REVIEW ARTICLE

Risks Associated With the Non-Medicinal Use of Cannabis

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SUMMARY

Background: Cannabis is the most commonly consumed illicit drug around the world; in Germany, about 4.5% of all adults use it each year. Intense cannabis use is associated with health risks. Evidence-based treatments are available for health problems caused by cannabis use.

Methods: Selective literature review based on a search of the PubMed database, with special emphasis on systematic reviews, meta-analyses, cohort studies, randomized controlled trials (RCTs), case–control studies, and treatment guidelines.

Results: The delta-9-tetrahydrocannabinol content of cannabis products is rising around the world as a result of plant breeding, while cannabidiol, in contrast, is often no longer detectable. Various medical conditions can arise acutely after cannabis use, depending on the user's age, dose, frequency, mode and situation of use, and individual disposition; these include panic attacks, psychotic symptoms, deficient attention, impaired concentration, motor incoordination, and nausea. In particular, intense use of high doses of cannabis over many years, and the initiation of cannabis use in adolescence, can be associated with substance dependence (DSM-5; ICD-10), specific withdrawal symptoms, cognitive impairment, affective disorders, psychosis, anxiety disorders, and physical disease outside the brain (mainly respiratory and cardiovascular conditions). At present, the most effective way to treat cannabis dependence involves a combination of motivational encouragement, cognitive behavioral therapy, and contingency management (level 1a evidence). For adolescents, family therapy is also recommended (level 1a evidence). No pharmacological treatments can be recommended to date, as evidence for their efficacy is lacking.

Conclusion: Further research is needed to elucidate the causal relationships between intense cannabis use and potential damage to physical and mental health. Health problems due to cannabis use can be effectively treated.

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Recreational use of cannabis has recently been legalized in several states of the USA. At the same time, scientific research is improving our knowledge of the therapeutic potential of medicinal drugs containing cannabis (1). In this light, it is not surprising that more and more patients are asking their doctors and other healthcare professionals for information about the health risks and medical benefits of cannabis.

Cannabis is the most widely consumed illegal substance across the world (2). According to United Nations estimates, 125 to 227 million people consume cannabis worldwide (2). A recent national epidemiological survey of addiction in Germany showed that 4.5% of the adult population had used cannabis in the previous year (3). Consumption is particularly common among 18- to 20-year-olds (12-month prevalence: 16.2%). An estimated 1% of the population of the European Union (12 million persons) are daily users of cannabis (4). Cannabis is mostly consumed in the form of marijuana (dried flowers and leaves) or hashish (the delta-9-tetrahydrocannabinol [THC]-containing resin of the inflorescences) (4). Oil containing THC is also sometimes ingested in foodstuffs. Police reports indicate that cannabis plants are increasingly being grown in European countries and less cannabis is being imported (4).

The content of THC, the principal psychotropic substance in cannabis, has increased sharply in the past decade (4). Another active ingredient, cannabidiol (CBD), is no longer present in many strains (e1, e2). The anxiolytic, antipsychotic, anti-inflammatory, antiemetic, and neuroprotective actions that are ascribed to CBD (e3) may compensate the adverse effects of THC (5). The consumption of cannabis products high in THC and low in CBD is thought to cause undesired effects in persons with a corresponding predisposition (e4). The total number of addiction treatments owing to cannabis consumption is increasing in Europe and the USA (2, 4, e5).

Goal

The aim of this review is to summarize the current state of knowledge with regard to the potential physical and mental adverse effects of intensive recreational use of cannabis and outline the options for treatment of health impairments resulting from cannabis consumption.

BOX

Acute cannabinoid intoxication

Dysfunctional behavior or distorted perceptions can be recognized by the presence of at least one of the following:

1. Euphoria and disinhibition
2. Anxiety or agitation
3. Mistrust or paranoid delusions*
4. Altered sense of time (a feeling that time is passing extremely slowly or a feeling of racing thoughts)
5. Limited power of judgment
6. Attention disorder
7. Impaired reaction time
8. Acoustic, optic, or tactile illusions
9. Hallucinations without lack of orientation
10. Depersonalization
11. Derealization
12. Impaired personal performance

Moreover, at least one of the following signs may be present:
Appetite loss, dry mouth, conjunctival injection, tachycardia

*May persist for as long as a week; the other symptoms subside within a few hours of cannabis consumption

Method

Selective surveys of clinical data were carried out in PubMed. This narrative review included systematic reviews, meta-analyses, narrative reviews, randomized controlled trials (RCTs), cohort studies, case–control studies, guidelines, and reports from public institutions *(eTable 1)*. The evidence was evaluated according to the guidelines of the Oxford Centre for Evidence-Based Medicine (6) *(eTable 2)*.

