Canadian Mental Health Association
Waterloo Wellington
Association canadienne pour la santé mentale
Waterloo Wellington

May 31, 2020

City of Guelph Committee of Adjustment
Council Chambers, Guelph City Hall
1 Carden St.
Guelph, ON N1H 3A1

To Whom It May Concern:

As a psychiatrist who works with the children and adolescents of Guelph daily, I feel obliged to warn against current plans to open a cannabis store next to the long-awaited (and desperately needed) Canadian Mental Health Association's Children's Mental Health Building. The children I will be working with there have a range of mental health concerns that often make them even more susceptible to addiction. I am aware the minors I work with will not legally be able to purchase cannabis from the proposed retail store. However, many of these children have adults in their lives who are willing to buy for them. Even for those who don't, passing a cannabis store immediately after an appointment may be all it takes to prompt them to use again as quickly as possible, from whatever source they usually access.

I spend a great deal of time educating the children under my care about the negative effects of cannabis, because many of them believe it's entirely harmless. In fact, for children like these with additional mental health concerns, the risks are actually significantly amplified. Cannabis has been proven to be addictive, to cause mood and anxiety disorders, and prompt psychotic illnesses. Cannabis use is a common reason for loss of focus and motivation with a devastating impact on school, work, and community involvement in the youth I see. There is substantial evidence that cannabis can cause changes in the developing brain that are long-lasting and negative. Further, there is no evidence cannabis has therapeutic value for youth, or for mental health more generally and it is not approved in Canada for treatment of youth or mental health conditions.

It is not unusual for me to have multiple adolescents a month end up in the emergency room with acute anxiety attacks or brief psychotic episodes secondary to cannabis use. It is not unusual for me to have adolescents develop a cyclical vomiting syndrome known to be caused by cannabis. Most, if not all, of the adolescents I see who do not finish high school are chronic cannabis users.

While I understand that cannabis is legal, opening a store next to a building that works night and day to educate the youth of Guelph about the negative impact this substance is having on their lives is sending the wrong message. There are many locations in Guelph where a Cannabis store would be a good fit: next to the city's primary access point for mental health and wellness for children and adolescents isn't it.

Sincerely,

M MacSween

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Reference for Dr. MacSween's Letter dated May 31, 2020

Cannabis use and disorder: Epidemiology, comorbidity, health consequences, and medico-legal status

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2020. | **This topic last updated:** May 24, 2019.

INTRODUCTION

Cannabis (also called marijuana) is the most commonly used illegal psychoactive substance worldwide [1]. Its psychoactive 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, which may have contributed to increased rates of cannabis-related adverse effects. Cannabis use disorder develops in approximately 10 percent of regular cannabis users, and may be associated with cognitive impairment, poor school or work performance, and psychiatric comorbidity such as mood disorders and psychosis.

The medico-legal context, epidemiology, comorbidity, and health consequences of cannabis use and cannabis use disorder in adults are reviewed here. The pathogenesis, pharmacology, clinical manifestations, course, assessment, diagnosis, and treatment of cannabis use disorder are reviewed separately. Acute cannabis intoxication is also reviewed separately. (See "Cannabis use and disorder in adults: Pathogenesis, pharmacology, and routes of administration" and "Cannabis use and disorder in adults: Clinical manifestations, course, assessment, and diagnosis" and "Treatment of cannabis use disorder in adults" and "Cannabis (marijuana): Acute intoxication".)

EPIDEMIOLOGY

Cannabis grows in nearly every country in the world.

Canna 4 million) worldwide in 2016, approximately 3.9 percent (range 3.4 to 4.8 percent) of the global population age 15 to 64 years [1]. This is a 16 percent increase in prevalence since 2006. Cannabis use is most prevalent in West and Central Africa (13.2 percent, 34.3 million users), North America (12.9 percent, 41.5 million users), and Oceania (11.0 percent, 2.9 million users), and least prevalent in East and South-East Asia (0.6 percent, 9.7 million users), Eastern and South-Eastern Europe (2.4 percent, 5.5 million users), the Caribbean (2.2 percent, 630 thousand users), and Central America (2.8 percent, 820 thousand users) [1].

A large, nationally representative, community-based, epidemiologic survey estimated the 2016 prevalence rate of past-year cannabis use in the community-dwelling United States population (12 years or older) at 13.9 percent (estimated 37.6 million users) and past-month use of 8.9 percent (estimated 24.0 million users) [3]. Cannabis use during the past month increased from 6.2 percent (estimated 14.5 million users) in 2003. The increase in cannabis use over the past decade has occurred largely in adults, rather than adolescents [4]. Cannabis use was initiated by 2.6 million individuals in 2016, almost half (46 percent) 12 to 17 years old [3].

Risk and protective factors for cannabis use include:

- Age – Cannabis use varies with age. The highest past-year prevalence is among young adults (18 to 25 years old) (33.0 percent); the lowest prevalence is among early adolescents (0.5 percent among 12 year olds and 2.8 percent among 13 year olds); past year prevalence is 11.0 percent among those 26 years or older [3]. Cannabis use is rare in those 65 years or older (3.3 percent). In 2016, the mean age of first-time cannabis users was 19.4 years [3].

- Sex – Men are almost twice as likely as women to have used cannabis over the past month, 11.3 versus 6.7 percent, respectively [3]. Men and women initiate cannabis use in roughly comparable numbers and at roughly comparable mean ages [3], suggesting that women may stop cannabis use at higher rates. Pregnant women are less than half as likely as nonpregnant women to have used cannabis in the past month, with rates substantially lower during the third trimester (2.3 percent) than the first trimester (10.4 percent) [3].

- Race and ethnicity – Cannabis use over the past month is more prevalent among those of mixed race (17.7 percent), , blacks or African Americans (11.1 percent), and Native Americans (13.6 percent) compared with the overall non-Hispanic United States population

(9.1 percent), and less prevalent among Asians (3.3 percent) [3]. Cannabis use among whites (9.0 percent), Pacific Islanders (8.6 percent), and Hispanics (7.7 percent) is comparable to that of the general population.

- Education – College graduates have a lower prevalence of cannabis use during the past month (6.6 percent) than do those with less education (8.3 to 11.3 percent) [3]. Full-time college students have the same rate of current use as do their non-student peers.

  The school experience strongly influences risk of cannabis use. Among adolescents enrolled in school, two- threefold greater prevalence of cannabis use during the past month is seen among adolescents with (compared with without) the following characteristics [3]:

  - Failing grades
  - Nonparticipation in extracurricular activities
  - Dislike of school
  - Others in grade who use cannabis, alcohol, or cigarettes

- Employment status – Those employed full-time or not in the labor force (eg, students, retired, disabled) have lower prevalence of cannabis use during the past month than do those working part-time (11.6 percent) or unemployed (7.5 and 4.8 versus 15 percent) [3].

- Income – Adults with income less than $20,000 USD annually have 2.5-times higher rates of cannabis use during the past year than adults with income of at least $70,000 USD annually (15.6 versus 5.9 percent) [5].

- Marital status – Unmarried adults are more likely to have used cannabis during the past year than are married adults or those widowed/separated (21.0 versus 5.5 versus 8.3 percent) [5].

- Legal status – Adults on parole, probation, or supervised release status are approximately three times more likely to have used cannabis in the past month than are individuals not in such legal status [3]. Adolescents with violent or illegal behavior in the past year are at least twice as likely as those without such behavior [3].

- Social network – Among adolescents, a positive relationship with parents and having parents, friends, or peers who disapprove of cannabis use are all associated with at least twofold lower prevalence of cannabis use over the past month [3].

- Religion – Adolescents with frequent attendance at religious services or strong religious beliefs are two to three times less likely to have used cannabis over the past month than those without such protective factors [3].

- Other substance use – Cigarette smokers and alcohol drinkers are each five to six times more likely than nonsmokers and nondrinkers to use cannabis [3]. Binge alcohol drinkers (binge means four to five drinks per drinking occasion) and heavy drinkers (five or more binges per month) are two and three and a half times more likely, respectively, to use cannabis than are non-binge alcohol drinkers [3].

- Geography – Prevalence of cannabis use over the past month in the United States varies somewhat by geographic characteristics [3]. Highest rates are found in the West (11.7 percent) and in large (>1 million population) metropolitan areas (9.5 percent). Lowest rates are found in the South (7.2 percent) and in rural areas (5.5 percent).

Patterns of use — Frequency of cannabis use varies widely among those not in treatment [3]. Almost one-quarter of current users use only one to two days per month, while two-fifths use at least 20 days monthly. Prospective longitudinal studies suggest several distinct patterns of use over time [6]:

- Early onset with persisting chronic use
- Late onset with increasing use over time
- Use limited to adolescence
- Occasional use which never increases

As an example, a prospective, longitudinal study that assessed a nationally representative sample of 26,204 community-dwelling United States adults at baseline and one year later found that 97.46 percent of the 12,786 individuals who had never used cannabis remained nonusers one year later [7]. Of the 5421 current (past-year) cannabis users at baseline, 72.5 percent were still using one year later, while 27 percent had stopped cannabis use. Of the 8074 past cannabis users (those who had stopped use more than one year before baseline), 89.31 percent remained nonusers one year later, while 10.42 percent had resumed use.

Two models have been proposed to explain the sequence of cannabis use in relationship to other psychoactive substance use: the sequential gateway model and the common liability model:

- **Sequential gateway model** – The classical “gateway” model holds that there is a typical sequence of initiation of use of psychoactive substances: first use (usually in adolescence) of legal substances (alcohol, tobacco), followed by cannabis use, and then use of more harmful illegal drugs such as stimulants, opiates, or hallucinogens. The model assumes a causal relationship across the sequence, so that prevention of cannabis use would likely prevent later use of other illegal drugs [8,9].

