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Wolters Kluwer

Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects

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Literature review current through: **Oct 2023.**
This topic last updated: **Nov 10, 2023.**

INTRODUCTION

Cannabis (also called marijuana) is the fourth most commonly used psychoactive substance worldwide, after alcohol, caffeine, and tobacco [1]. Its euphorigenic ("high"), sedative, and analgesic properties are primarily due to one cannabinoid: delta-9-tetrahydrocannabinol (THC); THC concentration is commonly used as a measure of cannabis potency [2].

The legal status of cannabis use, for medical as well as recreational purposes, varies internationally as well as across the United States. The potency of cannabis has increased around the world in recent decades [2], which may have contributed to increased rates of cannabis-related adverse effects.

The epidemiology, pharmacology, comorbidity, and adverse effects of cannabis use and disorder in adults are reviewed here. Effects of acute intoxication, and treatment of cannabis use disorder and cannabis withdrawal are reviewed separately. (See "Cannabis use disorder: Clinical features, screening, diagnosis, and treatment" and "Cannabis (marijuana): Acute intoxication" and "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment".)

EPIDEMIOLOGY

Cannabis use

Incidence and prevalence — Cannabis was used by an estimated 219 million people worldwide in 2021, approximately 4.3 percent of the global population age 15 to 64 years [1].

A large, nationally representative, community-based, epidemiologic survey (the National Survey on Drug Use and Health [NSDUH]) estimated the prevalence rates of lifetime, past-year, and past month cannabis use in the community-dwelling United States population (12 years or older) in 2021 to be 45.7, 18.7, and 13 percent, respectively [3].

Cannabis use was initiated by 2.6 million individuals in 2021, one-third (33.2 percent) between age 12 and 17 years [3].

Frequency of use — Adolescents (12 to 17 years old) use cannabis less frequently and are less likely than older individuals to be heavy users [3].

As examples, according to the 2021 NSDUH survey, the approximate average number of days of past year, and past month use for each group was:

- Adolescents (12 to 17 years) – 88.9 days past year, 11.4 days past month
- Adults (>17 years) – 148.6 days past year, 16.4 days past month

Additionally, the percentage of individuals with >300 days use in the past year, and >20 days in the past month for each group was:

- Adolescents (12 to 17 years) – 9.7 and 29.1 percent, respectively
- Adults (>17 years) – 26.1 and 48.8 percent, respectively

Routes of administration — Cannabis can be consumed by a variety of routes of administration, most commonly smoked (typically as a "joint" [plant material rolled in paper], "blunt" [rolled in tobacco] or in a pipe), vaporized ("vaping"), and oral ("edibles") [4]. Topical and transmucosal (typically sublingual) routes are used for some medicinal cannabis products but rarely for recreational purposes (only 1 percent of users in one study) [5]. Cross-sectional surveys suggest that approximately three-quarters of users smoke cannabis [5]. Among adolescent/young adult users, approximately one-third use oral cannabis and approximately one-quarter are vaping (ie, inhaling from electronic drug delivery devices or "e-cigarettes"). The prevalence of vaping among adolescents has more than doubled over the past decade [6].

Sociodemographic groups — Cannabis use is present in all sociodemographic groups, but some groups show greater prevalence than others [3,7,8]. These variations do not imply that any specific sociodemographic characteristic plays a causal role in cannabis use or use disorder.

- **Age** – Past year prevalence rates of cannabis use by age show young adults have the highest rate while use is less common in early adolescents or individuals age 65 and over.
  - Adolescents (12 to 17) – 10.5 percent
  - Young adults (18 to 25) – 35.4 percent
  - Adults (26 to 49) – 24.6 percent
  - Older adults (>65) – 7.1 percent
- **Gender** – Men have a greater prevalence of past-month cannabis use than women overall (15.1 versus 11 percent, respectively). However, men have a higher rate among adults, while women have a higher rate among adolescents.
- **Pregnancy** – An estimated 143,000 women used cannabis during their pregnancy in 2021. Pregnant women are approximately one-half as likely as nonpregnant women to have used cannabis in the past month (7.2 versus 17.3 percent, respectively). Rates of use appear to be lower during the third trimester as compared with the first trimester (4.5 versus 9.9 percent, respectively).
- **Other demographic characteristics** – White and Black Americans have relatively similar prevalence of past-month cannabis use (13.5 and 15.4 percent, respectively), while American Indians/Native Hawaiians have significantly higher prevalence (27.0 percent), and Asian Americans have lower prevalence (5.4 percent).

  Education level is inversely associated with cannabis use. College graduates (16.8 percent) and those with some college (17.1 percent) have higher cannabis use prevalence than the national average, while those without a high school diploma (12.1 percent) have lower than the national average.

  Unemployed individuals have a higher prevalence than the national average (24.2 percent), while those living in rural areas have a lower than national average prevalence (9.3 percent).

Cannabis use disorder — Cannabis use disorder refers to problematic cannabis use (table 1).

The 2021 NSDUH estimated a 5.8 percent (standard error 0.16) past-year prevalence of cannabis use disorder among United States community-dwelling residents age 12 years or older [3]. The highest prevalence (14.4 percent [standard error 0.50]) was among those 18 to 25 years old. Among adolescents, the prevalence was 4.80 percent (standard error 0.34). The lowest prevalence (1.8 percent [standard error 0.19] was among those 50 years or older.

Nearly 57 percent of those with a current cannabis use disorder had a mild disorder; only 16.1 percent had a severe disorder.

A meta-analysis of 10 published international studies (Australia, Europe, United States) found the median age of onset for cannabis use disorder as 22 years. Only 3.2 percent of cases appeared by age 14 years; 75 percent appeared by age 29 years [9].

Risk factors for cannabis use and disorder

Frequency of use — The primary risk factor for developing cannabis use disorder is the frequency of cannabis use [10,11]. A nationally representative survey of 43,093 community-dwelling United States adults (National Epidemiologic Survey of Alcohol and Related Conditions wave I) found higher rates of past-year moderate-severe cannabis use disorder among respondents with more frequent cannabis use: 9 percent among those using at least once, 22 percent among those using weekly, and 30 percent among those using daily [10].

Duration of use — Duration of cannabis use is also a risk factor for developing cannabis use disorder [12-14]. For example, a secondary analysis of the 2015 to 2018 NSDUH surveys found a significant positive association between lifetime duration of cannabis use and prevalence of past-year cannabis use disorder among respondents 12 to 17 or 18 to 25 years old [14]. Among 12- to 17-year-olds, prevalence of past-year cannabis use disorder increased from 11 percent (95% CI 9.3-12.3 percent) among those using up to one year to 15 percent (95% CI 13.2-16.2 percent) among those using one to two years, 17 percent (95% CI 15-18.8 percent) using two to three years, and 20 percent (95% CI 18-22.3 percent) among those using more than three years [14].