Disorders associated with cannabinoids

Acute intoxication, harmful and addictive use of cannabis

When cannabis is smoked, THC passes from the lungs into the bloodstream, reaching the internal organs and the brain within minutes. In the brain, THC exerts its effect principally via the CB1 cannabinoid receptors, located mainly in regions of the cerebrum associated with locomotion, learning, memory, and the reward system. The smoking of herbal cannabis can lead to acute intoxication (7–9) *(Box)*. The effect depends on the composition of the cannabis preparation, the dose, the frequency and form of intake, and the circumstances, as well as the user's individual disposition and experience of cannabis consumption (7, e6). When the pharmacological effect has worn off, the symptoms disappear (10, 11). The cannabis metabolite THC-COOH can be demonstrated in urine for 2 to 6 weeks after last use (e7).

Further cannabinoid-associated disorders are defined in DSM-5 (e8) and in ICD-10 (e9). While ICD-10 distinguishes between harmful and addictive use of cannabis, in DSM-5 the severity of health impairment can be classified in three segments (mild, moderate, severe) of a continuum. Both classifications also describe a specific cannabis withdrawal syndrome, which can occur within 24 h of consumption (10, 11, e8, e9). For cannabis withdrawal syndrome to be diagnosed, at least two mental symptoms (e.g., irritability, restlessness, anxiety, depression, aggressiveness, loss of appetite, sleep disturbances) and at least one vegetative symptom (e.g., pain, shivering, sweating, elevated body temperature, chills) must be present. The symptoms are at their most intensive in the first week and can persist for as long as a month. Clinically, withdrawal from cannabis is usually uncomplicated (10, 11, e10, e11).

In the German general population, around 1% of adults fulfill the DSM-IV criteria of cannabis abuse (0.5%) or cannabis addiction (0.5%) (3). For comparison, higher rates of prevalence are found for alcohol abuse and dependence (3.1% and 3.4% respectively) and for nicotine addiction (10.8%) (3). Dependence on other illegal substances, e.g., amphetamines (0.2%) or cocaine (0.3%) is less common (3). Overall, around 9% of all cannabis consumers become dependent on cannabis at some time during their lives (e12). This rate rises to 17% for those who started using cannabis in adolescence (e13) and 25 to 50% if cannabinoids are consumed daily (e14). As yet there are no data for Germany on the prevalence of health impairments as a result of cannabis use according to DSM-5.

The amotivational syndrome, characterized by reduced motivation to perform the activities of daily living, disorders of concentration and attention, and blunting of affect (e15), has been insufficiently investigated to date and empirical proof is lacking (e16). In regular consumers of cannabis this pattern of symptoms may be produced by a disturbance of focused attention (e17) or a prolonged intoxication effect (12).

Cognitive consequences

A meta-analysis (13) (evidence level: 1a) reported mild negative effects on learning capacity (effect strength [ES] = –0.24, 99% confidence interval [CI] –0.39 to –0.02) and memory (ES = –0.27, 99% CI –0.49 to –0.04) in non-abstinent habitual consumers of cannabis. These effects were also demonstrable after at least 24 h abstinence. Attentiveness and reaction time were not impaired. A more recent meta-analysis (14) (evidence level: 1a) also shows low-level global cognitive impairments in acute cannabis consumption (global ES = –0.29, 95% CI –0.46 to –0.12). Compared with abstinent persons, non-abstinent cannabis users exhibited mild impairments in the following areas:

- Abstract thinking or executive performance (ES = –0.21, 95% CI –0.38 to –0.05)
- Attention (ES = –0.36, 95% CI –0.56 to –0.16)
- Retentiveness (ES = –0.25, 95% CI –0.47 to –0.07)

