Drug Abuse Management - Intoxication

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01

Alcohol Intoxication

Acute Intoxication

Transient and clinically significant disturbances in consciousness, cognition, perception, affect, behaviour, or coordination that develop during or shortly after the consumption or administration of alcohol.

The symptoms must be compatible with the known pharmacological effects of alcohol, and their intensity is closely related to the amount of alcohol consumed.

Presenting Features

Impaired Attention

Poor Coordination

Inappropriate Behaviour

Unsteady Gait

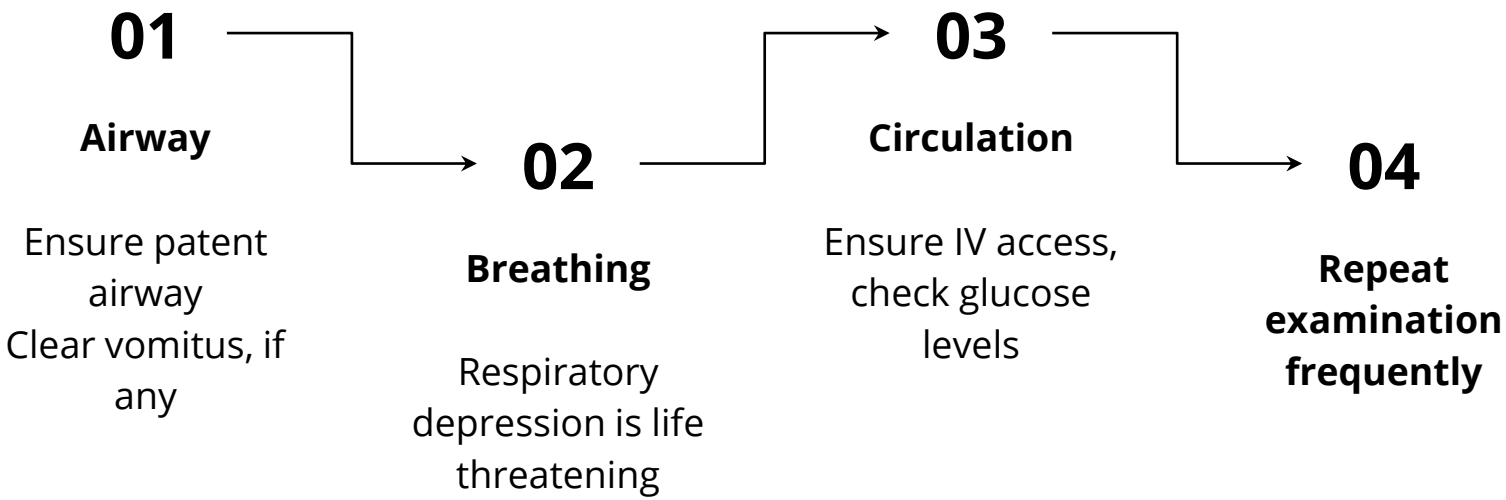
Emotional Lability

Slurred Speech

Differential Diagnosis

- Head injury, meningitis and encephalitis
- Diabetic ketoacidosis or hypoglycaemia
- Hepatic or other metabolic encephalopathy
- Wernicke’s encephalopathy
- Electrolyte disturbance
- Hypoxia or hypercapnia
- Systemic infection

Approach to Alcohol Intoxication



Supportive Treatment

IV Fluids

Address dehydration and electrolyte imbalance

Thiamine

To prevent Wernicke's Encephalopathy

Agitation

Low dose psychotropics or injectable sedatives

Monitor

Vitals, potential violence/suicidality, medical issues

Disposition and Follow-Up

Admission

Detoxification, Medical/surgical comorbidites

Referral

De-addiction services for long-term management

Psychoeducation

Family members, addressing caregiver burden

Harm Reduction

Utilize the window of opportunity

02

Opioid Intoxication

Acute Intoxication

Transient and clinically significant disturbances in consciousness, cognition, perception, affect, behaviour, or coordination that develop during or shortly after the consumption or administration of opioids.

The symptoms must be compatible with the known pharmacological effects of opioid, and their intensity is closely related to the amount of opioids consumed.

Presenting Features

Psychomotor Retardation

Respiratory Depression

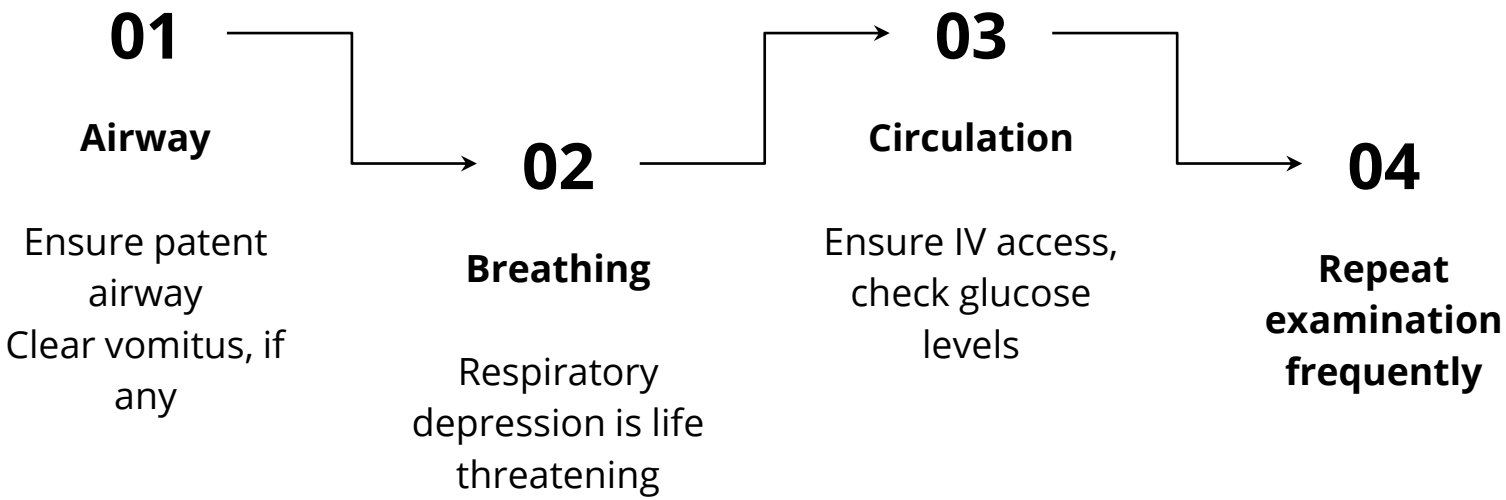
Impaired Judgement

Pupillary Constriction

Mood Changes

Stupor/Coma

Approach to Opioid Intoxication



Opioid Reversal with Naloxone

Dose

- Initial: 0.4–2 mg IV every 2–3 min; max 10 mg.
- In opioid-tolerant patients: start with 0.04–0.1 mg to avoid withdrawal

Routes

IV, IM, IN (intranasal), subcutaneous, endotracheal

Goal

- Restore breathing, not full alertness.
- May need repeated doses or continuous infusion for long-acting opioids

Supportive Treatment

IV Fluids

Address dehydration and electrolyte imbalance

Activated Charcoal

Oral ingestion, patent airway, within 2-3 hours

Bowel Irrigation

Suspected body packers

Monitor

Vitals, potential violence/suicidality, medical issues

Disposition and Follow-Up

Admission

Detoxification, Medical/surgical comorbidites

Referral

De-addiction services for long-term management

Psychoeducation

Family members, addressing caregiver burden

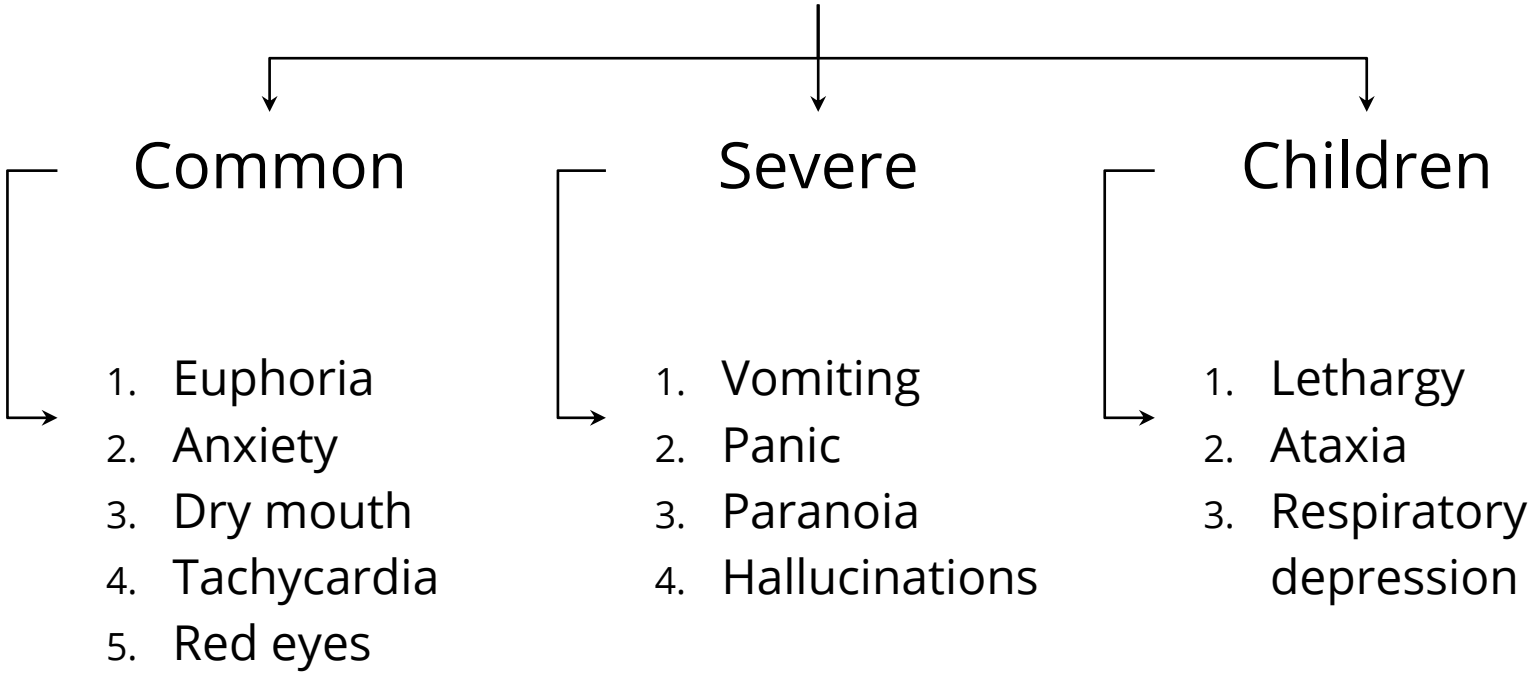
Harm Reduction

Utilize the window of opportunity

03

Cannabis Intoxication

Presenting Features



Presenting Features

Sluggishness

Intensified Ordinary Experiences

Increased Appetite

Conjunctival Injection

Perceptual Alterations

Impaired Judgement

Treatment

Supportive

Calm, quiet environment, hydration

Agitation

Benzodiazepines, antipsychotics

Cannabinoid Hyperemesis Syndrome

Cyclical vomiting, relieved by hot showers

Monitor

Vitals, potential violence/suicidality, medical issues

Disposition and Follow-Up

Admission

Most will not require inpatient management

Referral

De-addiction services for long-term management

Psychoeducation

Family members, addressing caregiver burden

Harm Reduction

Utilize the window of opportunity

Thanks!

Do you have any questions?
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STANDARD TREATMENT GUIDELINES

Management of Alcohol Dependence

Full Background document (Draft)
February 2016

सत्यमेव जयते

Ministry of Health & Family Welfare
Government of India

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SCOPE OF THE GUIDELINES

The areas that will be addressed by the guideline on alcohol dependence are described in the following sections.

Population

Groups that will be covered

The guideline will cover the individuals with alcohol dependence who require medical management for their alcohol use disorders. This will include those diagnosed with alcohol dependence. It will cover those individuals who require medical services per se for their alcohol use disorder. It will not cover the groups as specified in the subsequent section.

Groups that will not be covered

The guideline will not cover the management of the medical conditions associated with alcohol use. The guideline shall also not specifically cover individuals with co-morbid alcohol use disorders, psychiatric disorders and alcohol (methanol) poisoning. Although, the clinicians might find these guidelines useful while planning management for these patients as well.

Healthcare setting

The guideline will cover care provided in primary, secondary and tertiary hospital settings.

Clinical management

- The guideline will provide advice on diagnosis of individuals presenting with alcohol dependence.
- The guideline will provide advice on investigations to be carried out while managing a patient with alcohol dependence.
- The guideline will provide advice on short-term medical management of individuals with alcohol dependence.
- The guideline will provide advice on long- term medical management of patients with alcohol dependence.
- The guideline will provide advice on psycho-social interventions for patients with alcohol dependence.

- The guideline will provide advice on situations that warrant in-patient care as well as indications for referral.
- The guideline will provide advice on patient psycho- education to improve patient and care giver satisfaction.

BACKGROUND

- Excessive use of alcohol is a major public health problem. It causes 5.9% of all deaths globally and is responsible for 5.1% of the DALYs (Disability Adjusted Life Years) (WHO, 2014). Excessive use of alcohol is a component cause of more than 200 disease and injury conditions. Excessive use of alcohol is preceded only by tobacco as the largest modifiable risk factor for morbidity and mortality globally. Alcohol use has been identified as one of the priority modifiable risk factors to bring down burden due to NCDs.
- It has been estimated that around one-fourth to one-third of male population in South Asian countries drink alcohol. Additionally, an increasing trend of alcohol use among women has been observed in these countries. Disease burden per litre consumption of alcohol has been found to be relatively higher among Low and Middle Income countries (LMIC). It has been recommended that addressing excessive alcohol use shall serve as a low cost effective strategy to reduce the burden of disease in LMIC.

PREVALENCE OF ALCOHOL DEPENDENCE IN INDIA

The National Household Survey of Drug Use was the first systematic effort to document the nation-wide prevalence of (psychoactive) substance use in India. **Alcohol was the primary substance used (apart from tobacco) in 21.4% of the subjects** (Ray, 2004). Additionally, 17- 26% of alcohol users qualified for ICD- 10 diagnosis of dependence. This corresponded to an average prevalence of about 4%. The alcohol use prevalence varied across different states of the country with a low of 7% (for current use) in Gujarat to a high of 75% (for current use) in Arunachal Pradesh. The **National Family Health Survey (NFHS)** suggested an increase in alcohol use among males in the NFHS-3 as compared to NFHS-2. The **Drug Abuse Monitoring System reported data from the government de-addiction centres** across the country. Alcohol was reported as the most commonly used substance (apart from tobacco) with 43.9% of the treatment seekers reporting its current use. According to the **Global Status Report on Alcohol and Health 2011**, 25% and 15% of male and female drinkers, respectively were identified as heavy episodic drinkers. Additionally, it has been estimated that unrecorded alcohol consumption is at least two thirds of all alcohol consumption in the Indian subcontinent.

There has been limited literature from India that has explored the problems associated with alcohol use. As per the reports of the industry association sources, 15% to 20% of absenteeism and 40% of accidents at work are due to alcohol consumption. **Hospital-based studies from India report alcohol-related problems to account for over a fifth of hospital admissions**. It has a disproportionately high association with **deliberate self-harm, high-risk sexual behavior, human immunodeficiency virus (HIV) infection, tuberculosis, esophageal cancer, liver disease, and duodenal ulcer.**

I. WHEN TO SUSPECT/ RECOGNISE?

Introduction

Alcohol use disorders are a major contributor to global burden of disease. Problematic alcohol use is associated with significant morbidity and mortality. Patients with problematic alcohol use are common in all kinds of medical care settings. Often, those seeking treatment for their medical or surgical conditions in other clinical departments/ specialities may have an underlying alcohol dependence that may be complicating the medical/ surgical condition. Moreover, many cases of alcohol dependence go undetected for years because of poor motivation on part of the patient as well as failure of the treatment providers to screen for it. At times, individuals with alcohol dependence are brought to the treatment setting after they have come in conflict with law as in case of drunken driving.

Alcohol dependence represents a set of biological, psychological and social manifestations. It represents a maladaptive pattern of alcohol use that leads on to clinically significant impairment or distress or both. One can suspect possibility of alcohol dependence when alcohol use turns problematic.

A history of intense, irresistible, compulsive desire to use alcohol (known as **craving)**; a gradual increase in amount of alcohol used over time because of reduction in the effect experienced with previous amount (known as **tolerance)**; and appearance of **withdrawal symptoms** including sweating, increased pulse rate, hand tremor, nausea, vomiting, insomnia, psychomotor agitation, anxiety, transient visual, tactile, or auditory hallucinations or illusions on stopping or reducing the amount usually consumed are indicators of psychological and physical dependence on alcohol.

An individual with alcohol dependence tends to plan the day around procuring, using and experiencing its effects. **History of neglect of other pleasures** and **responsibilities** at school, home or work and loss of control over the amount or pattern of use are pointers towards possibility of alcohol dependence**. Use that persists in spite of being aware of the harms associated with alcohol** use is another pointer towards dependence on alcohol.

Presence of one or more of the aforementioned is an indicator for evaluation for possibility of alcohol dependence. Interpersonal difficulties consequent to alcohol use, difficulties at work place, and emergence of a physical or mental disorder commonly associated with alcohol use also suggest possibility of heavy alcohol use, and should raise the suspicion for possibility of alcohol dependence.

Case definition

An individual presenting with history of excessive (regular/ periodic) use of alcohol, especially when associated with medical, psychological, vocational, financial, familial and social problems needs to be assessed for presence of alcohol dependence. Presence of craving, tolerance and/or withdrawal symptoms lends further support to the possibility of alcohol dependence and warrants detailed evaluation for presence of alcohol dependence.

II. DIAGNOSIS

Alcohol dependence

As mentioned in the previous section, alcohol dependence represents a maladaptive pattern of alcohol use that leads on to clinically significant impairment or distress or both. One can suspect possibility of alcohol dependence when alcohol use turns problematic.

A history of craving; tolerance; appearance of withdrawal symptoms on stopping or reducing the amount usually consumed are indicators of psychological and physical dependence on alcohol. An individual with alcohol dependence tends to plan the day around procuring, using and experiencing its effects. History of neglect of other pleasures and responsibilities at school, home or work and loss of control over the amount or pattern of use are pointers towards possibility of alcohol dependence. Use that persists in spite of being aware of the harms associated with alcohol use is another pointer towards dependence on alcohol.
A description of criteria for diagnosis of alcohol dependence syndrome as specified in the WHO's ICD-10 Classification of Mental and Behavioral Disorders is provided in Box 1.

Alcohol intoxication and alcohol withdrawal

Presence of clinical features associated with alcohol dependence make the diagnosis of the condition fairly straight forward. These features are unlikely to be confused with any other psychiatric disorder. However, at times it might be challenging to reach at a diagnosis of alcohol dependence if the adequate information is not available**. A patient who is unavailable for interview due to being under intoxication or withdrawal might require a reassessment once the acute medical condition has settled** and the patient is in a position to participate in the interview. Even during such conditions of intoxication and withdrawal, **presence of clinical features associated with intoxication (along with alcohol on breath) and withdrawal can help establish the diagnosis of alcohol intoxication and alcohol withdrawal, respectively.**
Alcohol intoxication is characterized by disinhibition, argumentativeness, aggression, lability of mood, impaired attention, impaired judgment, interference with personal functioning, unsteady gait, difficulty standing, slurred speech, nystagmus, decreased level of consciousness (e.g. stupor,

coma), flushed face, and conjunctival injection. These clinical features develop following recent use of alcohol at sufficiently high dose levels to be consistent with intoxication.