Potency of cannabis — A systemic review including six published cross-sectional studies (five rated as poor quality) found a positive association between potency of cannabis used (assessed in terms of THC concentration) and probability of developing cannabis use disorder [15]. All studies compared only two levels of potency (high versus low) and one study found no significant association.

Genetic factors — Family and twin studies suggest that there is a substantial degree of heritability for certain patterns of cannabis use and development of cannabis use disorder. No single gene or single nucleotide polymorphism has been robustly associated with these traits in replicated studies [16,17]. A substantial proportion of genetic influence on cannabis use and use disorder is shared with other psychoactive substances, rather than being specific to cannabis [16-18].

Twin and population-based studies suggest that genetic factors account for one-quarter to one-third of the variability in initiation of cannabis use [19,20] and age at first use [21] and two-thirds to three-quarters of the variability in frequency of cannabis use [22] and development of cannabis use disorder [19,22,23]. There is limited evidence of genetic influence on the acute subjective effects of cannabis, such as dysphoria and cannabis craving [24,25].

Psychosocial factors — Large, population-based observational studies and smaller prospective longitudinal studies [26] suggest several risk and protective factors associated with cannabis use and the development of cannabis use disorder during adolescence and young adulthood, after controlling for sociodemographic characteristics and other substance use [27-31]. However, study results are not always consistent and many studies are of low quality [32].

- **Psychological factors** – Depressed mood, anxiety, abnormal negative mood regulation, persisting conduct problems as a child or adolescent [26,33], or a pre-existing psychiatric disorder are associated with increased risk of initiating cannabis use among adolescents and young adults and of developing cannabis use disorder. In many instances, this appears to be a bidirectional comorbidity as discussed in detail below. (See 'Comorbidities' below.)

- **Other substance use** – Use of alcohol and tobacco and other substances is associated with greater risk of cannabis use, daily use of cannabis, and of developing cannabis use disorder. This association appears to be bidirectional as discussed below. (See 'Comorbidities' below.)

  The evidence is more consistent with this association being due to common pre-existing environmental and genetic factors that contribute to all substance use and substance use disorders (so-called “common liability” model), rather than to cannabis use at a specific time contributing to subsequent use of other substances (so-called “sequential gateway” model) [34-37].

- **Education** – More years of education are associated with lower prevalence of cannabis use [27], but not with the development of cannabis use disorder [29].

- **Others** – Other factors associated with cannabis use and development of cannabis use disorder include parental cannabis use [38,39], adverse childhood experiences (eg, physical, emotional, or sexual abuse) [40], and stressful life events (such as unemployment, financial difficulties) [29,40,41]. Experiencing positive subjective effects (eg, euphoria) during early cannabis use is associated with increased probability of later developing a cannabis use disorder; there is no consistent association with experiencing negative subjective effects (eg, paranoia) [42].

- **Protective factors** – Protective factors against initiating cannabis use or developing cannabis use disorder include close parental monitoring and opposition to cannabis use [43], and attendance at religious services [44].

PHARMACOLOGY OF CANNABINOIDS

Naturally occurring cannabinoids — The cannabis plant contains a mixture of more than 400 identified phytocannabinoids, terpenoids, and flavonoids, few of which have been fully characterized pharmacologically [45-47].

Pharmacokinetics, site of action, and cannabis formulations are discussed in detail separately. (See "Cannabis (marijuana): Acute intoxication", section on 'Pharmacology and toxicity'.)

Synthetic cannabinoids — Synthetic compounds with cannabinoid-like action, but not necessarily a phytocannabinoid chemical structure, are known as synthetic cannabinoids. Many physiologic effects of synthetic cannabinoids are similar to the effects of cannabis; however, the effects of illicit synthetic cannabinoids (ie, those not approved by the US Food and Drug Administration [FDA]) are more intense or longer lasting (sometimes for days) and have greater potential for life threatening toxicity [48,49].

Synthetic cannabinoids include illicit, misused substances (so-called “spice” and “K2”) as well as FDA-approved medications that can be legally prescribed (such as dronabinol [synthetic delta-9-tetrahydrocannabinol]).

The clinical presentation and management of acute intoxication and withdrawal from synthetic cannabinoids are reviewed separately. (See "Synthetic cannabinoids: Acute intoxication" and "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment", section on 'Synthetic cannabinoids' and "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment", section on 'Synthetic cannabinoid withdrawal'.)

Use of synthetic cannabinoids in the treatment of cannabis withdrawal and other medical conditions is discussed elsewhere.

- (See "Management of cancer anorexia/cachexia", section on 'Not recommended'.)
- (See "Management of poorly controlled or breakthrough chemotherapy-induced nausea and vomiting in adults", section on 'Cannabinoids and medical marijuana'.)
- (See "Assessment and management of anorexia and cachexia in palliative care", section on 'Cannabis and cannabinoids'.)

- (See "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment", section on 'Delta-9-tetrahydrocannabinol: Dronabinol, nabiximols'.)

COMORBIDITIES

There is substantial bidirectional comorbidity between cannabis use or cannabis use disorder and psychiatric disorders including several substance use disorders. It is often unclear to what extent this is due to a direct causal relationship, the chance co-occurrence of two common conditions, or the presence of risk factors common to both conditions. Regardless of etiology, the presence of comorbid cannabis use or use disorder often worsens the clinical course of the psychiatric disorder [50,51]. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis", section on 'Etiologic theories'.)

Substance use disorders — Large, community-based surveys have established the following comorbidities associated with cannabis use disorder [11,27-29,52-60]:

- **Alcohol** – Adults with current (past 12 months) alcohol use disorder are six times more likely than adults without current alcohol use disorder to have current cannabis use disorder (adjusted odds ratio 6, 95% CI 5.10-6.97) [55].

  Adults with current cannabis use disorder are nearly three to four times more likely than adults without current cannabis use disorder to have current alcohol use disorder (adjusted odds ratio 2.8, 95% CI 2.19-3.60 for men; adjusted odds ratio 3.8, 95% CI 2.33-6.48 for women) [55].

  The mechanisms of these associations are unclear. Two large-scale cross-sectional studies using Mendelian randomization to control for potential confounding variables found no significant association between genetic liability to cannabis use and to alcohol use [37,61].

  Use of cannabis and alcohol within several hours of each other may result in more intense intoxication than use of either substance alone [62].

