Drug Abuse Management - Withdrawal

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01

Alcohol

Alcohol Withdrawal Timeline

Onset

Within 6-8 hours of cessation / reduction in prolonged use

Peak

Within 2-3 days, necessitating vigilant clinical monitoring

Resolution

Begins by day 4-5, indicating progression towards remission

Types of Withdrawal Manifestations

Simple

Tremors, insomnia, anxiety, and autonomic hyperactivity

Complicated

Seizures and delirium tremens

Assessment of Withdrawal

History

Physical and Mental Status Examination

Comorbidities

Past Withdrawal Complications

Types of Management

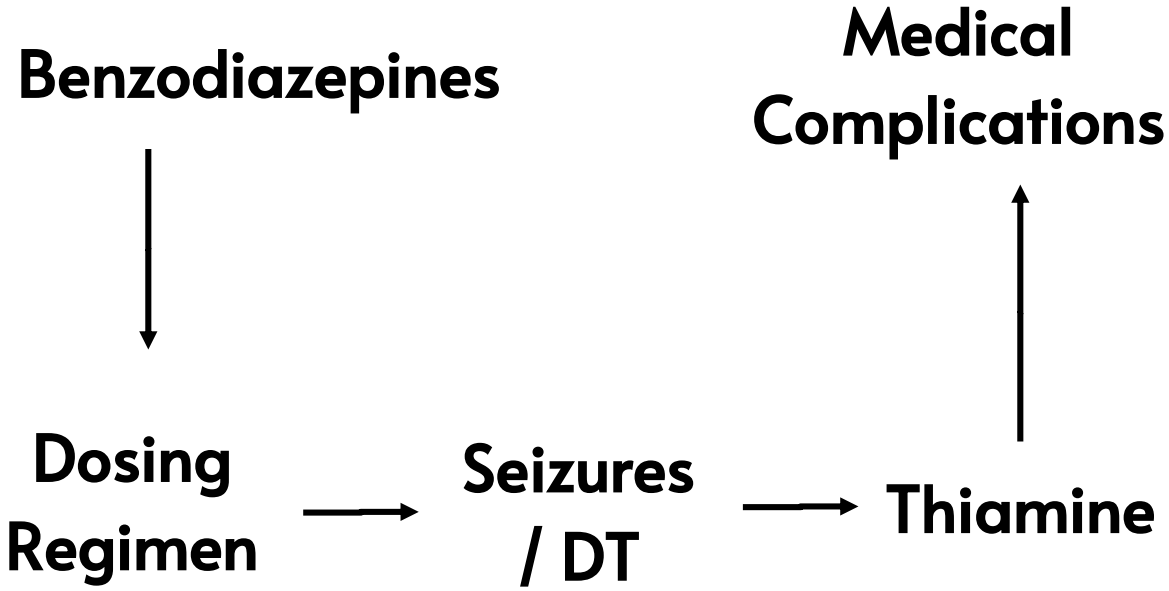
Pharmacological

Medical management of withdrawal, and complications

Non-pharmacological

Supportive measures and therapy

Pharmacological Management



Benzodiazepines

- Cross tolerant with alcohol (**mainstay**)
- **Long acting** ones preferred e.g., chlordiazepoxide, diazepam
- **Short acting** reserved for special cases e.g., lorazepam, oxazepam

Dosing Regimen

- **Fixed dose:** Standard schedule, taper 20% daily
- **Symptom-triggered:** Based on CIWA-Ar scores
- **Front-loading:** High initial dose followed by taper

Seizures and Delirium Tremens

- Intravenous **diazepam** or **lorazepam** for acute control of withdrawal seizures and delirium tremens.
  - Delirium tremens has high morbidity and mortality, may require liaison with general medicine
  - No long term anti-epilectic medications required for withdrawal seizures

Thiamine and Hypo-gycemia

Image Credit: *AI generated*

Medical Comorbidities

- Chronic Liver Disease
- Cirrhosis
- Portal Hypertension
- Hemoptysis and Ascites
- Hepatic Encephalopathy

Non-pharmacological Management

Group Therapy & Family Support

Non-pharmacological Management

Peer Support & Lifestyle Modification

Key Points

- Alcohol withdrawal can be **life-threatening** → prompt recognition is vital
- **Benzodiazepines** are first-line; choose regimen based on setting
- Always give **parenteral thiamine** before glucose
- **Non-pharmacological** interventions enhance outcomes
- **MET and family involvement** key in long-term abstinence

02

Opioids

Opioid Withdrawal Timeline

Onset	Peak	Resolution
Within 6-24 hours	Within 2-4 days	Within 4-20 days

Assessment of Withdrawal

History

Physical and Mental Status Examination

Comorbidities

Past Withdrawal Complications

Withdrawal Symptoms

Early-phase

Yawning, lacrimation, rhinorrhea, perspiration

Mid-phase

Cramps, vomiting, diarrhoea, piloerection, mydriasis, muscle aches

Later-phase

Craving

Conditioned Withdrawal

Types of Management

Pharmacological

Medical management of withdrawal, and complications

Non-pharmacological

Supportive measures and therapy

Pharmacological Management

Opioids

Buprenorphine (preferred) 2-4 mg upto 10-12 mg, OST

Non-opioids

Clonidine (0.1-0.2 mg every 4 hours)
NSAIDs, loperamide, benzodiazepines, etc

Medical Comorbidities

- Dehydration and electrolyte disturbances
- HIV, Hepatitis B, TB, etc

Non-pharmacological Management

Individual Therapy

Non-pharmacological Management

Group Therapy & Family Support

Non-pharmacological Management

Peer Support & Lifestyle Modification

Key Points

- Opioid withdrawal is uncomfortable but manageable
- **Buprenorphine** is preferred pharmacological agent
- **Clonidine** can be used when opioids not available
- Non-pharmacological support essential
- Use withdrawal period to initiate **long-term treatment planning (eg OST)**

03

Cannabis

Cannabis Withdrawal

Onset

Within 24-48 hours

Symptoms

Restlessnes,
Irritability,
Anxiety,
Insomnia,
Dreams,
Tremors

Severity

Mild

No medical complications

Types of Management

Pharmacological

Medical management of withdrawal, and complications

Non-pharmacological

Supportive measures and therapy

Pharmacological Management

Avoid long term sedatives

Benzodiazepines, melatonin, etc

Symptom-based Approach

Non-pharmacological Management

Individual Therapy

Non-pharmacological Management

Group Therapy & Family Support

Non-pharmacological Management

Peer Support & Lifestyle Modification

Key Points

- Cannabis withdrawal is **mild and self-limiting**
- No need for specific detox
- Treat insomnia and anxiety **symptomatically**
- Educate about **non-life-threatening** nature
- Use withdrawal as window for behaviour change