Box 1. Diagnostic criteria for alcohol dependence syndrome as specified in The ICD-10 Classification of Mental and Behavioral Disorders (adapted for alcohol)

A cluster of physiological, behavioral, and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take alcohol. There may be evidence that return to alcohol use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.

A definite diagnosis of alcohol dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

(a)a strong desire or sense of compulsion to take alcohol;

(b)difficulties in controlling alcohol-taking behavior in terms of its onset, termination, or levels of use;

(c)a physiological withdrawal state when alcohol use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for alcohol; or use of alcohol (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;

(d)evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses;

(e)progressive neglect of alternative pleasures or interests because of alcohol use, increased amount of time necessary to obtain or take alcohol or to recover from its effects;

(f)persisting with alcohol use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy alcohol use, or alcohol-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Alcohol withdrawal is characterized by tremors of the outstretched hands, tongue or eyelids, sweating, nausea, retching or vomiting, tachycardia or hypertension, psychomotor agitation, headache, insomnia, malaise or weakness, transient visual, tactile or auditory hallucinations or illusions, and generalized seizures. These features **develop on recent cessation or reduction of alcohol after repeated, and usually prolonged and/or high-dose use.** At times, patient develops what is known as 'complicated withdrawal'. It is characterized by presence of seizures or delirium (known as delirium tremens) along with other features associated with alcohol withdrawal.

Alcohol intoxication is not a direct indicator of alcohol dependence and can occur independent of it. Similarly, while alcohol withdrawal is one of the clinical features of alcohol dependence, in itself is not sufficient (or necessary) to make a diagnosis of alcohol dependence. However, those presenting with alcohol intoxication or withdrawal should be assessed for presence of alcohol dependence.

Differential Diagnosis

- **Sedative/ hypnotic/ anxiolytic dependence**

Features of alcohol intoxication and withdrawal have some overlap with other depressant psychoactive substances such **as sedatives/ hypnotics/ anxiolytics**. However, history of use of these substances, along with clinical features specifically associated with these can help differentiate dependence on these substances from alcohol dependence. **Sedative/ hypnotic/ anxiolytic intoxication is** characterized by slurred speech, incoordination, unsteady gait, nystagmus, impairment in attention or memory, stupor or coma during, or shortly after their use. Sedative/ hypnotic/ anxiolytic withdrawal is characterized by autonomic hyperactivity in form of sweating, increased pulse rate; hand tremor; insomnia; nausea; vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety and grand mal seizures. These features follow cessation of (or reduction in) sedative/ hypnotic/ anxiolytic use that has been heavy and prolonged.

- **Alcohol abuse and harmful use**

Harmful use (used in ICD 10) represents a maladaptive patterns of alcohol use that leads to some kind of harm. Harmful use of alcohol refers to a pattern of alcohol use that leads to either physical or psychological harm. On the other hand, **alcohol abuse refers to a**

pattern of alcohol use that leads to failure to fulfill major role obligations; or recurrent use in situations in which it is physically hazardous; or associated with recurrent substance-related legal problems; or continued use despite having persistent or recurrent social or interpersonal problems. The diagnostic criteria for alcohol, harmful use and alcohol abuse have been presented in table 3.

Table 1. Diagnostic criteria for alcohol, harmful use (as per ICD 10)
I. Diagnostic criteria for alcohol, harmful use (as per ICD 10) (adapted for alcohol) A pattern of alcohol use that is causing damage to health. The damage may be physical or mental. The diagnosis requires that actual damage should have been caused to the mental or physical health of the user.

Co-morbid conditions

- **Psychiatric disorders**

Excessive use of alcohol, particularly in dependent pattern, is associated with different psychiatric disorders collectively known as **alcohol induced disorders**. These include **dementia, amnestic disorder, psychotic disorder (with delusions or with hallucinations), mood disorder, anxiety disorder, sexual dysfunction, sleep disorder.** These need to be differentiated from independent psychiatric disorders. Alcohol induced psychiatric disorders resemble their independent counterparts in terms of clinical features. However, these tend to have temporal association with pattern of alcohol use, are usually short lasting, and tend to remit with abstinence. However, in clinical practice it might be difficult to differentiate between the two. Consequently, those presenting with any of the psychiatric disorders should be assessed for presence of underlying alcohol dependence as well.

III. PREVENTION AND COUNSELING

Prevention has been recommended as an important public health intervention to address the problem of alcohol dependence. Prevention helps by preventing the onset of alcohol use or problematic alcohol use (in case alcohol use has set in).

Some of such strategies include:

- Raising awareness and commitment among the general public regarding harmful effects of alcohol use
- Health services' response;
- Community action;
- Strict action against drunk-driving;
- Regulating availability and marketing of alcohol;
- Alcohol pricing policies;
- Reducing the negative consequences of drinking and alcohol intoxication;
- Reducing the public health impact of illicit alcohol and informally produced alcohol;
- Monitoring and surveillance of sell of alcohol

Counseling plays a key role in management of alcohol dependence both during the short term as well as long term phase of management. It has been described in greater details in the subsequent sections.

IV. DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

ASSESSMENT

While assessing an individual for alcohol dependence, it is important to carry out complete clinical assessment. This includes medical history, physical examination, mental status examination (MSE) and investigations. Assessment is targeted:

- To ascertain the diagnosis of alcohol dependence
- To establish rapport with the patient
- To assess complications associated with alcohol use (including physical and psychological)
- To assess level of motivation
- To assess support and resources available
- To assess suitable setting for management
- To assess need for referral

Screening

There is a significant time lag between emergence of alcohol dependence and treatment seeking for the same. It is not uncommon for the patient with alcohol dependence to come in contact with medical facility for some unrelated medical condition. It is important for the clinician to enquire about alcohol use from every patient. Simple, brief and validated tools can be used to screen those with problem drinking. Those who screen positive on these instruments should then be assessed in greater detail for alcohol dependence. Two such screening instruments include CAGE questionnaire and the Alcohol Use Disorders Identification Test(AUDIT) (Table 4)

Table 2. Screening tools for problem alcohol use
CAGE questionnaire
Items
1. Have you ever felt that you should **C**ut down on your drinking?
2.Have people **A**nnoyed you by criticizing your drinking?
3.Have you ever felt bad or **G**uilty about your drinking?
4.Have you ever had a drink first thing in the morning to steady your nerves or get rid of

a hangover (**E**ye-opener)?

Interpretation[#]

Answering Yes to 2 questions – Strong Indication for alcohol dependence

Answering Yes to 3 questions – May be taken as evidence for alcohol dependence

The Alcohol Use Disorders Identification Test (AUDIT)

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I amgoing to ask you some questions about youruse of alcoholic beverages during this past year. "Explain what is meant by "alcoholic beverages"by using local examples of beer, wine, vodka,etc. Code answers in terms of "standard drinks".Place the correct answer number in the box atthe right.

1.How often do you have a drink containing alcohol?

(0) Never [Skip to Qs 9-10]
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

2. How many drinks containing alcohol do youhave on a typical day when you aredrinking?

(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

3.How often do you have six or more drinkson one occasion?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

4. How often during the last year have youfound that you were not able to stop drinking once you had started?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

5. How often during the last year have youfailed to do what was normally expectedfrom you because of drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

7. How often during the last year have youhad a feeling of guilt or remorse after drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

8.How often during the last year have youbeen unable to remember what happened the night before because you had been drinking?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

9. Have you or someone else been injured as aresult of your drinking?

(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

10. Has a relative or friend or a doctor or an-other health worker been concerned aboutyour drinking or suggested you cut down?
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

Skip to Questions 9 and 10 if total score forquestions 2 and 3 = 0

Interpretation-

Total scores of 8 or more are recommended asindicators of hazardous and harmful alcohol use,as well as possible alcohol dependence. AUDIT scores in the range of 8-15 represent amedium level of alcohol problems whereasscores of 16 and above represented a high levelof alcohol problems.

History

Sources of information

While assessing an individual for alcohol dependence, the information can be obtained from the patient, family members, significant others including friends and treatment records. Denial and minimization are commonly observed among individuals with alcohol dependence. It is helpful to corroborate the information from different sources. However, even in case the clinician suspects that the information is being withheld by the patient, it should not become a barrier to the therapeutic process. More information can be expected during the subsequent interviews.

Information to be obtained

Apart from socio-demographic details, information should be obtained with regards to pattern of alcohol use, type of alcohol beverage used, duration of use, features of alcohol dependence, alcohol related complications (physical, psychological, familial, social, vocational, financial, legal), past abstinence attempts, and level of motivation. Information should also be obtained for possible high- risk sexual behavior.

Past history of any medical illness, psychiatric disorder, family history and personal history should also be obtained. All this information is important in psychosocial management.

Physical examination

A thorough general and systemic examination must be carried out for all patients with alcohol dependence. Physical examination can reveal features of alcohol intoxication or withdrawal (described in the previous section).

Additionally, physical examination helps identify presence of physical complications associated with alcohol use. Since patients with alcohol dependence may suffer from other medical

disorders, physical examination helps identify the associated medical conditions. One needs specifically to look at:

- Pulse: Could be low (intoxication) or high (withdrawal)
- Blood Pressure could be low (intoxication) or high (withdrawal or hypertension as a medical complication)
- Pallor: Seen in co-morbid anaemia
- Icterus: Indicative of hyperbilirubinemia (hepatic dysfunction)
- Generalised oedema: Indicates hypoproteinaemia (due to hepatic dysfunction)
- Abdomen examination: Look for hepatomegaly and signs of portal hypertension (caput medusa)

Chronic medical conditions that are associated with problematic alcohol use are listed in table 5. It is recommended to look for presence of clinical features associated with these medical conditions.

Table 3. Chronic medical conditions that are associated with problematic alcohol use (list is not all inclusive) (Shield et al, 2013)
A. **Chronic medical conditions that may be attributed to alcohol** • Alcoholic gastritis • Alcoholic liver disease • Alcoholic fatty liver • Alcoholic hepatitis • Alcoholic fibrosis and sclerosis of liver • Alcoholic cirrhosis of liver • Alcoholic hepatic failure • Alcoholic liver disease, unspecified • Alcohol-induced acute pancreatitis • Alcohol-induced chronic pancreatitis • Alcoholic polyneuropathy • Degeneration of nervous system attributed to alcohol • Amnesic syndrome • Psychotic disorder • Residual and late-onset psychotic disorder • Other mental and behavioral disorders • Unspecified mental and behavioral disorder

• Alcoholic myopathy • Alcoholic cardiomyopathy • Fetus and newborn affected by maternal use of alcohol • Fetal alcohol syndrome (dysmorphic)
B. **Chronic medical conditions for which alcohol consumption is a component cause** • Hypertensive heart disease • Ischemic heart disease and ischemic stroke • Alzheimer's disease and other dementias • Epilepsy • Unipolar depressive disorders • Diabetes • Cancer of various organs

Mental Status Examination (MSE)

Mental Status Examination (MSE) includes following assessments.

- General appearance and behaviour: Gait incoordination, abusiveness, dressing pattern, smell of alcohol from the body or during conversation
- Psychomotor activity: Increased or decreased
- Speech: Coherence/relevance
- Affect: Irritable, depressed
- Thought: Presence of any delusions, ideas of hopelessness, helplessness, worthlessness, suicidal ideation and risk
- Perception: Visual/auditory hallucinations
- Orientation: Disorientation to time/place/person in alcohol withdrawal delirium
- Attention and concentration, memory, intelligence, abstraction
- Judgment- intact/impaired
- Insight
- Level of motivation.

MSE identifies presence of any co-occurring psychiatric disorders, level of motivation and presence of complicated alcohol withdrawal.

INVESTIGATIONS

The **diagnosis of alcohol dependence is clinical** and is based primarily on the information obtained from history. Findings from the physical examination and MSE can help support the diagnosis. Investigations do not **help establish or refute presence of diagnosis of alcohol dependence. However, the investigations are warranted in a case of alcohol dependence for the following reasons-**

- To assess presence of **medical illness** (secondary to alcohol use or independent)
- To monitor side effects/ adverse effects associated with medications used for management of alcohol dependence
- To rule out possible differential diagnosis of complicated alcohol withdrawal (delirium tremens)

The choice of investigations is guided by the information obtained from history and findings during examination. These can include biochemical investigations such as liver function test, neuroimaging such as CT scan, other radiological investigations such as endoscopy. Table 6 summarizes the important investigations indicated in a patient with alcohol use disorder.

It is recommended to get a base line haemogram (including haemoglobin, total leucocytes count, differential leukocyte count, peripheral blood smear); random blood sugar; liver function tests (serum bilirubin, SGOT, SGPT); and renal function test (serum creatinine, blood urea) for all patients with alcohol dependence.

Table 4. Investigations along with indications in a patient with alcohol dependence (list is not all inclusive)

Investigations	**Indications**
Haemoglobin	Nutritional deficiency
Peripheral blood smear	Nutritional deficiency
Total Leucocyte Count and Differential Leucocyte Count	Infection (possible cause of delirium)
Blood glucose	Hypoglycaemia (possible cause of delirium)

Serum electrolyte levels	Dyselectrolytemia (possible cause of delirium)
Serum bilirubin	Hepatic dysfunction
SGOT/ SGPT	Hepatic dysfunction

Table 5. Specific investigations along with indications (for higher centres)	
Investigations	**Indications**
Prothrombin time	Hepatic dysfunction
Serum albumin/ globulin ration	Hepatic dysfunction
CT scan- Head	Head injury (possible cause of delirium)
USG abdomen	Hepatic damage
Upper Gastro-intestinal tract endoscopy	Oesophageal varices
Fibroscan	Cirrhosis of liver

TREATMENT

Phases of treatment

Treatment of alcohol dependence can be discussed under two distinct, but complimentary phases- the initial short- term management phase (also known as detoxification) and the later long- term management phase.

Short- term management phase

As mentioned earlier, the short- term management phase is also known as **detoxification.**

Aims

Aims of detoxification are as follows-

- To manage alcohol withdrawal
- To prevent complicated alcohol withdrawal
- To manage complicated alcohol withdrawal
- To manage the associated medical (including psychiatric) complications
- To establish rapport with the patient
- To prepare the patient for the long term management phase

Setting

The treatment for alcohol dependence can be carried out in the out-patient as well as in-patient settings. The choice for the setting can be guided by the patient, clinician as well as treatment facility related variables. **Some of the indicators for in-patient management are as follows-**

- Presence of **severe alcohol dependence** (drinks over 30 units of alcohol per day or regularly drinks between 15 and 30 units of alcohol per day and have significant psychiatric or physical co-morbidities)
- Presence of or **anticipated severe withdrawal**
- Presence of complicated withdrawal (withdrawal with seizures or delirium)
- History of complicated withdrawal (withdrawals with seizures or delirium)
- Co-occurring significant physical illness
- Co-occurring significant psychiatric disorder
- Concurrent abuse/ dependent use of other psychoactive substances including benzodiazepines
- Poor psychosocial support
- Distance from treatment centre that precludes regular follow up
- Failure of out-patient detoxification in past
- Pregnancy
- Children and adolescents
- Elderly
- Personal preference for in-patient treatment

Simple alcohol withdrawal

Specific assessment for alcohol withdrawal is based on clinical history and examination (physical and mental status) of the patient.

There is history of recent cessation of alcohol use that has been heavy and prolonged. Additionally, there is **presence of clinical features associated with alcohol withdrawal**. These include tremor of the outstretched hands, tongue or eyelids, sweating, nausea, retching or vomiting, tachycardia or hypertension, psychomotor agitation, headache, insomnia, malaise or weakness, transient visual, tactile or auditory hallucinations or illusions, and grand mal convulsions.

Alcohol withdrawal **typically develops 6 to 8 hours after the cessation of drinking**. Tremulousness is usually one of the earliest signs of alcohol withdrawal. The **psychotic and perceptual symptoms begin in 8 to 12 hours after cessation of alcohol** use. The withdrawal reaches peak intensity on the second or third day, and markedly diminishes by the fourth or fifth day.

It is important to rule out other causes of the clinical presentation based on history, examination and relevant investigations.

Complicated alcohol withdrawal

At times, patient with alcohol dependence develops what is known as '**complicated withdrawal'**. It is observed among **3-5% of dependent users**, and is characterized by presence of **seizures or delirium** (known as delirium tremens) along with other features associated with alcohol withdrawal.

The alcohol withdrawal seizures typically develop 12 to 24 hours after cessation of drinking. These are generalized and tonic-clonic in character. Patients often have more than one seizure 3 to 6 hours after the first seizure. Status epilepticus is relatively rare.

Delirium tremens develops between 2- 5 days of cessation of alcohol use, but can appear even up to a week after stopping alcohol use. It is characterized by disturbance of consciousness, reduced ability to focus, to sustain, or to shift attention, a change in cognition (such as memory deficit, disorientation, or language disturbance), and perceptual disturbance. Additionally there can be disturbance of mood or sleep wake cycle, impairment in recent memory, delusion and

evening worsening of symptoms, with severe agitation and coarse tremors of limbs and body. Delirium is potentially life threatening if left unattended.

It is important to exclude other possible causes of delirium like fluid and electrolyte disturbance, physical conditions like hepatic dysfunction, possibility of head injury, etc.

Medications

Benzodiazepines share tolerance with alcohol (cross tolerance) and hence can be used for management of alcohol withdrawal. Several meta-analyses have supported efficacy of benzodiazepines in reducing the severity of withdrawal, prevention of delirium and withdrawal seizures. These are recommended as the first line of treatment of alcohol withdrawal. Long acting benzodiazepines (such as chlordiazepoxide and diazepam) are preferred over short acting benzodiazepine for this purpose. Short acting benzodiazepines (such as **oxazepam and lorazepam) are preferred in liver damage, in elderly and in people with cognitive dysfunction**. However, the short acting benzodiazepines have to be administered more frequently to manage withdrawal. The equivalent dose of different benzodiazepines that are commonly used in management of alcohol withdrawal have been provided in table 8.

Table 6. Approximate therapeutic dose equivalent of different benzodiazepines commonly used in management of alcohol withdrawal

Benzodiazepine	**Dose equivalent (mg)**
Chlordiazepoxide	25
Diazepam	10
Lorazepam	2
Oxazepam	30
#Dosing frequency, duration and dose reduction depends on the regimen used for withdrawal management	

Treatment regimen

Benzodiazepines for management of alcohol withdrawal (detoxification) can be administered using either of the three administration regimens. These include **fixed dose schedule, symptom triggered dosing, and front loading schedule (table 7).**

A fixed dose schedule involves starting treatment with a standard dose determined by the recent severity of alcohol dependence and/or typical level of daily alcohol consumption, followed by reducing the dose to zero usually **over 7 to 10 days.** The starting dose of benzodiazepine is guided by the severity of dependence and expected severity of the withdrawal. The starting dose of benzodiazepine can vary **from 15 mg four times a day (q.d.s.) to 50 mg four times a day (q.d.s.) of chlordiazepoxide dose equivalent (or 10 mg three times a day to 25 mg three times a day of diazepam dose equivalent)**. The same dose is usually maintained over the next two days. The dose reduction is made at the rate of 20% every day or 25% every alternate day.