- **Tobacco** – Adults with current (past 12 months) tobacco (nicotine) use disorder are six times more likely than those without current tobacco use disorder to have current cannabis use disorder (adjusted odds ratio 6.2, 95% CI 5.24-7.34) [56]. Cigarette smoking is significantly associated with eventual development of cannabis use disorder among those without cannabis use (adjusted odds ratio 1.62, 95% CI 1.35-1.94), persistence of cannabis use disorder in those who have it (adjusted odds ratio 1.63, 95% CI 1.30-2.00), and relapse

to cannabis use disorder in those in remission (adjusted odds ratio 1.23, 95% CI 1.09-1.45) [63].

Adults with current cannabis use disorder are three times more likely than adults without current cannabis use disorder to have current tobacco use disorder (adjusted odds ratio 3.0, 95% CI 2.43-3.66 for men; adjusted odds ratio 3.7, 95% CI 2.61-5.26 for women) [55].

A bidirectional Mendelian randomization study found a significant positive association between genetic liability to lifetime cannabis use and risk of lifetime cigarette smoking and intensity (pack-years) of lifetime cigarette use but no significant association between genetic liability to lifetime cigarette smoking and risk of lifetime cannabis use [61].

Cannabis is often smoked simultaneously with tobacco in the form of "blunts" (cannabis within hollowed-out cigar wrappings) or "spliffs" (cannabis and tobacco mixed within a joint) [64]. Such co-use of cannabis and tobacco is associated with less likelihood of cessation of use of either substance [65,66].

- **Opioids** – Individuals with opioid use disorder appear to have a high prevalence of cannabis use. A systematic review of 41 studies of adults receiving medication treatment for opioid use disorder (majority receiving methadone) found that the median prevalence of cannabis use at treatment baseline was 23 percent (range 12 to 67 percent) and of frequent use (five to seven days/week) was 18.5 percent (range 16 to 33 percent) [67]. Cannabis use did not significantly influence treatment outcome.

  Individuals with current cannabis use disorder are nearly five times more likely than those without current cannabis use disorder to have current opioid use disorder (adjusted odds ratio 4.6, 95% CI 3.0-6.8) [58].

- **Stimulants** – Individuals with current cannabis use disorder are more likely than those without current cannabis use disorder to have current cocaine use disorder (adjusted odds ratio 9.3, 95% CI 5.6-15.5) or prescription stimulant use disorder (adjusted odds ratio 4.3, 95% CI 2.3-7.9) [58].

- **Other psychoactive drugs** – Individuals with current cannabis use disorder are significantly more likely than those without current cannabis use disorder to have current sedative/hypnotic use disorder (adjusted odds ratio 5.1, 95% CI 2.9-9) or "club drug" (eg, 3,4-methylenedioxymethamphetamine [MDMA], methamphetamine) use disorder (adjusted odds ratio 16.1, 95% CI 6.3-40.8) [58].

Individuals with current cannabis use disorder have a higher prevalence of current hallucinogen use disorder and current inhalant/solvent use disorder than those without current cannabis use disorder. However, adjusted odd ratios were not reported [58].

Psychiatric disorders — Large, community-based surveys suggest that after, controlling for potentially confounding sociodemographic factors, a variety of psychiatric disorders are comorbid with cannabis use and cannabis use disorder [50].

- **Depressive disorders** – While a bidirectional relationship between cannabis use and depressive disorders is demonstrated in prospective surveys and meta-analyses, not all data support this relationship.

  Individuals with depression and other mood disorders are more likely to use cannabis in some studies:

  - Large prospective surveys of community-living adults in the United States show a bidirectional comorbidity between cannabis use and major depression [68].
  - Individuals with depression have nearly twice the odds of past-month cannabis use compared with those without depression (odds ratio 1.9, 95% CI 1.62-2.24) [69]. Additionally, individuals with a lifetime mood disorder are more likely to develop cannabis use disorder after starting cannabis use as compared with those without any psychiatric disorder [70,71].

  Individuals who use cannabis appear to be at risk of developing a mood disorder in some studies:

  - In a meta-analysis of 14 prospective longitudinal studies, heavy cannabis users were more likely than light or nonusers to develop clinically diagnosed major depression or depressive symptoms (odds ratio 1.62, 95% CI 1.21-2.16) [72].
  - A meta-analysis of seven prospective longitudinal studies found that adolescents who used cannabis were more likely those who did not use cannabis to develop depression (clinically significant symptoms or major depressive episode; odds ratio 1.37, 95% CI 1.16-1.63), suicidal ideation (three studies; odds ratio 1.5, 95% CI 1.11-2.03), or suicide attempt (three studies; odds ratio 3.46, 95% CI 1.53-7.84) during young adulthood [73].
  - A prospective, longitudinal, population-based study using Danish national health registries found a significant association between having a diagnosis of cannabis use disorder and later receiving a diagnosis of unipolar depression (adjusted hazard ratio

1.84, 95% CI 1.78-1.90), after adjusting for sex, educational level, other substance use disorder, and parental substance use disorders or affective disorders [74].

- A Mendelian randomization study that included 126,291 British men age 40 to 70 years found a significant association between lifetime cannabis use and depression (odds ratio 1.64, 95% CI 1.59-1.70) [75].

However, a prospective community based study found users of cannabis at no increased risk of developing a mood disorder over three years of follow-up (odds ratio 1.1, 95% CI 0.8-1.4) [54].

- **Bipolar disorders** – While large, cross-sectional surveys support a bidirectional relationship between cannabis use and disorder and bipolar disorders, not all data support this relationship.

  Individuals with bipolar disorder appear to be at risk of cannabis use and disorder and for worsening symptoms of disease:

  - A meta-analysis including 36 published studies found that among adults with bipolar disorder, the prevalence of lifetime cannabis use was 24 percent (95% CI 18-29 percent) and of lifetime cannabis use disorder 20 percent (95% CI 14-29 percent) [76].

  - A meta-analysis of two studies of individuals with bipolar disorder found cannabis use associated with a threefold increased risk (odds ratio 2.97, 95% CI 1.80-4.90) for new onset of manic symptoms [77]. Additionally, cannabis use has been found to be associated with earlier age of onset of first manic symptom and more frequent mood episodes [78].

  Individuals who use cannabis appear to be at risk for developing bipolar disorders:

  - A large, cross-sectional study of a representative sample of community-living adults found that adults with lifetime cannabis use disorder had almost four times the odds of having bipolar I disorder (adjusted odds ratio 3.8, 95% CI 3.1-4.59) and almost three times the odds of having bipolar II disorder (adjusted odds ratio 2.8, 95% CI 1.51-5.23), compared with those without lifetime cannabis use disorder [50].

  - In contrast, in a three-year longitudinal study of community living adults in the United States, the association between cannabis use and bipolar disorder was unclear [79].

  A bidirectional Mendelian randomization study found a significant association between genetic liability to bipolar disorder and risk of lifetime cannabis use, but no significant

association between genetic liability to lifetime cannabis use and risk of developing bipolar disorder [80].