04

Nicotine

Nicotine Withdrawal Timeline

Onset	Peak	Resolution
Within 4-6 hours	Within 2-3 days	Within 2-4 weeks

Withdrawal Symptoms

Difficulty concentrating

Irritability, Anxiety, Restlessness

Craving

Decreased sleep, Increased appetite

Types of Management

Pharmacological

Medical management of withdrawal, and complications

Non-pharmacological

Supportive measures and therapy

Pharmacological Management

Nicotine Replacement Therapy

2-4mg gums OR 21mg patch

Other Medications

Bupropion 150-300mg; Varenicline 1mg To be started at least 1 week prior to quit date

Non-pharmacological Management

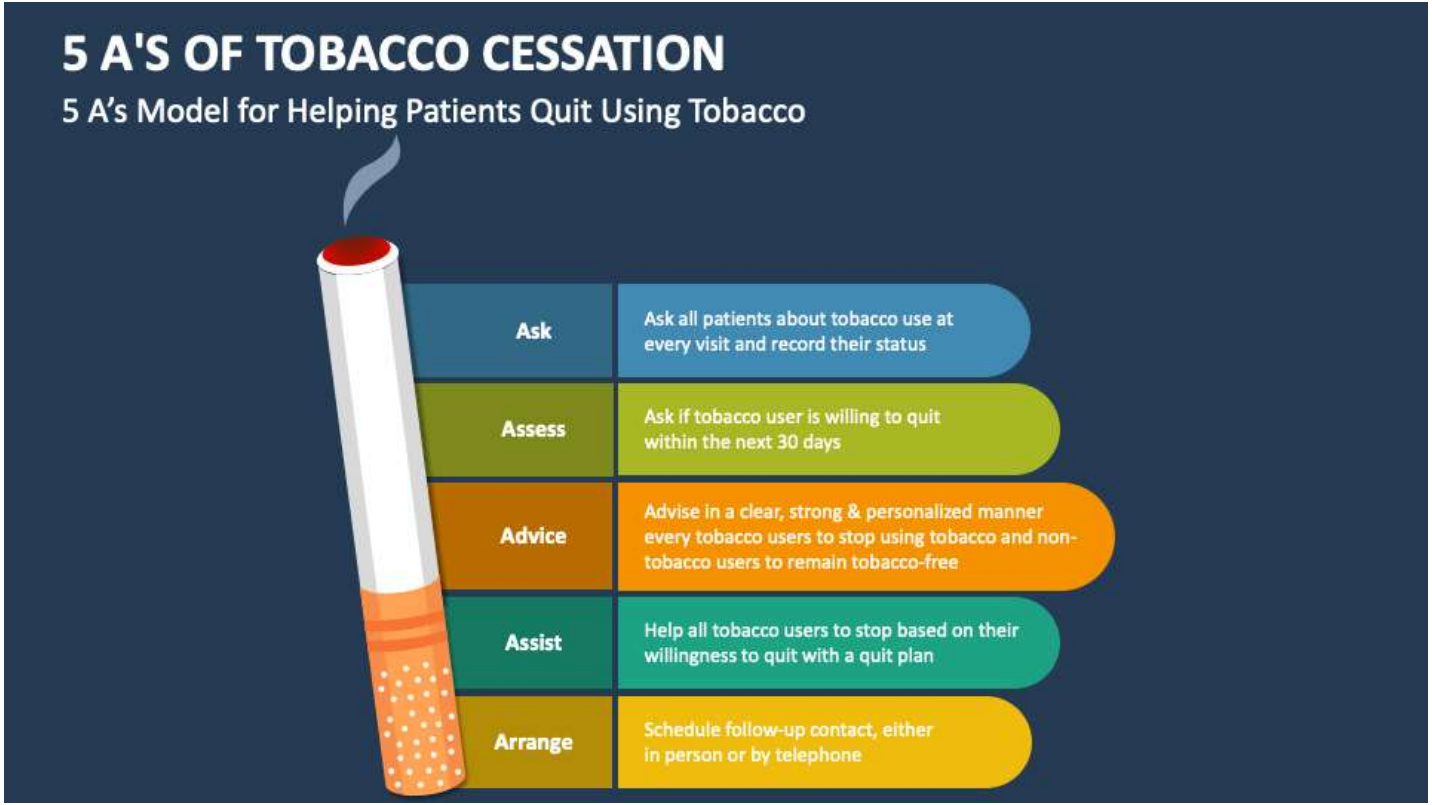


Image Credit: *https://www.collidu.com/presentation-5-as-of-tobacco-cessation*

Non-pharmacological Management

	06:00	08:30	11:00	13:30	16:00	18:30	21:00
Day 1							
Day 2							
Day 3							
Day 4							
Day 5							
Day 6							
Day 7							

Non-pharmacological Management

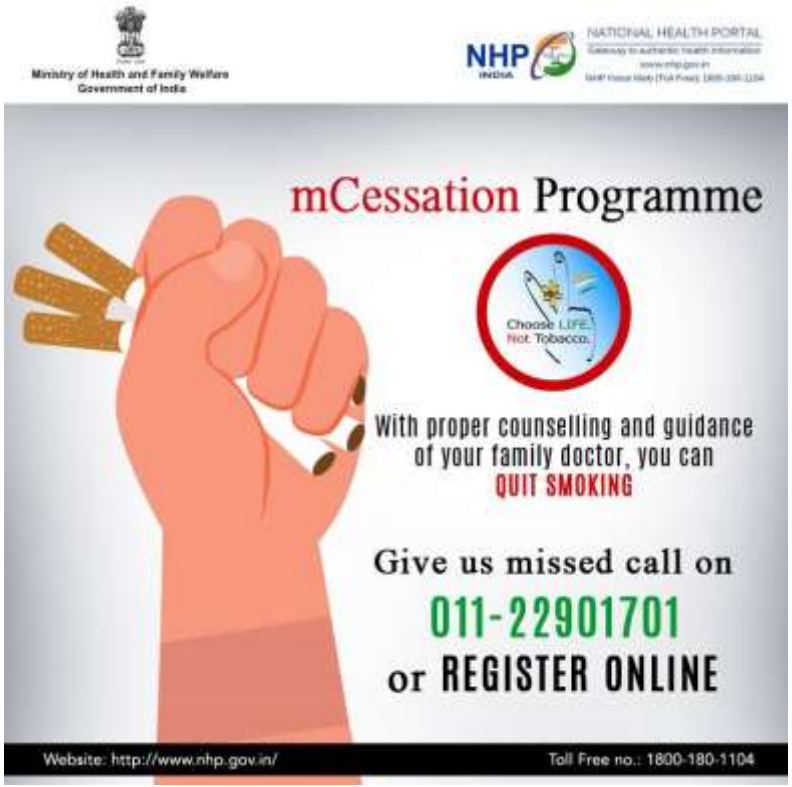


Image Credit: *National Tobacco Control Programme* https://ntcp.mohfw.gov.in/

Thanks!