A **symptom triggered dosing approach involves monitoring of the patient on a regular basis and pharmacotherapy is** administered according to the patient's level of withdrawal symptoms (ranging from 10-20 mg dose equivalent of diazepam per administration). Pharmacotherapy continues as long as the patient is displaying withdrawal symptoms and the administered dose depends on the assessed level of alcohol withdrawal. The severity of the alcohol withdrawal and response to treatment can be assessed objectively using structured rating scales. One of the most commonly used and recommended instrument for this purpose is revised **Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar).** It includes 10 items which are the common symptoms and signs of alcohol withdrawal- nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbance, headache, orientation and clouded sensorium. All items are scored from 0-7 with the exception of the orientation category, scored from 0-4. Scoring is done as 0-9 absent or minimal withdrawal, 10-19 mild to moderate withdrawal, and severe with score greater than 20.

A **front-loading regimen involves providing the patient with an initially high dose of medication (30-40 mg dose equivalent of diazepam**), and then using either a fixed dose schedule or symptom triggered dosing approach. Usually, very little additional medication is necessary after initial loading in this regimen.

Table 7. Different regimens for alcohol withdrawal management (detoxification)		
Fixed dose schedule	Starting treatment with a standard dose determined by the recent severity of alcohol dependence	Reducing the dose to zero usually over 7 to 10 days at the rate of 20% every

	and/or typical level of daily alcohol consumption	day or 25% every alternate day
Symptom triggered dosing	Pharmacotherapy is administered according to the patient's level of withdrawal symptoms.	Pharmacotherapy continues as long as the patient is displaying withdrawal symptoms and the administered dose depends on the assessed level of alcohol withdrawal
Front loading schedule	An initially high dose of medication is adminitered and subsequently either a fixed dose schedule or symptom triggered dosing approach is used	Depends on the regimen used.

There is some evidence to indicate the superiority of symptom-triggered regimens. The use of fixed dosing schedule is recommended for general care in community and symptom triggered dosing is preferred when close observation is possible. Symptom triggered dosing is not recommended in the patients with a past history of withdrawal seizures.

Benzodiazepine doses **may need to be reduced by about 50% in the geriatric population**, and in persons with liver impairment.

Dose and duration of drug treatment depends on quantity of alcohol daily used/last dose, time elapsed after the last dose of alcohol, severity of alcohol withdrawal symptoms at the initiation of treatment, presence of medical co-morbidities (specifically liver dysfunction) and psychiatric co-morbidities. So, the dose and duration needs to be individualized.

Along with benzodiazepines, the alcohol withdrawal management includes general nursing care in form of maintaining **hydration and nutritional** status. There is no consensus on adequate dose and duration of thiamine supplementation during management of alcohol withdrawal. In all cases of alcohol detoxification it is recommended to give **oral thiamine for minimum of three months**. All patients in alcohol withdrawal should receive at least **250 mg thiamine by the parenteral route once a day for the first 3-5 days.** Those with **suspected**

Wernicke's encephalopathy should receive 500 mg/day thiamine for 3-5 days. The symptoms of Wernike's encephalopathy are confusion, ataxia and nystagmus. Ophthalmoplegia may occur in severe cases. After receiving the parenteral thiamine, the supplementation can then be continued orally. Also, any parenteral administration of glucose during withdrawal management should not be done without addition of thiamine.

Management of alcohol withdrawal seizures

Effective management of alcohol withdrawal is preventive against emergence of withdrawal seizures. The **alcohol withdrawal seizures can be managed by both short acting (lorazepam-considered to be more effective by some) and long acting (diazepam) benzodiazepine**s. Benzodiazepines can be given either orally or parenterally. However, diazepam should only be given through intravenous route if administered parenterally because of their erratic absorption by intra-muscular route.

Seizure prophylaxis with lorazepam 2 mg intravenously must be given to all patients with seizures in the current withdrawal period at presentation and also in those with past history of withdrawal seizure. The dose should be tapered down starting at a high dose that should be gradually reduced once the seizures have been controlled. Sufficient benzodiazepines should be given to keep the patient calm and sedated, and manage other alcohol withdrawal symptoms.

Prophylactic use of anticonvulsants such as phenytoin is not recommended except in cases of co-occurring (non- alcohol withdrawal related) seizure disorder and alcohol use. A thorough neurological and general medical evaluation should be done to exclude any other possible cause of seizures among all patients who develop seizures during alcohol withdrawal.

Management of delirium tremens

Delirium tremens should be managed in inpatient setting. The patient should be kept under close supervision. Safety of the patient against any physical harm should be ensured. Water and electrolyte balance and nutritional status should be maintained. **The benzodiazepines are more effective than antipsychotic medicines in reducing mortality in alcohol withdrawal delirium**. These can be administered through parenteral route in sufficient dosages with an aim

to make the patient clam and sedated. An initial **dose of 10 mg diazepam is given intravenously**. Further doses of 10 mg can be r**epeated every 5-20 min interval. The aim is to make the patient calm and sedated**. The dose can be increased to 20 mg per bolus for the subsequent boluses if the first two boluses do not calm the patient down. The patient with delirium tremens can have lucid intervals in between. Hence it is important to be vigilant about reemergence of the clinical features of delirium. Subsequently the patient can be shifted to oral benzodiazepines and the dose can be gradually tapered down.

General Nursing Care

Nurses should consider patient safety and injury prevention.The patient should be appropriately monitored and emergency airway equipment kept at the bedside, especially for those who require injectable benzodiazepines.

- **Restraints:** The critically ill patient experiencing moderate to severe AWS symptoms may require both chemical and physical restraints to avoid immediate threat behavior to self and others. Use of bed rails is advisable.
- **Managing behavioural disturbance:** If the patient is confused and disoriented or hallucinating, a supportive and reassuring approach is to be used and patient should not be confronted.
- **Managing environment**. The patient's room should be kept quiet everyone should move around quietly. Interaction should be minimal and questions limited.
- **Nutritional needs.** The patient may be malnourished, causing folate, thiamine, or vitamin B12 deficiency. If the patient is unable to eat, tube feedings or total parenteral nutrition (TPN) should be initiated early. If a feeding Ryle's tube is used it is taped at the nose and cheek area, with the tubing running toward the head and behind the bed.
- **Involving family:** A complete care plan should involve family members in a therapeutic alliance to provide optimal symptom relief and formulate acceptable behavior objectives for the patient.

Motivational Enhancement Therapy (MET)

Patients with alcohol dependence can be in different stages of change with regards to their alcohol use. These include **pre-contemplation stage** (when an individual has not yet

contemplated bringing in a change), **contemplation stage** (when an individual is still debating the pros and cons of continuing with alcohol use or quitting it), **preparation stage** (when an individual has recognized the need to change and is making preparations towards the same), **action stage** (when an individual, has taken steps towards quitting alcohol use, e.g. seeking treatment) and **maintenance stage** (when an individual has modified his alcohol use pattern and maintaining the same). The short-term management phase for alcohol dependence can be used to further enhance the motivation of the patient and strengthen the commitment to change towards an alcohol-free life style. **Motivational enhancement therapy (MET)** can help achieve this. It utilizes different principles such as **expressing empathy through reflective listening, developing discrepancy between clients' goals or values and their current behavior, avoiding argument and direct confrontation, adjust to client resistance rather than opposing it directly, supporting self-efficacy and optimism**.

Appropriate motivational strategies for each stage of change could be as follows:

Precontemplation: Establish rapport, build trust. Raise doubts or concerns in the person about substance using pattern. Explore the meaning of vents that brought the patient to treatment or the results of previous treatment. Elicit the patient's perception of the problem. Give factual information about the risk of sub-stance use. Provide personalized feedback about assessment findings. Explore the pros and cons of substance use. Examine the discrepancies between the patient and others perception of the problem behavior. Express concern and keep the door open.

Contemplation: Normalize ambivalence; help the patient tip the decisional balance scale to-wards change by eliciting and weighing pros and cons of substance use and change. Change extrinsic and intrinsic motivation. Examine the patient's personal values in relation to change. Emphasize the choice of responsibility and self-efficacy. Elicit self-motivational statements of intent and commitment. Elicit ideas regarding perceived self-efficacy and expectations to-wards treatment. Summarize self-motivational statements.

Preparation: Clarify the patient's own goal and strategies for change. Offer a menu of options. With permission, offer advice. Negotiate a change or treatment plan and behavior contract. Counter and lower barriers to change. Help the patient enlist social support. Explore treatment expectancies and the patient's role. Elicit what has worked in the past for him or others whom he

knows. Assist the patient to negotiate finances, child care, work or other barriers. Have the person publicly announce plans to change.

Action: Engage the patient in treatment and reinforce the importance of remaining in recovery. Support a realistic view of change through small steps. Acknowledge difficulties for the person in early stages of change. Help in identifying high risk situation and develop appropriate coping strategies to overcome them. Assist in finding new reinforcers of the change. Help in assessing whether the person has strong family and social support.

Maintenance: Help in identifying and sample drug free sources of pleasure. Support life style change. Affirm person's resolve and self-efficacy. Assist in practicing the use of new coping strategies to avoid return to drug use. Maintain supportive contact. Develop a 'fire-escape' plan if the patient resumes substance use. Review long term goals (Substance Use Disorder Manual).

Long-term management phase

While the short-term management phase is an important and essential stage in management of alcohol dependence, it in itself is not sufficient to achieve the long-term abstinence from alcohol. In order to reduce the risk of relapse and improve treatment outcome, it is important to **integrate the short-term management phase into the long-term management p**hase. There is no clear-cut demarcation between the short-term and long-term management phases, but long-term management phase usually begins, once the initial withdrawal management from alcohol has been achieved and the patient is reasonably comfortable to participate in the long-term management phase.

Aims

Aims of the long term management phase are as follows-

- To consolidate the progress made during the short-term management phase
- To maintain abstinence from alcohol
- To prevent and delay relapse
- Management of physical and psychological complications associated with alcohol use
- Vocational rehabilitation
- Addressing other familial, social and legal complications associated with alcohol dependence

Setting

The long-term management phase does not require hospitalization and can be carried out from the **outpatient setting**. However, in case a patient requires longer hospitalization (e.g. due to management of a medical complication of alcohol use), the long-term management phase can start in the in-patient setting itself.

Medications

Various medications that can be used in long-term management of alcohol dependence include **acamprosate, naltrexone, disulfiram**.

Acamprosate: Acamprosate is **an anti-craving medication** that is used for **long-term management of alcohol dependence.** It is hypothesized that it acts as a functional glutamatergic NMDA antagonist. It has been found to be more effective than placebo in maintaining abstinence and in preventing relapse in meta-analysis. it is relatively safe in lid to moderate hepatic dysfunction.

It is available as 333mg tablets. The usual **daily dose of acamprosate ranges from 1332 mg/day (body weight < 50 kg; dosing schedule- Tab. Acamprosate (333 mg) 1-1-2- one tablet each in morning and afternoon and two tablets at bedtime) to 1998 mg/day (body weight> 50 kg; dosing schedule- Tab. Acamprosate (333 mg) 2-2-2, two tablets thrice a day).**

Disulfiram: Disulfiram is a **deterrent medication**, used for long-term management of alcohol dependence. It is an irreversible inhibitor that **blocks aldehyde dehydrogenase**, causing accumulation of acetaldehyde if alcohol is consumed, resulting in what is known as **disulfiram-ethanol reaction (DER**).

Disulfiram should always be started after a **written informed consent** of the patient. The patients using disulfiram also need to be informed to **avoid all forms of alcohol containing items (including alcoholic beverages, after shave lotions, food items containing vinegar, medications such as metronidazole etc.).**

The usual dose of disulfiram is 250 mg/ day. The first dose of disulfiram should be administered at least 24 hours after the last dose of alcohol. It is advisable to administer the dose under supervision. In case a patient fails to experience DER with 250 mg/day, the dose can be increased to 500 mg/ day, which can further be increased up to 750 mg/ day. However, one should ensure compliance prior to hiking the dose.

The **DER** includes **sweating, warmth and flushing, hyperventilation, respiratory difficulty, respiratory depression, blurred vision, throbbing headache**, thirst, nausea, vomiting, chest pain, palpitations, hypotension, tachycardia, cardiovascular collapse, arrhythmia, myocardial infarction (in individuals with preexisting coronary artery disease), acute congestive heart failure (in individuals with preexisting myocardial dysfunction), vertigo, syncope, marked uneasiness, confusion, seizures, unconsciousness, death (rarely, in case of very severe reaction).

Severity of DER depends on the amount of alcohol consumed and individual related variables. There is potential for a reaction with alcohol for up to 2 weeks after stopping disulfiram. The fall in blood pressure should be controlled on a priority basis. If DER is mild, assurance and oral fluids suffice. In patients with moderate or severe DER, intravenous fluids and, in some patients, dopamine infusion is necessary to control the severe hypotension.

Liver function tests (especially SGOT and SGPT levels) should be carried out at base line prior to initiation of disulfiram and then every 2 weeks for the first 2 months of therapy. Subsequently it can be performed once every three months.

Naltrexone

Naltrexone is another anti-craving agent used for long-term management of alcohol dependence. It is thought to act by preventing the opiate receptor mediated euphoric and rewarding effects of alcohol by blocking the opioid receptors. Oral naltrexone has been shown to reduce return to heavy drinking.

Oral Naltrexone is given at dose of 50mg/ day.

It is recommended to get baseline liver function tests prior to starting naltrexone. Liver function test should be repeated periodically (monthly for the first three months, and subsequently once every three months) to monitor for emergence of hepatic side effects of the medication.
Additionally, naltrexone and acamprosate can be used in combination. Also, disulfiram can also be used in combination with naltrexone and acamprosate.

Table 10 summarizes some of the common side effects and contraindications to use of these medications.

Table 8. Common side-effect of the medicines used in long term management phase for alcohol dependence

Medicine	**Common side-effects and contraindications to use**	**Dose**	**Frequency**	**Duration**
Acamprosate	Diarrhea with abdominal pain, nausea, vomiting, pruritus **Contraindications**- hypersensitivity reaction, pregnancy and breastfeeding, renal insufficiency (serum creatinine more than 120 micromoles per litre), severe hepatic failure FDA pregnancy category C	1332 mg/day (body weight < 50 kg) to 1998 mg/day (body weight> 50 kg	TDS	One year
Disulfiram	Drowsiness, fatigue, abdominal pain, headache, nausea, diarrhea, allergic dermatitis, metallic or garlic like after taste **Contraindications (absolute)**- hypersensitivity reaction , pregnancy and breast feeding **Contraindications (relative)-** cardiovascular problems, severe personality disorder, suicidal risk,	250mg/day	OD	One year

	psychosis FDA pregnancy category C			
Naltrexone	Nausea, headache, abdominal pain, reduced appetite and tiredness **Contraindications-** acute liver failure (caution is suggested when serum aminotransferases are four to five times above normal) FDA pregnancy category C	50 mg/day	OD	One year

Duration of treatment

There is limited consensus on duration of use for medications used in long term phase of management of alcohol dependence. It is **advisable to continue these medications for a period of 9-12 months.** These can be continued even longer if deemed appropriate by the clinician and the patient. Risk of relapse, status of rehabilitation of the patient and patient's confidence to live without the support of the medications are some of the factors that can help decide on the duration of treatment.

Psychosocial interventions

It has been shown that **utility of pharmacological therapies** can be enhanced when combined with non-pharmacological interventions. It is recommended to offer pharmacological interventions for alcohol dependence in conjunction with psychosocial interventions.

The **goal of psychosocial interventions in long term management of alcohol dependence include improved therapeutic adherence, achieving sustained drug free status, encouraging and supporting drug free life style and rehabilitation** of the patient.

Psycho-social interventions include **motivational enhancement therapy (MET), cognitive behavior therapy (CBT), relapse prevention (RP), contingency management (CM) and family therapy.**

MET has been discussed in the section on short-term management of alcohol management.

CBT is based on the social learning theories aimed at improving self-control and social skills. This leads to promotion of a drug free life style.

RP is aimed at helping the alcohol dependent individuals to delay lapse and prevent relapse. It involves various steps used to help patients develop greater self-control over alcohol use behaviors.

CM is a behavioral therapy that helps support alcohol free life style by making rewards contingent of alcohol free status.

Family therapy help address the issues in the context of family of alcohol dependent individual. These include inter-personal problems, expressed emotions, etc.

Additionally, it is important to help the patient with vocational rehabilitation.

Timing of psychosocial interventions

The **psychosocial interventions should be started as early as possible in the management of alcohol dependence**. The relevant psychosocial interventions can be initiated once the patient is physically comfortable and in a position to attend the sessions. This can be done even during the short-term phase of management.

Settings for psychosocial interventions

The psychosocial interventions can be offered both in inpatient as well as outpatient settings. When a patient receives the short-term management for alcohol dependence in inpatient setting, psychosocial interventions can start in the inpatient setting and then can be continued on the outpatient basis.

Brief interventions (BI)

Those who are using alcohol but not in a dependent pattern could also be at increased risk of experiencing harms associated with alcohol use in immediate future or even later. Individuals having harmful or hazardous pattern of alcohol use can benefit from Brief

Intervention (BI). Such individuals usually do not require medicines and can be helped using short term interventions aimed at changing their behavior by helping them understand how their alcohol use puts them at risk and to reduce or give up their alcohol use. Brief Interventions usually last from 5 minutes of brief advice to 15-30 minutes of brief counseling. While BI help address the problematic or risky substance use, these are not intended to treat people with alcohol dependence.

The consistent features in BI have been summarized by Millerand Sanchez (1993) using the acronym **FRAMES: Feedback, Responsibility, Advice, Menu of options, Empathy and Self-efficacy (confidence for change).**

- The provision of giving personally relevant feedback after assessment such as individual's drug use and problems and associated personal risks is a key component of brief intervention.
- Personal responsibility is emphasized so as to bring about change in behavior.
- Advice about changing the drug taking behavior is given in a non-judgemental manner.
- Alternative strategies to cut down or stop their substance use are given.
- Empathic counselling and understanding approach to encourage the patient's confidence so as to promote self- efficacy in their behaviour is used.

REFERRAL CRITERIA

The following are the indications for referral to a higher centre:

- Presence of **co-morbid psychiatric condition** that cannot be managed at the primary care or secondary care level
- **Physical comorbidity of serious nature** for which adequate infrastructure and support may not be available (e.g., decompensated cirrhosis with imminent risk of hepatic encephalopathy; actively bleeding peptic ulcer; pancreatitis, uncontrolled seizures, etc.). In such circumstances, liaison should be made for transfer to other specialist departments or to emergency services for stabilization of patient's physical condition first.
- **Presence of a co-morbid substance use** disorder for which treatment is not available at primary/secondary hospital setting (e.g. opioid substitution therapy for opioid dependence)
- Non-availability of professionals to administer psycho-social interventions

VI. WHO DOES WHAT AND TIMELINES

The roles and responsibilities of various members of treatment team in management of alcohol dependence are as follows-

a. Doctor

The doctor shall be the overall in-charge of the treatment team. The doctor coordinates and supervises other members of the treatment team. Additionally, he will be responsible for the clinical assessment (history taking, physical examination, MSE), formulation of management plan, selection of investigations, initiation and continuation of the pharmacological treatment. The doctor shall also make the decision regarding the requirement of referral to a higher center.

b. Clinical psychologist/ counsellor

The clinical psychologist/ counselor is responsible for psychosocial assessment and interventions.

c. Nurse

The nurse is responsible for general nursing care, regular observation and monitoring of the patient, administration of medications, offering feedback to the team regarding the patient based on observations made.