Individuals with cannabis use disorder appear to be at increased risk for developing bipolar disorder. A prospective, longitudinal, population-based study using Danish national health registries found an association between having a diagnosis of cannabis use disorder and later receiving a diagnosis of bipolar disorder (adjusted hazard ratio 2.96, 95% CI 2.73-3.21 for men; 2.54, 95% CI 2.31-2.80 for women), after adjusting for sex, educational level, other substance use disorder, and parental substance use disorders or affective disorders [74].

- **Nonaffective psychosis and schizophrenia** – Individuals with schizophrenia are two to three times more likely to use cannabis and to develop cannabis use disorder than those without any psychiatric disorder [70,71].

Additionally, cannabis use may be a risk factor for schizophrenia and other psychotic disorders. This is discussed below. (See 'Psychiatric effects' below.)

- **Anxiety disorders** – Prospective longitudinal studies have conflicting results regarding the association between long-term cannabis use and anxiety disorders [50,54,81,82].

  Individuals with a lifetime anxiety disorder are two to three times more likely to have lifetime cannabis use than those without any psychiatric disorder [70] and to develop a cannabis use disorder after starting cannabis use [70,71].

  However, a meta-analysis of three prospective longitudinal studies found that adolescents who used cannabis during adolescence were no more likely than nonusers to develop anxiety (clinically significant symptoms or anxiety disorder) during young adulthood (18 to 32 years; odds ratio 1.18, 95% CI 0.84-167) [73].

- **Posttraumatic stress disorder (PTSD)** – Several community-based national epidemiologic studies found comorbidity rates of approximately 10 percent for current PTSD among adults with current cannabis use disorder and for current cannabis use disorder among those with current PTSD [55,56]. The prevalence of cannabis use disorder among United States veterans with PTSD is substantially higher, almost three-quarters in some studies [83]. Cannabis use by adults with PTSD is associated with more severe PTSD symptoms [84], especially intrusive symptoms among veterans [85].

- **Attention-deficit hyperactivity disorder (ADHD)** – Studies of large, unselected adult populations suggest a 10 to 30 percent prevalence of cannabis use disorder among adults

with ADHD [86,87].

Childhood/adolescent ADHD, especially if untreated, is a risk factor for later development of cannabis use disorder [88,89].

Conversely, a cross-sectional survey of a convenience sample of 341 United States veterans with lifetime cannabis use found a 29 percent prevalence of lifetime adult ADHD (based on self-report using a validated screening instrument) [90].

A bidirectional Mendelian randomization study found a significant association between genetic liability to ADHD and risk of lifetime cannabis use, but no significant association between genetic liability to cannabis use and risk of lifetime ADHD [91].

- **Other psychiatric disorders** – More limited evidence suggests that there is comorbidity between obsessive-compulsive disorder [92] and cannabis use and use disorder. Additionally, there is evidence for comorbidity between lifetime or current cannabis use disorder and several personality disorders, especially antisocial, dependent, and borderline personality disorders [50,55,92,93].

ADVERSE EFFECTS OF CANNABIS USE

Disability and all-cause mortality — Much of the morbidity associated with cannabis use disorder may be due to comorbid psychiatric and substance use disorders, rather than to cannabis use disorder itself [94]. Cannabis use disorder constitutes a very small proportion of the global burden of disease relative to other substance use disorders. The Global Burden of Disease Project, using data from 195 countries, estimated that cannabis use disorder was associated with only 6.4 percent of the more than 6.1 million disability-adjusted life years attributed to substance use disorders (excluding tobacco) in the United States and Canada [95].

There is insufficient evidence to assess whether cannabis use is associated with an increased all-cause mortality [96].

- A population-based, longitudinal cohort study of all individuals born in Sweden 1955 to 1980 found that those identified as having cannabis use disorder had a higher mortality than the general population (hazard ratio 10.93, 95% CI 11.36-12.03) [97].

- In contrast, a prospective longitudinal study of 11,253 participants in the 1970 British Birth Cohort Study found no significant association between past-year cannabis use at age 30 years and all-cause mortality by age 44 years (median follow-up 7.2 years, interquartile range 3.5 to 10.1 years; adjusted hazard ratio 1.27, 95% CI 0.82-1.96) after controlling for

sex [98]. This finding was materially unchanged by further adjustment for childhood socioeconomic disadvantage, childhood mental health, or maternal psychological morbidity.

The most common causes of death associated with cannabis use are accidents (primarily motor vehicle), suicide, and medical conditions (primarily cardiovascular and pulmonary disease) [96,99,100]. Other psychoactive substances are found in the majority of cases (most commonly alcohol).

Medical and systemic effects

- **Pulmonary** – Smoking cannabis may contribute to respiratory symptoms and possibly respiratory disease.

  Individual studies [101-103] and a meta-analysis [104] with low-quality evidence suggest that smoking cannabis is associated with cough (relative risk 2.04, 95% CI 1.02-4.06), sputum production (relative risk 3.84, CI 1.62-9.07), wheezing (relative risk 2.83, CI 1.89-4.23), and dyspnea (relative risk 1.56, CI 1.33-1.83) [104].

  In addition, cannabis inhalation can acutely exacerbate asthma; however, the association between chronic cannabis use and asthma remains unclear [105]. A retrospective review of electronic health records from a large metropolitan health system found that adults who were regular cannabis users, compared with nonusers, had a greater risk for asthma (adjusted odds ratio 2.13, 95% CI 1.75-2.59) whether they had a diagnosis of tobacco use disorder [106]. Evidence on the association between cannabis use and chronic obstructive lung disease and pulmonary function was inconclusive due to methodologic issues [104]. A large Mendelian randomization study including 79,055 participants found no significant association between genetic liability to cannabis use or use disorder and impaired pulmonary function [107].

  Cannabis smoke and vapor acutely irritate the airways. However, chronic cannabis use is not clearly associated with impaired pulmonary functioning. A prospective longitudinal study of 1037 individuals born in Dunedin, New Zealand and followed through age 45 years found that cumulative cannabis use, in individuals with no tobacco use, was significantly associated with increased lung volumes (total lung capacity, forced vital capacity) but not with measures of airway resistance, airway conductance, or diffusion capacity [108]. While cannabis smoke contains many of the same respiratory irritants and carcinogens as tobacco smoke, the effects of cannabis smoke may be moderated by the absence of nicotine and the presence of cannabinoids with anti-inflammatory action [101,102]. Cannabis vapor contains fewer toxic compounds than cannabis smoke [109];

however, use of electronic drug delivery devices (so-called “e-cigarettes”) containing cannabis or pure delta-9-tetrahydrocannabinol (THC) is associated with acute lung injury (e-cigarette or vaping-associated lung injury) [110]. (See "E-cigarette or vaping product use-associated lung injury (EVALI)".)