- **Common liability model** – Pre-existing environmental and genetic factors contribute to all

substance use and substance use disorders, so that use of a specific substance at one time is not a major factor in determining what substance is used at a later time [9].

Data from large, well-controlled, community-based epidemiologic studies and twin studies are generally not consistent with the sequential gateway model, but are often suggestive of the common liability model [9,10]. Cross-national studies suggest that the underlying prevalence of substance use in the population also influences the sequence of substance use [11].

Cannabis use disorder — An estimated 13.1 million individuals world-wide had moderate-severe cannabis use disorder in 2010, a point-prevalence of 0.19 percent [12]. Prevalence was greatest in young adult (20 to 24 years old) males living in high-income regions.

An estimated 4.0 million community-dwelling residents had current (use during past year) cannabis use disorder in the United States in 2016, a prevalence rate of 1.5 percent [3]. Approximately one in eight cannabis users had a cannabis use disorder (12.7 percent). A smaller, more detailed community-based epidemiologic survey found a doubling of the cannabis use disorder rate among adults over a comparable period, from 1.5 percent (standard error 0.08) in 2001 to 2002 to 2.9 percent (standard error 0.13) in 2012 to 2013 [5].

Users of cannabis over the past year are 7.6 (95% CI 4.8-12.0) times more likely than nonusers to develop cannabis use disorder over the next three years, after controlling for potential confounders [13]. Risk of developing cannabis use disorder increases with greater intensity of cannabis use.

There are substantial differences in population rates of cannabis use disorder over the past year among different sociodemographic groups. The risk of cannabis use disorder over the past year among cannabis users (so-called “conditional” cannabis use disorder) varies much less, suggesting that much of the variation in cannabis use disorder rates is more due to differences in rates of cannabis use than to differences in development of cannabis use disorder.

- Age – Prevalence of cannabis use disorder declines substantially with age in adults: 7.5 percent among young adults (18 to 29 years old), 1.3 percent among the middle-aged (45 to 64 years old), and 0.3 percent among older adults 65 years or older [5]. Adolescents (12 to 17 years old) have an intermediate prevalence (2.3 percent) [3].

- Sex – Adult men are more than twice as likely as adult women to have cannabis use disorder over the past year (4.2 versus 1.7 percent, respectively) [5].

- Education – Adults with at least some college education are less likely to have cannabis use disorder over the past year (2.5 percent) than are high school dropouts (3.3 percent) and high school graduates (3.7 percent) [5].

- Race and ethnicity – Native Americans (5.5 percent) and blacks (4.6 percent) have higher cannabis use disorder rates over the past year than whites (2.7 percent) and Asians (1.3 percent) [5]. Hispanics have a rate (2.8 percent) comparable to the general population (2.9 percent).

- Income – Cannabis use disorder rates decline with increasing income from less than $20,000 USD annually to at least $70,000 USD annually [5].

- Urban residence – The cannabis use disorder rate over the past year is greater in urban (3.1 percent) than in rural (2.3 percent) areas [5].

PSYCHIATRIC COMORBIDITY

Cannabis use and use disorder have high rates of comorbidity, in both directions, with several psychiatric disorders, including other 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 "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis", section on 'Etiologic theories'.)

The most rigorous information comes from large, representative community-based studies, preferably prospective longitudinal studies, rather than cross-sectional. Case series of patients in treatment are less informative, and subject to selection bias.

Alcohol — There is substantial bidirectional comorbidity between cannabis use or cannabis use disorder and alcohol use or alcohol use disorder. A cross-sectional survey of 36,309 community-living adults in the United States found those with current (past 12 months) alcohol use disorder were six times more likely compared with those without alcohol use disorder to have current cannabis use disorder (prevalence rate 10.9 percent [standard error 0.55], adjusted odds ratio 6.0, 95% CI 5.10-6.97). Those with current cannabis use disorder were three to four times more likely to have current alcohol use disorder (prevalence rate 59.4 percent [standard error 2.46], adjusted odds ratio 2.8, 95% CI 2.19-3.60 for men; 59.5 percent [standard error 3.52], adjusted odds ratio 3.8, 95% CI 2.33-6.48 for women) [14]. Prospective longitudinal surveys suggest that cannabis users are 2.0 (95% CI 1.4-2.7) [13] to 5.43 (95% CI 4.54-6.49) [15] times more likely to develop alcohol use disorder over the next three years than are nonusers. Among adults with a history of alcohol use disorder, cannabis use is associated with increased likelihood of persistent alcohol use disorder over the next three years compared with those without cannabis use (odds ratio 1.74, 95% CI 1.56-1.95) [15]. A majority of daily recreational cannabis users also binge

drink alcohol [16].

Tobacco — There is substantial bidirectional comorbidity between cannabis use or cannabis use disorder and cigarette smoking [17]. A cross-sectional survey of 36,309 community-living adults in the United States found those with current (past 12 months) tobacco (nicotine) use disorder about six times more likely than those without tobacco use disorder to have current cannabis use disorder (prevalence rate 8.1 percent [standard error 0.43], adjusted odds ratio 6.2, 95% CI 5.24-7.34) [18] and those with current cannabis use disorder about three times more likely to have current tobacco use disorder (prevalence rate 63.4 percent [standard error 2.31], adjusted odds ratio 3.0, 95% CI 2.43-3.66 for men; 64.8 percent [standard error 3.24], adjusted odds ratio 3.7, 95% CI 2.61-5.26 for women) [14]. A prospective longitudinal study of 34,653 United States adults found that cannabis users, compared with nonusers, were more likely to become cigarettes smokers (adjusted odds ratio 4.45, 95% CI 3.97-5.00) or daily smokers (adjusted odds ratio 2.90, 95% CI 2.10-4.00) [19] and to develop a moderate to severe tobacco use disorder (adjusted odds ratio 1.8, 95% CI 1.2-2.7) over the next three years, after controlling for demographic characteristics and presence of psychiatric disorders [13].

Opiates — A cross-sectional, nationally representative survey of 36,309 community-living United States adults found that individuals with current cannabis use disorder, compared with those without, were more likely to have current opioid use disorder (adjusted odds ratio 4.6, 95% CI 3.0-6.8), after controlling for sociodemographic characteristics, alcohol and cigarette use, and psychiatric diagnoses [20].

Stimulants — A cross-sectional, nationally representative survey of 36,309 community-living United States adults found that individuals with current cannabis use disorder, compared with those without, were more likely 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), after controlling for sociodemographic characteristics, alcohol and cigarette use, and psychiatric diagnoses [20].

Other psychoactive drugs — A cross-sectional, nationally representative survey of 36,309 community-living United States adults found that individuals with current cannabis use disorder, compared with those without, were more likely to have current sedative/hypnotic use disorder (adjusted odds ratio 5.1, 95% CI 2.9-9.0) or “club drug” (eg, MDMA, methamphetamine) use disorder (adjusted odds ratio 16.1, 95% CI 6.3-40.8), after controlling for sociodemographic characteristics, alcohol and cigarette use, and psychiatric diagnoses [20]. Individuals with current cannabis use disorder, compared with those without, had higher prevalence of current hallucinogen use disorder (1.7 percent [95% CI 1.0-3.0] versus 0.0 [95% CI 0.0-0.0]) and current inhalant/solvent use disorder (1.1 percent [95% CI 0.4-2,8] versus 0.0 [95% CI 0.0-0.1],

respectively), but adjusted odds ratios could not be calculated.

Mood disorders — There is substantial comorbidity between cannabis use/cannabis use disorder and mood disorders (depression, bipolar disorder). Secondary analyses of data from a representative sample of 43,093 community-based adults in the United States found that individuals with a lifetime mood disorder were two to three times more likely to have used cannabis during their lifetime compared with those without any psychiatric disorder [21] and to develop a cannabis use disorder after starting cannabis use [21,22]. Cross-sectional studies have found lifetime rates of cannabis use of approximately 70 percent and cannabis use disorder of approximately 30 percent among patients with bipolar disorder [23].

A systematic review of nine published community-based national epidemiologic surveys found a mean prevalence of 17 percent (range 10 to 30 percent) for current cannabis use disorder among respondents with bipolar disorder and a prevalence of 10 to 25 percent for bipolar disorder among respondents with current cannabis use disorder [24]. A systematic review by the same research group that included 78 published studies of inpatient and outpatient clinical populations found a 20 percent prevalence rate for cannabis use disorder among patients with bipolar disorder [25].

A systematic review of seven published prospective longitudinal cohort studies of adults with current mood disorder (five bipolar, two depressive) at baseline found that recent (prior six months) cannabis use was associated with higher levels of mood symptoms over time (2.5-month to five-year follow-up), compared with less intense or nonuse) [26].

Schizophrenia (nonaffective psychosis) — There is substantial comorbidity between cannabis use and schizophrenia; some experts believe that early cannabis use is a causal factor in developing schizophrenia. (See 'Psychotic disorders' below.)

Cross-sectional studies indicate that cannabis users have two- to threefold increased prevalence of schizophrenia compared with nonusers [27]. This association is stronger with earlier age of onset of use (eg, early adolescence), more intense cannabis use, and use of cannabis with high delta-9-tetrahydrocannabinol (THC) content and THC:cannabidiol ratio [28]. Secondary analyses of data from a representative sample of 43,093 community-living adults in the United States found that individuals with lifetime schizophrenia were two to three times more likely to have lifetime cannabis use than those without any psychiatric disorder [21] and to develop cannabis use disorder [21,22].