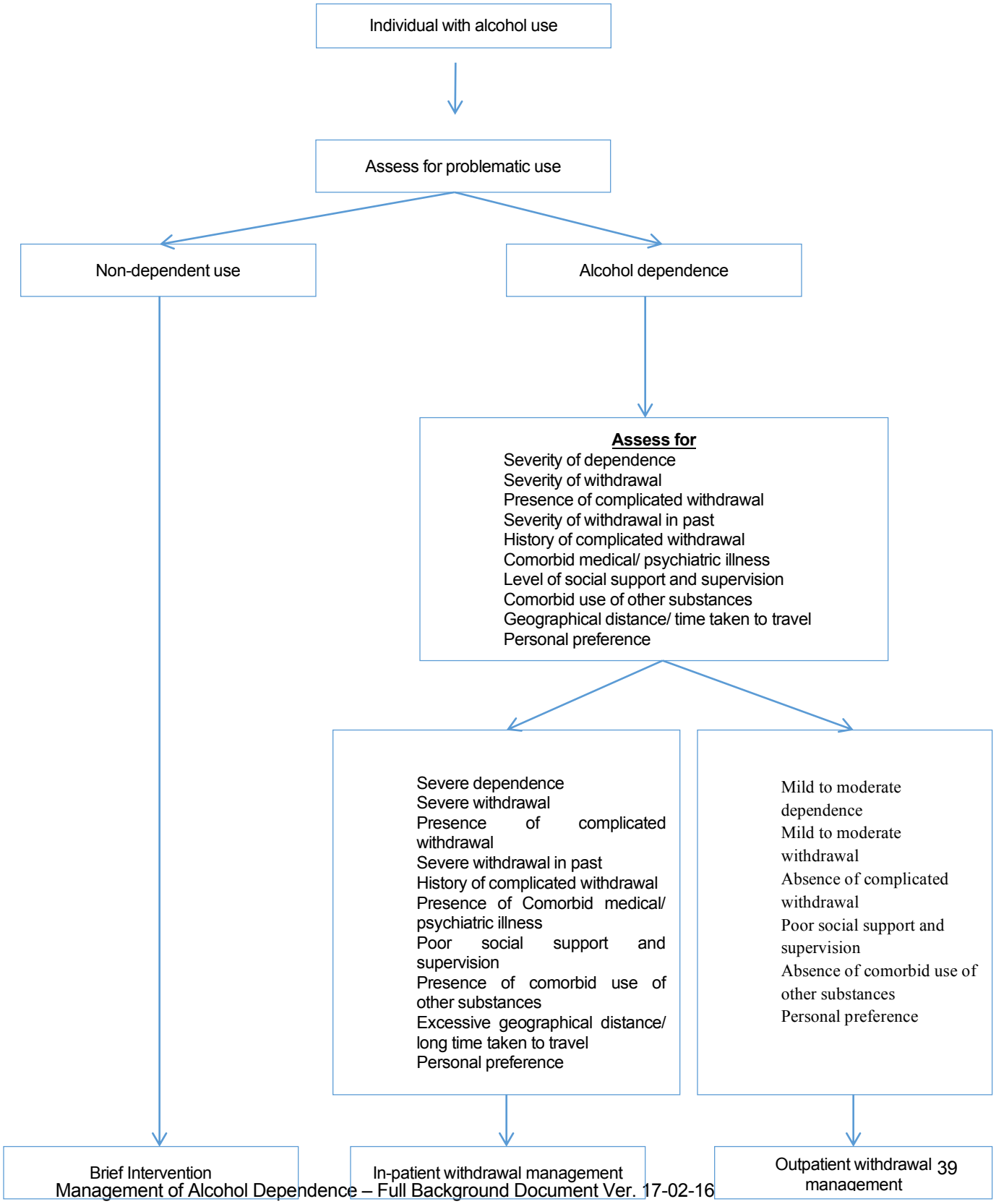
d. Medical Social Worker (MSW)

The Medical Social Worker (MSW) carries out assessment of the patient on psychosocial issues and helps the patient in vocational rehabilitation. MSW also be establishes contact with the family members/ significant others and contacts the patient in case of treatment drop out.

Timeline of various activities/ interventions

A suggested time line for various activities/ interventions in the management of alcohol dependence is shown in figure 1. It can be modified and individualized, based on the requirements of a particular patient based on the clinical judgment of the patient.

VII. Clinical Pathways for Management of Alcohol Dependence



VIII. How these Guidelines were developed

Background

A Task Force was constituted in December 2014 to guide the development of Standard Treatment Guidelines (STG) in India for application in the National Health Mission. The Task Force subsequently approved the draft STG development manual of India (Part 1) for development of adapted guidelines. In addition, it approved a list of 14 topics recommended by a subgroup of the task force appointed to select prioritized topics for STG development. These 14 topics are from 10 clinical specialties for which the first set of STGs will be developed. The topic of Management of Alcohol Dependence was included in this first list and was the dealt with by the Psychiatry clinical subgroup.

Formation of STG Group on Psychiatry

A multidisciplinary group composed of a mix of primary care practitioners, academicians and practicing psychiatrist was constituted with Dr. Rakesh Chadda as the facilitator of the group. Following were the members of group-

Coordinator	Dr Rakesh Chadda Professor of Psychiatry AIIMS, New Delhi drrakeshchadda@gmail.com
Experts	Prof Rakesh Lal Professor of Psychiatry Deptt of Psychiatry & National Drug Dependence Treatment Centre (NDDTC) AIIMS, New Delhi 110029 rakeshlall@rediffmail.com Prof Debashis Basu Professor of Psychiatry PGIMER, Chandigarh 160012 db_sm2002@yahoo.com Dr Nitin Gupta Associate Professor Department of Psychiatry Govt Medical College & Hospital, Chandigrah nitingupta659@yahoo.co.in Dr Yatan PS Balhara Asstt. Professor Deptt of Psychiatry & NDDTC AIIMS, New Delhi 110029

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The group was constituted 7 August 2015. All the members signed the declaration of Interest. First face to face Meeting was held on 17 August 2015 attended by Drs Chadda, Lal, Balhara, Rachna,, Bichitra. Scope decided as guidelines on alcohol dependence for use in different settings. Uncomplicated cases can be managed as outpatient and management does not differ across different setting. Complicated cases and those with co morbid problems need specialist input and can be managed only in secondary or tertiary care.
First draft got ready on 10th Sept 2015; shared on email amongst the group.
Second Face to Face Meeting was held on 13 Sept 2015. Draft modified as per discussion and submitted on 6 Oct 2015 to the Internal Harmonization Group of STG Taskforce. The draft document was reviewed by Internal Harmonization Group on 24th of October 2015 consisting of Dr. Sangeeta Sharma (IBHAS), Dr. Anil Gurtoo (LHMC), Dr. Om Sai Ramesh (LHMC), Dr. Babban Jee (ICMR) and Dr. Nikhil Prakash (NHSRC). The comments of internal harmonization group were received on 8th of Novemeber 2015. Third Face to Face Meeting was called on 13 Nov 2015 Attended by Drs Chadda, Lal, Balhara, Rachna,, Bichitra. The Revised draft was prepared and further discussed meeting on third 3 Dec 2015.

Search and Selection of Evidence Based Guidelines

In view of the paucity of time available to develop this guideline, a decision was taken by the Task Force for the Development of STGs for the National Health Mission that these STGs would be adopted and/or adapted from existing evidence based guidelines to make them relevant to our context, resource settings and priorities.

A search was conducted for evidence based guidelines which had been framed using evidence based methodology and using international guideline development criteria.

Following guidelines were selected for Adapting/Adopting recommendations based strength of evidence, currency of guidelines and suitability to Indian context.

Table 9. List of available guidelines on management of alcohol dependence and the guidelines referred to for the purpose of the current guideline

List of the available guidelines	Guidelines consulted for the current guideline	Rationale for considering the source guideline
Alcohol use disorders- Diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE clinical guidelines. National Institute for Health and Clinical Excellence, UK, 2011.	Alcohol use disorders- Diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE clinical guidelines. National Institute for Health and Clinical Excellence, UK, 2011.	These guidelines are evidence based, have been created systematically, are some of the most recent documents on this topic, represent diverse settings across various countries including India and cover various aspects related to management of alcohol dependence.
Clinical practice guideline for Management of Substance Use Disorders (SUD). Department of Veterans Affairs Department of Defense, USA, 2009.	Clinical practice guideline for Management of Substance Use Disorders (SUD). Department of Veterans Affairs Department of Defense, USA, 2009.	
Clinical Practice Guidelines for the assessment and management of substance use disorders. Indian Psychiatric Society, 2014.	Clinical Practice Guidelines for the assessment and management of substance use disorders. Indian Psychiatric Society, 2014.	
Detoxification and Substance Abuse Treatment. *Treatment Improvement Protocol (TIP) Series, No. 45.* Center for Substance Abuse Treatment. Substance Abuse and Mental Health Services Administration (US); 2006.	Detoxification and Substance Abuse Treatment. *Treatment Improvement Protocol (TIP) Series, No. 45.* Center for Substance Abuse Treatment. Substance Abuse and Mental Health Services Administration (US); 2006.	
Drug and Alcohol Withdrawal Clinical Practice Guidelines – NSW. Mental Health and Drug & Alcohol Office, NSW Department of Health, Australia, 2007.	Global strategy to reduce the harmful use of alcohol. World Health Organization, 2010.	
Global strategy to reduce the harmful use of alcohol. World Health Organization, 2010.	Guidelines on treatment of alcohol problems. Australian Government Department of Health and Ageing, The University of Sydney, Australia, 2009.	
Guidelines on treatment of alcohol problems. Australian Government Department of Health and Ageing, The University of Sydney, Australia, 2009.	Incorporating Alcohol Pharmacotherapies Into Medical Practice. *Treatment Improvement Protocol (TIP) Series, No. 49.* Center for Substance Abuse Treatment. Substance Abuse and Mental Health Services Administration (US); 2009.	
Incorporating Alcohol Pharmacotherapies Into Medical Practice. Treatment Improvement Protocol (TIP) Series, No. 49.	Manual for Long Term Pharmacotherapy. NDDTC, AIIMS, New Delhi, 2013.	

Center for Substance Abuse Treatment. Substance Abuse and Mental Health Services Administration (US); 2009.		
Manual for Long Term Pharmacotherapy. NDDTC, AIIMS, New Delhi, 2013.	Quick reference guide to the treatment of alcohol problems. Australian Government Department of Health and Ageing, The University of Sydney, Australia, 2009.	
mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings. Mental Health Gap Action Programme. World Health Organization, 2010.	Substance Use Disorders. Manual for Physicians. NDDTC, AIIMS, New Delhi, 2013.	
Naltrexone and Alcoholism Treatment. Treatment Improvement Protocol (TIP) Series, No. 28. Center for Substance Abuse Treatment. Center for Substance Abuse Treatment. Substance Abuse and Mental Health Services Administration (US); 1998.	The Maudsley Prescribing Guidelines in Psychiatry, 2015.	
Practice guideline for the Treatment of Patients With Substance Use Disorders, Second Edition. American Psychiatric Association, USA, 2006.		
Quick reference guide to the treatment of alcohol problems. Australian Government Department of Health and Ageing, The University of Sydney, Australia, 2009.		
Substance Use Disorders. Manual for Physicians. NDDTC, AIIMS, New Delhi, 2013.		
The Maudsley Prescribing Guidelines in Psychiatry, 2015.		

Adoption/Adaption of Recommendations

Recommendations selected from various source guidelines are considered for adaptations/Adoption. Following is the summary of adaption/adoption of the key recommendations.

Table 10. Status of the adoption/ adaptation for the various recommendations used in the current guideline

Recommendations in the source guidelines	Whether adopted/ adapted	Rationale for adaptation
The diagnosis of alcohol dependence can be done using ICD-10 diagnostic criteria	Adapted	While some of the guidelines did not specify the process of reaching at a diagnosis of alcohol dependence, others recommended use of DSM. Since ICD- 10 is the WHO approved nosological system

		the same has been recommended for diagnosing.
The indicators for in-patient management during the short term phase of management are as follows: -Presence of severe alcohol dependence (drinks over 30 units of alcohol per day or regularly drinks between 15 and 30 units of alcohol per day) -Presence of or anticipated severe withdrawal or complicated withdrawal (withdrawal with seizures or delirium) -Co-occurring significant physical and psychiatric illness -Poor psychosocial support -Distance from treatment centre that precludes regular follow up -Failure of out-patient detoxification in past -Pregnancy, children and adolescents and elderly	Adopted	
Benzodiazepines are recommended as the first line of treatment of alcohol withdrawal.	Adopted	
Long acting benzodiazepines (such as chlordiazepoxide and diazepam) are preferred over short acting benzodiazepine for this purpose.	Adopted	
Short acting benzodiazepines (such as oxazepam and lorazepam) are preferred in liver damage, in elderly people.	Adopted	
Benzodiazepines for management of alcohol withdrawal can be administered using either of the following three administration regimens. -Fixed dose schedule -Symptom triggered dosing -Front loading schedule	Adopted	
Along with benzodiazepines, the alcohol withdrawal management includes general nursing care in form of maintaining hydration and nutritional status.	Adopted	
In all cases of alcohol detoxification it is recommended to give oral thiamine for minimum of three months.	Adopted	
All patients in alcohol withdrawal should receive at least 250 mg thiamine by the parenteral route once a day for the first 3-5 days.	Adopted	
Any parenteral administration of glucose during withdrawal management should not be done without addition of thiamine.	Adopted	
Management of alcohol withdrawal includes general nursing care aimed at: - Keeping the environment quiet - Prevention of injury to the patient and others - Maintaining hydration and nutrition		
Management of alcohol withdrawal seizure: -Effective management of alcohol withdrawal is	Adopted	

preventive against emergence of withdrawal seizures. -The alcohol withdrawal seizures can be managed by both short acting (lorazepam- considered to be more effective by some) and long acting (diazepam) benzodiazepines. -Benzodiazepines can be given either orally or parenterally.		
Management of delirium tremens: -Delirium tremens should be managed in inpatient setting. Safety of the patient against any physical harm should be ensured. -Water and electrolyte balance and nutritional status should be maintained. -The benzodiazepines are to be administered through parenteral route in sufficient dosages with an aim to make the patient clam and sedated. -An initial dose of 10 mg diazepam is given intravenously. Further doses of 10 mg can be repeated every 5-20 min interval. The dose can be increased to 20 mg per bolus for the subsequent boluses if the first two boluses do not calm the patient down. -Subsequently the patient can be shifted to oral benzodiazepines and the dose can be gradually tapered down.	Adopted	
Long-term management phase: The aim is to maintain abstinence from alcohol and to prevent and delay relapse.	Adopted	
The medications that can be used for this phase include acamprosate, naltrexone, dislufiram, baclofen.	Adopted	
Recommended psycho-social interventions: -Motivational enhancement therapy -Cognitive behavior therapy -Relapse prevention -Contingency management -Family therapy	Adopted	
Referral criteria: -Presence of co-morbid psychiatric condition that cannot be managed at the primary care or secondary care level -Physical comorbidity of serious nature for which adequate infrastructure and support may not be available -Presence of a co-morbid substance use disorder for which treatment is not available at primary/secondary hospital setting -Non-availability of professionals to administer psycho-social interventions -A complete care plan should involve family members to identify treatment options, appropriate supportive care beyond medication and monitoring may help decrease morbidity and mortality rates.	Adopted	
Prevention strategies: -Raising awareness and commitment among the	Adopted	

general public regarding harmful effects of alcohol use -Health services' response; -Community action; -Strict action against drunk-driving; -Regulating availability and marketing of alcohol; -Alcohol pricing policies; -Reducing the negative consequences of drinking and alcohol intoxication; -Reducing the public health impact of illicit alcohol and informally produced alcohol; -Monitoring and surveillance of sell of alcohol		

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Ethanol Toxicity

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Continuing Education Activity

Ethanol toxicity results from the ingestion of large amounts of ethanol, usually in the form of alcohol. It affects multiple organ systems in both the acute and chronic phases. This activity outlines the evaluation and management of ethanol toxicity and reviews the interprofessional team's role in managing patients with this condition.

Objectives:

- Identify the etiology of ethanol toxicity.
- Outline the appropriate evaluation of ethanol toxicity.
- Review the management options available for ethanol toxicity.
- Describe interprofessional team strategies for improving care coordination and communication of ethanol toxicity and improving outcomes.

Access free multiple choice questions on this topic.

Introduction

Ethanol toxicity results from the ingestion of ethanol, usually in large quantities. This can occur from the ingestion of beverage ethanol, commonly known as alcohol, and non-beverage ethanol, present in substances such as mouthwash, cologne, and cough medicine. Alcohol is the most common form of ethanol and is a widely used and abused substance, mostly in Western culture, representing the oldest and most widely abused substance. The demographic most likely to present for acute alcohol intoxication are adolescents and young adults. Emergency departments see disproportionately more of these patients than in other settings.[1][2]

Etiology

Ethanol toxicity can occur in both acute and chronic settings, representing two different spectrums of disease. Acute ethanol intoxication usually follows the ingestion of a large amount of alcohol and is a clinically harmful condition.[1]

Epidemiology

No demographic group is unaffected by alcohol, but adolescents and young adults are most likely to present for intoxication and toxicity. They are also most likely to present for traumatic injuries sustained while drinking alcohol. Approximately 3.3 million deaths can be attributed to alcohol use; it is the fourth leading preventable cause of death in the United States. One in 12 adults has alcohol use disorder, which is defined as more than 3 drinks a day in men and more than 2 drinks a day in females or binge drinking.[2][3]

Pathophysiology

Alcohol is absorbed through the proximal GI tract. It is primarily metabolized in the liver by alcohol dehydrogenase to acetaldehyde. The primary site of action in acute toxicity is the central nervous system, where it increases central nervous system (CNS) inhibition and decreases excitation. Gamma-aminobutyric acid (GABA) is the primary CNS inhibitory neurotransmitter. GABA binds to receptors allowing chloride to enter the cell, which decreases cellular excitability. Alcohol binds strongly to GABA receptors, activating the inhibitory cascade, which results in sedation, cognitive dysfunction, and decreased coordination.

With chronic alcohol use, the number of GABA receptors is increased, requiring more and more alcohol to create the same level of inhibition. This is a phenomenon known as tolerance. This tolerance partly explains the alertness of chronic alcohol users at blood alcohol levels that, in others, would cause coma or death. Benzodiazepines also bind to the GABA receptor, making them useful in alcohol withdrawal. Alcohol also inhibits the primary excitatory neurotransmitter in the CNS, glutamate. Patients with alcohol use disorder have increased numbers of NMDA receptors and increased sensitivity of these receptors to glutamate. Due to the increased sensitivity of these receptors, patients with alcohol use disorder are at risk for seizures and hallucinations when alcohol is withdrawn.[2][4][5]

History and Physical

Criteria for diagnosing alcohol intoxication include known or admitted ingestion of alcohol, behavior change, clinical signs including slurred speech, incoordination, nystagmus, memory loss, and lack of another condition to account for the symptoms. The signs and symptoms associated with alcohol toxicity depend on the blood alcohol concentration (BAC). As the BAC increases, so does the severity of the symptoms. At a BAC of 0 to 0.05%, one would expect to see relaxation, increased talkativeness, and decreased fine motor control. At a BAC of 0.05% to 0.1%, patients develop impaired judgment and coordination. From 0.1% to 0.2%, one sees gait instability, slurred speech, and mood and behavior changes. At a BAC of 0.2% to 0.4%, patients develop nausea and vomiting, hypothermia, dysarthria, amnesia, diplopia, and nystagmus. With a BAC of greater than 0.4%, patients can develop respiratory depression followed by coma and even death. The extent and severity of these symptoms vary depending on how quickly the alcohol is ingested and the rapidity of the rise and fall of the BAC.