Do you have any questions?

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Acute alcohol toxicity and withdrawal in the emergency room and medical admissions unit

Author: Marsha Y Morgan[A]

ABSTRACT

Alcohol-related hospital attendances and admissions continue to escalate despite a fall in alcohol consumption levels in the UK population overall. People with alcohol-related problems pose a significant and often disproportionate burden on acute medical services as their management is often complex and challenging. This article focuses on the management of alcohol intoxication, with particular emphasis on aggressive and possibly violent behaviour; alcohol withdrawal; fitting; and the prevention and treatment of Wernicke's encephalopathy.

Introduction

People with alcohol problems are frequent attendees at accident and emergency departments and medical admission units. They manifest a wide range of problems, including alcohol intoxication, alcohol withdrawal and fitting, and aggressive and sometimes violent behaviour. In addition, they may have a whole host of other alcohol-related physical and psychosocial problems. Management of these individuals needs skill, knowledge and fortitude. However, opportunities should not be lost, whether patients are admitted or not, to assess their needs and refer appropriately to alcohol liaison services or other statutory/non-statutory bodies.

Alcohol intoxication

In naïve drinkers, blood alcohol concentrations of 150–250 mg/100 ml are usually associated with clinically apparent intoxication; concentrations of 350 mg/100 ml are associated with stupor and coma; while concentrations of >450 mg/100 ml are often fatal. Individuals who habitually misuse alcohol often develop tolerance to its effects and are significantly less likely to develop intoxication than non-habitual drinkers.

Adults with mild to moderate intoxication can be managed satisfactorily in relatively simple surroundings with a minimum of medical support, but those who are severely intoxicated should be admitted and nursed in a high-dependency setting. Their level of consciousness should be assessed at least hourly; their cardiac activity should be continuously monitored; their urine output should be carefully recorded; and blood glucose, plasma electrolytes and blood gases should be measured every 4 hours until recovery is assured.

Intravenous fluids should be given to counter dehydration and to maintain urine output and plasma expanders may be required if circulatory collapse occurs; inotropic support may be necessary if severe hypotension persists. Hypoglycaemia should be corrected as quickly as possible with oral glucose, if the conscious level permits, or else with 5% or 10% IV dextrose, as required. Assisted ventilation may be needed if respiration is severely depressed. Haemodialysis may have a place in the management of individuals with exceptionally high blood alcohol concentrations, particularly if there are other metabolic complications, evidenced by an arterial pH of <7, or if other dialysable drugs have been ingested.

Key points

Alternative causes of impaired consciousness should be sought in adults with blood alcohol levels below 350 mg/100 ml.

Aggressive, intoxicated individual should be assessed, if possible, to identify factors such as injury or infection which might confound the clinical picture.

Individuals who are alcohol dependent should be admitted to hospital for assisted withdrawal if they have previously experienced severe withdrawal symptoms, have a history of fitting, significant comorbidities or complex social needs.

Fitting is associated with both alcohol intoxication and alcohol withdrawal and is best managed with benzodiazepines; prophylactic anti-epileptic medication should not be given.

Maintain a low threshold for provision of prophylactic thiamine supplementation to patients with alcohol problems, particularly those who are malnourished, have comorbid liver disease or are withdrawing from alcohol.

KEYWORDS: Alcohol intoxication, alcohol withdrawal, aggression, benzodiazepines, fitting, thiamine, Wernicke's encephalopathy ■

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Table 1. Features of acute alcohol withdrawal.

Type	Onset[a]	Features	Offset	Fitting	Other features
Minor symptom complex (majority)	6–8 h	Generalised hyperactivity, anxiety, tremor, sweating, nausea, retching, tachycardia, systemic hypertension, mild pyrexia (Peak 10–30 h)	40–50 h	Yes: first 12–48 h	Auditory/visual hallucinations: may last for 5–6 days
Delirium tremens (<5%)	48–72 h	Coarse tremor, agitation, fever, tachycardia, profound confusion, delusions and hallucinations	Fatal if not effectively treated	No: may herald the syndrome but is not part of it	Hyperpyrexia, ketoacidosis and profound circulatory collapse if not effectively curtailed

[a]following abrupt cessation or a substantial reduction in alcohol intake.

Several further complications can arise which will need additional skilled management; these include ketoacidosis, lactic acidosis, cardiac arrhythmias, hypokalaemia, inhalation pneumonia, venous thromboembolism and hyperpyrexia; hypoglycaemia may be delayed for up to 36 hours and is easily missed.

Alternative or additional causes for the change in conscious level should also be sought in adults who present in coma with blood alcohol concentrations of <350 mg/100 ml. Cerebral trauma, cerebrovascular events and meningitis should be excluded, as far as possible. The presence of narcotic or other sedative drugs should be considered and information sought from the National Poisons Information Service (NPIS) in the UK and the National Poisons Information Centre in Ireland (NPIC). This service is accessed via www.toxbase.org and is freely available to UK NHS hospitals and general practices, NHS Departments of Public Health and HPA units. Severe or complex cases, including multiple ingestions and people with significant comorbidity, can be discussed with the relevant poisons service: UK NPIS 0844 892 0111; Ireland NPIC (01) 809 2566. Clinicians treating women who are pregnant can contact the UK Teratology Information Service 0844 892 0909.

Metadoxine (pyridoxal L-2-pyrrolidine-5-carboxylate) has been shown to accelerate the elimination of alcohol in adults leading to faster recovery from intoxication and a more controlled withdrawal from alcohol.[1–3] It is given as a single intravenous administration and has few, if any, side-effects. This product is not, however, licensed for use in the UK.

The aggressive intoxicated drinker

Although most intoxicated patients are cooperative, some may be belligerent, abusive and violent. The overriding priority in this situation is to ensure the patient's safety and that of attending staff, relatives/friends and bystanders. It is equally important to try to assess whether the patient is aggressive and disinhibited simply because they are intoxicated or because other factors, such as injury or infection, have added a component of confusion or delirium.

Every attempt should be made to create a calm environment. Those not immediately concerned with the patient's management should be asked to leave. Ensure that the room is clear of objects that can be thrown or used as weapons and that staff can exit easily and safely, if necessary. Try to defuse escalating anger by adopting a concerned and non-threatening demeanour. Remember there is little point in arguing with someone who is very drunk.

