed.
Moore et al.[48]	Cohort study Recreational marijuana use	6,728 adults aged 20 to 59 years who completed the drug, tobacco, and health sections of the NHANES III questionnaire in 1998 and 1994.	Marijuana smokers reported smoking an average of 10.2 days of the previous 30 days. Approximately 16% reported daily or nearly daily use. Smokers were more likely to be male, white, younger, and single compared to nonsmokers. Approximately 77% of marijuana smokers also smoked tobacco cigarettes.	Reports of chronic bronchitis 8.1% vs. 3.2%), cough (21.7% vs. 3.8%), phlegm (16.9% vs. 3.5%), and chest sounds (23.5% vs. 5.8%) were significantly associated with marijuana smoking compared to non smokers. (P<0.05). Shortness of breath (23.7% vs. 33.4%) and FEV1/FVC ratio < 70% was observed more frequently with tobacco smoking compared to marijuana smoking (p<0.05). Wheezing (40.1 vs. 25.2%) occurred more frequently with marijuana smokers compared to tobacco smokers (p<0.05).	Marijuana use was associated with an increased risk of many respiratory symptoms.
Mental health disorders					
Wilkinson et al.[51]	Longitudinal observational study	N= 2,276 veterans Mean age: 51.7 (SD =8.6(years, 96.7% male, 21.2 African American, married: 40.7%, mean education level: 12.9 years (SD 1.9). Mean length of	Never-users (group 1, n=850) Stoppers (group 2, n=299) Continuing users (group 3, n=296) Starters (group 4, n=831)	PTSD symptom severity (groups 3,4 > 1,2) Never-users: 37.71 (0.228) Stoppers:36.64 (0.383) Continuing users: 38.92 (0.383) Starters: 39.67 (0.226) *P*<0.001	Marijuana use was associated with higher PTSD symptoms at follow up compared to never users. Marijuana use after treatment was associated with more violent behavior and

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
		stay 42.5 days		Violence (group 4 >1,2,3) Never-users: 0.87 (0.041) Stoppers: 0.76 (0.068) Continuing users: 0.93 (0.068) Starters: 1.25 (0.040) *P* <0.001 Alcohol abuse (group 4>1,2,3; 3>3) Never-users: 0.096 (0.007) Stoppers: 0.079 (0.011) Continuing users: 0.129 (0.011) Starters:0.229 (0.006) *P*<0.001 Drug abuse (Groups 3, 4 > 1 ,2) Never-users:0.037 (0.0033) Stoppers:0.034 (0.0056) Continuing users: 0.128 (0.0056) Starters: 0.130 (0.0033) *P*<0.001 Employment status Never-users:0.578 (0.007) Stoppers: 0.575 (0.011) Continuing users: 0.594 (0.011) Starters:0.577 (0.007) *P*=0.5752	alcohol use.

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Greer et al.[53]	Retrospective chart review Medical cannabis study to assess differences in PTSD symptoms with and without the use of cannabis.	First 80 patients evaluated for participation in the New Mexico Department of Health's Medical Cannabis Program for PTSD Clinical Administered Posttraumatic Scale (CAPS) for DSM-IV was assessed.	No patient characteristics were discussed.	Significant reductions of total CAPS scores were observed when patients were using cannabis (22.5±16.9) compared with no cannabis use (98.8±17.6). The majority of patients experiencing benefits had reductions in core symptom cluster of re-experiencing (Criterion B) which decreased from 29.5±6.4 to 7.3 ±5.9; p<0.0001; numbing and avoidance (Criterion C) which decreased from 38.2 ± 8.4 to 8.7 ± 8.0; p<0.0001); and hyperarousal (Criterion D) which decreased from 31±6.2 to 6.6±6.0; p<0.0001. No adverse effects were reported.	Cannabis use is associated with PSTD reduction in symptoms in some patients; however, additional clinical trials need to be conducted to determine the efficacy of cannabis in treating PTSD.
Bonn-Miller et al.[54]	Retrospective cohort	Male patients (n=432) admitted to VA residential rehabilitation program	Substance use patterns of male, VA patients who were admitted to treatment residency program.	Change in PCL-M scores was not a significant predictor of alcohol or opiate use. A post hoc analysis indicated that change in PTSD re-experiencing symptom severity was not significantly predictive of	Military veterans who experienced lower levels of change in PTSD symptom severity during the course of residential treatment for PTSD were more likely to use cannabis after discharge from treatment.

Reference	Study Design	Patient Demographics	Patient Characteristics	Results	Conclusion
				cannabis use during the 30 days before 4-month follow up.	
Hospitalizations					
Kim et al.[56]	Cross-sectional study of an urban academic hospital in Aurora, CO	Colorado residents from 2012 -2014 and residency was determined by the zip codes.	Hospital has 100,000 emergency department (ED) visits per year. Findings were confirmed with data from more than 100 hospitals reported to the Colorado Hospital Association from 2011 through 2014. Female: 35% Black: 38% White: 46% Reason for visit: Cardiopulmonary (16%) Gastrointestinal (27%) Psychiatric (26%)	ED visits possibly related to cannabis use among out-of-state residents doubled from 85 per 10,000 visits in 2013 to 168 per 10,000 visits in 2014 (p=0.001). No significant change in ED rates between 2013 and 2014 among CO residents were observed between 2013 and 2014. The rates did not change significantly between 2012 and 2013 among out of state residents or CO residents.	Emergency department visits related to cannabis use appear to be increasing more rapidly among out-of-state residents compared to Colorado residents.