A systematic review of 53 published studies found that patients with schizophrenia-spectrum disorders had a 23.1 percent prevalence (range 4.5 to 81.1 percent) of cannabis use over the past 6 months and a 42.2 percent (range 19.2 to 89.1 percent) prevalence of lifetime use [29]. A

systematic review of 35 published studies found that patients with schizophrenia-spectrum disorders had a 16.0 percent (8.6 to 28.6 percent interquartile range) prevalence of current cannabis use disorder and a 27.1 percent (12.2 to 38.5 percent interquartile range) prevalence of lifetime cannabis use disorder [30].

The increased prevalence of cannabis use by people with schizophrenia is not likely explained by a shared genetic liability. A cross-sectional study of 6931 adults in the Netherlands Twin Registry found that a polygenic risk score for schizophrenia (derived from a large genome-wide association meta-analysis) accounted for no more than 0.5 percent of the variance in several cannabis use phenotypes, including lifetime and regular use, frequency and quantity of use, and age at initiation of use [31].

A prospective, national, register-based, birth cohort study in Denmark that followed 41,470 people with schizophrenia born in 1955 or later found an increased risk of all-cause mortality in those with cannabis use disorder (hazard ratio 1.24, 95% CI 1.04-1.48, p = 0.0174) [32].

Anxiety disorders — There is substantial comorbidity between anxiety disorders and cannabis use. A meta-analysis of 31 studies involving 112,000 individuals in 10 countries found associations between anxiety disorder and cannabis use (odds ratio = 1.24, 95% CI 1.06-1.45) or cannabis use disorder (odds ratio = 1.68, 95% CI 1.23-2.31) [33].

Secondary analyses of a representative survey of 43,093 community-based adults in the United States found that individuals with a lifetime anxiety disorder were two to three times more likely to have lifetime cannabis use than those without any psychiatric disorder [21] and to develop a cannabis use disorder after starting cannabis use [21,22].

A community-based, nationally representative survey of 36,309 adults in the United States found that one-quarter or more (23.4 percent, standard error 2.30 among men; 36.1 percent, standard error 3.74 among women) of respondents with current cannabis use disorder had a current anxiety disorder, although the adjusted odds ratios were not significant (1.2, 95% CI 0.88-1.56 for men; 0.8, 95% CI 0.58-1.23) [14]. Current prevalence rates for individual anxiety disorders among men and women were specific phobia 8.6 (standard error 1.50) and 9.9 (standard error 1.93) percent, respectively; generalized anxiety disorder 12.2 (standard error 1.88) and 19.9 (3.19) percent, respectively; social phobia 7.1 (standard error 1.42) and 7.2 (standard error 1.76) percent, respectively; and panic disorder 7.4 (standard error 1.20) and 15.2 (standard error 2.81) percent, respectively. None of the adjusted odds ratios were significant.

Posttraumatic stress disorder — Several community-based national epidemiologic studies found comorbidity rates of around 10 percent for current cannabis use disorder and posttraumatic stress disorder (PTSD). For example, a cross-sectional, nationally representative

survey of 36,309 community-living United States adults found the prevalence of current cannabis use disorder among those with current PTSD to be 9.4 percent (standard error 0.94) (adjusted odds ratio 4.3, 95% CI 3.15-4.67) [18] and the prevalence of current PTSD among those with current cannabis use disorder to be 12.3 percent (standard error 1.66) (adjusted odds ratio 1.7, 95% CI 1.12-2.57) for men and 26.9 percent (standard error 3.37) (adjusted odds ratio 1.6, 95% CI 1.01-2.48) for women [14].

A systematic review of four prospective longitudinal cohort studies of adults with PTSD at baseline found that current (prior month) cannabis use was associated with higher levels of PTSD symptoms over time, compared with comparison groups (less intense use or no use) [26].

Obsessive-compulsive disorder — A cross-sectional, nationally representative, household survey of 8841 adult Australians found a 19.9 percent (standard error 7.4) prevalence of obsessive-compulsive disorder among respondents with current cannabis use disorder, compared with 4.6 percent (standard 1.2) among current cannabis users without cannabis use disorder and 2.4 percent (standard error 0.2) among current nonusers [34]. However, the odds ratios for having obsessive-compulsive disorder were not different from one for current cannabis users with cannabis use disorder versus current users without cannabis use disorder (odds ratio 2.3, 95% CI 0.6-8.7) or for current nonusers versus current users without cannabis use disorder (odds ratio 0.8, 95% CI 0.4-1.6).

Attention deficit hyperactivity disorder — Two studies of large, unselected populations suggest a 20 to 30 percent comorbidity rate between attention deficit hyperactivity disorder (ADHD) and cannabis use disorder. A nationally representative survey of 33,488 community-living United States adults found about a 30 percent prevalence of lifetime cannabis use disorder (varying by ADHD subtype: inattentive, hyperactive-impulsive, or combined) among the 965 respondents with ADHD, compared with 5 percent among the 15,614 respondents without ADHD or ADHD-type symptoms (adjusted odds ratio 2.14 [adjusted for socioeconomic characteristics, conduct disorder, major depression, and anxiety disorder], 95% CI 1.58-2.90) [35]. The 17,009 respondents with ADHD-type symptoms (but not meeting full DSM-IV diagnostic criteria for ADHD) also had greater prevalence of lifetime cannabis use disorder (10 percent; adjusted odds ratio 1.29, 95% CI 1.20-1.38). A 2010 to 2011 study of 5103 male Swiss Army conscripts found a 21.9 percent prevalence of current cannabis use disorder among the 215 conscripts with current ADHD, compared with an 8.0 percent prevalence among conscripts without current ADHD (chi-square 48.43, $p < 0.001$) [36].

Personality disorders — There is substantial comorbidity between cannabis use disorder and several personality disorders, especially antisocial and obsessive-compulsive personality disorders. A community-based, nationally representative study of 36,309 adults in the United

States found high rates of current personality disorder in men and women with current cannabis use disorder: 48.2 (standard error 2.51) and 58.6 (standard error 3.17), respectively, two to three times the rate of those without cannabis use disorder (adjusted odds ratios 2.0, 95% CI 1.56-2.65 for men; 3.1, 95% CI 2.14-4.35 for women) [14]. Current prevalence of specific personality disorders included:

- Antisocial personality disorder: 21.8 (standard error 2.12) percent (adjusted odds ratio 1.5, 95% CI 1.08-2.02) for men; 16.1 (standard error 1.95) percent (adjusted odds ratio 1.7, 95% CI 1.13-2.58) for women.
- Borderline personality disorder: 39.1 (standard error 2.32) percent (adjusted odds ratio 2.0, 95% CI 1.46-2.67) for men.
- Schizotypal personality disorder: 24.9 (standard error 2.17) percent (adjusted odds ratio 1.3, 95% CI 0.98-1.85) for men; 33.5 (standard error 3.21) percent (adjusted odds ratio 2.0, 95% CI 1.26-3.18) for women.

Secondary analysis of an earlier community-based, nationally representative study of 43,093 adults in the United States found that cannabis users with any lifetime personality disorder were more than twice as likely to develop cannabis use disorder than those without any disorder (adjusted odds ratio 2.36, 95% CI 2.05-2.71) [22].

Respondents with lifetime cannabis use disorder were 10-fold more likely (odds ratio 10.2, 95% CI 8.77-11.88) to have lifetime antisocial personality disorder than those without cannabis use disorder [37]. Respondents with lifetime cannabis use disorder were also twice as likely to have lifetime childhood conduct disorder (2.2, 95% CI 1.65-3.03) and seven times more likely to have lifetime adult antisocial behavior (7.1, 95% CI 6.47-7.88). Women show this increased prevalence of personality disorders two-three times more than men.

A cross-sectional, population-based study of 1419 adult Norwegian twins found associations between antisocial personality disorder and lifetime cannabis use (beta = 0.23, 95% CI 0.19-0.28) and cannabis use disorder (beta = 0.26, 95% CI 0.21-0.31), after adjusting for age and sex [38]. Similar associations were found between borderline personality disorder and cannabis use (beta = 0.20, 95% CI 0.14-0.26) and cannabis use disorder (beta = 0.12, 95% CI 0.06-0.18). Genetic risks for these two personality disorders explained 32 to 60 percent of the total variance in cannabis use and cannabis use disorder.

ADVERSE EFFECTS OF CANNABIS USE

Cannabis use disorder constitutes a small proportion of the global burden of disease relative to other substance use disorders. Of the approximately two million total disability adjusted life-years lost to substance use disorders (not including tobacco), individual substance use disorders were [12]:

- Alcohol – 47 percent
- Opioids – 24.3 percent
- Amphetamines – 7.0 percent
- Cannabis – 5.5 percent
- Cocaine – 2.9 percent
- Other illicit drugs – 13.4 percent

Large-scale cross-sectional epidemiological studies and smaller prospective longitudinal studies have not found cannabis use to be associated with serious or chronic medical conditions or death from medical conditions [12,39]. Cannabis use is associated with injury and death from motor vehicle accidents [40-43]. As examples:

- A systematic review of 19 published studies found no evidence of an association between heavy cannabis use and adverse health outcomes, except for fatal motor vehicle crashes [39].