The speed of absorption can be affected by co-ingested food, female sex, cigarette use, and concentration of alcohol in the beverage. It is also affected by tolerance to alcohol; a significant history of alcohol use can allow a patient to be conscious, cohesive, and free of motor deficits at BACs that would cause severe symptoms in patients without tolerance. It is important to ascertain the quantity and type of alcohol consumed and over which period of time it was consumed. Patients may complain of nausea, vomiting, and diarrhea. A full physical exam is necessary, with special attention paid to the vital signs, nutritional status of the patient, and skin findings such as capillary prominence, spider naevi, telangiectasia, palmar erythema, and muscular atrophy. As with all physical exams, airway, breathing, and circulation should be the first focus. Acute alcohol intoxication can cause respiratory depression; establishing that the patient is protecting their airway is of primary importance. The physical exam should be repeated often as some patients will become aware of injuries as their intoxicated state improves.[1][2]

Evaluation

Acute alcohol intoxication causes several metabolic abnormalities, including lactic acidosis, hypoglycemia, hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia. Laboratory analysis should include a full electrolyte panel as well as liver function tests. Alcohol can cause acute effects on the cardiovascular system, such as atrial and ventricular tachydysrhythmias. An EKG should be obtained. One particular syndrome known as “holiday

heart syndrome" can develop, which is characterized by new-onset arrhythmias following acute ingestion of alcohol and can include new-onset atrial fibrillation. Serial EKGs should be done if an arrhythmia is found, as the majority will resolve with the elimination of alcohol. If the EKG changes persist, an alternate cause should be considered. In the case of altered mental status, when a full history cannot be elucidated, a CT scan of the brain should be obtained to rule out any intracranial pathology contributing to the patient's mental status. Many intoxicated patients may state suicidal thoughts or make such gestures. A psychiatric evaluation should be performed and may have to be repeated as the patient becomes more lucid.[1][6][7]

Treatment / Management

Treatment for acute ethanol toxicity is mostly supportive. The first priority, as always, is airway protection. The main life-threatening complication of alcohol intoxication is respiratory depression. Although most patients who present for alcohol intoxication receive intravenous fluids, there is no solid evidence to support this. Alcohol does act as a diuretic; thus, most patients who receive intravenous fluids are in an attempt to treat dehydration. As mentioned above, checking a point of care glucose is important, as many patients with alcohol use disorder will have depleted glycogen stores, and treating hypoglycemia is important, especially before replenishing vitamins such as thiamine. Few studies have shown vitamin deficiencies in intoxicated patients; thus, the routine use of IV multivitamins should be considered on a case-to-case basis. In contrast, routine use of thiamine is recommended for patients with alcohol use disorder, especially in the setting of altered mental status. Detecting occult thiamine deficiency and Wernicke encephalopathy is difficult, and this condition has a high mortality. Thus, the cost/benefit analysis falls in favor of administering thiamine. Patients with alcohol use disorder may not benefit from IV fluids, and consideration must be made for alcoholic cardiomyopathy in this patient population before administering fluids. Some patients may become agitated or violent. In these situations, sedative substances may be required, including droperidol or haloperidol, keeping in mind the potential interaction between the drug and alcohol. Depending on the severity of the intoxication and complications such as Wernicke encephalopathy, alcoholic hepatitis, or dysrhythmias, patients may have to be admitted to the hospital for further treatment.[1][2][5]

Differential Diagnosis

The differential diagnosis for alcohol toxicity is very broad and includes anything that can cause an altered mental status. Considerations include trauma, sepsis, CNS infections, seizure, nonalcoholic toxicologic ingestion, hypo- or hyperthermia, hypo- or hyperthyroidism, hypoxia, and metabolic derangements. Many of these can coexist with alcohol toxicity, so it is important to have a low threshold to obtain laboratory workup and CNS imaging. Complicating the diagnosis of alcohol toxicity is the potential for the patient to ingest non-beverage alcohol such as cologne, cough syrup, and isopropyl alcohol. This can be accidental, such as in pediatrics, or intentional, such as in patients with alcohol use disorder who do not have access to alcohol. Ethylene glycol, methanol, and isopropyl toxicity are discussed in separate articles, and please see these articles for further details. Once alcohol use has been confirmed, further diagnoses have to be considered, such as Wernicke encephalopathy and hepatic encephalopathy.[1][2]

Prognosis

The prognosis for ethanol toxicity depends on multiple factors, including chronicity of use, degree of intoxication, associated traumatic injuries, and end-organ damage. Patients who have uncomplicated ethanol toxicity have a good prognosis and need to be counseled on abstinence. Most of the chronic complications that can develop from ethanol toxicity can be helped and sometimes reversed with alcohol abstinence.[3][4][5]

Complications

Alcohol affects multiple organ systems and can cause complications with both acute and chronic use. Patients under the influence of alcohol are more likely to be involved in trauma-related injuries. Trauma patients under the influence of alcohol have a longer length of hospital stay, higher mortality, and are more likely to have traumatic injuries in the future. Alcoholic liver disease is one of the primary causes of chronic liver disease. Acute alcohol intoxication can cause alcoholic hepatitis and acute on chronic liver failure. This is usually in patients who are chronic alcohol abusers or patients already affected by alcoholic cirrhosis. Active excessive alcohol consumption is the second most frequent precipitating event for acute on chronic liver failure, with bacterial infection being the first. The most effective therapy for alcoholic liver disease is prolonged abstinence from alcohol. Alcohol can cause both acute and chronic effects on the cardiovascular system. Acutely, it can precipitate dysrhythmias such as atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia and can lead to lethal arrhythmias in patients with myocardial infarction. Also, it can cause contractile dysfunction leading to heart failure, stroke, and increased risk of cardiac death.

Heavy drinkers have a much higher risk of heart failure when compared to non-drinkers. Wernicke syndrome, also known as Wernicke encephalopathy, is due to thiamine deficiency and is characterized by the triad of ataxia, oculomotor abnormalities, and global confusion. It develops over days to weeks. While it is most commonly seen in conjunction with patients with alcohol use disorder, it can occur in any disorder leading to a thiamine deficiency. Neurobehavioral findings with Wernicke syndrome include decreased attention, impaired memory, and disorientation. In its severe form, it can lead to coma. Untreated, Wernicke encephalopathy can progress to Korsakoff syndrome, characterized by anterograde and retrograde amnesia without impaired alertness and attention or extraocular movement findings. Chronic alcohol use can lead to dementia, cerebellar degeneration, and peripheral neuropathy.[1][3][4][5][7][8][9][10]

Deterrence and Patient Education

All patients who present to the emergency department for acute alcohol intoxication should be screened for alcohol use disorder. If a patient is found to have alcohol use or dependence, they should be referred for alcohol treatment. In patients who consume alcohol at harmful levels, it is important to intervene early. Presentation to the emergency department for drunkenness should be considered an indicator of pathological use.[1][11]

Enhancing Healthcare Team Outcomes

Alcohol intoxication and use is and will likely remain prevalent in our culture. It is important to fully assess the intoxicated patient for acute organ dysfunction or injuries from their intoxication and educate them on the importance of moderation to prevent or slow the development of chronic diseases. In cases of suspected or known alcohol toxicity, the entire interprofessional healthcare team must work to achieve improved patient outcomes. This team includes clinicians, mid-level practitioners, nurses, pharmacists, and mental health professionals, who can play a crucial role in recovery following alcohol toxicity in those patients with alcohol use disorder. The interprofessional approach with shared information increases the chances of successful recovery. [Level 5]

Review Questions

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Marijuana Toxicity

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Continuing Education Activity

The term "marijuana" typically refers to the tobacco-like preparations of the leaves and flowers of the plant cannabis sativa. The active ingredient is believed to be tetrahydrocannabinol (THC), which is also responsible for intoxication. Different preparations of marijuana vary in strength. THC concentrations vary with climate, soil, and cultivation techniques. Additionally, THC absorption varies with the route of administration. This activity reviews the pathophysiology, diagnosis, and management of marijuana toxicity and highlights the role of the interprofessional team in caring for affected patients.

Objectives:

- Identify the epidemiology of marijuana toxicity.
- Describe the typical presentation of a patient with marijuana toxicity.
- Review the treatment and management options available for marijuana toxicity.
- Summarize interprofessional team strategies for improving care coordination and communication to advance the prevention and treatment of marijuana toxicity and improve outcomes.

Access free multiple choice questions on this topic.

Introduction

The term "marijuana" typically refers to the tobacco-like preparations of the leaves and flowers of the plant cannabis sativa and cannabis indica. The plant contains many psychoactive compounds, often referred to as cannabinoids. The primary psychoactive ingredient is believed to be tetrahydrocannabinol, which is also responsible for most of the intoxicating effects experienced by users. Different preparations of marijuana vary in strength, with THC concentration in cannabis varying with climate, soil, and cultivation techniques. Also, the amount absorbed by the body varies with the route of administration. The effects of cannabis depend on various things: the dose, mode of administration, user's prior experience with the drug, user's expectations/attitudes towards the drugs, and social environment when using the drug.[1][2][3]

Etiology

Marijuana intoxication is dose-related and has multiple names depending on the preparation: grass, ganja, hashish, etc. The amount absorbed by the body varies by the route of administration and concentration of the source being used, which can vary widely. Marijuana is commonly smoked or vaporized due to the rapid onset of symptoms, but marijuana can also be eaten (i.e., "grass" brownies) or drank (i.e., marijuana tea or marijuana tincture). Smoked marijuana has an increased potency, quoted as high as 2.6 times by some sources. Marijuana is used for both recreational and therapeutic purposes. Although some people promote the "harmless" nature of marijuana, acute and chronic intoxication can occur.[4][5][6][7]

Epidemiology

According to the World Health Organization (WHO), marijuana is the world's most widely cultivated, trafficked, and abused illicit substance. Approximately 2.5% of the world's population (147 million people) uses it. Its use is more prevalent among men than women—a gender gap that widened in the years 2007 to 2014. Use is widespread in the adolescent and young adult population. According to the Monitoring the Future survey, an annual survey of drug use in America's middle and high school students, rates of use within one year ranged from approximately 9% in 8 graders to 35% in 12 graders. In the United States, cannabis is still a Schedule 1, meaning it is not scheduled for federal medical use and has a high potential for abuse.[8]

History and Physical

The initial state of acute intoxication formulates recreational users' symptoms: euphoria, perception alterations such as time and spatial distortion, intensification of ordinary sensory experiences, and motor impairment. Not all effects of cannabis intoxication are welcomed by users, as some experience unpleasant psychological reactions such as panic, fear, or depression. Acute intoxication also affects the heart and vascular system, resulting in cannabis-induced tachycardia and postural hypotension. CNS and respiratory depression have been noted with high doses in animal models. Studies show that inhaled doses of 2 to 3 mg of THC and ingested doses of 5 to 20 mg THC can cause impairment of attention, memory, executive functioning, and short-term memory. Doses > 7.5 mg/m2 inhaled in adults and oral doses from 5 to 300 mg in pediatrics can produce more severe symptoms such as hypotension, panic, anxiety, myoclonic jerking/hyperkinesis, delirium, respiratory depression, and ataxia. Conjunctivitis is a consistent physical exam finding regardless of the route of administration. In children, neurological abnormalities such as lethargy and hyperkinesis can be signs of life-threatening toxicity. Although acute toxicity is uncommon in non-pediatric patients, those who come to medical attention are more likely to have hyperemesis, behavioral problems, or a medical emergency such as bronchospasm due to inhalation. There is disagreement about how long these impairments persist after taking cannabis, ranging from hours to days. Chronic use may lead to long-term effects on cognitive performance, "amotivational syndrome" (loss of energy and a will to work), and respiratory disorders. There have also been various reports of patients presenting with cyclic vomiting syndrome/cannabinoid hyperemesis. Cannabis intoxication can lead to acute psychosis in many individuals and can produce short-term exacerbations of pre-existing psychotic diseases such as schizophrenia. Psychiatric symptoms observed in some studies include depersonalization, fear of dying, irrational panic, and paranoid ideas.

Evaluation

The standard urine drug screen can be used to detect THC metabolites, primarily THC carboxylase. The lower limits range from 20 to 100 ng/mL. Second-hand exposure causing positive results is tough to achieve in adolescents and adults, although this has not been studied in children. Reported false positives for THC include dronabinol, efavirenz, PPIs, hemp seed oil, NSAIDs, and baby wash products in infants. Although, false positives are significantly less likely in testing laboratories with gas chromatography capabilities. Positive results for THC carboxylase have been reported up to 10 days after weekly use and up to 30 days after heavy daily use, making the timeline of exposure different and the severity of intoxication difficult to correlate.

Although less commonly used, other ways of detecting marijuana use are available. This includes detecting THC carboxylase in hair, which has the benefit of detection up to 3 months after use but often will not become positive until several weeks after use has been initiated. Detection of

THC can also be accomplished in the oral fluid within 24 hours of use and in blood within about 14 to 21 days of use. Breathalyzer tests have also been proposed, but since small amounts of cannabis continue to be released from fat into the blood long after short-term impairment wears off, this method has not been promoted.

Treatment / Management

Most adolescents and adults do not warrant testing for the diagnosis or treatment of cannabis intoxication. However, if chest pain is present, it is reasonable to obtain a 12-lead electrocardiogram and possibly cardiac markers to assess myocardial ischemia or infarction. There is thought to be an elevated risk up to 4.8 times for MI within 1 hour of marijuana use. Patients with toxic ingestion should also be screened for co-ingestion, especially if electrolyte abnormalities or OTc or QRS prolongation is noted on EKG. Some patients, particularly children, may require further testing if exposure is unknown, including rapid blood glucose, electrolytes, blood gas analysis, and neuroimaging (e.g., computed tomography of the head). Neuroimaging should be avoided in known cannabis exposures unless focal neurologic findings are also present or concerns for other etiologies such as head trauma exist.

The treatment for marijuana intoxication is symptomatic management. The extent of management has numerous factors, including the age of the individual and the amount of cannabis ingested. Several cases of accidental cannabis poisoning in geriatric patients have resulted in intensive care admissions due to central nervous system depression. Unintentional ingestion by children has also resulted in similar admissions. In cannabis-induced psychotic disorders, safe cannabis detoxication typically requires 24 hours but sometimes longer if persistent psychosis or unstable vital signs occur.[9][10][11]

Differential Diagnosis

- Allergic and environmental asthma
- Anxiety disorders
- Atrial tachycardia
- Benzodiazepine toxicity
- Brief psychotic disorders
- Delirium
- Depression
- Hallucinogen use
- Panic disorder
- Primary hypersomnia

Pearls and Other Issues

There is no experimental evidence to determine the lethal dose in humans, but the dose that kills animals ranges from 40 mg/kg to 130 mg/kg intravenously. Well-controlled studies have not implicated in utero marijuana exposure in any major fetal growth or physical abnormalities, but it may have long-term emotional and behavioral consequences. Marijuana has an affinity for lipids and accumulates in human milk, so its use is contraindicated during breastfeeding.

Enhancing Healthcare Team Outcomes

Marijuana toxicity is becoming common in emergency rooms all over the nation. The key reason is that there is limited quality control over the manufacturing of marijuana. Thus, many preparations contain varying levels of THC as well as toxic contaminants. Plus, many individuals consume marijuana with other illicit agents, including alcohol. The management of marijuana toxicity is commonly adequate with supportive measures. Because the agent can affect many organ systems, an interprofessional team including internists, psychiatrists, and occasionally cardiologists should assist with managing the patient.

Parents should be educated about the adverse effects of marijuana and urged to store the agent away from the reach of children.

Review Questions

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Tobacco Dependence Treatment Guidelines

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18th March 2011

FOREWORD

Tobacco use is a major public health challenge globally. As per Global Adult Tobacco Survey 2010 (GATS) India, more than one third (35%) of the adults (15 years and older) are using tobacco in the country. The prevalence of smokeless tobacco use is 26% while 14% adults are smokers.

WHO Framework Convention on Tobacco Control (FCTC) recommends many strategies to reduce the demand and supply of tobacco. India has ratified this treaty and is committed to implement guidelines prescribed for tobacco control under it. The Government of India also enacted a comprehensive legislation, the Cigarettes and Other Tobacco Products (prohibition of advertisement and regulation of trade and commerce, production , supply and distribution Act), COTPA, 2003. To fulfill the commitments under the law and WHO FCTC, National Tobacco Control Programme (NTCP) was launched in the 11th Five Year Plan.

Providing assistance to tobacco users for quitting tobacco use is an established policy under "WHO MPOWER", to reduce the demand of tobacco. The Government of India was amongst the first few countries in the world to set up a chain of tobacco cessation clinics in collaboration with WHO in 2001-02. Under the National Tobacco Control Programme, cessation facilities are being provided at the district level. Efforts have also been made to expand the existing cessation facilities by building capacity of the health care delivery system, including training of doctors and health workers in tobacco cessation. Tobacco cessation clinics are also being set up in some primary, secondary and tertiary care settings.

Tobacco Dependence Treatment Guidelines have been developed with an objective to sensitize, train and equip health care providers with the knowledge and skills of providing treatment for tobacco dependence.

I hope that these guidelines would prove useful to strengthen and expand the tobacco cessation services in the country so as to meet the needs of tobacco users for quitting tobacco use.

(K. Chandramouli)

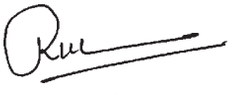
18/8/11

PREFACE

Tobacco epidemic has led to about 100 million deaths all over the world in the 20th century. Tobacco use is a risk factor for six of the eight leading causes of death. In India, 8-9 lakh persons die every year due to tobacco related diseases. At present, India is in the second stage of tobacco epidemic. There is an urgent need to reverse this entirely preventable epidemic. India faces huge challenge of tobacco control in view of high prevalence of tobacco use, as revealed by Global Adult Tobacco Survey (GATS) India 2010. With more than one third of adult population using large number of tobacco products, it becomes imperative to implement effective tobacco control strategies. The GATS India 2010 also revealed that there is demand for assistance to quit tobacco use in the community. It is a well established fact that in view of highly addictive nature of nicotine contained in tobacco, the tobacco users need assistance and treatment. The treatment for tobacco dependence may be in the form of behavioral counseling or pharmacotherapy.

The benefits of treatment for tobacco dependence have also been well documented. World Health Organization (WHO) has recommended "Brief Intervention" for tobacco cessation, which can be provided in different health care delivery settings. Studies have shown that people who quit tobacco live longer than people who continue to use tobacco. From the moment someone quit smoking, it only takes 20 minutes for the body to start undergoing beneficial changes. Thus cessation of tobacco use has extensive benefits and there is a need to make cessation facilities widely available.