TABLE

Somatic consequences of non-medicinal cannabis use

Region and symptoms or consequences	Study type, evidence level, statistical risk (reference)
Mouth and throat	
Gingival proliferation, inflammation of oral mucosa (stomatitis) or uvula (uvulitis)	Case reports (16), no statistical analysis
Respiratory tract	
Irritation of the respiratory system, damage to the bronchioles, and chronic bronchitis	Meta-analysis (17); (review [e24]; cohort study [e25]): association between cannabis consumption and cough (OR = 2.00; 95% CI: 1.32–3.01) (evidence level: 1b)
Dyspnea, hoarseness, chronic-obstructive lung disease, or pharyngitis with combined consumption of cannabis and tobacco; the findings for tobacco and cannabis inhalation do not go in the same direction; several cohort studies with differing results	Systematic review (e24, e26) (evidence level: 2a); case report (e27)
Life-threatening respiratory problems (experimentally unproved; in contrast, review points to a bronchodilatory effect)	Systematic reviews (e28, e29) (evidence level: 2a)
Emphysema: effects of cannabis controversial	Systematic reviews (17, e29, e30) (evidence level: 2a)
Gastrointestinal tract	
Worsening of hepatic steatosis (particularly in hepatitis C) with potential steatogenic and fibrotic effects	Systematic review (18), cohort study (e31) (evidence level: 2b); in cannabis users (N = 270) daily cannabis consumption predicted more rapid progression of hepatic fibrosis (>0.15) (OR = 3.6; 95% CI: 1.5–7.5).
Cannabis-hyperemesis syndrome: repeated episodes of nausea and vomiting	Case series (e32), review of these case reports (e33) (evidence level: 4)
Cardiovascular system	
Tachycardia, increased BP, arrhythmias up to and including atrial fibrillation	Reviews (19, 20), case reports, reviews of the cases (e.g., e34, e35; evidence level: 4)
Deaths due to cerebral and cardiac ischemia	Case reports (e36, e37), case–control study: increased risk of MI up to 60 min after cannabis consumption (OR = 4.8; 95% CI: 2.4–9.5) (e38) (evidence level: 1b); part of prospective study (e39) (evidence level: 1b): in n = 1913 patients (follow-up time: 3.8 years) there was a dose-dependent relationship between cannabis consumption and mortality after MI: cannabis consumption (<1 x per week) was connected with an HR of 2.5 (95% CI: 0.9–7.3), and the HR for weekly consumption was 4.2 (95% CI: 1.2–14.3). The age- and sex-adjusted HR for persons who had ever used cannabis was 1.9 (95% CI: 0.6–6.3) for cardiovascular and 4.9 (95% CI: 1.6–14.7) for other causes of death
Effects on skin and mucosae	
Conjunctivitis, inflammation of posterior palate	Individual cases, review (18) (evidence level: 4)
Isolated cases: urticaria, pruritus, excoriative prurigo, type-1 allergies (asthmatic and anaphylactic reactions)	Case reports (23), review (18) (evidence level: 4)
Consequences for hormone metabolism	
Elevated visceral fat deposition and insulin resistance	Case–control cohort study (e40): cannabis users had a higher proportion of abdominal fat, while other parameters (glucose, insulin, cholesterol, LDL, triglycerides) showed no difference. Adipocyte resistance to insulin and oral glucose tolerance results were lower ($p<0.05$) (evidence level: 2b)