- A 2016 40-year longitudinal cohort study of 50,373 Swedish male military conscripts found a small association between heavy cannabis use (>50 times) at baseline (age 18 to 19 years) and overall mortality (hazard ratio 1.4, 95% CI 1.1-1.8) [44]. The association was similar in those with and without a history of psychotic disorder, suggesting that schizophrenia was not a major factor driving the increased mortality. The only specific causes of death associated with heavy cannabis use were infections, cardiovascular, and injuries of unknown cause, all of which showed a positive dose-response relationship with intensity of baseline cannabis use.

- A 13-year prospective longitudinal study of 3124 randomly recruited United States young adults found no association between baseline cannabis use at least four times per month and subsequent decline in self-reported general health [45].

- A 20-year prospective longitudinal study of a representative birth cohort of 1037 individuals born in Dunedin, New Zealand in 1972 to 1973 and recruited at age 18 years found no association between cannabis use or cannabis use disorder and self-reported physical health [46].

- However, a retrospective cohort study using the electronic health records of a four million-

member integrated health system found that the 2752 patients with cannabis use disorder in 2010 were about twice as likely as 2752 demographically matched patients without cannabis use disorder to visit the emergency department or have an inpatient hospitalization over the next five years (all adjusted odds ratios around 2.0 [adjusted for socioeconomic characteristics, tobacco use disorder, and medical comorbidity, but not for psychiatric comorbidity]) [47].

- A cross-sectional survey of a nationally representative sample of 14,715 United States adults aged 50 years or older found that current (past-year) cannabis users, compared with nonusers, were more likely to experience an injury (odds ratio 1.48, 95% CI 1.18-1.85) and to visit an emergency department (odds ratio 6.14) [7].

- Two meta-analyses found that recent cannabis use increased the risk of injury from motor vehicle accident by 32 percent (odds ratio 1.32, 95% CI 1.09-1.59) [42,43] or by 42 percent (odds ratio 1.42, 95% CI 1.19-1.71) [40,41]. A meta-analysis limited to the 10 studies which verified recent cannabis use by blood analysis found an increased risk of 97 percent (odds ratio 1.97, 95% CI 1.35-2.87) [40,41].

Psychosocial functioning and health — Adolescent cannabis use is strongly associated with lower educational attainment and increased use of other drugs, but not with school performance or psychological health; even the strong associations are not clearly causal:

- A systematic review of 16 higher quality prospective longitudinal studies found consistent associations for cannabis use with lower educational attainment, and with increased use of other illegal drugs [48]. A prospective longitudinal study of 1103 French young adults (22 to 35 years old) who had been followed for 19 years found initiation of cannabis use by age 16 years associated with failure to earn a high school degree, compared with those not using cannabis (odds ratio 1.77, 95% CI 1.22-2.55) [49]. Those who initiated cannabis use older than age 16 years had educational attainment comparable to cannabis nonusers.

- The systematic review found inconsistent associations for cannabis use with poor psychological health, and with problematic or criminal behavior [48]. None of the associations was definitely causal, with the possibilities of reverse causation, potential bias, or confounding factors.

- Two 2015 prospective longitudinal studies found no association for adolescent cannabis use with high school academic performance or mental health problems, after controlling for concurrent alcohol and tobacco use [6,50].

Brain structure and function — 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 and no evidence for changes in whole brain volume; evidence for changes in other brain regions was inconsistent or inconclusive [51]. Functional neuroimaging studies (chiefly functional magnetic resonance imaging) suggested that adult cannabis users, relative to controls, have decreased neuronal activity in anterior cingulate cortex and right dorsolateral prefrontal cortex and increased functional connectivity across brain regions [51]. Findings for other brain regions were inconsistent or inconclusive. 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.

Neuropsychological effects — Cannabis acutely impairs a variety of neuropsychological functions in a dose-dependent manner, especially attention, concentration, episodic memory, and associative learning [52,53]. However, evidence of an association between regular cannabis use and long-term neurocognitive deficits is mixed [53,54].

While meta-analyses and systematic reviews of studies on cannabis-associated neuropsychological function in cannabis users generally show impairment, studies suggest its effects may be time limited [52-56]:

- A meta-analysis of 13 studies including cannabis users with at least one month of abstinence found no differences from nonusers on neuropsychological test performance [55]. This finding suggests that cannabis-associated impairment resolves over the time period needed to eliminate body stores of lipid-soluble cannabinoids.

- A systematic review and meta-analysis of 69 cross-sectional studies of adolescents and young adults (2152 cannabis users and 6575 comparison participants) showed a small overall effect size for reduced cognitive functioning in frequent cannabis users (d = -0.25; 95% CI -0.32 to -0.17) [56]. Five of eight domains were affected: learning, speed of information processing, delayed memory, attention, and aspects of executive function. Fifteen studies that required 72 hours or more of abstinence from cannabis before testing did not show an effect on cognitive functioning, suggesting the effects were time limited.

A review of three long-term prospective longitudinal studies suggested that greater cumulative intensity of cannabis exposure and earlier age of onset of cannabis use were associated with greater persistence of cannabis-associated impairment [57]. A more recent prospective longitudinal study of 5115 adults (aged 18 to 30 years at baseline) found that 84.3 percent were lifetime cannabis users at 25-year follow-up, while only 11.6 percent were current users [58]. Current cannabis use was associated with impaired verbal memory and slower cognitive processing speed. A linear regression analysis that excluded current cannabis users and

controlled for age, use of tobacco, alcohol, and other illegal drugs, and baseline cognitive function found cumulative lifetime cannabis use associated with impaired verbal memory, but not with processing speed or executive function.

Cannabis-induced psychosis — Cannabis use causes transient acute psychosis (cannabis-induced psychosis) in some users. It is not known whether this acute effect is related to the development of schizophrenia associated with chronic cannabis use. (See "Cannabis (marijuana): Acute intoxication", section on 'Toxic effects' and 'Psychotic disorders' below.)

A national registry study that identified 1492 patients who received a diagnosis of cannabis-induced psychosis in the Danish Psychiatric Central Research Register between 1994 and 2014 and followed them through August 2014 found a 41.2 percent (95% CI 36.6-46.2) conversion rate to schizophrenia, with 50 percent of men converting within 2.0 years and 50 percent of women within 4.4 years [59]. 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).

Psychotic disorders — There is substantial evidence that chronic cannabis use, especially during adolescence, is associated with later development of schizophrenia. The mechanisms responsible for the association between cannabis use and schizophrenia remain unclear. Some experts believe that early cannabis use is a causal factor in developing schizophrenia.

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) [60]. 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). The review adjusted for several known confounding factors and excluded cohorts with identified mental illness or substance use problems at baseline.

A prospective longitudinal study of 6534 individuals born in northern Finland in 1986 and evaluated at age 15 to 16 years and again at age 30 years found an increased risk of psychosis for those who used cannabis at least five times by age 15 to 16 years, compared with those who had never used (adjusted hazard ratio 3.02, 95% CI 1.14-7.98) [61]. There was no increased risk for those who used cannabis one to four times. The analysis adjusted for several known confounding factors (eg, prodromal psychosis symptoms at baseline, parental psychosis, frequent alcohol use, daily tobacco smoking) and excluded individuals with a psychosis diagnosis at first evaluation.

Cannabis use exacerbates symptoms in patients 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, and positive symptoms (but not negative symptoms), and poorer level of functioning [62]. A two-year, prospective longitudinal study of 220 adults with first-episode psychosis found a increased risk of relapse with hospitalization during periods of cannabis use (odds ratio 1.13; 95% CI 1.02-1.24) [63]. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

Mood disorders — Most, but not all, prospective longitudinal studies have found that cannabis use or cannabis use disorder is associated with subsequent development of depression or bipolar disorder:

- **Depression** – A 2014 meta-analysis of 14 prospective longitudinal studies that controlled for depression at baseline found that heavy cannabis users had a 1.62 odds ratio (95% CI 1.21-2.16) for developing clinically diagnosed major depression or depressive symptoms, compared with light or nonusers [64]. As an example, a three-year prospective longitudinal study of a representative sample of almost 35,000 community-living United States adults found a bidirectional comorbidity between cannabis use disorder and major depressive disorder [65]. Individuals with cannabis use disorder at baseline had an adjusted odds ratio = 6.61 (95% CI 1.67-26.21) for major depressive disorder at follow-up, after controlling for likely confounding sociodemographic variables. However, a prospective longitudinal community-based study of 34,653 adults found cannabis users at no increased risk of developing a mood disorder (odds ratio 1.2, 95% CI 0.8-1.6) [13].

  A twin study concluded that comorbidity of cannabis dependence and major depressive disorder is probably due to genetic and environmental factors that predispose to both outcomes, rather than a direct causal relationship between cannabis use and depression [66].

- **Bipolar disorder** – 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 [67]. As an example, a three-year prospective longitudinal study of community-living United States individuals found that initiation of weekly to almost daily cannabis use was associated with increased incidence of bipolar disorder (adjusted odds ratio = 2.47 [95% CI 1.03-5.92]), while daily use was not associated with increased incidence (0.61 [0.36-1.04]) [68].

  Cannabis use has been found to be associated with earlier age of onset of first manic episode and more frequent mood episodes [23].

Anxiety disorders — Cannabis intake causes transient acute anxiety in many users. Two prospective longitudinal studies had conflicting findings regarding the association between long-term cannabis use and anxiety disorders:

- A prospective longitudinal community-based study of 34,653 United States adults found cannabis users at no increased risk of developing an anxiety disorder (odds ratio 1.0, 95% CI 0.8-1.3) [13].
- A 15-year prospective longitudinal study of 1943 Australian adolescents found daily cannabis use during adolescence associated with a 2.5-fold increased risk of anxiety disorder at age 29 years [69].