- **Cancer** – Molecular, cellular, and histopathological evidence plausibly suggests that cannabis smoking may cause cancer; however, epidemiologic studies do not consistently show an association [111]. This may be due, in part, to the fact that smokers of cannabis have less exposure to inhaled carcinogens than do smokers of tobacco or of both cannabis and tobacco [112,113].

  - **Lung cancer** – Case-control, cohort, and cross-sectional studies have inconsistent results regarding an association between cannabis smoking and lung cancer. Most studies had high risk of bias [111]. A pooled analysis including 5144 participants from six large, good-quality case control studies found no association between “habitual” cannabis use (at least one joint-year) and lung cancer when compared with nonhabitual or never use (odds ratio 0.96, 95% CI 0.66-1.38) [114]. However, a large Mendelian randomization study including 85,716 individuals found a significant association between genetic liability for lifetime cannabis use (but not for cannabis use disorder) and squamous cell carcinoma of lung (odds ratio 1.22, 95% CI 1.07-1.39) [107]. There was no such significant association with other forms of lung cancer. (See "Cigarette smoking and other possible risk factors for lung cancer", section on 'Marijuana and cocaine'.)

  - **Head and neck and oral cancer** – Meta-analyses have found no association between ever using cannabis and head and neck [111] or oral cancer [111]. (See "Epidemiology and risk factors for head and neck cancer", section on 'Tobacco products'.)

  - **Testicular cancer** – Cannabis use is associated with one form of testicular cancer. A meta-analysis of three case-control studies found cannabis use for more than 10 years associated with an increased risk for nonseminoma testicular cancer compared with never users (odds ratio 1.85, 95% CI 1.1-3.11) [111].

- **Cardiovascular** – Cannabis smoking has a possible association with the following conditions [115-117]:

  - **Myocardial infarction (MI)** – A cross-sectional survey of a nationally representative sample of 133,706 United States adults (18 to 74 years old) who were lifetime never cigarette smokers found significant associations between frequent cannabis use (at least 10 days per month) and risk of lifetime MI or coronary artery disease among the

entire sample (adjusted odds ratio 1.88, 95% CI 1.15-3.08) and among a younger subsample (men <55 years old, women <65 years old; adjusted odds ratio 2.3, 95% CI 1.2-4.3) [118].

Additionally, other data suggest that the risk of acute MI is significantly elevated in the 60 minutes after smoking cannabis (relative risk 4.8, 95% CI 2.4-9.5) [119].

- **Stroke** – A retrospective medical record review of 3,307,310 United States hospitalizations (2007 to 2014) among young adults (18 to 49 years old) found an association between lifetime cannabis use and any stroke (adjusted odds ratio 1.16, 95% CI 1.14-1.19) or acute ischemic stroke (adjusted odds ratio 1.41, 95% CI 1.31-1.51) [120].

- **Arrhythmias** – Cardiac arrhythmias of any type (except sinus tachycardia) are rare among adolescent and young adult cannabis users [120,121]. Low-quality case-control studies and case series suggest a possible association between cannabis use and atrial fibrillation and ventricular tachycardia [122]. A medical record review of 67.7 million United States inpatients hospitalized between 2010 to 2014 (Nationwide Inpatient Sample) found current cannabis use disorder associated with increased risk of cardiac arrhythmia among younger patients, after adjusting for race, sex, alcohol and tobacco use disorders, obesity, and medical comorbidities: relative risk 1.28 (95% CI 1.23-1.35) among 15- to 24-year-olds and 1.52 (95% CI 1.47-1.58) among 25- to 34-year-olds [123]. The most common arrhythmia among patients with cannabis use disorder was atrial fibrillation (42 percent).

Due to methodologic issues in most studies, including recall bias, inadequate assessment of cannabis exposure, and failure to control for all potential confounding factors (such as other substance use), the evidence is insufficient to conclusively establish the association between cannabis use and these cardiovascular outcomes [115]. However, the known acute cardiovascular effects of cannabis smoking, such as tachycardia, vasodilation, increased myocardial oxygen demand, and reduced myocardial oxygen supply, provide plausible pathophysiological mechanisms for producing these outcomes [116,117,119,124-130].

- **Hyperemesis syndrome** – Cannabinoid hyperemesis syndrome is a well-defined syndrome involving episodic severe nausea and vomiting and abdominal pain associated with heavy or chronic cannabis use and which is often relieved by exposure to hot water (shower or bath) [131]. Differential diagnosis from other cyclic vomiting disorders depends on a history of recent cannabis use [132]. The true population prevalence is unknown, but

presentations to emergency departments have increased over the past decade [133]. Symptoms typically resolve within one to two days of cessation of cannabis use. This syndrome is described in detail separately. (See "Cyclic vomiting syndrome", section on 'Chronic cannabis use' and "Cannabis (marijuana): Acute intoxication", section on 'Cannabis hyperemesis syndrome'.)

- **Sexual function**, **reproductive system, and neonatal outcomes**

  - **Sexual function** – Several large, cross-sectional surveys suggest that cannabis use does not impair male or female sexual function in healthy individuals [134-136] nor delay the time to pregnancy in healthy couples trying to conceive [137]. There is no good-quality evidence associating cannabis use with erectile dysfunction. A meta-analysis of case-control studies involving 3395 healthy men found a significant difference in prevalence of erectile dysfunction between cannabis smokers and nonusers in one of three statistical metrics [138]. There was substantial heterogeneity across studies and only one study controlled for potential confounds such as other substance use and depression. That study found no significant difference in prevalence.

  - **Spermatogenesis** – Cannabis use is associated with reduced spermatogenesis and impaired sperm function in most [139,140], but not all [141] studies. (See "Causes of male infertility", section on 'Drugs and radiation'.)

  - **Breast milk** – THC, cannabidiol, and perhaps other cannabinoids appear in the breast milk of lactating women who use cannabis [142,143]. THC concentration in breast milk is two- to sixfold higher than its concentration in plasma. THC is detectable in breast milk for several weeks after the mother stops cannabis use. The effects on the infant of cannabinoids in breast milk are uncertain. (See "Prenatal substance exposure and neonatal abstinence syndrome (NAS): Clinical features and diagnosis", section on 'Cannabis' and "Prenatal substance exposure and neonatal abstinence syndrome (NAS): Management and outcomes", section on 'Cannabis'.)

  - **Pregnancy and neonatal outcomes** – Cannabis use by the mother during pregnancy (ie, prenatal cannabis exposure) is associated with increased risk of low birth weight, small for gestational age, and neonatal intensive care admission in most, but not all studies [144-146].