Region and symptoms or consequences	Study type, evidence level, statistical risk (reference)
Comatose states	
Individual cases of comatose states in children who had ingested cannabis	Case reports (e41) (evidence level: 4)
Overall mortality	
Some unfavorable effects of cannabis use (e.g., increased risk of road traffic accidents and tumors) can influence overall mortality	Systematic review of studies (12, 21, 22), some of them with low case numbers; no epidemiological findings (evidence level: 3a)
Consequences for the reproduction system	
In women: adverse effects on frequency of menstrual cycle, oogenesis ("maturation of oocytes"), implantation of embryo, development of brain in embryo, increased risk of birth complications, decreased birth weight of child	Systematic reviews (24, 25), cohort studies (e42, e43) (evidence level: 2a): low birth weight (OR = 1.7; 95% CI: 1.3–2.2), preterm births (OR = 1.5; 95% CI: 1.1–1.9), reduced gestation (OR = 2,2; 95% CI: 1.8–2.7), admission to neonatal intensive care unit (OR = 2.0; 95% CI: 1.7–2.4)
In children of women exposed to cannabis during pregnancy: increased impulsiveness, impairment of learning, memory, and executive functions, particularly following exposure in the third trimester	Systematic review without statistical analysis, cohort study (e44) (evidence level: 3a)
In men: ejaculation problems, decreased sperm count, libido loss or impotence	Systematic review (25) (evidence level: 3a)
Tumor diseases	
Nasopharyngeal tumors (independent of tobacco consumption)	Case–control cohort study (e45) (evidence level: 2b): for intensive cannabis consumption (>2000 x in total) the OR was 2.62 (95% CI: 1.00–6.86) after statistical control for tobacco consumption
Increased risk of lung tumors, although simultaneous tobacco consumption is a potential confounding factor	Cohort study (e46) (evidence level: 2b): in cannabis users the OR for lung tumors was 2.4 after statistical adjustment for various factors, e.g., tobacco consumption (95% CI: 1.6–3.8). If the amount of tobacco consumed is taken into account (cigarettes/d), the risk (compared with non-users of cannabis) rises to 10,9 (95% CI: 6.0–19.7). Case–control study (e47) (evidence level: 2b): the risk of a lung tumor rose by 8% with every year of cannabis use (95% CI: 2.00–15.00), after controlling for tobacco consumption. The risk of a lung tumor rose by 7% with every year of tobacco consumption (95% CI: 5–9) after controlling for cannabis use.
Tumors of head and neck	Systematic reviews (18), cohort study (e48) (evidence level: 2b): cannabis smoke is carcinogenic and cannabis use can cause tumors of the upper respiratory tract, the GIT, the lungs, and the bladder; cohort case–control study (e48): n = 75 patients and n = 319 controls; cannabis consumption (even at a high level) was not associated with an increased risk of head and neck tumors (after adjusting for potential confounding variables) (evidence level: 2b).
Effects on the immune system	
Immunosuppressive effect in a number of autoimmune diseases or inflammatory processes (e.g., multiple sclerosis, atherosclerosis, asthma, rheumatic, gastrointestinal, and liver diseases)	Basic science–oriented review without statistical analysis (26) (evidence level: 4)

Evidence level according to Oxford CEBM classification; CI: confidence interval of OR; OR: odds ratio; LDL: low-density lipoprotein; HR: hazard ratio; MI: myocardial infarction; GIT: gastrointestinal tract; BP: blood pressure; d: day

- Learning (ES = –0.35, 95% CI –0.55 to –0.15)
- Psychomotor functions (ES = –0.34, 95% CI –0.57 to –0.11)

After abstinence for at least a month, these differences were no longer detectable (ES = –0.12, 95% CI –0.32 to 0.07). The effects may be reversible in adults. Other studies show that especially in consumers who began using cannabis in adolescence, cognitive impairments may still be present after 4 weeks' abstinence. Persisting mild to moderate deficits were found in the following areas:

- Psychomotor velocity (β = –0.32, ES = 0.09, $p<0.05$)
- Attention (β = –0.33, ES = 0.06, $p<0.04$)
- Memory (β = –0.34, ES = 0.06, $p<0.04$)
- Planning ability (β = –0.53, ES = 0.30, $p<0.001$) (e18, e19).

A long-term study in New Zealand yields evidence of an unfavorable influence of regular cannabis consumption in adolescence on intelligence in later life (e20) (evidence level: 1b). In persons who had regularly used cannabis before reaching the age of majority, the mean intelligence quotient at the age of 38 years was eight points lower than at the age of 13 years. These effects were not evident in probands whose long-term consumption of cannabis had begun when they were already adult. The study excluded any possibility that the effects were due to acute cannabis intoxication, addiction to other substances, schizophrenia, or a lower level of education. These findings indicate elevated vulnerability to neurocognitive impairments among adolescents who regularly use cannabis, with questionable reversibility (e21) (evidence level: 2a).