Pulmonary — Cannabis smoke contains many of the same respiratory irritants and carcinogens as tobacco smoke [70], although their effects may be moderated by the absence of nicotine [71]. Cannabis smoking acutely irritates the airways and is associated with transient cough, sputum production, wheezing, chest tightness, and airway inflammation, as well as bronchodilatation, which may account for past use of cannabis to treat asthma [70,72].

Cannabis smoking produces acute, transitory respiratory symptoms, but chronic cannabis use is not clearly associated with impaired pulmonary function:

- A systematic review and meta-analysis of 22 published, English-language studies (10 prospective cohort, 12 cross-sectional) found low-strength evidence suggesting that smoking marijuana is associated with cough (risk ratio, 2.04 [95% CI, 1.02 to 4.06]), sputum production (risk ratio, 3.84 [CI 1.62-9.07]), wheezing (risk ratio, 2.83 [CI 1.89-4.23]), and dyspnea (risk ratio, 1.56 [CI 1.33-1.83]) [73]. Evidence on the association between marijuana use and obstructive lung disease and pulmonary function was inconclusive, in part because many cannabis users had little exposure to cannabis, and some studies included smokers of both cannabis and tobacco.
- A systematic review of 12 interventional studies that evaluated the effect of a smoked cannabis challenge on lung function found an 8 to 48 percent decrease in airway resistance lasting up to one hour (eight studies), a 0.15 to 0.25 L increase in forced expiratory volume one (FEV1) (five studies), a 10 percent increase in peak airflow (one study), and immediate reversal of methacholine-induced or exercise-induced bronchospasm in asthma patients (one study) [72].
- A subacute study in which 28 healthy, young adult male cannabis users smoked cannabis cigarettes (2.2 percent delta-9-tetrahydrocannabinol) ad lib for 47 to 59 days (mean of 5.2 cigarettes/day) found decreases, compared with baseline, in FEV1 (3±1 percent), maximal

mid-expiratory flow rate (11±2 percent), plethysmographic specific airway conductance (16±2 percent), and diffusing capacity (8±2 percent) [74]. These findings suggest that regular cannabis smoking for six to eight weeks causes mild airway obstruction.

- A cross-sectional survey (2007 to 2010) of 6723 United States community-living adults (18 to 59 years old) found no association between cumulative cannabis use up to 20 joint-years and performance on standard spirometry tests (forced vital capacity [FVC], forced expiratory volume [FEV], or FEV/FVC) [75]. Greater cumulative use was associated with an odds ratio of 2.1 (95% CI 1.1, 3.9) for an abnormally low (<70 percent) FEV/FVC, which was due to increased FVC, rather than decreased FEV (unlike obstructive lung disease, which is typically associated with decreased FEV).

Limited evidence from small case series and case-control studies suggests that inhalation of cannabis vapor generated by electronic devices may be less irritating to the lungs than inhalation of cannabis smoke [76-78]. This suggestion has some biological plausibility, in that cannabis vapor has less hot gases and less toxic pyrolytic breakdown products, but remains to be confirmed by larger systematic studies.

Cancer — Molecular, cellular, and histopathological evidence, both in vivo and in vitro, plausibly suggests that cannabis smoking may cause cancer [79,80]; however, epidemiologic studies do not consistently show an association. The failure to observe an association may be due, in part, to substantial methodologic limitations in many studies, such as the difficulty controlling for important confounding factors, especially cigarette smoking, the assessment of cannabis use by retrospective self-report, and the small sample sizes for heavy cannabis users.

- **Lung cancer** – A 2006 systematic review of 19 studies evaluating the association between cannabis smoking and lung cancer found associations with alveolar macrophage dysfunction, oxidative stress, and bronchial mucosal abnormalities, but no association with lung cancer after adjusting for tobacco use [80]. A more recent review of six epidemiologic studies also found no association [79]. (See "Cigarette smoking and other possible risk factors for lung cancer", section on 'Marijuana and cocaine'.)

- **Head and neck cancer** – A review of 11 studies found some increased risk and some decreased risk associated with cannabis smoking, possibly due in part to differences in human papillomavirus status (a known causal factor in such cancers) [79]. A pooled analysis of five case control studies including 4029 cases and 5015 controls did not find an association between cannabis use and cancer of the head and neck [81]. (See "Epidemiology and risk factors for head and neck cancer", section on 'Tobacco products'.)

- **Testicular cancer** – A meta-analysis of three case-control studies found cannabis use at

least weekly associated with an increased risk (odds ratio of 2.59 [95% CI 1.60, 4.19]) for non-seminoma testicular cancer compared with never users [82]. There was inconsistent evidence regarding an association with seminoma tumors.

Cardiovascular — Cannabis intake acutely increases sympathetic activity and decreases parasympathetic activity, resulting in release of catecholamines, tachycardia, vasodilation, and an increase in cardiac output and myocardial oxygen demand with little or no increase in blood pressure [83,84]. These acute changes probably account for the orthostatic hypotension associated with cannabis use [85] and the association between cannabis smoking and acute myocardial infarction (although the absolute risk appears to be small).

A 2018 systematic review of 11 published English-language studies concluded that the overall evidence was of insufficient quality to judge whether cannabis use is associated with acute myocardial infarction or stroke, largely because of recall bias, inadequate assessment of cannabis exposure, and the predominance of low-risk cohorts with minimal cannabis exposure [86].

- **Myocardial infarction** – Cannabis smoking may be associated with a modest, short-lived increase in risk of acute myocardial infarction, even in individuals without a history of angina or hypertension. A prospective study followed 3886 adult inpatients with an acute myocardial infarction, 3.2 percent of whom had smoked cannabis within the prior year [87]. Cannabis smokers were less likely than nonsmokers to have a history of angina (12 versus 25 percent) or hypertension (30 versus 44 percent) at their index hospitalization. A case-crossover analysis found a 4.8-fold (95% CI 2.4, 9.5) increased risk of myocardial infarction in the first 60 minutes after cannabis use, which became nonsignificant by the second hour [87]. After a median 3.8 years of follow-up (1913 subjects), weekly cannabis users had a hazard ratio of 4.2 (95% CI 1.2-14.3) for subsequent mortality, compared with nonusers [88]. After up to 18 years of follow-up of the entire cohort, there was no longer any difference in mortality rate between cannabis smokers and nonsmokers (29 percent higher rate, 95% CI 0.81, 2.05) [89].

- **Stroke** – Cannabis use has been associated with stroke, although the absolute risk appears to be small. A review of 64 published cases of stroke associated with cannabis use found that the majority had characteristics suggesting causality, ie, a close temporal relationship, exclusion of other likely causes, and another stroke after reuse of cannabis [90]. A cross-sectional national survey of patients hospitalized for acute ischemic stroke found that cannabis users had a 17 percent increased likelihood of acute ischemic stroke compared with nonusers (odds ratio 1.17, 95% CI 1.15, 1.20) [91].

- **Atrial fibrillation** – Cannabis use has been associated with atrial fibrillation in a growing

number of case reports, although the absolute risk appears to be small [92,93].

Hyperemesis syndrome — Cannabinoid hyperemesis syndrome is a well-defined but apparently relatively rare syndrome involving episodic severe nausea and vomiting and abdominal pain which is relieved by exposure to hot water (shower or bath) [94-96]. Topical capsaicin has shown some benefit, but standard antiemetics and antidopamine agents are of little or no value [97]. The pathophysiology remains unknown, but patients are almost always daily cannabis users for at least one year and symptoms resolve within one to two days of cessation of cannabis use. (See "Cyclic vomiting syndrome", section on 'Chronic cannabis use'.)

Reproductive — Cannabis use has been found to be associated with several reproductive processes:

- **Spermatogenesis** – The endocannabinoid system is involved in regulation of the male reproductive system. In vitro and in vivo studies suggest that cannabis disrupts the hypothalamic-pituitary-adrenal axis, reduces spermatogenesis, and impairs several sperm functions, including motility, capacitation, and the acrosome reaction [98]. A cross-sectional study of 1215 Danish male military recruits who had smoked cannabis within the prior three months found that weekly or more frequent users had a 28 percent (95% CI -48, -1) lower sperm concentration and a 29 percent (95% CI -46, -1) lower total sperm count compared with less frequent users [99].

- **Prolactin** – Acute cannabis use probably has no effect on plasma prolactin levels, although some earlier, small studies showed either increases or decreases [100]. Chronic cannabis users have approximately 20 percent lower plasma prolactin levels than healthy nonusers [100].

- **Neonatal outcomes** – Cannabis use by pregnant women does not appear to affect fetal health or neonatal outcome [101]. As an example, a meta-analysis of 24 studies of the association between cannabis use during pregnancy and neonatal outcomes found a pooled odds ratio of 1.77 (95% CI 1.04-3.01) for low birthweight with any cannabis use (pooled mean difference 109.4 g, 95% CI 38.72-180.12) and increased risk of placement in the neonatal intensive care unit (pooled odds ratio 2.02, 95% CI 1.27-3.21) [102]. There was no cannabis-use association with neonatal body length, head circumference, gestational age, or Apgar score.