Many hospitals have security staff and police on standby; they should be summoned promptly if initial attempts to defuse the situation fail. Their intervention is rarely necessary but their presence is important to convey a clear message that violence will not be tolerated.

The patient should be offered 'something to calm them down'; sedatives should be used sparingly because of the danger of oversedation in an intoxicated patient and of masking other conditions affecting cerebral function. If the patient refuses help and their aggression continues to escalate it is probably best to try to isolate them in a safe environment rather than to forcibly restrain and sedate them. Restraint, if eventually necessary, should be undertaken by staff trained in the correct procedures. The drug of choice in this situation is haloperidol, administered parenterally. Subsequent, careful monitoring will be required, watching specifically for features of alcohol withdrawal.

If the patient is mentally ill, confused, disorientated, suicidal or significantly depressed then detention under the Mental Health Act may be needed; however, this is not justified in most situations of intoxication and aggressive behaviour.

Alcohol withdrawal effects

Approximately 40% of individuals who misuse alcohol will develop an acute withdrawal syndrome when they abruptly

Box 1. High-risk patients who should be considered for admission to hospital for medically assisted withdrawal from alcohol.

- History of seizures or delirium tremens during previous attendances/admissions.
- Significant or multiple comorbidities
  eg severe chronic depression, psychosis, unstable angina, heart failure, chronic liver or renal disease, malnutrition
- Significant learning difficulties or cognitive impairment
- Inadequate social support
- Age <18 years
- Older persons particularly if also frail
- Pregnant women
- Homeless persons

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Table 2. Sample fixed dose regimen for treatment of alcohol withdrawal with chlordiazepoxide.

Time	Dosage
Day 1, ie first 24 h	30 mg qds
Day 2	20 mg tds 30 mg nocté
Day 3	10 mg tds 20 mg nocté
Day 4	5 mg tds 10 mg nocté
Day 5	5 mg mane 10 mg nocté
Day 6	5 mg nocté
THEN STOP	

A variable 5–10 mg 'prn' dose can be prescribed for breakthrough symptoms occurring during the withdrawal period

Box 2. Treatment of Wernicke–Korsakoff syndrome.

A presumptive diagnosis of Wernicke–Korsakoff syndrome should be made in patients with a history of alcohol misuse and one or more of the following otherwise unexplained symptoms:

- ataxia
- ophthalmoplegia
- nystagmus
- hypotension
- memory disturbance
- comatosed/unconscious
- confusion
- hypothermia

Treat with the following:

- IV high-potency Pabrinex® tds for three days
- dilute ampoules 1 and 2 with 50–100 ml normal saline or 5% glucose and infuse over 15–30 minutes
- flush the giving set with at least 50–100 ml normal saline or 5% glucose at the end of the infusion.

NO RESPONSE: discontinue and reassess.

RESPONSE: IV Pabrinex® od IV for five days or until no further improvement: then oral supplements for 2–4 weeks.

stop or substantially reduce their alcohol intake. Most patients manifest a 'minor symptom complex or syndrome', while a relatively small proportion develop delirium tremens which, if untreated, can be fatal (Table 1).

Not all patients attending acute services with features of alcohol withdrawal need to be admitted. The decisions around this are complex and primarily driven by local practices and facilities. Some patients in early withdrawal, with no other risk factors, can be referred to alcohol liaison services and their withdrawal managed in the community. Clearly admission is mandatory for patients with symptoms of severe alcohol withdrawal, fitting and established delirium tremens. Admission is also recommended for patients thought to be at particular risk, including those who have a history of fitting, significant comorbidities or complex social needs (Box 1).[4,5]

Medically assisted withdrawal from alcohol in generally managed using a fixed-dose regimen of benzodiazepines. The benzodiazepines differ little in efficacy from one another but the longer acting drugs, diazepam and chlordiazepoxide, have a smoother more protracted effect. However, accumulation may cause problems in patients with respiratory or hepatic impairment. The shorter acting drugs have little tendency to accumulate but their use is associated with a higher incidence of fitting. The drug of choice is given in high dosage on days 1– 3 and is then tapered over the next 4–7 days in response to the patient's condition. Patients' needs are extremely variable and so the dosage of medication is difficult to predict accurately. As a guide, the daily dosages commonly employed in the early phase of treatment might be diazepam 40 mg, chlordiazepoxide 120 mg and lorazepam 8 mg. After the third day, dose reduction of at least 25% daily is required (Table 2).

Consideration can be given, in settings where 24-hour assessment and monitoring are available, for adoption of a symptoms-triggered withdrawal regimen tailored to the individual patient's needs; patients are assessed at set time points and drug treatment provided if they need it, but withheld if they are comfortable/without symptoms.

Convulsions can be treated with intravenous diazepam in a dose of 0.15–0.25 mg/kg body weight (usually 10–20 mg) every 4 hours by slow intravenous injection or infusion. Diazemuls (diazepam emulsion injection) is preferred to plain diazepam as it is less likely to cause thrombophlebitis. Lorazepam, given in a dose of 2–4 mg (0.7 µg/kg: maximum 4 mg) by rapid bolus injection, is an alternative. Hallucinations may require treatment with lorazepam, haloperidol or olanzapine. Delirium tremens is best managed with lorazepam which may need to be given parenterally; haloperidol and olanzapine are alternatives.

Care must be taken to maintain the patient's general condition during the withdrawal period. Dehydration should be corrected by use of oral fluids; intravenous fluids should be avoided as overhydration is a serious potential hazard. Several biochemical abnormalities may be observed during the withdrawal period, for example, hypokalaemia and hypomagnesaemia, but these are usually transient and do not need specific correction; more persistent abnormalities will need to be corrected appropriately.

Fitting

Individuals who misuse alcohol may develop fitting when intoxicated. Fitting may also develop in alcohol-dependent individuals when they withdraw from alcohol. The fits should be brought under control with parenteral benzodiazepines but with great care as the blood alcohol concentration may still be significantly elevated. An electroencephalogram should be undertaken in all individuals experiencing this type of fitting for the first time, together with some form of cerebral imaging, either CT or MRI, in order to exclude potential underlying pathology. There is no indication for use of prophylactic anti-epileptic medication in this setting.

Individuals who chronically misuse alcohol may suffer head trauma resulting in cerebral injury or subdural/

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Table 3. Recommended regimens for prophylactic vitamin supplementation in alcohol misusers.