These results are complementary to age-dependent structural changes in the gray and white matter of the brain. In a study of young cannabis users (e22), the decrease in volume of the right amygdala and the hippocampus on both sides of the brain correlated with the severity of dependence on cannabis ($R^2 = 0.54$) and the amount of cannabis consumed weekly ($R^2 = 0.43$). There is also evidence of changes in the axonal fiber pathways (e23) (evidence level: 1b): cannabis users showed a loss of axonal integrity (reduction of fiber pathways by up to 84%) in the area of the right fimbria and bilaterally in a region of the corpus callosum, as well as a decrease of 88% in the fiber bundle from the splenium of the corpus callosum to the right precuneus. In both cases the age at which regular cannabis use had begun correlated significantly with radial ($t = 2.5$, $p = 0.02$ versus $t = 4.0$, $p = 0.002$) and axial ($t = 1.9$, $p = 0.06$ versus $t = 3.2$, $p = 0.002$) density.

Influence on education

A meta-analysis of three prospective cohort studies with a total of over 6000 participants suggests a connection between early cannabis use (before the age of 15 years) and an increased risk of leaving school early or attaining a lower level of education (15) (evidence level: 1a).

Somatic risks

The *Table* provides an overview of the possible somatic consequences of acute and chronic use of cannabis.

Mental comorbidity

Affective disorders, suicidality, anxiety disorders: Between 50% and 90% of cannabis-dependent persons are diagnosed with a further mental disorder or health impairment from consumption of alcohol or other substances at some point in their lives (e49). Some studies suggest a positive relationship between cannabis consumption and bipolar disorders (27, 28, e50–e52) or between augmented manic symptoms and cannabis use (e52, e53). The relationship of cannabis use with depression is less clear. A few longitudinal studies (29) have found a slightly increased risk for the development of unipolar depression (odds ratio [OR] 1.17–1.62) (evidence level: 2a), particularly in persons with early onset of cannabis use and consumption of large amounts of cannabis, while others have not (e54). Especially in adolescents and young adults who use cannabis, increased occurrence of suicidal thoughts has been described (OR 1.80–4.55) (30, e55) (evidence level: 3a). The data are heterogeneous, so no confident statement can be made with regard to the extent of the risk for suicidality (31), and no consistent causal link has been found (31, 32, e56, e57).

Chronic intoxication, withdrawal symptoms, additional addictions, adaptational or personality disorders, and—particularly in adolescents—disorders of emotional development and social behavior are assumed to be further additional factors in the development of depression and suicidality in cannabis users (30, 33, e54, e58). In bipolar disorders, above all, accompanying cannabis use is associated with a less favorable course, poorer adherence, elevated risk of suicide, and decreased response to lithium (e59). Treatment of the affective disorder may lead to reduction of the accompanying cannabis use (34). Treatment of the cannabis dependency is also probably advantageous for the course of the affective disorder. To date this assumption is based exclusively on clinical observation, with no empirical support. More evidence exists for a connection between cannabis use and anxiety disorders, particularly panic disorders. The risk of an anxiety disorder was significantly elevated in persons who consumed cannabis weekly up to the age of 29 years (OR 3.2, 95% CI 1.1 to 9.2) (e60) (evidence level: 2b). Furthermore, epidemiological investigations have revealed a 2.5– to 6-fold risk of anxiety disorders in those dependent on cannabis (e61).

Psychoses: Early, regular, long-term, and heavy consumption of cannabis, in association with other stressors such as experience of violence and abuse in childhood or psychoses in the original family, has been connected with increased risk of psychotic disorders (30, 35, e62–e64). The pooled data in a meta-analysis quantified the increased risk of psychoses after frequent cannabis consumption with an OR of 2.09 (95% CI 1.54 to 2.84) (evidence level: 2a). In the presence of a

certain genetic pattern, as shown in an animal experiment, cannabinoids and stress can favor the development of a psychosis (36–38).

Consumption of cannabis and other substances: Various studies have demonstrated a link between early, regular cannabis use and continuing consumption of other illegal drugs or alcohol (33). However, there are no empirical data to support the gateway hypothesis, i.e., the notion that use of cannabis leads directly to use of other substances (e65, e66).