  Three retrospective studies of representative cohorts of pregnant women, each containing 8000 to 12000 women, controlled for known confounds such as alcohol and tobacco use [103-105]. All three studies found no adverse neonatal outcomes associated with cannabis use. The second study found that concurrent use of cannabis and tobacco was associated

with increased risks over tobacco use alone: preterm birth (adjusted odds ratio 2.6, 95% CI 1.3, 4.9), low birth weight (adjusted odds ratio 2.8, 95% CI 1.6, 5.0), and increased rates of pre-eclampsia (adjusted odds ratio 2.5, 95% CI 1.4, 5.0) [104]. Secondary analysis of data from a cohort of 1610 singleton, nonanomolous live births identified 2.7 percent with maternal cannabis use during pregnancy (self-report and/or testing of umbilical cord homogenate) [106]. Maternal cannabis use was not associated with adverse pregnancy outcomes (small for gestational age, spontaneous preterm birth, hypertensive disorders of pregnancy) (adjusted odds ratio 1.29, 95% CI 0.56-2.96 [adjusted for maternal tobacco use status and clinical and socioeconomic characteristics]), but was associated with increased neonatal morbidity (chiefly infection and neurologic) or death (adjusted odds ratio 3.11, 95% CI 1.40-6.91 [adjusted for tobacco and illicit drug use status and race]). (See "Substance use by pregnant women", section on 'Marijuana'.)

- **Breast milk** – Cannabinoids appear in breast milk, at levels estimated at 0.8 to 2.5 percent of the maternal dose [101,107]. Limited preclinical evidence suggests that cannabis use may reduce lactation by inhibiting prolactin secretion [108].

Liver — Cannabis use is not associated with acute hepatotoxicity [109]. Daily cannabis use worsens the progression of chronic viral hepatitis C infection. Two cross-sectional studies with a combined 585 consecutive patients with chronic hepatitis C infection undergoing liver biopsy (approximately half cannabis users) found daily cannabis smoking associated with more severe fibrosis (odds ratio 3.4, 95% CI 1.5-7.4) [110] and more severe steatosis (odds ratio 2.1, 95% CI 1.01-4.5) [111].

Dental — Cannabis smoking is associated acutely with dry mouth and irritated oral mucosa, chronically with leukoplakia, inflamed oral mucosa (cannabis stomatitis), increased risk of periodontal disease (gingivitis), and oral candidiasis [112]. A 20-year prospective longitudinal study of a representative birth cohort of 1037 individuals born in Dunedin, New Zealand in 1972 to 1973 and recruited at age 18 years found that cannabis use was associated with poorer periodontal health (beta = 0.10, 95% CI 0.05-0.16) [46].

Ophthalmologic — Cannabis causes conjunctival vasodilation (red eyes) and reduces intraocular pressure [113]. Effects of cannabis on vision are poorly understood, but may include increased photosensitivity and decreased visual acuity

MEDICO-LEGAL CONTEXT

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”; cannabis and cannabis resin are also in Schedule IV, meaning use should be limited to “medical and scientific research” [114]. In practice, the legal status of cannabis and its use in health care varies widely internationally [115]. Possession of small amounts is officially legal in Spain, Uruguay, and Canada (effective October 2018) and decriminalized in more than two dozen countries, chiefly in Europe and Latin America. Medical use is legal in more than two dozen countries, including Canada, Australia, and much of Europe. In the United States, cannabis is subject to contradictory legal regulation under state and federal law.

Cannabis and all phytocannabinoids (ie, compounds found in the Cannabis sativa plant) are classified as schedule I compounds under the United States Controlled Substances Act [116]. 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.

Medical use — As of August 2018, thirty-one US states, the District of Columbia, Puerto Rico, and Guam authorize medical use of cannabis, although not all programs are operational [117]. An additional 15 states have limited programs that authorize use of high cannabidiol/low delta-9-tetrahydrocannabinol (THC) cannabis formulations for treatment of childhood epilepsy, especially refractory seizures. Cannabidiol is a phytocannabinoid without psychoactive effects, so has little or no abuse liability. (See "Seizures and epilepsy in children: Refractory seizures and prognosis", section on 'Cannabinoids'.)

In these states, licensed clinicians can recommend or certify patients with certain specified conditions (which vary by state) to obtain medical cannabis from state-licensed dispensaries (or, in a few states, grow their own) [118]. Federal courts have ruled that such recommendations to patients are free speech protected under the First Amendment and do not violate federal laws regulating “prescribing” of controlled substances.

There are a handful of approved medical uses in numerous countries for cannabis, cannabis-derived products, or synthetic cannabinoids. (See 'Synthetic cannabinoids' below.)

A cannabis extract with equal proportions of THC and cannabidiol (nabiximols, Sativex) is approved for medical use in 27 countries (including Canada), but not in the United States, for treatment of pain and muscle spasticity due to multiple sclerosis. (See "Symptom management of multiple sclerosis in adults", section on 'Cannabinoids'.) A cannabis extract containing only cannabidiol (Epidiolex) was approved by the US Food and Drug Administration for the treatment of intractable childhood epilepsy but is not yet on the market.

Clinicians recommending cannabis for medical treatment should consider:

- Prior experience with cannabis – Patients with no prior experience with cannabis are more likely to experience the psychoactive effects as dysphoric rather than pleasurable. Patients who are regular cannabis users are more likely to be tolerant to some of the adverse effects, eg, cognitive and psychomotor impairment.

- Cannabinoid content – “Dosing” of cannabis is determined by the means of administration, frequency, and amount used as well as the cannabinoid content of the recommended strain (especially in terms of THC and THC:cannabidiol ratio). Some states require labeling of medical cannabis strains or dosing units with their content of major cannabinoids such as THC and cannabidiol. States that have legalized only low THC:high cannabidiol medical cannabis typically have a maximum permitted THC content.

- Route of administration:

  - Smoked and inhaled cannabis have a rapid onset of effect (typically minutes) and relatively short duration of action (typically two to four hours). These routes are preferred by some patients because they allow frequent and precise titration of dose to effect (eg, analgesia).

  - Oral cannabis has a slow onset of effect (typically half to one hour) and long duration of action (typically 4 to 12 hours). This may lead to inadvertent overdosing; when patients don’t experience effects as soon as they expect, they may take another dose, resulting in a cumulative overdose. This is especially likely by patients familiar with the rapid onset of smoked or inhaled cannabis.

- Drug interactions – THC has potential drug-drug interactions with other medications [119]. THC is a substrate for the CYP2C9 and CYP3A4 drug-metabolizing enzymes, so may interact pharmacokinetically with other substances metabolized by these enzymes, such as tricyclic antidepressants (2C9), protease inhibitors (3A4), or sildenafil (2C9, 3A4) [120]. The clinical significance of these interactions has not been established.

- Sedative effect – As a central nervous system (although not respiratory) depressant, THC potentiates the sedative effects of other central nervous system depressants such as alcohol and benzodiazepines. This additive interaction is especially relevant when driving or operating heavy machinery. As an example, a 2015 blinded controlled study of the effects of inhaled (vaporized) cannabis and oral alcohol on simulated driving performance found that a 5 mcg/L blood THC concentration combined with a 0.05 g/210 L breath alcohol concentration produced the same impairment as a 0.08 g/210 L alcohol concentration [121].

There is little information from controlled clinical trials regarding contraindications to use of medical cannabis. Based on known adverse effects of recreational cannabis use, it seems prudent to avoid recommending medical cannabis to individuals with a history of schizophrenia, a recent acute myocardial infarction or episode of cardiac tachyarrhythmia, or who must drive or operate heavy machinery.

Recreational use — As of January 2019, nine states and the District of Columbia will have authorized cannabis for recreational (as well as medicinal) use under state law. Not all the state programs were operational as of August 2018 [117]. Canada will have a recreational cannabis program operational in October 2018.

Synthetic cannabinoids — Synthetic cannabinoids have been approved in some countries for specific clinical indications.

Dronabinol (Marinol synthetic THC) and nabilone (a THC analogue, eg, Cesamet) are classified under schedule III of the Controlled Substances Act in the United States (and similar schedules in other countries) and approved by the US Food and Drug Administration for oral administration in the treatment of:

- Anorexia associated with weight loss in patients with AIDS. (See "Assessment and management of anorexia and cachexia in palliative care", section on 'Cannabis and cannabinoids'.)
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. (See "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults", section on 'Poor emesis control/rescue therapy'.)

Dronabinol and nabilone are psychoactive, which is often experienced as an adverse effect by cannabis-naïve patients. They appear to have little abuse or diversion liability [122], perhaps because the oral route of administration does not provide the rapid onset and intense euphoria desired by the typical recreational drug user.

Synthetic cannabinoids are discussed further separately. (See "Cannabis use and disorder in adults: Pathogenesis, pharmacology, and routes of administration", section on 'Synthetic cannabinoids'.)

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".)

SUMMARY

- Cannabis is the most commonly used illegal psychoactive substance, used by an estimated 192 million individuals worldwide (3.9 percent of the 15- to 64-year-old population in 2016 and an estimated 37.6 million community-living individuals (13.9 percent of those 12 years and older) in the United States in 2016. (See 'Cannabis use' above.)

- Rates of cannabis use in the United States are higher in young adult men with low incomes and no college education than among other population groups. Approximately one in eight current regular cannabis users develops a cannabis use disorder. (See 'Cannabis use' above and 'Cannabis use disorder' above.)

- Cannabis use before age 17 years is strongly associated with lower educational attainment and increased use of other drugs, but these associations are not clearly causal. (See 'Psychosocial functioning and health' above.)

- Individuals with cannabis use or cannabis use disorder often use other psychoactive substances, especially alcohol and tobacco. Substantial bidirectional comorbidity is seen between cannabis use disorder, schizophrenia, and several other psychiatric disorders, including depression, bipolar disorder (mania), anxiety disorders, and antisocial personality disorder. (See 'Psychiatric comorbidity' above.)