    - A systematic review and meta-analysis that included 53 published studies of women who used no illicit drug other than cannabis found significant associations between cannabis use during pregnancy and premature birth (adjusted odds ratio

1.42, 95% CI 1.19-1.69), small for gestational age (adjusted odds ratio 1.76, 95% CI 1.52-2.05), and perinatal mortality (adjusted odds ratio 1.5, 95% CI 1.39-1.63), after adjusting for use of alcohol and tobacco [147].

- A separate review that included several studies that reported on the frequency and timing of cannabis use found higher adjusted odds ratios for premature birth and small for gestational age among women who used cannabis more frequently or used during the second and third trimester, after controlling for cigarette smoking and illicit drug use [148].

Cannabis use during pregnancy is not generally associated with adverse outcomes for the mother, such as gestational diabetes or pre-eclampsia [144,146].

- **Cognitive effects and neuroimaging changes**

  - **Cognitive effects** – Cannabis (primarily THC) use acutely impairs cognitive functions including attention, concentration, episodic memory, and associative learning in a dose-dependent fashion [149-151]. These effects are time limited, with the duration of impairment dependent on dose taken, route of administration, and degree of tolerance. (See "Cannabis (marijuana): Acute intoxication", section on 'Clinical manifestations'.)

    The association of long-term cannabis use with long-term cognitive impairment is supported by some, but not all, studies [151-153]. As examples:

    - In a prospective longitudinal study involving a cohort of all individuals born in Dunedin, New Zealand over a one-year period (n = 1037; 91 percent of eligible births), participants were periodically assessed from birth through age 45 years for cognitive function and cannabis use and dependence [154]. Long-term cannabis use was defined at age 45 as at least weekly cannabis use or a diagnosis of cannabis dependence in the prior year and at least weekly cannabis use at one or more previous assessments. Among long-term users of cannabis, the mean decline in intelligence quotient (IQ) was greater (n = 86; -5.5 points) than among lifetime nonusers of cannabis (n = 196; -0.7 points), long-term users of tobacco (n = 75; -1.5 points), and long-term users of alcohol (n = 57; -0.5 points). Long-term users of cannabis showed declines in tests of learning and processing speed and self-reported memory and attention, after controlling for other substance use, family history, and other factors. Similar cognitive decline was not seen in those who used cannabis less than weekly during mid-life (32 to 45 years) and were never diagnosed with cannabis dependence (n = 65), those who were not using cannabis

at age 45 years but had previously used at least four times per week or been diagnosed with cannabis dependence (n = 60), and long-term users of tobacco or alcohol.

- Longitudinal studies have suggested an association with long-term cognitive impairment, especially in the domain of episodic memory; however, effect sizes are small and group differences are often attenuated or eliminated after controlling for potential confounds such as other substance use and psychiatric comorbidity [155]. One longitudinal study of 804 European teenagers followed over five years did not find evidence to support the presumption that cannabis consumption leads to a decline in neurocognitive ability [156].

- A systematic review and meta-analysis of 69 cross-sectional studies of adolescents and young adults (2152 cannabis users [in most studies, at least weekly users or with cannabis use disorder] and 6575 comparison participants with no or "minimal" cannabis use) found small but significant impairment in neurocognitive domains of learning, processing speed, delayed memory, executive functioning, and attention [157]. The 15 studies that conducted cognitive testing more than 72 hours after last cannabis use found no significant cognitive impairment. Additionally, a meta-analysis of 13 studies examining neurocognitive performance in users of cannabis with at least 25 days of abstinence versus nonusers of cannabis found similar global performance on neuropsychological testing [158].

- **Neuroimaging changes** – Neuroimaging studies show associations between cannabis use and reduced hippocampal volume [154] and gray matter density, thinning orbitofrontal cortex, and smaller cerebellar white matter volume. As examples:

  - A systematic review of 56 published neuroimaging studies of brain structure and function in adult cannabis users found consistent evidence of reduced hippocampal volume and lower hippocampal gray matter density in cannabis users relative to controls [152]. No evidence for changes in whole brain volume was noted. Evidence for changes in other brain regions was inconsistent or inconclusive.

  - A cross-sectional study comparing 129 European adults who were regular cannabis users (mean 349 doses/month for men, 264 doses/month for women) with 114 healthy nonusers found that the regular cannabis users had significantly smaller volume of the orbitofrontal cortex and cerebellar white matter, after controlling for age, intelligence quotient, intracranial volume, and alcohol and tobacco use [159].

- A prospective longitudinal study of 799 European adolescents followed from age 14 years (prior to any cannabis use) to 19 years found a significant dose-dependent association between frequency of cannabis use and thinning of the frontal cortex bilaterally, after controlling for age, sex, handedness, total brain volume, and alcohol intake [160].

However, these associations are stronger in adult than in younger users of cannabis, perhaps due to longer duration of exposure. For example:

- A systematic review and meta-analysis of 16 cross-sectional studies including 830 adolescents/young adults (mean age 22.5 years, range 14 to 26 years, 386 cannabis users, 444 controls) found similar volumes of total brain gray or white matter, or regional brain volumes [161].

Functional neuroimaging studies (chiefly functional magnetic resonance imaging) suggested that adult cannabis users have decreased neuronal activity in anterior cingulate cortex and right dorsolateral prefrontal cortex relative to controls [152]. In addition, increased functional connectivity across brain regions relative to controls has been noted. Abnormalities of neuronal activity were observed even when cognitive task performance was normal, suggesting that cannabis users may need to engage different levels of neuronal activation to achieve normal performance.

- **Other systemic effects**

  - **Hepatic** – Cannabis use is not associated with acute hepatotoxicity [162] or with worsening progression of hepatic fibrosis in patients with chronic viral hepatitis C [163]. Cannabis use disorder is associated with increased risk of hepatic encephalopathy among inpatients hospitalized with chronic viral hepatitis C, after controlling for age, race, sex, alcohol use disorder, HIV/AIDS, viral hepatitis B, diabetes, and obesity (odds ratio 2.2, 95% CI 1.48-3.35) [164].

  - **Renal** – Cannabis use (recreational or medical) is not associated with nephrotoxicity in healthy individuals [165,166], nor is cannabis use disorder associated with adverse outcomes after kidney transplantation [167]. Cannabis use may accelerate the decline in kidney function among men with hypertensive kidney disease [168].

  - **Endocrine** – Cannabis use is not associated with the development of type II diabetes (and is protective in some studies) [169-171], but is associated with poorer glycemic control and increased risk of diabetic ketoacidosis in adults with type I or type II diabetes [172,173]. Cannabis use is not associated with obesity [174].

- **Ophthalmologic** – Cannabis use causes acute and transient ophthalmologic effects (ie, decreased intraocular pressure, increased photosensitivity, reduced tear production ["dry eyes"], conjunctival injection ["red eye"], but is not associated with chronic ophthalmologic dysfunction) [175,176].