The "Tobacco Dependence Treatment Guidelines" have been developed recognizing the need for professional help to tobacco users to quit. It is imperative that these guidelines are widely distributed to reach all relevant stakeholders to ensure maximum output in terms of reduction of tobacco use. The document has been divided in to four sections to make it user friendly.



Dr R. K. Srivastava

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INTRODUCTION

Tobacco use is a leading cause of preventable deaths all over the world.[1] Tobacco is also one of the major causes of deaths and diseases in India, accounting for almost a million deaths every year.[2]

Global Adult Tobacco Survey (GATS) India (2010) data revealed that more than one out of three adults in India (35%) used tobacco in some form or the other. Among them, 21 % of adults used only smokeless tobacco, 9% only smoked and 5 % smoked as well as used smokeless tobacco. Overall tobacco use is much higher among Indian males at 48 percent but is also a serious concern among females among whom prevalence is 20 per cent.[3]

In India, *khaini* or tobacco-lime mixture (12%) is the most commonly used smokeless tobacco product, followed by gutkha *(*a mixture of tobacco, lime and areca nut) (8%), betel quid with tobacco (6%) and tobacco dentifrice (5%).[3] Bidi (9%) is most commonly used smoking product, followed by cigarette (6%) and hukkah (1%).[3]

As per the Global Health Professions Student Survey (GHPSS), India, 2009, 6.5% third year dental students smoked cigarettes and 8.6% used other tobacco products.[4] Among medical students, 13.4% third year medical students smoked cigarettes and 11.6% used other tobacco products.[4] Global Youth Tobacco Survey(GYTS) India, 2009 revealed that 14.6% of 13-15 years school going children in India used tobacco products out of which 4.4% smoked cigarettes and 12.5% used other forms of tobacco.[5] These figures are alarming because these professional students will themselves lead the war against tobacco, and because earlier initiation increases chances of long term dependence.

Article 14 of WHO FCTC (Framework Convention on Tobacco Control) prescribes demand reduction measures concerning tobacco dependence and cessation. It states that “each party (country) shall develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices, taking in to account national circumstances and priorities, and shall take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence”.

To help countries fulfill the obligations under FCTC, WHO has established MPOWER, the policies of which are proven to reduce tobacco use

M – Monitor tobacco use and prevention policies.

P – Protect people from tobacco smoke.

O – Offer help to quit tobacco use.

W – Warn about the dangers of tobacco.

E – Enforce bans on tobacco advertising, promotion and sponsorship.

R – Raise taxes on tobacco.

India is a signatory to the FCTC. The Government of India passed the Cigarettes and Other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act in 2003. Under National Tobacco Control Programme, being implemented in the XI Five Year Plan, cessation facilities are being made available at the district hospital level.

TOBACCO DEPENDENCE

Tobacco dependence is defined as, “Cluster of behavioral, cognitive and physiological phenomena that develop after repeated tobacco use and that typically include a strong desire to use tobacco, difficulties in controlling its use, persistence in tobacco use despite harmful consequences, a higher priority given to tobacco use than other activities and obligations, increased tolerance and sometimes a physical withdrawal state”. (ICD – 10)

Both smoked and smokeless forms of tobacco contain nicotine, a highly addictive chemical, making it difficult for habituated tobacco users to quit.[6][7] In fact, it is as addictive, or even more, than heroin or cocaine. Over time, users become dependent on nicotine and suddenly stopping produces both physical and psychological withdrawal symptoms.[8][9][10][11]

Nicotine is readily absorbed from the respiratory tract, buccal mucosa and skin.[12] There is minimal absorption through the gastrointestinal tract when administered orally. Cigarettes are highly effective mechanism for delivering nicotine. Inhaled nicotine takes about 10-19 seconds to reach the brain and its stimulation releases chemicals which ensure feeling of goodness, alertness and energy.[6][7][9]

As the person stops tobacco use, these chemicals decrease in the body and withdrawal symptoms start. These can be very distressing for the unprepared tobacco user. Thus, the tobacco user is compelled to continue using tobacco, hence trapped in the vicious cycle.

Studies have shown that tobacco users must effectively deal with both the physical and psychological symptoms of withdrawal to quit and stay quit.[15]

TOBACCO DEPENDENCE TREATMENT

Tobacco dependence is a chronic condition that often requires repeated interventions. Because effective tobacco dependence treatments are available, **every patient who uses tobacco should be offered at least one of these treatments.** Tobacco dependence treatments are both clinically effective and cost effective in relation to other medical and disease prevention interventions.

BEHAVIOUR INTERVENTIONS:

A variety of behavior therapies, ranging in complexity from simple advice offered by a physician or other health care providers or much more extensive therapy offered by counselors, have been shown to be efficacious for tobacco cessation.[32]

Brief Advice – This consists of Advice to stop using tobacco, usually taking only a few minutes, given to all tobacco users, usually during the course of a routine consultation or interaction.[33]

Behavioral support – This involves support, other than medications, aimed at helping people stop their tobacco use. It can include all cessation assistance that imparts knowledge about tobacco use and quitting, provides support and teaches skills and strategies for changing behavior.

Basic knowledge, certain competencies and skills are required to provide effective counseling for tobacco cessation.

STRATEGIES FOR TOBACCO CESSATION - THE 5 "A"S AND 5 "R"S

The Five A's (Ask, Advise, Assess, Assist and Arrange) and Five R's (Relevance, Risk, Rewards, Repetitions, Roadblocks) is a five to fifteen minute research based counseling approach that has proven global success.[13]

STEP 1: ASK

Systematically identify all tobacco users at every visit. It should be an essential part of evaluation that for every tobacco user at every consultation, tobacco-use status be queried and documented. (Refer Annexure 1)

STEP 2: ADVISE "STRONGLY URGE ALL TOBACCO USERS TO QUIT".

Advice should have:

- **Clear Message**: "I think it is important for you to quit tobacco now and I can help you." "Cutting down while you are ill is not enough".
- **Strong message**: "As your health carer, I need to advise you that quitting tobacco smoking/ chewing/sniffing is the most important thing you can do for your health and your family's health." . "I can surely help you in this matter."
- **Personalized message:** Relate the tobacco use to current health/illness, and /or its social and economic cost, motivation level/readiness to quit, and /or the impact of tobacco use on children and others in the household.

All tobacco users should be firmly advised to quit in a way that is supportive and non-confrontational. Tell them about benefits of quitting.

BENEFITS OF QUITTING

It is important to tell the tobacco user about the benefits of quitting. Some hints are presented below. Individual users may have other motives to quit, which should be explored and documented for future use.

Begin thus - From the moment you quit smoking, it only takes 20 minutes for your body to start undergoing beneficial changes.

20 Minutes:

Blood pressure drops to normal; Pulse rate drops to normal; Temperature of hands and feet increases to normal.

Within 8 Hours:

Carbon-monoxide level in blood drops to normal; Oxygen level in blood becomes normal.

Within 24 Hours to 48 hours:

Chance of heart attack decreases.

Nerve endings start regenerating; Ability to smell and taste begins to improve.

Within 72 hours:

Bronchial tubes relax, making breathing easier.

Within 2 Weeks to 3 Months:

Circulation improves. Lung function increases up to 30%

Within 6 Months:

Coughing, sinus congestion, fatigue and shortness of breath decrease. The lungs function better, as congestion reduces, so does the chance of infection.

Within 1 Year:

Risk of coronary heart disease decreases to half that of a smoker.

Within 10 Years:

Risk of dying from lung cancer is reduced to half.

Within 15 Years:

Risk of dying from a heart attack is equal to a person who never smoked.

STEP 3: ASSESS

Assess: Determine willingness to make a quit attempt.

To be able to assist a tobacco user with tobacco cessation, assess his/ her willingness to commit to this change. Ask every tobacco user if he/she is willing to make a quit attempt at this time (e.g. within the next 30 days).

The stages of Readiness to change model is a valuable model for assessing a tobacco user's readiness to change the behaviour. Cessation is explained as a process, and tobacco users may go through the steps of being ready, quitting and relapsing, an average of three to four times, before achieving success. Tobacco users will be in different stages of readiness at different times, hence, readiness needs to be re-evaluated constantly. [15][16][17]

The stages may be,

i) Not ready (Pre contemplation)

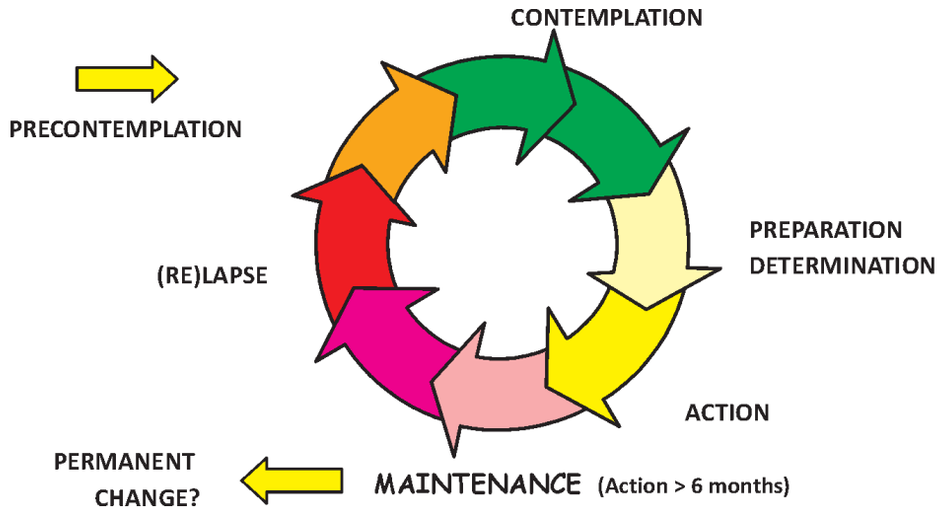
ii) Unsure (Contemplation)

iii) Ready (Preparation)

iv) Action

v) Maintenance.

MOTIVATIONAL INTERVIEWING TECHNIQUES – STAGES OF READINESS TO CHANGE MODEL



Not ready (Pre contemplation)

These tobacco users are not seriously considering quitting in the near future. They only see the positive aspects of tobacco and do not like to acknowledge the disadvantages.

- *Encourage such a person to think about his/her tobacco use and make an offer of help. Offer them written information on the harms of tobacco use and benefits of quitting.*

Unsure (Contemplation)

These tobacco users are seriously considering quitting in the near future. This group is particularly amenable to brief motivational interviewing. Talk to them about the relevant health effects of tobacco use and barriers to cessation.

- *Provide them the written information and inform them that quitting is possible with will power and support from the family, friends, peer group and health professionals.*

Ready (Preparation)

These tobacco users are planning and ready to quit and have usually made a 24-hour quit attempt in the past year. This group is motivated to quit soon and is the group most likely to attempt to quit in the near future.

➢ *This is the best opportunity, which may be available for only a short time, and is the group most likely to ask for help with quitting.*

Action

These are former tobacco users who have quit in the last 6 months. This is when the risk of relapse is highest with about 75% of relapses occurring in this stage, within the first week. This is a period where support and strategies to prevent relapse are important.

➢ If relapse occurs, it is important that this should not be seen as failure, but considered a learning experience and as part of quitting process.

Maintenance

These are tobacco users who quit for more than 6 months. The non-tobacco use behavior is established and the threat of tobacco use gradually diminishes. The chances of relapse diminish over time.

➢ Only about 4% of those who quit for more than two years ever go back to tobacco use.

Assessment of nicotine dependence— if the tobacco user is in the ready stage

Assess willingness to quit, and determine the level of Nicotine addiction. This can be measured by **Fagerstrom Scoring** (Annexure-2). The tool has six simple questions. Scoring is done as followed:

- A high level of addiction will rank between 7 and 10 points.
- A medium level of addiction will rank between 4 and 6 points.
- A low level of addiction will rank between 0 and 3 points.

STEP 4 - ASSIST

The following strategies are suggested to assist tobacco users in motivational stage:

Action	Strategies for implementation
Help in making a **QUIT PLAN**.	**Preparations for quitting;** **Set** a quit date; ideally, the quit date should be within 2 weeks. **Tell** family, friends, and co-workers about quitting, plan and seek their support. **Anticipate** challenges to planned quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. **Remove** tobacco products from surroundings. **Avoid –** *Avoid Smoking or Using tobacco in places where a lot of time is spent e.g. work place.* Avoid all forms of tobacco, do not substitute one tobacco product for another.

Action	Strategies for implementation
Provide practical counseling (Problem solving / skills training)	**Past quit experience**-Identify what helped and what failed in previous quit attempts. **Anticipate triggers** or challenges in upcoming attempt – Discuss challenges and how user will successfully overcome them. **Alcohol**- The tobacco user should consider limiting/abstaining from alcohol while quitting. **Other tobacco users in the household/ workplace** - Quitting is more difficult when there is another smoker/ tobacco user in the household/ workplace. Other housemates/ coworkers/ peers should also be encouraged to quit.
Provide intra-treatment social support.	Provide a supportive environment by encouraging tobacco users in their quit attempts.
Help in obtaining extra-treatment social support.	Provide help in developing social support for quit attempt in the environment outside of treatment. "Ask your spouse / partner, friends and coworkers to support you in your quit attempt."
Recommend Pharmacotherapy.	Explain how the medications improve success rates and reduce withdrawal symptoms.

There is a strong dose response relation between the intensity of tobacco cessation counseling and its effectiveness.

PHARMACOTHERAPY

Medications available for tobacco cessation can broadly be divided into two groups:

1. Nicotine Replacement Therapy (NRT)
2. Non Nicotine Replacement Therapy

Nicotine replacement therapy: Nicotine Replacement Therapy (NRT) is a method of substituting the nicotine in tobacco products by an approved nicotine delivery product so that the tobacco user does not have uncomfortable withdrawal symptoms upon stopping the tobacco product. The dose of NRT is monitored and gradually reduced to make the process of cessation comfortable for the tobacco user. As compared to blood levels of nicotine following tobacco smoke inhalation, NRT blood levels increase relatively slowly. Nicotine through tobacco smoke reaches brain within few seconds compared to medicinal nicotine which take few minutes to hours. Hence motivation and patience are essential for the user. All types of NRTs viz. Nicotine patch, nicotine gum, nicotine inhaler, and nicotine nasal spray have been shown to have more or less similar success rates.[18][19][20]

Nicotine Gum:

It acts as an oral substitute and provides a source of nicotine that reduces the withdrawal symptoms experienced when tobacco use is stopped. The gum is available in different strengths and can be used on either at regular intervals or on an as needed basis. Tapering can be considered after 8 to 12 weeks.

How it is used-

- Should be used orally as a chewing gum and not swallowed.

- Treatment is usually started by using 2 mg gum.
- Heavy smokers/ tobacco users may start the treatment by using 4 mg gum.
- Nicotine gum may be used by chewing one piece of gum every 1-2 hours at first, or by chewing one piece of gum whenever there is an urge to use tobacco.
- The gum should be chewed slowly until the taste of nicotine or slight tingling is felt in the mouth.
    - Stop chewing and place (park) the gum between cheek and gum.
    - Parking the nicotine gum is essential for the absorption of nicotine through the buccal mucosa, not doing so will lead to more nicotine being swallowed which might result in side effects such as nausea and vomiting.
    - Once the tingling is almost gone (almost one minute), start chewing again.
    - Repeat this procedure for about 30 minutes.
- Precautions –
    - Don't chew nicotine gum too fast.
    - Don't chew more than one piece of gum at a time.
    - Don't chew one piece too soon after another.
    - Don't chew more than 30 pieces of 2mg gum in a day if under supervision.
    - Don't chew more than 24 pieces of 2 mg gum in a day if not under supervision.
- Avoid eating and drinking (especially acidic beverages such as coffee or soft drinks) for 15 minutes before and during chewing of nicotine gum to prevent reduced absorption of nicotine.
- Gradually reduce the amount of nicotine gum use after 2-3 months, which prevents nicotine withdrawal symptoms.

Weaning of Nicotine Gum (NRT)

- Start decreasing the total number of nicotine gum pieces being used per day by about one piece in every 4-7 days.
- Decrease the chewing time with each piece from the normal 30 minutes to 10-15 minutes for 4-7 days. Then gradually decrease the total number of pieces used per day.
- Increase the duration between use of nicotine gum pieces.
- Increase intake of drinking water.
- Start substituting one or more pieces of nicotine gum with sugarless gums and gradually increase it over a period of time.
- If using 4 mg gum, replace it with 2 mg gum and apply any of the aforesaid steps.
- Consider stopping the use of nicotine gum when the craving for nicotine is satisfied by chewing just one or two pieces of gum per day.
- Avoid using nicotine gum for durations longer than 3 months.

Availability of Nicotine gum in India

Composition: Nicotine Polacrilex

Dosages: 2 mg and 4 mg

Nicotine pastilles have also been introduced in India. Here, the procedure to use is to roll the pastille in the mouth rather than chew.

Nicotine patches, inhalers and sprays are not presently available in India.

Non Nicotine Replacement Therapy:

In this type of therapy , medications which act on the similar set of neurotransmitters that are affected by nicotine and provide effective and behavioural regulation are used. This tackles the need, or impulse to use nicotine and to minimize withdrawal effects. While with nicotine replacement therapy, the tobacco user immediately quits tobacco use upon starting NRT, in the case of non NRT medication, the user sets a quit date one to two weeks after initiation of the medicine.

First Line drugs

1. Bupropion : Bupropion is a non-nicotine drug for treating tobacco dependence.[21] It is an atypical antidepressant that has both dopaminergic and adrenergic actions. A quit date is decided preferably within 7 to 14 days of starting treatment with bupropion. This is because the steady state plasma concentration of bupropion and its active metabolites are achieved in approximately 8 days after initiation of therapy.[22]

2. Varenicline: This is a partial nicotine agonist that selectively binds to the alpha (4) and beta (2) nicotinic acetylcholine receptors in the brain. It lessens the physical pleasure from taking in nicotine and helps lessen the symptoms of nicotine craving.[23] Tobacco use may be stopped one week after initiating treatment with Varenicline.

TABLE : PHARMACOTHERAPY FOR TOBACCO CESSATION

1. Nicotine Replacement Therapy (NRT)*			
	Dosage and duration	Side effects	Contraindications**
a. Nicotine gum	For 1-24 cigarettes/ bidis - 2mg gum (up to 24 pieces/day) for 12 weeks For ≥25 cigarettes/ bidis – 4mg gum (up to 24 pieces/day) for 12 weeks Chewers need about half or a quarter of the dose as prescribed for smokers.	Mouth soreness, burning in the mouth, throat irritation, dyspepsia, nausea, vomiting, hiccups and excess salivation	Gastric Ulcers, myocardial infarction or stroke in the past two weeks or poorly controlled cardiovascular disease.*** If a patient has any serious medical condition, refer to an appropriate specialist.

* Only Nicotine gum is available in India (in 2 mg and 4 mg strengths).
** For pregnant and lactating mothers, shorter-acting NRTs such as gums are recommended.
*** NRT can be prescribed to persons with underlying stable cardiovascular disease, including angina and previous myocardial infarction.