- Cannabis acutely impairs attention, concentration, episodic memory, associative learning, and motor coordination in a dose-dependent manner. Long-term cannabis use is associated with impairment of verbal memory and cognitive processing speed, which resolves after at least a month of abstinence. (See 'Neuropsychological effects' above.)

- Substantial evidence suggests that chronic cannabis use, especially during adolescence, is associated with later development of schizophrenia. The mechanisms responsible for the association between cannabis use and schizophrenia remain unclear. Some experts believe that early cannabis use is a causal factor in developing schizophrenia. (See 'Psychotic disorders' above.)

- Chronic cannabis use has not been found to be associated with serious or chronic medical conditions or death from medical conditions. Cannabis use is associated with injury and death from motor vehicle accidents. (See 'Adverse effects of cannabis use' above.)

- Cannabis smoking is associated with acute, transient respiratory symptoms, but chronic use is not associated with impaired lung function. (See 'Pulmonary' above.)
- Cannabis smoking acutely increases sympathetic activity and myocardial oxygen demand, and is associated with a small increased risk of myocardial infarction and stroke. (See 'Cardiovascular' above.)
- Cannabis use is also associated with periodontal disease, hyperemesis syndrome, and a lower sperm count. Hyperemesis syndrome is a relatively rare condition involving episodic severe nausea and vomiting and abdominal pain. Frequent cannabis smoking has been associated with a lower sperm count; the clinical significance of this finding is unknown. (See 'Dental' above and 'Hyperemesis syndrome' above and 'Reproductive' above.)

ACKNOWLEDGMENTS

The editorial staff at UpToDate would like to acknowledge John Bailey, MD, Robert DuPont, MD, and Scott Teitelbaum, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. United Nations Office on Drugs and Crime, World Drug Report 2018, Vienna 2018.
2. Swift W, Wong A, Li KM, et al. Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile. PLoS One 2013; 8:e70052.
3. Center for Behavioral Health Statistics and Quality, 2016 National Survey on Drug Use an d Health: Detailed Tables, Substance Abuse and Mental Health Services Administration, R ockville 2017.
4. Mauro PM, Carliner H, Brown QL, et al. Age Differences in Daily and Nondaily Cannabis Use in the United States, 2002-2014. J Stud Alcohol Drugs 2018; 79:423.
5. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. JAMA Psychiatry 2015; 72:1235.
6. Bechtold J, Simpson T, White HR, Pardini D. Chronic adolescent marijuana use as a risk

factor for physical and mental health problems in young adult men. Psychol Addict Behav 2015; 29:552.

7. Choi NG, DiNitto DM, Marti CN. Marijuana use among adults: Initiation, return to use, and continued use versus quitting over a one-year follow-up period. Drug Alcohol Depend 2018; 182:19.

8. Van Gundy K, Rebellon CJ. A Life-course Perspective on the "Gateway Hypothesis". J Health Soc Behav 2010; 51:244.

9. Vanyukov MM, Tarter RE, Kirillova GP, et al. Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. Drug Alcohol Depend 2012; 123 Suppl 1:S3.

10. Richmond-Rakerd LS, Slutske WS, Deutsch AR, et al. Progression in substance use initiation: A multilevel discordant monozygotic twin design. J Abnorm Psychol 2015; 124:596.

11. Degenhardt L, Dierker L, Chiu WT, et al. Evaluating the drug use "gateway" theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug Alcohol Depend 2010; 108:84.

12. Degenhardt L, Ferrari AJ, Calabria B, et al. The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. PLoS One 2013; 8:e76635.

13. Blanco C, Hasin DS, Wall MM, et al. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. JAMA Psychiatry 2016; 73:388.

14. Kerridge BT, Pickering R, Chou P, et al. DSM-5 cannabis use disorder in the National Epidemiologic Survey on Alcohol and Related Conditions-III: Gender-specific profiles. Addict Behav 2018; 76:52.

15. Weinberger AH, Platt J, Goodwin RD. Is cannabis use associated with an increased risk of onset and persistence of alcohol use disorders? A three-year prospective study among adults in the United States. Drug Alcohol Depend 2016; 161:363.

16. Hughes JR, Naud S, Budney AJ, et al. Attempts to stop or reduce daily cannabis use: An intensive natural history study. Psychol Addict Behav 2016; 30:389.

17. Agrawal A, Budney AJ, Lynskey MT. The co-occurring use and misuse of cannabis and tobacco: a review. Addiction 2012; 107:1221.

18. Hasin DS, Kerridge BT, Saha TD, et al. Prevalence and Correlates of DSM-5 Cannabis Use Disorder, 2012-2013: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Am J Psychiatry 2016; 173:588.

19. Weinberger AH, Platt J, Copeland J, Goodwin RD. Is Cannabis Use Associated With Increased Risk of Cigarette Smoking Initiation, Persistence, and Relapse? Longitudinal Data From a Representative Sample of US Adults. J Clin Psychiatry 2018; 79.

20. Hayley AC, Stough C, Downey LA. DSM-5 cannabis use disorder, substance use and DSM-5 specific substance-use disorders: Evaluating comorbidity in a population-based sample. Eur Neuropsychopharmacol 2017; 27:732.

21. Martins SS, Gorelick DA. Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the U.S. population. Drug Alcohol Depend 2011; 119:28.

22. Lev-Ran S, Imtiaz S, Rehm J, Le Foll B. Exploring the association between lifetime prevalence of mental illness and transition from substance use to substance use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Am J Addict 2013; 22:93.

23. Bally N, Zullino D, Aubry JM. Cannabis use and first manic episode. J Affect Disord 2014; 165:103.

24. Hunt GE, Malhi GS, Cleary M, et al. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: Systematic review and meta-analysis. J Affect Disord 2016; 206:321.

25. Hunt GE, Malhi GS, Cleary M, et al. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: Systematic review and meta-analysis. J Affect Disord 2016; 206:331.

26. Mammen G, Rueda S, Roerecke M, et al. Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. J Clin Psychiatry 2018; 79.

27. Gage SH, Hickman M, Zammit S. Association Between Cannabis and Psychosis: Epidemiologic Evidence. Biol Psychiatry 2016; 79:549.

28. van Winkel R, Kuepper R. Epidemiological, neurobiological, and genetic clues to the mechanisms linking cannabis use to risk for nonaffective psychosis. Annu Rev Clin Psychol 2014; 10:767.

29. Green B, Young R, Kavanagh D. Cannabis use and misuse prevalence among people with psychosis. Br J Psychiatry 2005; 187:306.

30. Koskinen J, Löhönen J, Koponen H, et al. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr Bull 2010; 36:1115.

31. Verweij KJ, Abdellaoui A, Nivard MG, et al. Short communication: Genetic association between schizophrenia and cannabis use. Drug Alcohol Depend 2017; 171:117.

32. Hjorthøj C, Østergaard ML, Benros ME, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. Lancet Psychiatry 2015; 2:801.

33. Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population--a meta-analysis of 31 studies. BMC Psychiatry 2014; 14:136.

34. Teesson M, Slade T, Swift W, et al. Prevalence, correlates and comorbidity of DSM-IV Cannabis Use and Cannabis Use Disorders in Australia. Aust N Z J Psychiatry 2012; 46:1182.

35. De Alwis D, Lynskey MT, Reiersen AM, Agrawal A. Attention-deficit/hyperactivity disorder subtypes and substance use and use disorders in NESARC. Addict Behav 2014; 39:1278.

36. Vogel T, Dom G, van de Glind G, et al. Is attention deficit/hyperactivity disorder among men associated with initiation or escalation of substance use at 15-month follow-up? A longitudinal study involving young Swiss men. Addiction 2016; 111:1867.

37. Compton WM, Conway KP, Stinson FS, et al. Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 2005; 66:677.

38. Gillespie NA, Aggen SH, Neale MC, et al. Associations between personality disorders and cannabis use and cannabis use disorder: a population-based twin study. Addiction 2018;

113:1488.

39. Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev 2010; 29:318.

40. Hostiuc S, Moldoveanu A, Negoi I, Drima E. The Association of Unfavorable Traffic Events and Cannabis Usage: A Meta-Analysis. Front Pharmacol 2018; 9:99.

41. Hostiuc S, Moldoveanu A, Negoi I, Drima E. Corrigendum: The Association of Unfavorable Traffic Events and Cannabis Usage: A Meta-Analysis. Front Pharmacol 2018; 9:564.

42. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction 2016; 111:1348.

43. Rogeberg O, Elvik R, White M. Correction to: 'The effects of cannabis intoxication on motor vehicle collision revisited and revised' (2016). Addiction 2018; 113:967.

44. Manrique-Garcia E, Ponce de Leon A, Dalman C, et al. Cannabis, Psychosis, and Mortality: A Cohort Study of 50,373 Swedish Men. Am J Psychiatry 2016; 173:790.

45. Kertesz SG, Pletcher MJ, Safford M, et al. Illicit drug use in young adults and subsequent decline in general health: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Drug Alcohol Depend 2007; 88:224.

46. Meier MH, Caspi A, Cerdá M, et al. Associations Between Cannabis Use and Physical Health Problems in Early Midlife: A Longitudinal Comparison of Persistent Cannabis vs Tobacco Users. JAMA Psychiatry 2016; 73:731.

47. Campbell CI, Bahorik AL, Kline-Simon AH, Satre DD. The role of marijuana use disorder in predicting emergency department and inpatient encounters: A retrospective cohort study. Drug Alcohol Depend 2017; 178:170.