Situation	Regimen
> Well nourished > No history of dietary neglect > Adequate dietary intake > No neuropsychiatric symptoms/signs	No need for additional supplements but monitor
> Mild malnutrition > At risk of malnutrition > Compensated cirrhosis > Acute alcohol withdrawal	Oral thiamine hydrochloride: 100 mg tds for 2–4 weeks
> Moderate/severe malnutrition > Significant dietary neglect > Poor/negligible dietary intake > Peripheral neuropathy > Decompensated cirrhosis > Severe acute withdrawal	IV Pabrinex® bd for three days then oral supplementation for 2–4 weeks

extradural haematomas. These injuries may result in fitting, either at the time of the initial insult, or subsequently. These individuals are extremely difficult to manage. They may require long-term, antiepileptic medication but, if they continue to misuse alcohol, control may be difficult, if not impossible, to achieve.

Wernicke's encephalopathy

Individuals with alcohol problems are often thiamine deficient and are therefore at risk for developing Wernicke–Korsakoff syndrome. The classical triad of ophthalmoplegia, ataxia and confusion is rarely seen and a high threshold of suspicion should be maintained in patients with otherwise unexplained neurological findings (Box 2). Thiamine supplementation is required, and invariably provided in the UK, as the mixed vitamin preparation Pabrinex®. However, there is little or no evidence base on which to determine the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of Wernicke–Korsakoff syndrome in this setting.[6] Several sets of guidance exist based primarily on pragmatic clinical consensus,[4,7,8] resulting in a lack of consistency, confusion and poor uptake of best practice.[9,10]

If there is any suspicion of Wernicke's encephalopathy treatment should be instituted promptly (Box 2). Prophylactic vitamin supplementation should also be prescribed in individuals identified as at risk with the dosage and route varied in relation to the perception of risk severity. It is not clear how long treatment should be continued to ensure adequate replenishment of thiamine stores – a safe margin should be allowed (Table 3).

Caution should be exercised when adopting the recommended practice of giving one dose of parenteral Pabrinex® to individuals attending acute services.[7] Provision might mask the signs of impending Wernicke's with possible disastrous consequences making it vital that the patient is also given an adequate supply of oral thiamine supplementation to take away with them and clear advice about the need for compliance.

Summary

Patients with alcohol problems presenting to accident and emergency department and medical admissions unit are challenging and their management, as a consequence, is often suboptimal. These patients should be reviewed, and their management directed, by members of staff with relevant experience rather than by departmental juniors. Guidelines exist for the management of these patients, which can be modified to reflect local preferences and services, and should be used to facilitate application of best practice. ■

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Cannabis Use Disorder

Jason Patel; Raman Marwaha.

Author Information and Affiliations

Last Update: March 20, 2024.

Continuing Education Activity

Cannabis is a plant of the Cannabaceae family that contains multiple biologically active compounds. The most potent compounds are delta-9-tetrahydrocannabinol and cannabidiol. Cannabis use can cause intoxication, withdrawal, and biopsychosocial issues. A range of disorders are associated, including psychosis, sleep disorders, withdrawal, and a scale of intoxication that leads to the diagnosis of a substance use disorder. Treatment should include counseling such as cognitive behavioral therapy, family therapy, and psychiatric assessment for comorbid disorders, alongside innovative interventions like PNC-txt and intensive outpatient programs, while considering individual needs such as pain management or sleep studies.

Participants explore symptomatology, distinguishing between cannabis use and misuse, and navigate the complex regulatory landscape. The course details the evaluation and management of cannabis use disorder, emphasizing the interprofessional team's pivotal role. Clinicians facilitate comprehensive patient care through collaborative efforts, ensuring tailored interventions and addressing multifaceted aspects of cannabis-related issues for improved patient outcomes.

Objectives:

- Evaluate patients on the risks and benefits of cannabis use, fostering open dialogue and shared decision-making in treatment planning.
- Interpret the presentation of a patient with cannabis intoxication to recognize the signs and symptoms indicative of cannabis use disorder.
- Screen patients for the diagnostic criteria for cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
- Implement care coordination amongst the interprofessional team to optimize long-term outcomes for patients with cannabis use disorder.

Access free multiple choice questions on this topic.

Introduction

According to the United States Food and Drug Administration (FDA), cannabis is considered a Schedule I drug. According to this classification, the drug has no accepted medical purpose at the federal level and has a high potential for abuse. The FDA-approved cannabis-derived and cannabis-related products are only approved for the treatment of particular conditions. These products contain purified cannabidiol (CBD) or synthetic delta-9- tetrahydrocannabinol (THC), which are used for the treatment of seizure disorder and anorexia associated with acquired immunodeficiency syndrome.

Cannabis is a plant of the Cannabaceae family that contains multiple biologically active compounds. The most potent compounds are THC and CBD. The FDA continues to categorize cannabis as a Schedule I drug with no accepted medical use at this time despite the increasing number of states that have allowed the medical use of cannabis and its derivatives. The FDA

emphasizes its high potential for abuse and has attempted to introduce federal regulation to help curb the misuse.

Despite their efforts, cannabis (marijuana) is still one of the most commonly used drugs in the United States.[1] The most common users are teenagers and adolescents, and usage declines as these groups age into adulthood due to careers, marriage, cohabitation, and parenthood.[2][3] As expected, cannabis use has increased in recent years due to state-directed legislature. The Diagnostic and Statistical Manual of Mental Disorders, DSM–5, defines cannabis use disorder as the presence of clinically significant impairment or distress in 12 months, manifested by at least 2 of the following:

- Cannabis is taken in larger amounts or used over a longer period than intended
- Persistent desire to cut down with unsuccessful attempts
- Excessive time spent acquiring cannabis, using cannabis, or recovering from its effects
- Cravings for cannabis use
- Recurrent use resulting in neglect of social obligations
- Continued use despite social or interpersonal problems
- Important social, occupational, or recreational activities foregone to be able to use cannabis
- Continued use despite physical harm
- Continued use despite physical or psychological problems associated with cannabis use
- Tolerance
- Withdrawal symptoms when not using cannabis [4]

Etiology

Reasons for cannabis use vary based on demographics. Research shows college students and young adults most commonly use cannabis to conform socially (42%), experiment (29%), and for “enjoyment” (24%). Twelve percent primarily use the drug to manage stress or relax, consistent with other studies associating its use with depression, anxiety, social anxiety, and post-traumatic stress disorder.[5][6][7][8] During pregnancy, mothers who reported using marijuana say they did so primarily to manage depression, anxiety, and stress (63%); pain (60%); nausea or vomiting (48%); and for recreational purposes (39%).[9] Biologically speaking, impaired inhibition can predispose individuals to substance use disorders. However, clinicians are unsure if this is true for marijuana.[10]