	Dosage and duration	Side effects	Contraindications**
b. Nicotine patch	21mg/24 hours for 4 weeks then 15mg/24 hours for 2 weeks then 7mg/ 24 hours for 2 weeks.	Local skin reaction, insomnia	Myocardial infarction or stroke in the past two weeks or poorly controlled cardiovascular disease.*** If a patient has any serious medical condition, refer to an appropriate specialist.
c. Nicotine inhaler	6-16 cartridges/day for 6 months	Local irritation of mouth and throat	- As above -
d. Nicotine nasal spray	1-2 doses/hour for 3 to 6 months	Nasal irritation, irritation of throat, coughing and watering of eyes.	- As above -
2. Non Nicotine Replacement Therapy (Non- NRT)			
	Dosage and duration	Side effects	Contraindications**
a. Bupropion	150mg OD for 3days followed by 150mg BD for 7 to 12 weeks.	Agitation, restlessness, insomnia, gastrointestinal upset, anorexia, weight loss, headache and lowering of seizure threshold (at doses above 600 mg/day). Rarely allergic reactions can occur, including skin rashes, fever, muscle and joint pain.	History of allergy, tumours of central nervous system, severe liver diseases, undergoing unsupervised withdrawal of alcohol or benzodiazepenes, uncontrolled seizures, pregnant and lactating women, those below 18 years, and persons on monoamine oxidase inhibitors.
b. Varenicline	Initially 0.5 mg once daily for the first three days, increased to 0.5 mg twice daily for the next four days, and then increased to 1mg twice daily for 12 weeks. The person can quit one week after initiating Varenicline	Agitation, depression, restlessness, insomnia, bad dreams, suicidal ideations, gastrointestinal upset and headaches. Allergic reactions may occur rarely.	Pregnant women, children or people with mental illness. Stop treatment if changes in mood & behavior, agitation and suicidal ideations occur.

Combination Therapy:

Combined behavioral and pharmacological therapies appear to be the best approach for treating tobacco dependence. Because these therapies operate by different mechanisms, complementary and potentially additive effects may be expected. Nicotine Replacement Therapies (NRT) combined with supportive counseling are the most widely used and intensively reached treatment method. Although self help strategies alone marginally affect quit rates, individual and combined pharmacotherapies and counseling either alone or in combination can significantly increase cessation.[25]

> The tobacco cessation experience in India has shown that counseling with regular follow-up by health care provider also presents encouraging quit rates, more so among smokeless tobacco users.

** For pregnant and lactating mothers, shorter-acting NRTs such as gums are recommended.

*** NRT can be prescribed to persons with underlying stable cardiovascular disease, including angina and previous myocardial infarction.

WITHDRAWAL SYMPTOMS:

Commonly experienced withdrawal symptoms on stopping tobacco use include:[8][9][10][11]

- Depressed mood
- Insomnia
- Irritability, frustration , anger
- Anxiety
- Craving and difficulty in concentration
- Restlessness
- Decreased heart rate
- Increased appetite or weight gain

Withdrawal symptoms of tobacco products should be discussed in advance with the tobacco user who is planning to quit. In addition, behavioral coping methods should be taught at the outset and it should be explained clearly that the worst of the physical symptoms are over within 2-3 days and most have passed after 10-14 days but in some, can last up to 4 weeks.

Some Common Withdrawal Symptoms and Coping Strategies are as follows:

Symptom	Coping Strategy
Irritability	Take walk, take bath, relax and talk to friends, listen to favourite music, do breathing exercises/ Yoga.
Fatigue	Relax, take naps, increase intake of fluids
Insomnia	Avoid tea, coffee, aerated drinks after 6pm; develop habit of reading books
Cough	Drink plenty of fluids, use lozenges, steam inhalation
Nasal Drip	Drink plenty of fluids
Dizziness	Change positions slowly, relax
Lack of Concentration	Plan workload, avoid stress, time management
Constipation	Add fiber to your diet through fresh fruits, vegetables etc; drink plenty of fluids
Headaches	Drink plenty of fluids, and practice relaxation, eat small snacks
Hunger	Increase intake of fruits/ vegetables/ fluids; avoid heavy meals, take smaller meals at shorter intervals
Craving for tobacco	Distract yourself – Drink water, read, exercise, talk to family members/friends. Remind yourself that the urge will die down in a few minutes

THE 5 "R"s APPROACH[35]

For tobacco users who are not ready to make a quit attempt, provide a brief intervention designed to promote the motivation to quit and information about harmful effect of tobacco. The tobacco user may have fears and concerns about quitting, or may be demoralized because of previous unsuccessful attempts and relapse. This group may respond to a motivational intervention designed to educate, reassure and motivate and build around the 5 "R"s; i.e. Relevance, Risk, Rewards, Roadblocks and Repetition.

Relevance	Encourage the tobacco user to consider the personal relevance of cessation. Take into account the disease status (if any), family or social situation, health concerns, age and gender.
Risks	Discuss short term, long term and environmental risks of continued tobacco use, including effects of exposure to second hand smoke on the family members especially children. Relate with the symptoms.
Rewards	Encourage tobacco user to identify benefits of cessation. These may include withdrawal symptoms, fear and concern associated with quitting, depression, lack of social support, weight gain etc. Discuss strategies to address potential barriers.
Roadblocks	Barriers that the tobacco user may face in his/her quit attempt should be identified. Withdrawal symptoms, fear and concern associated with quitting, depression, lack of social support, enjoyment of tobacco are some of the barriers that the tobacco user may face in an attempt.
Repetition	This information should be reviewed regularly with tobacco users who are not yet ready to quit. It is also important for tobacco users who have not yet successfully quit to understand that most people attempting cessation quit several time before finally succeeding in quitting.

The health care provider should renew the strong message to quit and renew the offer of help

STEP 5: ARRANGE

Arrange - Schedule a follow-up contact

Time- Follow up contact should occur soon after the quit date, preferably during the first week. A second follow up contact is recommended within the first month. Schedule further follow up contact as indicated. Follow up visits after advice to quit have been shown to increase the likelihood to successful long term abstinence.

During the follow up, quitters have some common problems and a solution should be suggested accordingly. Some of these are described below:

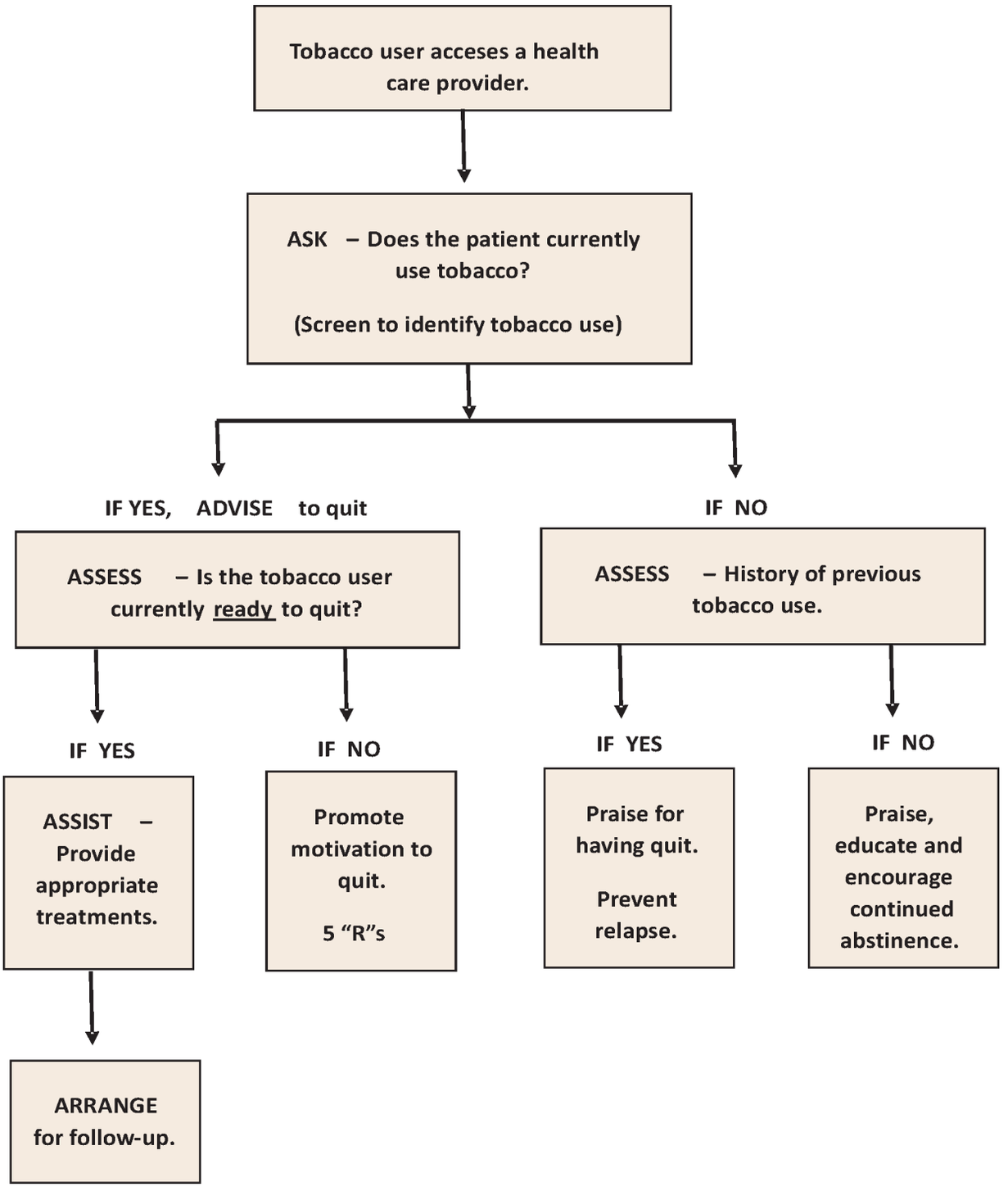
Problems	Responses
Lack of support for cessation	• Schedule follow-ups or telephone calls with the tobacco user. • Help in identifying sources of support.
Negative mood or depression	• Provide counseling, prescribe appropriate medications, or refer to a specialist.
Strong or prolonged withdrawal symptoms	• Use an approved pharmacology or adding/combining pharmacologic medications to reduce strong withdrawal symptoms.
Weight gain	• Recommend starting or increasing physical activity. • Emphasize the importance of a healthy diet. • Reassure the tobacco user that weight gain is normal and will not increase beyond a point, and that there is just a need to watch it.
Flagging motivation/feeling deprived	• Reassure the tobacco user that these feelings are common. • Recommend rewarding activities. • Emphasize that (even a puff or chew) will increase urges.

Identify all tobacco users.

Document tobacco use and treatment offered.

Follow up.

Intervention Method Algorithm for Quitting Tobacco Use



TOBACCO CESSATION IN SPECIAL SITUATIONS

Pregnant and lactating females

Women who use tobacco during pregnancy and breast-feeding should strongly be advised against it. They should be asked to quit using the behavioral strategies that were mentioned earlier, to deal with withdrawal. However if they are unable to quit just by behavior counseling, then use of NRT may be considered. Pregnant and breast-feeding women who opt for NRT should be advised to use shorter acting products to minimize overnight foetal exposure to nicotine. (e.g. Nicotine gum)

Cardiovascular disease

In stable cardiovascular disease conditions, use of NRT is safe. Caution should be taken while considering NRT in patients of unstable angina, myocardial infarction, or stroke as nicotine is a vasoconstrictor. In these cases, rapidly reversible NRT like nicotine gum is preferable.

Patients with tobacco use related diseases

This is a group where tobacco cessation is an urgent clinical need, as continued tobacco use greatly increases the risk of further illness. There is evidence that pharmacotherapy with bupropion can increase cessation rates in chronic tobacco users with co-morbidity and those with mild to moderate Chronic Obstructive Pulmonary Disease. People with tobacco use related diseases may benefit from a multidisciplinary care plan.

Patients with mental illness

Patients with mental health problems have higher rates of smoking/tobacco use and are prone to serious health problems both on account of their mental illness and on account of tobacco use. The treatment of mental illness needs to be monitored carefully during tobacco cessation.

Persons with substance-use disorders

Smoking and tobacco use is common in persons with substance use disorders. Tobacco cessation must be offered to such persons in inpatient and outpatient settings.

Tobacco users with apprehension of weight gain

Some tobacco users are apprehensive of quitting tobacco use as it may lead to weight gain. Such persons should first be reassured that weight gain can be minimized by proper diet and exercise and the need to quit must be emphasized. Bupropion or nicotine gum has been shown to delay weight gain. Continuing reassurance and support are vital for successful quitting.

SETTING UP TOBACCO CESSATION SERVICES

While all health care providers must provide brief counseling for tobacco cessation as part of routine health care, dedicated tobacco cessation services can be set up in different health care settings at primary, secondary and tertiary care settings. Specialist care may be provided particularly to help people with more severe tobacco dependence.

Tobacco cessation services can be set up preferably in different departments of a hospital/ medical college e.g. dental, medicine, surgery, ENT, psychiatry, community medicine, TB & chest diseases, paediatrics, obstetrics & gynae etc.[29]

A specialized setting can be run by a team consisting of a trained physician, counselor or social worker attendant. A trained nurse, pharmacist or health worker can also provide counseling services.

DISSEMINATION STRATEGIES FOR THE GUIDELINES

The Guidelines may be disseminated to following suggested stakeholders:

- Resource Centers for Tobacco Control (RCTCs) – Such centres have been set up under GOI-WHO collaboration programme.
- Professional Organisations –
    - Indian Medical Association (IMA)
    - Indian Dental Association (IDA)
    - Indian Pediatric Association
    - Indian Psychiatry Society
    - The Tuberculosis Association of India
    - Indian Chest Society
    - Indian Network of Chronic Respiratory Diseases
    - Indian Association for Chest Diseases
    - The Federation of Obstetrics and Gynaecological Societies of India
- Specialised Institutions – Regional Cancer Centres (RCCs), Public health institutions.
- Training Institutions
    - Medical/ Dental colleges
    - Nursing colleges
    - Pharmacy colleges

For more information access following websites :

http://chooselifenottobacco.org/

http://www.mohfw.nic.in/National%20Programme%20for%20Tobacco%20Control.htm

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ANNEXURE – 1

(SUGGESTED PROFORMA FOR PATIENT INPUTS)

TOBACCO CESSATION SERVICES - INTAKE AND FOLLOW-UP FORM

Note: This is the minimum required information for the database. Each health care facility is encouraged to maintain a detailed clinical record for each client.

Client No. ☐☐ ☐☐ ☐☐☐☐

Date ☐☐ ☐☐ ☐☐☐☐

1. Name : _____

2. Age : _____

3. Gender : Male ☐ Female ☐

4. Address : _____ Ph. No. _____

5. Education (Numbers of years of formal education) _____

6. Marital Status: Unmarried ☐ Married ☐ Widowed ☐

Separated or Divorced ☐ Not Applicable ☐

8. Occupation: Professional and Semiprofessional ☐

Skilled, Semiskilled & Unskilled worker ☐ Retired ☐

Housewives ☐ Students ☐ Others/ Not Classified. ☐

Unemployed ☐

9. Details of Tobacco use:

Type	Age at Starting Tobacco use	Smokeless tobacco/bidi/cigarette years (Numbers of cigs/*bidis*/sachets of tobacco used per day X No. of years of regular tobacco use)	Average numbers of cigarette/ sachets amount of tobacco chewed per day in the last one month
Smokeless 1. 2. 3.			
Smoking 1. 2. 3.			

11. Expense per month on tobacco (Average month last year) Rs. _____

12. Alcohol use in the last 1 year: Daily Drinking ☐
Regular Drinking (3 or more times a week) ☐
Social Drinking (<3 times/ week) ☐
None ☐

13. Average units per drinking day (30 ml spirit/60ml wine/1/2 mug beer= 1 unit) _____Units

14. Others Substance use: Yes ☐ No ☐ If Yes specify substance: _____

15. Number of previous attempts at quitting which lasted for at lasted one month _____.

16. Apply Fagerstrom Test (Annexure 2)

17. Tobacco use in first \-degree relatives: Smoking ☐ Smokeless ☐ Both ☐ None ☐

18. History & Symptoms suggestive of: Hypertension (yes, No) ☐ Diabetes (Yes, No) ☐
Heart Attack (Yes, No) ☐ Stroke (Yes, No) ☐
Asthma/ Bronchitis (Yes, No) ☐
Oral/ Lung Cancer (Yes, No) ☐

Physical Examination

19. Weight_____ Kgs. 20. Height _____ cms. 21. Pulse____ 22. BP Systolic_____ Diastolic____

23 Oral Cavity: Leukoplakia Yes, No ☐ Erythroplakia Yes, No ☐
Sub mucous fibrosis Yes, No ☐ Denta Caries Yes, No ☐

24. Significant current co-morbid disorder:

a)_____

b)_____

c)_____

25. Intervention: Behavioral Counselling ☐ Behavioral Counselling+ Medication ☐
Behavioral Counselling + NRT ☐

26. Follow up

	Date	No Change (or<50% reduction from baseline*)	Reduced use (50% or greater reduction from baseline*)	Stopped Use	Lost to follow up	Cotinine test (+ve or_ve) or not done
2 weeks						
4 weeks						
6 weeks						
3 months						
6 months						

Any other remarks:

ANNEXURE – 2

(FAGERSTROM TEST)

Screening for nicotine dependence

The Fagerstrom test for nicotine dependence is widely used as a screening test for the physical aspects of nicotine dependence. There are scales for both smoking and smokeless tobacco. Based on the score, the level of addiction can be low (score less than 4), medium (score 4-6) or high (score more than 6).

Fagerstrom test for smoking	**Modified Fagerstrom test for smokeless tobacco users**
1. How soon after you wake up do you smoke your first cigarette/bidi? Within 5 minutes 3 6 to 30 minutes 2 31 to 60 minutes 1 More than 60 minutes 0	1. How soon after you wake up do you use your first dip/chew? Within 5 minutes 3 6 to 30 minutes 2 31 to 60 minutes 1 After 60 minutes 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden? Yes 1 No 0	2. How often do you intentionally swallow tobacco juice? Always 2 Sometimes 1 Never 0
3. Which cigarette/bidi would you hate to give up most? The first one in the morning 1 All others 0	3. Which tobacco chew would you hate to give up most? The first one in the morning 1 All others 0
4. How many cigarettes/bidis do you smoke per day? 10 or less 0 11-20 1 21-30 2 31 or more 3	4 . How many cans/pouches of tobacco do you use per week? More than 3 2 1-3 1 Less than 1 0
5. Do you smoke more frequently in the first hours after waking up than during the rest of the day? Yes 1 No 0	5. Do you chew tobacco more frequently in the first hours after waking up than during the rest of the day? Yes 1 No 0
6. Do you smoke when you are so ill that you are in bed most of the day? Yes 1 No 0	6. Do you chew tobacco when you are so ill that you are in bed most of the day? Yes 1 No 0
Total score:	Total score:
Level of dependence: ➢ **6: high** ➢ **4-6: moderate** ➢ **Less than 6: low**	

Clinical Practice Guidelines for Assessment and Management of Patients with Substance Intoxication Presenting to the Emergency Department

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INTRODUCTION

The International Statistical Classification of Diseases and Related Health Problems, revision 10 (ICD-10) describes intoxication as "a transient condition following the administration of alcohol or other psychoactive substance, resulting in disturbances in level of consciousness, cognition, perception, affect or behavior, or other psychophysiological functions and responses."[1] Intoxication is generally an acute phenomenon, the intensity and effects of which wear off with time and disappear completely in the absence of further use of the substance.