48. Macleod J, Oakes R, Copello A, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. Lancet 2004; 363:1579.

49. Melchior M, Bolze C, Fombonne E, et al. Early cannabis initiation and educational attainment: is the association causal? Data from the French TEMPO study. Int J Epidemiol 2017; 46:1641.

50. Meier MH, Hill ML, Small PJ, Luthar SS. Associations of adolescent cannabis use with

academic performance and mental health: A longitudinal study of upper middle class youth. Drug Alcohol Depend 2015; 156:207.

51. Nader DA, Sanchez ZM. Effects of regular cannabis use on neurocognition, brain structure, and function: a systematic review of findings in adults. Am J Drug Alcohol Abuse 2018; 44:4.

52. Crane NA, Schuster RM, Fusar-Poli P, Gonzalez R. Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. Neuropsychol Rev 2013; 23:117.

53. Curran HV, Freeman TP, Mokrysz C, et al. Keep off the grass? Cannabis, cognition and addiction. Nat Rev Neurosci 2016; 17:293.

54. Volkow ND, Swanson JM, Evins AE, et al. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry 2016; 73:292.

55. Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp Clin Psychopharmacol 2012; 20:420.

56. Scott JC, Slomiak ST, Jones JD, et al. Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018; 75:585.

57. Schulte MH, Cousijn J, den Uyl TE, et al. Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. Clin Psychol Rev 2014; 34:531.

58. Auer R, Vittinghoff E, Yaffe K, et al. Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. JAMA Intern Med 2016; 176:352.

59. Starzer MSK, Nordentoft M, Hjorthøj C. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. Am J Psychiatry 2018; 175:343.

60. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007; 370:319.

61. Mustonen A, Niemelä S, Nordström T, et al. Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. Br J Psychiatry 2018; 212:227.

62. Schoeler T, Monk A, Sami MB, et al. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 2016; 3:215.

63. Schoeler T, Petros N, Di Forti M, et al. Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis: A Quasi-Experimental Investigation Within an Observational Study. JAMA Psychiatry 2016; 73:1173.

64. Lev-Ran S, Roerecke M, Le Foll B, et al. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med 2014; 44:797.

65. Pacek LR, Martins SS, Crum RM. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J Affect Disord 2013; 148:188.

66. Lynskey MT, Glowinski AL, Todorov AA, et al. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. Arch Gen Psychiatry 2004; 61:1026.

67. Gibbs M, Winsper C, Marwaha S, et al. Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord 2015; 171:39.

68. Feingold D, Weiser M, Rehm J, Lev-Ran S. The association between cannabis use and mood disorders: A longitudinal study. J Affect Disord 2015; 172:211.

69. Degenhardt L, Coffey C, Romaniuk H, et al. The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. Addiction 2013; 108:124.

70. Gates P, Jaffe A, Copeland J. Cannabis smoking and respiratory health: consideration of the literature. Respirology 2014; 19:655.

71. Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. Harm Reduct J 2005; 2:21.

72. Tetrault JM, Crothers K, Moore BA, et al. Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 2007; 167:221.

73. Ghasemiesfe M, Ravi D, Vali M, et al. Marijuana Use, Respiratory Symptoms, and

Pulmonary Function: A Systematic Review and Meta-analysis. Ann Intern Med 2018; 169:106.

74. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. N Engl J Med 1976; 294:125.

75. Kempker JA, Honig EG, Martin GS. The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National Health and Nutrition Examination Study. Ann Am Thorac Soc 2015; 12:135.

76. Loflin M, Earleywine M. No smoke, no fire: What the initial literature suggests regarding vapourized cannabis and respiratory risk. Can J Respir Ther 2015; 51:7.

77. Biehl JR, Burnham EL. Cannabis Smoking in 2015: A Concern for Lung Health? Chest 2015; 148:596.

78. Lee DC, Budney AJ, Brunette MF, et al. Outcomes from a computer-assisted intervention simultaneously targeting cannabis and tobacco use. Drug Alcohol Depend 2015; 155:134.

79. Huang YH, Zhang ZF, Tashkin DP, et al. An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol Biomarkers Prev 2015; 24:15.

80. Mehra R, Moore BA, Crothers K, et al. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med 2006; 166:1359.

81. Berthiller J, Lee YC, Boffetta P, et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev 2009; 18:1544.

82. Gurney J, Shaw C, Stanley J, et al. Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer 2015; 15:897.

83. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014; 113:187.

84. Pacher P, Steffens S, Haskó G, et al. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. Nat Rev Cardiol 2018; 15:151.

85. Gorelick DA, Heishman SJ, Preston KL, et al. The cannabinoid CB1 receptor antagonist rimonabant attenuates the hypotensive effect of smoked marijuana in male smokers. Am Heart J 2006; 151:754.e1.

86. Ravi D, Ghasemiesfe M, Korenstein D, et al. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. Ann Intern Med 2018; 168:187.

87. Mittleman MA, Lewis RA, Maclure M, et al. Triggering myocardial infarction by marijuana. Circulation 2001; 103:2805.

88. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J 2008; 155:465.

89. Frost L, Mostofsky E, Rosenbloom JI, et al. Marijuana use and long-term mortality among survivors of acute myocardial infarction. Am Heart J 2013; 165:170.

90. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. Stroke 2015; 46:852.

91. Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. J Neurol Sci 2016; 364:191.

92. Korantzopoulos P, Liu T, Papaioannides D, et al. Atrial fibrillation and marijuana smoking. Int J Clin Pract 2008; 62:308.

93. Korantzopoulos P. Marijuana smoking is associated with atrial fibrillation. Am J Cardiol 2014; 113:1085.

94. Schreck B, Wagneur N, Caillet P, et al. Cannabinoid hyperemesis syndrome: Review of the literature and of cases reported to the French addictovigilance network. Drug Alcohol Depend 2018; 182:27.

95. Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. J Med Toxicol 2017; 13:71.

96. Lapoint J, Meyer S, Yu CK, et al. Cannabinoid Hyperemesis Syndrome: Public Health Implications and a Novel Model Treatment Guideline. West J Emerg Med 2018; 19:380.

97. Richards JR. Cannabinoid Hyperemesis Syndrome: Pathophysiology and Treatment in the Emergency Department. J Emerg Med 2018; 54:354.

98. du Plessis SS, Agarwal A, Syriac A. Marijuana, phytocannabinoids, the endocannabinoid system, and male fertility. J Assist Reprod Genet 2015; 32:1575.

99. Gundersen TD, Jørgensen N, Andersson AM, et al. Association Between Use of Marijuana and Male Reproductive Hormones and Semen Quality: A Study Among 1,215 Healthy Young Men. Am J Epidemiol 2015; 182:473.

100. Ranganathan M, Braley G, Pittman B, et al. The effects of cannabinoids on serum cortisol and prolactin in humans. Psychopharmacology (Berl) 2009; 203:737.

101. Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol 2015; 213:761.

102. Gunn JK, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 2016; 6:e009986.

103. Conner SN, Carter EB, Tuuli MG, et al. Maternal marijuana use and neonatal morbidity. Am J Obstet Gynecol 2015; 213:422.e1.

104. Chabarria KC, Racusin DA, Antony KM, et al. Marijuana use and its effects in pregnancy. Am J Obstet Gynecol 2016; 215:506.e1.

105. Ko JY, Tong VT, Bombard JM, et al. Marijuana use during and after pregnancy and association of prenatal use on birth outcomes: A population-based study. Drug Alcohol Depend 2018; 187:72.

106. Metz TD, Allshouse AA, Hogue CJ, et al. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol 2017; 217:478.e1.

107. Baker T, Datta P, Rewers-Felkins K, et al. Transfer of Inhaled Cannabis Into Human Breast Milk. Obstet Gynecol 2018; 131:783.

108. Barnett E, Sussman S, Smith C, et al. Motivational Interviewing for adolescent substance use: a review of the literature. Addict Behav 2012; 37:1325.

109. Pateria P, de Boer B, MacQuillan G. Liver abnormalities in drug and substance abusers. Best Pract Res Clin Gastroenterol 2013; 27:577.

110. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology 2005; 42:63.

111. Hézode C, Zafrani ES, Roudot-Thoraval F, et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterology 2008; 134:432.

112. Cho CM, Hirsch R, Johnstone S. General and oral health implications of cannabis use. Aust Dent J 2005; 50:70.

113. Yazulla S. Endocannabinoids in the retina: from marijuana to neuroprotection. Prog Retin Eye Res 2008; 27:501.

114. Wikipedia. Legality of cannabis by country. https://en.wikipedia.org/wiki/Legality_of_cannabis_by_country (Accessed on August 12, 2018).

115. Wikipedia. Legality of cannabis by country. https://en.wikipedia.org/wiki/Legality_of_cannabis_by_country (Accessed on September 28, 2016).

116. National Conference of State Legislatures. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (Accessed on August 12, 2018).

117. National Conference of State Legislatures. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (Accessed on February 12, 2018).

118. Sachs J, McGlade E, Yurgelun-Todd D. Safety and Toxicology of Cannabinoids. Neurotherapeutics 2015; 12:735.

119. Lindsey WT, Stewart D, Childress D. Drug interactions between common illicit drugs and prescription therapies. Am J Drug Alcohol Abuse 2012; 38:334.

120. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev 2014; 46:86.

121. Hartman RL, Brown TL, Milavetz G, et al. Cannabis effects on driving lateral control with and without alcohol. Drug Alcohol Depend 2015; 154:25.

122. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). J Psychoactive Drugs 1998; 30:187.

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