The frequency of use is a major risk factor for the development of cannabis use disorder.[11] However, when using relatively low amounts, specific populations are at high risk of this disorder. According to one study, a significant proportion of marijuana users, particularly adolescents, are at high risk for developing cannabis use disorder at relatively low levels of use.[12]

Epidemiology

Nearly 4% of the global population was using cannabis in 2015.[13] Among teenagers, 8% in the United States and 16% in Europe report use. Nine percent of all users experience addiction, of which nearly a fifth begin to use in adolescence.[14] Limited evidence currently exists for cannabis use among older patients. In the medical profession, first-year psychiatry residents are

more likely to have cannabis use disorder and seek out experiences to be disinhibited; these individuals also have a history of sedative use and anxiety.[15]

During pregnancy, 4% of mothers admit to using drugs, most commonly cannabis. A retrospective cohort study of more than 12 million pregnant women revealed nearly a tripling of cannabis abuse or dependence from 1999 through 2003 and a significant association for perinatal complications.[16] Thirty-five percent of mothers who have used marijuana have done so during pregnancy, and 18% used it when breastfeeding.[9]

As consumption increases among adults, so does the unintended consequence of exposure to children. Between 2005 and 2009, 985 unintentional exposures to children (median age of 1.7 years) were reported. States legalizing marijuana have had a 20-fold increase in calls to poison centers and admissions to critical care units for its exposure.[17] Overall, the trend for cannabis use is increasing over time for most, if not all, demographics.

Pathophysiology

Researchers know that prolonged and heavy cannabis use can alter brain circuitry. However, the specific pathophysiological mechanisms are unclear. In terms of addiction, THC is the primary molecule responsible for the reinforcing properties of marijuana.[18][19][20] Interestingly, the striatal dopamine system is typically involved with substances of abuse, such as alcohol and opioids. Meta-analysis reveals insufficient evidence to support a conclusion about cannabis and suggests that dopamine receptors may not be involved.[21]

At a symptomatic level, heavy use modifies conscious experience by altering the brain's network for self-awareness. By reducing anxiety and impairing memory, cannabis also affects motivation and personal experience.[22] The botanical provides over 500 active chemical compounds interacting with numerous molecular targets at a molecular level, modulating the transmission of endocannabinoids, gamma-aminobutyric acid, glutamate, and serotonin. Psychoactive effects are primarily derived from THC, which binds cannabinoid receptors CB1 and CB2.

CB1 receptors are located throughout the central nervous system (CNS), lungs, liver, and kidneys. CB2 receptors predominate within the immune hematopoietic cells. Binding these receptors modulates G-protein-coupled inhibition of cyclic adenosine monophosphate, influencing pain, mood, appetite, nausea, and sexual activity.[23] CNS effects are mediated by glial cells, particularly microglia and astrocytes. In vitro studies show microglial cells produce greater endocannabinoids than neurons, and astrocytes may play a role in signaling by regulating endocannabinoid turnover.[24][25] Thus, an influence of the neuropil, not just the neurons, may better describe the CNS changes mediated by cannabis.

Toxicokinetics

Unlike synthetic substances and alcohol, cannabis is a more complex drug. Consumption or inhalation of the botanical exposes the user to hundreds of compounds, including cannabinoids (eg, THC and cannabidiol) and non-cannabinoids (eg, terpenes and flavonoids), many of which are bioactive.[23] Compared to isolated pharmaceutical derivatives (eg, dronabinol and cannabidiol), the sheer complexity of the plant makes a comparison between the two difficult. What is currently known about marijuana is derived from studies of a single active constituent, tetrahydrocannabinol, and less so from the plant itself. This problem is primarily due to the federal status as a Schedule I substance and the prohibition of federal research funds for the study.

THC, the principal psychoactive and addictive component, is most commonly smoked. The substance is rapidly absorbed by the lungs and distributed systemically via perfusion. The rapid influence on the brain contributes to pleasure and abuse potential.[26] Oral ingestion typically

follows a more gradual course and delays peak blood concentration. THC is extensively bound to lipoproteins, with only 3% in the free state.[27][28] Metabolism through the liver can produce over 80 metabolites of THC, with the most common pathway involving allylic hydroxylation at the 11-position followed by oxidation to a carboxy derivative. Conjugation occurs with some metabolites. Bioavailability varies greatly amongst individuals depending on their smoking topography, such as number, duration, spacing of puffs, hold time, and inhalation volume.[29] THC remains in the body for extended periods due to lipophilic properties, allowing accumulation and slow release from adipose tissue and further processing via the enterohepatic circulation, which produces active metabolites.

Chronic daily smokers can produce detectable levels of THC and the metabolites up to 1 month after their last intake.[30] Lipophilic metabolites are suggested to form conjugates, allowing for greater stability and prolonging their metabolism and half-life, so release from adipose tissue is the rate-limiting step.[31][32][33] This high lipophilicity explains why withdrawal from the substance is a slow-onset phenomenon. The pharmacokinetics of THC are further complicated by factors such as its physical or chemical form, route of administration, genetics, and concurrent consumption of alcohol.[34]

History and Physical

The individual's mental status is a critical part of the exam and can point to the phase of cannabis use. Intoxication can include euphoria, anxiety, uncontrollable laughter, increased appetite, inattentiveness, forgetfulness, restlessness, tachycardia, conjunctival injection, and dry mouth. Less common adverse events may include delusions, hallucinations, and derealization. Prolonged continuous use or withdrawal typically causes a depressed mood characterized by apathy, lack of motivation, irritability, loss of interest in typical activities, difficulty concentrating, and isolation. Cognition can be assessed by testing 3-word recall, asking multi-step math problems, or recalling details from a brief fictional story, as demonstrated on the St. Louis University Mental Status Exam.

In patients with prolonged use or withdrawal, the depressed mood must be differentiated from persistent depressive disorder and major depressive disorder. Substance use and a mood or anxiety disorder are not necessarily mutually exclusive and frequently co-occur. Suicidality and homicidal tendencies can result from dysregulated mood, a recent stressor, or substance use. Differentiation requires an understanding of the intensity and temporality of the symptoms. Persistent symptoms during periods of sobriety can indicate a comorbid primary psychiatric disorder.

Classifying cannabis use disorder in the United States is dictated by the DSM-5. Generally, it can be understood as having acute and chronic phases. The acute phase includes intoxication and withdrawal states, along with secondary complications such as delirium, psychosis, anxiety, and insomnia. Chronic regular use is characterized by disordered behavior.

History and physical exam findings seen in various cannabis use-associated conditions are outlined below:

Cannabis Intoxication

- A recent use of cannabis can cause intoxication.
- Intoxication can include clinically significant, problematic, behavioral, or psychological changes (eg, impaired motor coordination, euphoria, anxiety, a sensation of slowed time, impaired judgment, social withdrawal) that developed during or shortly after cannabis use.