- **Oral** – Chronic cannabis use is associated with a variety of adverse oral health effects, including xerostomia ("dry mouth"), leukoplakia, and periodontitis [177].

Psychiatric effects

- **Psychosis and psychotic disorders** – Individuals who use cannabis appear to be at greater risk of psychosis than those who do not use cannabis:

  - **Cannabis-associated psychosis** – Cannabis use causes transient acute psychosis (cannabis-induced psychosis) in some users. (See "Cannabis (marijuana): Acute intoxication".)

    - A systematic review of 35 longitudinal studies found an increased risk of psychosis for those who ever used cannabis compared with those who did not (adjusted odds ratio 1.41, 95% CI 1.20-1.65) [178]. There was a significant dose-response relationship, with a twofold increase in risk among those who used cannabis most frequently (odds ratio 2.09, 95% CI 1.54-2.84).

    - In a subsequently published prospective longitudinal study, 6534 individuals born in northern Finland were evaluated at age 15 to 16 years and again at age 30 years. Those individuals who used cannabis at least five times by age 15 to 16 years of age had an increased risk of psychosis compared with those who had never used cannabis (adjusted hazard ratio 3.02, 95% CI 1.14-7.98) [179]. There was no increased risk for those who used cannabis one to four times.

    There is a genetic influence on the propensity to develop cannabis-induced psychosis.

    - A systematic review including 18 published studies found a consistent association between polymorphisms in genes involved with dopaminergic function (such as the dopamine D_2 receptor, dopamine transporter, the dopamine metabolizing enzyme catechol-O-methyltransferase) and the probability of developing cannabis-induced psychosis [180]. However, a genome-wide association study found no significant association between cannabis-induced hallucinations and any dopamine-related gene [181].

- A systematic review including six published studies of varying designs (three cross-sectional, one prospective longitudinal, two case-control) and quality (poor to fair) found a significant positive association between potency of cannabis used (assessed in terms of THC concentration) and probability of developing psychosis [15].

Some evidence suggests that the severity of cannabis use (eg, frequent use, diagnosis of cannabis use disorder), but not cannabis use per se, may be associated with increased probability of transition to frank psychosis in individuals at clinical high risk for psychosis.

- A review of published meta-analyses found suggestive, but not conclusive, evidence that severity of cannabis use was associated with increased probability of transition to psychosis. There was no such association with use of alcohol or tobacco. Clinical high risk was diagnosed in an individual if they had attenuated or subthreshold psychotic symptoms, brief and limited psychotic symptoms that resolved spontaneously, or a family history of psychosis [182].

- A two-year prospective longitudinal study (not included in the above review) of 334 individuals at clinical high risk for psychosis found no significant association between cannabis use variables at baseline (frequency of use, potency of cannabis, presence of cannabis dependence) and probability of developing psychosis [183].

- **Cannabis use as a risk factor for schizophrenia –** Some experts believe that early cannabis use is a causal factor in developing schizophrenia.

  There is substantial evidence that chronic cannabis use, especially during adolescence, is associated with later development of schizophrenia. Cross-sectional studies indicate that cannabis users have two- to threefold increased prevalence of schizophrenia and schizophrenia spectrum disorders compared with nonusers [184]. This association is stronger with earlier age of onset of use (eg, early adolescence), more intense cannabis use, and use of cannabis with high THC content and THC:cannabidiol ratio [185,186]. For example:

  - A Danish national registry-based prospective study of 7,186,834 individuals who were 16 years or older between 1972 and 2016 found that the adjusted hazard ratio for schizophrenia among those with cannabis use disorder, compared with those without cannabis use disorder, was approximately 4 (95% CI 3-6) throughout the time period, after adjusting for age, sex, birth outside of Denmark, other psychiatric diagnoses (including other substance use disorders), parents' education level, and parents'

psychiatric history [187]. The population-attributable risk fraction of schizophrenia attributable to cannabis use disorder increased from two in 1992 to six to eight in 2010 to 2016, paralleling the increasing incidence of cannabis use disorder (0.02 percent in 1992 to 0.18 percent in 2016).

Genetic liability to cannabis use disorder is strongly associated with schizophrenia, but evidence for a causal association is mixed [188].

Individuals who have had an episode of cannabis-induced psychosis may be at particularly high risk. As examples:

- A systematic review and meta-analysis of six studies involving 3040 participants with cannabis-induced psychosis found a transition rate to schizophrenia of 34 percent (95% CI 25-46 percent) [189].

- A Danish national registry study followed 1492 individuals with a diagnosis of cannabis-induced psychosis for up to 20 years [190]. Forty-one percent (95% CI 36.6-46.2) of these individuals converted to a diagnosis of schizophrenia, with 50 percent of men converting within 2 years and 50 percent of women within 4.4 years. The hazard ratio for conversion to schizophrenia, compared with matched comparison subjects without a history of substance-induced psychosis, was 101.7 (95% CI 74.1-139.7).

- **Cannabis use in patients with established psychotic disorder** – Cannabis use exacerbates symptoms in individuals with established psychotic disorders such as schizophrenia. A systematic review and meta-analysis of 24 published longitudinal studies involving 16,565 participants found that cannabis use was associated with increased relapse, rehospitalization, more severe positive symptoms (but not negative symptoms), and poorer level of functioning and treatment adherence than nonusers or those who discontinued cannabis use [191]. Additionally, in individuals with first episode of psychosis, cannabis use is associated with an increased risk of psychotic experiences [192] and of relapse and re-hospitalization [193]. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

- **Mood and anxiety disorders** – Studies provide mixed evidence as to the association between cannabis use and mood or anxiety disorders. (See 'Psychiatric disorders' above.)

Other effects

- **Education** – Systematic reviews and prospective longitudinal studies find consistent associations for cannabis use with lower educational attainment. However, none of the associations was clearly causal and potential bias and confounding factors were noted [194,195]. Adolescent cannabis use was not found to be associated with high school academic performance or mental health problems in prospective longitudinal studies [196,197].

- **Motor vehicle crashes** – Cannabis or THC alone acutely impair driving performance in controlled studies in driving simulators, with impairment typically resolving within five to seven hours after inhalation (smoked or vaporized; somewhat longer after oral ingestion) [149,198]. Impairment is due primarily to THC, as cannabidiol itself has no effect on driving performance [199,200]. However, assigning a causal role to recent cannabis use is more difficult in real-world observational studies, partly because, unlike with alcohol, there is no tight association between impairment and blood/plasma or oral fluid concentrations of THC [201].

  A meta-analysis including 13 of the more rigorous published studies found recent cannabis use associated with a one-third increased risk of motor vehicle crashes (odds ratio 1.37, 95% CI 1.10-1.69) [202]. This is comparable to the 1.38 to 1.75 odds ratio associated with a blood alcohol concentration of 0.05 and less than the 1.68 to 2.29 odds ratio associated with opiates [203].