Secondary cannabis consumption: Many consumers may use cannabis to alleviate troublesome psychic or physical symptoms (e67). This has been reported for patients with posttraumatic stress syndrome (e68, e69) or chronic pain (e70). Cannabis is also smoked by some persons with schizophrenic psychoses, perhaps because of the antipsychotic action of CBD (e3), and increases the risk of more and longer-lasting paranoid syndromes (e71) and intoxication phenomena (e72, e73) in 40% of user.

Further research is required to clarify the causal nature of the links between cannabis consumption patterns and adverse events. In future studies particular care should be taken to control for confounding variables.

Treatment

In Europe, cannabis consumption is the most common reason for a first drug treatment due to use of an illegal substance (4). The number of first treatments rose from 45 000 to 61 000 between 2006 and 2011 and remained stable at 59 000 in 2012.

In Germany, patients with cannabis-related disorders are usually treated as outpatients, e.g., in dependency outreach services, addiction clinics, or specialist centers. Uncomplicated withdrawal is also treated on an outpatient basis.

Qualified inpatient treatment is indicated in the case of:

- Complicated course of intoxication
- Severe withdrawal syndrome and/or severe aftereffects
- High danger of relapse
- Comorbid mental disorders (39)

The treatment is divided into acute and post-acute phases. The acute phase (duration 2 to 4 weeks; in adolescents, 4 to 12 weeks) can include physical detoxication, diagnosis, and treatment of withdrawal symptoms, as well as detection and possibly treatment of any coexisting disorders. In addition to intensive counseling and structuring of daily activities, accompanied by psychopharmaceutical support if indicated, the patient is encouraged to begin abstinence-stabilizing treatment in cases where treatment motivation is lacking in the presence of impairment of psychosocial function (i.e., difficulties in organizing the daily routine and structuring activities).

More complicated episodes of intoxication may be characterized by panic attacks or by psychotic or delirious symptoms. In these cases it is helpful to talk to the patient and, if applicable, to administer antipsychotics (preferably atypical) and/or sedatives for a limited period of time (39).

Rehabilitational postacute treatment (duration: 6 to 9 months) serves to ensure abstinence, prevent relapse, stabilize the patient's mental, social, and occupational situation, and treat any comorbidity. In adolescents, attention needs to be paid to educational support, reintegration into school, and the situation regarding family and residence.

Psychotherapeutic interventions

A meta-analysis (40) and several systematic reviews of RCTs (evidence level: 1a) (e74–e76) demonstrate that short interventions (6 to 12 sessions) with combinations of measures to promote motivation, cognitive-behavioral therapy, and contingency management (learning via systematic rewards) have the greatest effect. Furthermore, family therapy interventions have proved effective in children and adolescents (evidence level: 1a) (e74). The abstinence rates lie between 10 and 50% (40, e77–e81). Around half these patients relapse within a year (40, e77–e81).

More successful than the attempt to achieve abstinence from cannabis are measures to reduce the frequency and intensity of consumption and ameliorate the psychosocial problems and other health impairments associated with cannabis use (e75).

Internet- and computer-based interventions are effective in reaching young people at the time when their use of cannabis is becoming problematic and in achieving a reduction in consumption (e82).

Pharmacotherapy

No medications are yet licensed for the treatment of cannabis-related disorders. Drug treatment is necessary only in the presence of severe withdrawal symptoms (e.g., with gabapentin, benzodiazepines, sedative antipsychotics), psychoses (with antipsychotics), or panic attacks (with benzodiazepines, sedative antipsychotics) (39). Two RCTs investigated treatment of cannabis withdrawal with synthetic THC (dronabinol) or cannabis extracts (e.g., nabiximols). These medications were superior to placebo with regard to compliance and amelioration of withdrawal symptoms, but not for reduction of consumption (e83, e84).

Buspirone and the CB1-receptor antagonist rimonabant have also been shown to be effective (e85); however, rimonabant was taken off the market in 2008 because of its depressive action.

Summary

The use of cannabis is widespread, extending from experimental consumption to dependence. Empirical data have now clearly shown that starting early in life and regularly using high amounts of cannabis for a long period of time increases the risk of various mental and physical disorders and endangers age-appropriate development. Because many studies have failed to control properly for confounding variables, it still cannot be

stated beyond doubt that there is a causal connection between cannabis consumption patterns and cognitive damage or the development of comorbid psychic or somatic disorders. The worldwide increase in the THC content of cannabis may increase the health risks, particularly for adolescent users. Further research is required to determine why some people are more affected than others by the unfavorable consequences.