- At least 2 of the following signs develop within 2 hours of cannabis use: conjunctival injection, increased appetite, dry mouth, and tachycardia.
- The symptoms must not be due to a general medical condition better accounted for by another mental disorder.
- Specify if perceptual disturbances are present: hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of delirium.

Cannabis Withdrawal

- This withdrawal accompanies cessation of cannabis use that has been heavy and prolonged (ie, usually daily or almost daily use over at least a few months). Three or more of the following signs and symptoms develop within 1 week after cessation of heavy, prolonged use:
- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (ie, insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least 1 of the following physical symptoms are causing significant discomfort: abdominal pain, shakiness or tremors, sweating, fever, chills, or a headache.
- The signs or symptoms are causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Evidence suggests that withdrawal only occurs in a subset of patients. Symptoms usually begin within the first 24 hours, peak by day 3, and last up to 2 weeks.[35] Increased use and more recent use can predict the severity of withdrawal.[36][37]

Cannabis Intoxication Delirium

This diagnosis relies on the definition of delirium and is appropriate when the following 2 symptoms predominate in someone who has taken cannabis:

- Disturbance in attention (ie, reduced ability to direct focus, sustain, and shift attention) and awareness
- An additional disturbance in cognition (ie, memory deficit, disorientation, language, visuospatial ability, or perception)

Cannabis-Induced Psychotic Disorder

- Presence of delusions or hallucinations
- Evidence from the history, physical examination, or laboratory findings of either one of the following:

- The symptoms in the first criterion developed during or soon after cannabis intoxication or withdrawal
- The disturbance was not accounted for by a psychotic disorder that is not substance-induced
- Evidence that the symptoms are accounted for by a psychotic disorder that is not substance-induced might include the following:
-
    - Symptoms precede the onset of substance use (or medication use)
    - Symptoms persist for a substantial period (eg, about 1 month) after the cessation of acute withdrawal or severe intoxication or are substantially more than what would be expected, given the type or amount of the substance used or the duration of use
    - Other evidence suggests the existence of an independent non–substance-induced psychotic disorder (eg, a history of recurrent non–substance-related episodes)
    - Disturbance does not occur exclusively during delirium
    - Disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning

Cannabis-Induced Anxiety Disorder

- Panic attacks or anxiety predominate in the clinical picture.
- Evidence from the history, physical examination, or laboratory findings of either of the following:
- Symptoms in the first criterion developed during or soon after substance intoxication or withdrawal
- Disturbance is not better accounted for by an anxiety disorder that is not substance-induced
- Evidence that the symptoms are better accounted for by an anxiety disorder that is not substance-induced might include the following:
- Symptoms precede the onset of substance use
- Symptoms persist for a substantial period (eg, about a month) after cessation of acute withdrawal or severe intoxication or are substantially more than expected, given the type or amount of the substance used or the duration of use
- Other evidence suggests the existence of an independent non–substance-induced anxiety disorder (eg, a history of recurrent non–substance-related episodes)
- Disturbance does not occur exclusively during delirium
- Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Cannabis-Induced Sleep Disorder

- A prominent and severe disturbance in sleep
- Evidence from the history, physical examination, or laboratory findings of both of the following:

- The symptoms in the first criterion had developed during or soon after the cannabis intoxication or after withdrawal from or exposure to it.
- The disturbance is not better explained by a sleep disorder that is not substance or medication-induced. Such evidence of an independent sleep disorder could include the following:
- Symptoms precede the onset of cannabis use
- Symptoms persist for a substantial period (ie, about a month) after the cessation of acute withdrawal or severe intoxication
- Other evidence suggests the existence of an independent non-substance or medication-induced sleep disorder (ie, a history of recurrent non-substance or medication-related episodes)
- Disturbance does not occur exclusively during delirium
- Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Cannabis Use Disorder

Cannabis abuse and dependence were combined in the DSM-5, capturing the behavioral disorder that can occur with chronic cannabis use and named cannabis use disorder defined as:

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within 12 months:

- Cannabis is often taken in more significant amounts or over a longer period than was intended.
- Persistent desire or unsuccessful efforts are attempted to cut down or control cannabis use.
- A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
- A craving or a strong desire or urge to use cannabis exists.
- Recurrent cannabis use results in failure to fulfill role obligations at work, school, or home.
- Continued cannabis use, despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
- Recurrent cannabis use even in situations in which cannabis is physically hazardous.
- Cannabis use continues despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
- The tolerance increases, defined by either (1) a need for markedly increased cannabis to achieve intoxication or desired effect or (2) a markedly diminished effect with continued use of the same amount of the substance.
- Having a withdrawal, as manifested by either (1) the characteristic withdrawal syndrome for cannabis or (2) cannabis is taken to relieve or avoid withdrawal symptoms.

The criteria have the following specifiers:

- In early remission, after full criteria for cannabis use disorder were previously met, none of the criteria for cannabis use disorder has been met for at least 3 months but less than 12 months (with an exception provided for craving).
- In sustained remission, after full criteria for cannabis use disorder were previously met, none of the criteria for cannabis use disorder has been met at any time during 12 months or longer (with an exception provided for craving).
- Severity is graded as mild, moderate, or severe, depending on whether 2 or 3, 4 or 5, or 6+ of the above criteria are present.

Evaluation

Laboratory testing of urine, blood, saliva, or hair can be useful to detect cannabis use, but results should be considered along with a clinical rationale. Assays typically rely on detecting the most common active metabolite, delta-9-tetrahydrocannabinol. The metabolite has been studied thoroughly and has become an established urinary marker of cannabis consumption in forensic, clinical, and environmental analyses.[34] A positive result can indicate usage, but not necessarily a substance use disorder or intoxication, and a negative result does not rule the drug out. Quantifying tolerance is possible by comparing the reported intake of cannabis to blood levels. Heavy or chronic cannabis smokers will take longer to clear THC compared to sporadic or one-time users. Additional tests to rule out related conditions may be beneficial. These include head imaging or laboratory testing for heavy metals, infection, immunological markers, electrolyte disturbances, or hormones.

Treatment / Management

The aim should be to improve the individual's multiphasic overall function. Supportive treatment may be provided during detoxification. Enabling access to psychiatric services allows the identification of underlying comorbid disorders. Psychological counseling can modify behavior and help develop healthier coping skills for stressors.