- **Emergency department visits and hospitalizations** – A retrospective cohort study of electronic health records of a 4 million-member integrated health system found that individuals with cannabis use disorder are more likely than individuals without cannabis use disorder to visit the emergency department or have an inpatient hospitalization [204].

  A study of all drug-related emergency department visits in 2022 at 53 United States hospitals generated a nationally weighted estimate of approximately 900,000 cannabis-related visits, representing 11.9 (95% CI 9.6-14.3) percent of all drug-related visits. This was tied for second with opioids and behind alcohol (12.7 [95% CI 8.9-16.6] and (45.0 [95% CI 39.9-50.2], respectively) [205]. Approximately half (47.6 percent) of cannabis-related visits involved one or more other drugs, chiefly alcohol (25 percent), cocaine (10 percent), or methamphetamine (6 percent). The highest prevalence of cannabis-related visits was among young adults (18 to 25 years old and 26 to 44 years old), the lowest was among adolescents and older adults. Men and women had equal prevalence of cannabis-related visits.

MEDICO-LEGAL CONTEXT

The legal status of cannabis and its use in health care varies internationally.

- **Classification** – Under the United Nations international Single Convention on Narcotic Drugs (as amended in 1972), the cannabis plant, cannabis resin and its extracts and tinctures are classified under schedule I, meaning use should be allowed only for "medical and scientific purposes" [206].

  Under the United States Controlled Substances Act, cannabis and all phytocannabinoids (ie, compounds found in the Cannabis sativa plant) are classified as schedule I compounds, with the exception of hemp (legally defined as a cannabis plant containing no more than 0.3 percent delta-9-tetrahydrocannabinol) [207]. Schedule I compounds, which are considered to have "high potential for abuse" and "no currently accepted medical use in the United States," are illegal to possess or use under federal law. The United States Department of Health and Human Services on August 30, 2023 recommended that cannabis be reclassified to Schedule III (low to moderate potential for abuse and some medically accepted use) [208]. This recommendation will be considered by the Drug Enforcement Administration, which makes the decision.

- **Medical use** – Medical use is legal in more than two dozen countries, including Canada. In the United States, medical cannabis is legal at the state level in 38 states, the District of Columbia, Puerto Rico, the United States Virgin Islands, and Guam, but remains illegal at the federal level [209]. Nine states allow high CBD/low THC products (primarily used to treat intractable childhood seizures). Only three states (Idaho, Kansas, Nebraska) have no form of medical cannabis program. An observational study utilizing state medical cannabis patient registries from 26 states and the District of Columbia found that nearly 3 million individuals were enrolled in medical cannabis programs in 2020, a 4.5-fold increase since 2016 [210]. The proportion of patients with conditions or symptoms for which there is conclusive or substantial evidence of medical cannabis efficacy (based on a review by the United States National Academy of Sciences, Engineering, and Medicine) [211] decreased from 84.6 percent to 68.2 percent over the same four-year period (based on data from 19 states). Medical use of cannabis and cannabinoids is discussed elsewhere. (See "Seizures and epilepsy in children: Refractory seizures", section on 'Cannabinoids'.)

- **Recreational use** – Possession of small amounts for adult recreational use is legal at the state level in 23 states, the District of Columbia, and two territories in the United States [209] and in five countries worldwide (Canada, Mexico, Uruguay, South Africa, Georgia).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cannabis use disorder and withdrawal".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Cannabis use disorder (The Basics)" and "Patient education: Cannabis hyperemesis syndrome (The Basics)")

SUMMARY

- **Epidemiology** – Cannabis is the fourth most commonly used psychoactive substance worldwide after alcohol, caffeine, and tobacco. Young adults age 18 to 25 years have the highest rates of cannabis use and disorder. (See 'Incidence and prevalence' above.)
- **Risk factors**
  - **Frequency and duration of use** – The primary risk factors for developing cannabis use disorder are frequency and duration of cannabis use. (See 'Risk factors for cannabis use and disorder' above.)
  - **Potency of cannabis** – Use of higher potency cannabis (in terms of THC concentration) is associated with greater probability of developing cannabis use disorder. (See 'Risk

factors for cannabis use and disorder' above.)

- **Genetic factors** – Family and twin studies suggest that there is substantial heritability for initiation of cannabis use and development of cannabis use disorder. However, no single gene nor nucleotide polymorphism is robustly associated with these traits. (See 'Risk factors for cannabis use and disorder' above.)

- **Psychosocial factors** – Other factors associated with increased risk of cannabis use include pre-existing psychiatric disorders, persisting conduct problems, other substance use, education level, adverse childhood experiences and stressful life events. (See 'Psychosocial factors' above.)

- **Comorbidities –** There is substantial bidirectional comorbidity between cannabis use or cannabis use disorder and psychiatric disorders including several substance use disorders. It is often unclear to what extent this is due to a direct causal relationship, the chance co-occurrence of two common conditions, or the presence of risk factors common to both conditions (See 'Comorbidities' above.)

- **Adverse effects**

  - **Disability and all-cause mortality** – Cannabis use disorder may be associated with higher a long-term mortality rate than the general population. This is largely associated with accidents (especially motor vehicle), suicide, and cardiopulmonary conditions. Much of the morbidity may be due to comorbid psychiatric (including substance use) disorders. (See 'Disability and all-cause mortality' above.)

  - **Medical and systemic effects** – Adverse systemic and medical effects of cannabis use may include pulmonary effects, cardiovascular effects, hyperemesis syndrome, and nonseminoma testicular cancer. The association between cannabis smoking and lung cancer is unclear due to high risk of bias in most studies. (See 'Medical and systemic effects' above.)

  - **Psychiatric and cognitive effects** - Cannabis acutely impairs attention, concentration, and coordination in a dose-dependent manner. While effects typically resolve after a month of abstinence, impairments may contribute to cannabis-related motor vehicle crashes. Chronic cannabis use, especially during adolescence, is associated with later development of schizophrenia. Some experts believe that early cannabis use is a causal factor in developing schizophrenia. There is mixed evidence as to the association between cannabis use and mood or anxiety disorders. (See 'Medical and systemic effects' above and 'Psychiatric effects' above.)

- **Medico-legal context** – Medical use is legal in more than two dozen countries worldwide. In the United States, medical cannabis is legal in 38 states, the District of Columbia, Puerto Rico, the United States Virgin Islands, and Guam. Possession of small amounts for adult recreational use is legal in five countries worldwide and in 23 states and the District of Columbia in the United States. (See 'Medico-legal context' above.)

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Topic 7797 Version 40.0