KEY MESSAGES

- Cannabis is the most frequently consumed illegal drug in Germany and the most common reason for a first drug treatment.
- Nine percent of all cannabis users, 17% of those who begin using cannabis in adolescence, and 25 to 50% of persons who consume cannabis daily become dependent.
- Starting in adolescence and high-dose, long-term, and regular use of cannabis increase the risk of various disorders of mental and physical health and endanger age-appropriate development. Other specific risk factors are currently being investigated.
- The worldwide continuing increase in the content of delta-9-tetrahydrocannabinol (THC) —the principal psychoactive ingredient—in cannabis products may be associated with greater risks to health, particularly for adolescent users.
- Combinations of measures to increase motivation, cognitive-behavioral therapy, and contingency management (specific rewards), together with family therapy interventions in adolescents, are currently the most effective approaches to the treatment of cannabis dependency.

Conflict of interest statement

Dr. Hoch has received honoraria from the publisher Hogrefe for authorship or co-authorship of a publication on a subject related to the topic of this article.

Prof. Bonnet has received honoraria for lectures and training courses from Actelion, Bristol-Myers Squibb, Esparma, GlaxoSmithKline, Lilly, Lundbeck, Merz, Otsuka, and Servier. He has received third-party funding for the conduct of a clinical application study from Servier. He has received personal honoraria for writing two CME articles published in the journal *Info Neurologie und Psychiatrie*—one on the addictive potential of propofol and one on the diagnosis and treatment of cannabis withdrawal syndrome.

Prof. Thomasius, Dr. Ganzer, Prof. Havemann-Reinecke, and Prof. Preuss declare that no conflict of interest exists.

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REVIEW ARTICLE

Risks Associated With the Non-Medicinal Use of Cannabis

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eTABLE 1

Literature survey

Search terms	
Cannabis, thc, marijuana, marihuana, hashish, mental health, physical health, comorbidity, neuro*, cognit*, assess*, abilit*, affect*, process*, function* or impair, residual, long-term, abstinen*, abstain*, lasting, non-acute, non-intox*, persist, consequences, treatment, therapy, effectiveness, efficacy	
Study type	**n**
Meta-analyses	9
Systematic reviews	7
Narrative reviews	44
Randomized controlled trials	6
Cohort studies	34
Case–control studies	9
Guidelines	1
Reports from public or publicly supported institutions: – United Nations Office on Drugs and Crime, World Drug Report 2014 (United Nations publication, sales no. E.14.XI.7) – European Monitoring Centre for Drugs and Drug Addiction: Drug Availability in Europe (EMCDDA). In: European Drug Report 2014: Trends and Developments. Luxembourg: Publications Office of the European Union 2014 – United States Department of Justice, Drug Enforcement Administration, National Drug Threat Assessment Summary 2013 (November 2013); 12	3

eTABLE 2

Evidence level according to Oxford Centre for Evidence-based Medicine (CEBM) (May 2001)*[1]

Level	Therapy/prevention, etiology/harm	Differential diagnosis/symptom prevalence study
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of prospective cohort studies
1b	Individual RCT (with narrow confidence interval)	Prospective cohort study with good follow-up
1c	All or none*[2]	All or none case series
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of 2b and better studies
2b	Individual cohort study (including low quality RCT)	Retrospective cohort study, or study with poor follow-up
2c	"Outcomes" research; ecological studies	Ecological studies
3a	SR (with homogeneity) of case–control studies	Systematic review (with homogeneity) of 3b and better studies
3b	Individual case–control study	Non-consecutive cohort study, or very limited population
4	Case series (and poor-quality cohort and case–control studies)	Case series or superseded reference standards
5	Expert opinion without critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without critical appraisal, or based on physiology, bench research or "first principles"

*[1] Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
*[2] Met when all patients died before a certain intervention became available, but some now survive on it; or when some patients died before the intervention became available, but none now die on it.
SR, systematic review; RCT, randomized controlled trial