As cannabis strains become more potent and accessible, the risk of cannabis use disorder will increase. For individuals with marked intoxication or withdrawal or cannabis use disorder, the goal should be to stop the drug altogether. Unlike abrupt cessation, a gradual decrease is likely to decrease the discomfort of the withdrawal and prevent relapse. Cannabis intoxication most often does not require medical management and will self-resolve. Supportive management, such as a calm, non-stimulating environment, helps patients. Symptomatic treatment can be considered for specific symptoms, such as α-2-adrenergic agonists or β-blockers for tachycardia, benzodiazepines for panic attacks, off-label use of first-generation antihistamines for anxiety and restlessness, and neuroleptics for psychosis. Monitoring psychological symptoms may predict features of withdrawal or continued primary psychiatric illness.

Pharmacologic detoxification is still under investigation. A systematic review indicates most studies are preliminary and cannot statistically support clinical rationale as they are small in size, inconsistent, and have a risk of attrition bias. No medication is FDA-cleared to treat cannabis use disorder. Tetrahydrocannabinol does show some potential in treatment, but more information is needed to demonstrate the validity and inform on the dose, duration, formulation, and adjunct therapies. Gabapentin and N-acetylcysteine are also used but have unclear benefits.[38] Another component of cannabis, cannabidiol, holds promise by modulating the serotonergic, glutamatergic, and endocannabinoid systems.[39]

Differential Diagnosis

The differential may include intoxication syndromes from other substances; these may include:

- Amphetamine intoxication
- Cocaine intoxication
- Benzodiazepine withdrawal
- Anxiety disorder
- Panic attacks

In patients with chronic use, it is imperative to rule out:

- Major depressive disorder
- Bipolar disorder

Toxicity and Adverse Effect Management

Side effects of short-term use of cannabis include impaired short-term memory, which can affect learning, impaired motor coordination in activities such as driving, and an increase in high-risk sexual behaviors.[14] Also, judgment is impaired when tasks are measured, such as the quality of decision-making and executive planning.[40] Children 12 and younger are a separate concern. Their exposure typically occurs via unintentional consumption of edibles, meaning the dosage is not considered. This has led to increased presentations to the emergency department, often for central nervous system depression such as lethargy and somnolence, and rarely for respiratory insufficiency.[41]

Prognosis

The likelihood of continuing cannabis abuse can vary from person to person. Impulsive individuals are more likely to experiment with substances, including cannabis. Using cannabis for experimentation is associated with less use and fewer problems. Factors such as enjoyment, habit, activity enhancement, and altered perception or perspectives are associated with heavier use and more problems.[5] Those more avoidant of punishment, boredom, or unpleasant events are less likely to discontinue use and are at risk for abuse. Individuals who experience withdrawal or those who use cannabis to avoid stressful situations can have perpetuated use.[42]

Complications

Heavy or chronic users are more likely to report a decreased sense of life satisfaction and achievement compared to the general population. Additionally, effects can impair neuropsychiatric, physical, and social domains. These include addiction, altered brain development, cognitive impairment, poor educational outcome, increased likelihood of dropping out of school, and lower intelligence quotient among frequent users during adolescence. In addition, individuals who chronically use cannabis develop cognitive and psychomotor driving impairments.[43][44][45][46]

Women may be more likely to demonstrate deficits in attentional inhibition.[47] Those with the tendency for chronic psychotic disorders are at increased risk of “unmasking the illness” with prolonged use. THC levels measured in hair among chronic heavy marijuana-only users were predictive of delusions, hallucinations, and organic brain dysfunction. Discontinuation of cannabis did not resolve these symptoms after 3 months, indicating organic neurological dysfunction.[48] Respiratory complications from smoking cannabis can lead to chronic bronchitis.[14] Chronic use may also affect fertility in both sexes.[49]

Perinatal exposure may result in cognitive impairments in the fetus, affecting intelligence, attention, visual-motor coordination, processing speed, visual memory, and interhemispheric transfer of information.[50][51][52][53] Evidence, albeit inconclusive, is apparent for potential risk for preterm delivery, low birth weight, and stillbirth.[54][55][56][57]

Deterrence and Patient Education

The increasing misconception among the general public suggests cannabis is “harmless.” Clinicians need to educate patients about the potential side effects and long-term complications of cannabis use, especially those 21 and younger, who are at a higher risk for long-term, potentially irreversible cognitive impairments. Patients who are pregnant should be counseled at length on the potential impact of cannabis on the fetus and the pregnancy. Adults should be informed that cannabis and its paraphernalia are best kept in a locked and hidden location to prevent pediatric intoxication. Though medical marijuana is legal in many states, employers may enforce policies.

Pearls and Other Issues

Clinicians across all specialties need to familiarize themselves with the effects of cannabis use. The evidence supporting the use of marijuana for specific conditions is limited and often derived from pharmaceutical preparations of isolated THC. Researchers struggle to gain funding for these studies given that the drug is a Schedule I controlled substance.

Permission to access medical marijuana for a given symptom does not restrict the patient to limited use. Based on the opinion, the dispensary’s employees can influence the strain, dosing, formulation, and indications. Also, continuous and heavy use of cannabis can increase the risk of intoxication or withdrawal, requiring medical attention and long-term complications that may be irreversible. Despite the more benign nature compared to opiate, benzodiazepine, and alcohol use, cannabis is still a substance with the potential for ill health effects and marked impairment of social and occupational functioning. With the expansion of evidence-based uses, delineating marijuana abuse from recreational use is important with a thorough history intake. Differences in state regulations governing medical indications for cannabis should be considered. Clinicians should be mindful that medical marijuana is not a product of the tightly regulated and scientifically backed pharmaceutical industry.

Enhancing Healthcare Team Outcomes

Deterring patients from substance use requires an interprofessional team of clinicians, including pharmacists. A non-judgmental approach to understanding the reasons for use is best. Among children, cannabis use can indicate coping with home or school stressors. In both environments, counseling, particularly cognitive behavioral therapy, and multidimensional family therapy, should be provided at school, home, or an outpatient clinic to improve behavioral issues.[58] Psychiatric assessment for comorbid mental health disorders is essential as a longitudinal relationship between reductions in cannabis use and improvements in anxiety, depression, and sleep quality is reported.[59]

Peer Network Counseling-txt, a 4-week, automated text-delivered cannabis treatment that focuses on close peer relations, was able to decrease usage and relationship problems.[60] Also, intensive outpatient programs for substance use disorders can be beneficial. For chronic pain, pain management or neurology is involved. For insomnia, sleep studies are useful. Clinicians should be aware that a patient with a history of substance use disorder is more likely to misuse controlled substances. In summary, an interprofessional approach to managing cannabis use disorder that collaboratively addresses the issue, oversees prescribed medical marijuana, and

openly shares patient data can help decrease the burden of this disease and ensure the best possible outcomes.

Review Questions

- Access free multiple choice questions on this topic.
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