While most episodes of intoxication do not need medical attention, intoxicated patients may sometimes present to the emergency department.[1] The reasons for seeking medical attention may either be due to the substance use itself (e.g., extreme agitation or violent behavior that may endanger the patient or others around them) or due to an adverse consequence of substance use (e.g., head injury in a road traffic accident that occurred due to driving while intoxicated).

Common substances of intoxication encountered in the emergency setting in India are alcohol, cannabis, opioids, and benzodiazepines. Cases of intoxication from other substances like inhalants, stimulants, hallucinogens, and newer psychoactive substances including synthetic cannabinoids and club drugs may also present to the emergency unit. Often the substance of intoxication may be unknown or falsely reported due to fear of legal ramifications or there may be use of more than one intoxicating substance, thereby complicating the clinical picture. Patients may present with decreased levels of consciousness, vomiting, seizures, or other symptoms that may resemble other medical or surgical emergencies. It is, thus, imperative that psychiatrists attending to patients in the emergency department be well-versed with identification, assessment, and management of patients with substance intoxication.[2]

Caring for intoxicated patients in the emergency department comes with various other issues that require a psychiatrist's time and effort. These patients may be brought into the emergency department against their wishes and refuse medical care. They may also be brought in for medical attention by law enforcement authorities with no available identification details and reliable history or even in association with an alleged crime or illegal activity, making it essential for the emergency care provider to be competent in dealing with the medicolegal aspects of intoxication and providing optimum medical services to the patient along with safeguarding the legal procedures. The present clinical practice guidelines deal with the assessment and management of patients with substance intoxication presenting to the emergency department. The guidelines present the general considerations while attending to a substance intoxicated patient, followed by general signs of intoxication. Thereafter, details of intoxication with specific substances are discussed, namely, alcohol, cannabis, opioids, benzodiazepines, and other substances. Features of intoxication, assessment, and management are discussed for each of these substances. Multiple substance intoxication is also discussed in the guidelines. Special populations are referred to in the guidelines, including children and adolescents, women, and the elderly population. The guidelines do not cover nicotine or caffeine intoxication (these are unlikely to be encountered in a clinical setting). Accidental ingestion of substances of use is not catered to in these guidelines. We also do not go into details of intoxication presenting with additional psychiatric and/or medical illnesses and each such case is likely to be unique with its own specific constraints and challenges in management.

General considerations while attending to a substance intoxicated patient

Patients with intoxication with a substance of abuse present several challenges during assessment and management [Figure 1]. One of the foremost concerns is the potential unreliability of history. Patients with substance intoxication may give inaccurate or unreliable history. This may be partly attributable to patients trying to minimize their substance use, not recollecting details adequately

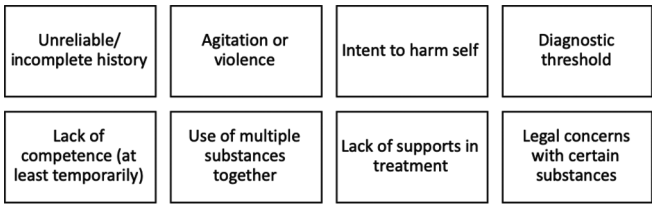

Figure 1: Challenges in assessment and management of patients with substance intoxication

due to cognitive impact of the substance, concealment of the details of substance use from the family, or avoiding sharing details to prevent legal ramifications. Thus, multiple sources of information can be referred to obtain a more comprehensive account of the patient's condition. Friends, family, and previous treatment records can be useful sources of collateral information about the patient. In some circumstances, physical examination and mental status examination of an uncooperative patient can be helpful to get a clearer clinical picture of the patient (e.g., injection track marks can hint at opioid overdose in an otherwise comatose patient).

Another challenge that comes across in patients with intoxication is the occurrence of agitation or violence. Some of the intoxications with substances like alcohol and stimulants like cocaine may be associated to aggression. Aggression may be due to disinhibition and impaired judgement associated with substance use. Furthermore, substance use disorder may be associated with other psychiatric or medical illnesses that may individually contribute to the state of agitation or aggression. Addressing aggression promptly is required to prevent harm to the self and others. Other relevant guidelines of the Indian Psychiatric Society may be referred to while addressing aggression and violence when patients with substance intoxication present to the emergency department.

A related issue is the consumption of substances or presentation with substance intoxication when the patient intends to kill themself. This may be a presenting feature in patients with overdose of opioids or sedative-hypnotics. Sometimes, patients may also consume large amounts of alcohol when they have an intent to die. Thus, self-harm should be considered as a possibility when patients present with substance intoxication, and suitable assessment measures should ascertain risk to self and the presence of concurrent psychiatric disorder. If required, additional treatment should be instituted for the patient.

A relevant aspect of consideration is to determine the line between simply the use of a substance or substance intoxication. Description in the ICD-11 mentions substance intoxication as occurrence of "clinically significant disturbances in consciousness, cognition, perception, affect, behavior, or coordination that develop during or shortly after the consumption or administration."[3] Hence there is a leeway for the clinician to determine what is considered as "clinically significant". One way to simply operationalize is to consider any clinical encounter with a patient having a recent history of substance use which has resulted in the abovementioned mental or neuropsychiatric disturbances and are brought to the emergency/clinical setting as "clinically significant" (those situations where these disturbances are expected by the person and are found to be pleasurable would be considered simply as use). The disturbances are described as transient and reversible, and hence they are expected to abate with time.

Patients with substance intoxication may have an issue related to their mental competence. Substance use may result in impairment of judgement or consciousness. This may result in impairment of competence, that is, the ability of the person to comprehend choices, decide a course of action, and communicate their choice back. This lack of competence has a bearing on treatment choices that should be instituted and promulgation of coerced treatment. It is generally accepted that when a person is not found to be competent, the nominated representative can be the proxy decisionmaker for the person. The treatment providers can also institute emergency treatment in the best interests of the patient. Furthermore, substance intoxication is a reversible process, so if emergency treatment is not required, then one can wait for the patient to re-attain competence as the substance intoxication wanes.

A clinical consideration for patients with substance use disorders is the concurrent use of many substances together. This may lead to the clinical picture being altered or complicated by features of intoxication or withdrawal from different substances. For example, a patient with opioid dependence may experience sedation during intoxication. If benzodiazepines or alcohol are used concurrently with opioids, then the sedation may be accentuated. In such a patient, reversal using naloxone may offset the features of intoxication from opioids, but not reverse the effects of benzodiazepines. Similarly, intoxication from cocaine and other stimulants may lead to paranoia, which may be accentuated by the consumption of higher than usual amounts of cannabis. Thus, a clinician needs to be open to the idea of multiple substance consumption in a patient with substance intoxication.

Another issue in the clinical management of patients with substance intoxication in the emergency setting is the potential lack of social support in the treatment process. Patients may be consuming substances alone, or it is possible that casual acquaintances do not intend to help or are not in a position to help (due to their own intoxication as well). Family and friends may be disinclined or burnt out due to the substance use disorder and hence may not be forthcoming in engaging with the care process. Thus, the ancillary supports

available in the treatment process of patients with substance intoxication may be few. Sometimes, police or other bystanders may bring a patient with substance intoxication to the emergency unit and the identity of the patient may be unknown to them. Thus, clinicians may have to work with limited information on occasions.

There may be legal concerns with the consumption of certain substances considered illegal under the Narcotic Drugs and Psychotropic Substances Act, 1985. This may make patients hesitant to disclose use of some of the substances; for example, heroin. Treating psychiatrists might also be apprehensive about documentation. However, it should be reiterated that clinicians can help patients better if they are able to get a reliable history of the patient. Thus, it would be preferable to gather detailed information and document suitably while ensuring confidentiality of the treatment records and providing reassurance about this to the patient. It might also be prudent to perform urine or blood testing for substance abuse, ensuring a safe chain of custody of the sample. It is unlikely that such treatment records are referred to by the legal process, but a psychiatrist may need to present the relevant information to courts when requested through due processing.

General signs of intoxication

As specified in the ICD-11,[3] intoxication from one or more psychoactive substances may be suspected in cases where the following features are present:

1. Transient, but clinically significant disturbances occur in consciousness, coordination, perception, cognition, affect, or behavior that develop during or shortly after the consumption/administration of the substance(s)
2. The symptoms are in accordance with the known pharmacological effects of the substance. The intensity of the symptoms is closely related to the amount of substance consumed/administered.
3. The symptoms are time-limited and subside as the substance is cleared away from the body.
4. The symptoms cannot be better explained by another medical condition or another psychiatric disorder.

Table 1 enumerates signs and symptoms of intoxication with different substances.

General management of intoxicated patients in the emergency setting

As mentioned earlier, patients presenting with intoxication may prove challenging to manage. Intoxicated behavior may often be confused with other disease conditions and vice versa. A brief outline on general management of a patient presenting with intoxication is given in Figure 2.

ALCOHOL INTOXICATION IN THE EMERGENCY SETTING

Alcohol (primarily) is a widely used psychoactive substance globally and in India. In people aged 20–39 years, approximately 13.5% of global deaths are attributable to alcohol. More than 200 disease and injury conditions are related to alcohol use. Data from the National Syndromic Surveillance Program of United States, which included non-fatal emergency department visits from facilities in 49 states and Washington, DC, indicated that in 2020 1.8% of the total annual emergency visits were related to alcohol use.

Of the many alcohol related disorders presenting to the emergency department in India, a vast majority presents with road traffic accidents due to driving under intoxication followed by acute alcohol poisoning, which is defined as ingestion of a large amount of alcohol in a short duration of time.[4]

Table 1: Features of intoxication with common psychoactive substances

Substance	Signs	Dysfunctional Behaviors
Alcohol	Unsteady gait, slurred speech, nystagmus, flushed face, conjunctival injection, decreased levels of consciousness	Disinhibition, argumentativeness, aggression, inattention, lability of mood, impaired judgement and functioning
Cannabis	Increased appetite (munchies), dry mouth, tachycardia, conjunctival injection	Euphoria, disinhibition, suspiciousness, anxiety, agitation, sense of slowing of time, rapid flow of ideas, inattention, slow reaction time, hallucinations and illusions, impaired judgement
Opioids	Slurred speech, drowsiness, constricted pupils, decreased levels of consciousness	Sedation, apathy, disinhibition, psychomotor retardation, inattention, impaired judgement and functioning
Benzodiazepines	Unsteady gait, slurred speech, nystagmus, flushed face, conjunctival injection, decreased levels of consciousness, erythematous skin lesions or blisters, hypothermia, hypotension, depressed gag reflex	Euphoria, apathy, disinhibition, sedation, lability of mood, aggression, inattention, anterograde amnesia, impaired psychomotor functioning
Stimulants (including cocaine)	Tachycardia, arrhythmias, hypertension, sweating and chills, nausea, vomiting, psychomotor agitation, dilated pupils, chest pain, muscle weakness, convulsions	Euphoria, increased energy, hypervigilance, ideas of grandiosity, aggression, lability of mood, suspiciousness, hallucinations and illusions
Hallucinogens	Tachycardia, sweating and chills, palpitations, tremors, blurring of vision, pupillary dilatation, incoordination	Anxiety, fearfulness, illusions and hallucinations, suspiciousness, lability of mood, hyperactivity, impulsivity, inattention
Volatile solvents	Unsteady gait, nystagmus, slurred speech, decreased levels of consciousness, muscle weakness, blurred vision, diplopia	Apathy, lethargy, aggression, lability of mood, impaired attention and memory, psychomotor retardation

Clinical features of alcohol intoxication

Alcohol is a global central nervous system (CNS) depressant. Acute ingestion generally results in elevation of mood, disinhibition, and increased confidence, leading to argumentative or combative behavior. In addition to those mentioned in Table 1, some features of alcohol intoxication seen with increasing blood alcohol concentration (BAC) are discussed in Table 2. In naïve drinkers, BAC of 150–250 mg per 100 ml result in clinically apparent intoxication; BAC of 350 mg per 100 ml cause stupor and coma; while levels

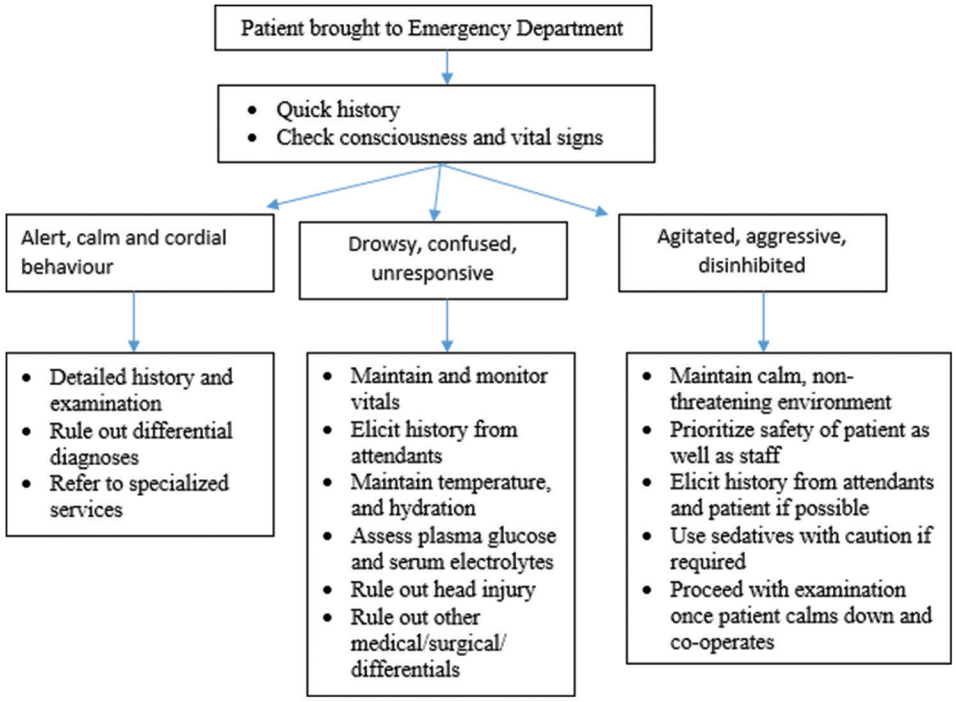

Figure 2: General management of intoxicated patients in an emergency setting

Table 2: Effects of increasing blood alcohol concentration

Stage	BAC (mg per 100 ml)	Clinical Features
Reduced awareness, information processing and visual acuity	10-100	Higher self confidence Shortened attention span Poor judgment Impulsiveness
Reduced muscle coordination	100-180	Poor judgment Delayed reaction time Incoordination Lack of concentration, impaired recent memory Blurry vision, delayed glare recovery Reduction in perceived sensation (hearing, tasting, feeling, seeing)
Confusion	180-250	Incoordination or staggered gait Slurred speech Confusion, disorientation to time and place Emotional lability Sedation
Stupor	250-350	Difficulty in moving Weak response to stimuli, if at all Nausea, vomiting May lapse in and out of consciousness
Coma	350-450	Unconscious Reflexes depressed Fixed pupils Hypothermia Breathing is slower and more shallow Bradycardia Arrhythmias may be precipitated (holiday heart syndrome) May result in death

more than 450 mg per 100 ml can be fatal. Regular users of alcohol often develop tolerance and are significantly less likely to manifest symptoms/signs of intoxication at the same BAC than non-regular drinkers.[5] Effects can last from 2 to 3 hours after a few drinks to up to 24 hours after heavy drinking.

Assessment of alcohol intoxication

An asssessment of a patient presenting with alcohol intoxication aims at identifying the immediate risks to the patient and attendants and uncovering maladaptive patterns of alcohol use that may require specialized management and care. Acute alcohol intoxication may result in several metabolic abnormalities, like hypoglycemia, lactic acidosis, hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia. Thus, these may be required on an urgent basis. Alcohol can cause acute effects on the cardiovascular system, such as atrial and ventricular tachy-dysrhythmias. Hence, an urgent electrocardiogram (ECG) may be required. Further discussed are the assessment measures for alcohol intoxication:

1. *Clinical history*
    a. Elicit details of current episode of alcohol use: amount, preparation, duration, mixing with other substances, etc.
    b. Ask for similar details about previous drinking episodes.
    c. Elicit, wherever possible, events of high-risk behavior under intoxication: driving, operating heavy machinery, self-harm, or violence toward others.
    d. Attempt should be made, wherever possible, to identify alcohol dependence or harmful use pattern.
2. *Physical Examination*
    a. Assess levels of consciousness (the Glasgow Coma Scale may be used), cardiac and respiratory parameters (heart rate, blood pressure, cardiac rhythm, respiratory rate), and urine output, if possible, with hourly intervals until parameters begin to normalize.
    b. Unresponsive patients may suffer from an occult head injury that may be identified from increased intracranial pressure. It is thus advised to perform a direct ophthalmoscopy looking for papilledema, which is a clinical sign for increased intracranial pressure. Papilledema without increased intracranial pressure may also be seen in methyl alcohol poisoning. Thus, imaging (CT/MRI) may be required to determine definitive management.
    c. In responsive patients, rule out diplopia and assess eye movements in all cardinal positions, any muscle weakness, and sensory deficits.
    d. Observe for any abnormal or involuntary movements.
    e. Check for other physical injuries and bleeding from the ear, nose, or mouth.
3. *Mental status examination*
    a. Assess for speech and behavioral abnormalities; pay special attention to aggressive behaviors, and ensure patient and staff safety.
    b. Assess thought and perceptual disturbances.
    c. Assess orientation to time and place: immediate, recent, and remote memory, insight, and reality testing.

Rule out other causes of altered sensorium:

1. Metabolic causes such as hypoglycemia, electrolyte imbalance, hyperosmolar hypoglycemic state, diabetic ketoacidosis, and metabolic acidosis may be detected by laboratory investigations including blood glucose, renal function tests, and arterial blood gases.
2. Cerebral trauma, cerebrovascular events, and meningitis may be identified by computed tomography (CT), magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analysis.
3. Encephalopathies and toxicity from other substances (methanol, lithium, barbiturates, benzodiazepines, and isoniazid) may be identified through laboratory investigations for serum ammonia, and levels of suspected agents in the blood. Higher serum levels than the therapeutic window indicates toxicity.

The abovementioned assessments and investigations are based on individual case considerations and clinical suspicion.

MANAGEMENT OF ALCOHOL INTOXICATION IN THE EMERGENCY SETTING

Individuals with some symptoms of alcohol intoxication (mild and moderate cases, i.e., without impairment of consciousness or significant medical issues) can be managed in relatively simple surroundings without much medical intervention. Those who are severely intoxicated should be admitted and further managed in a setting where high-dependency or intensive care can be provided.[4,6]

Treatment for acute alcohol toxicity is largely supportive. The first priority is airway protection and maintenance of breathing as respiratory depression due to alcohol intoxication may result in death. Alcohol acts as a diuretic; thus, patients with signs of dehydration (dry lips and mucosae and poor urine output) may be provided with intravenous fluids. Checking glucose is important, as many individuals with alcohol use disorder may have depleted glycogen stores. Hypoglycemia needs to be corrected with 5% dextrose intravenously.

Routine use of vitamins is not necessary for all cases of alcohol intoxication. However, thiamine supplementation is needed for patients with alcohol dependence to prevent the occurrence of Wernicke encephalopathy. Thus, prophylactic

thiamine may be administered to patients who appear at risk of developing thiamine deficiency (prolonged use of alcohol, poor nutritional status, confused mental state, gait abnormalities, and ophthalmoplegia).[7] Usual dose should be at least 250 mg of thiamine daily intramuscularly for 3–5 days, followed by oral thiamine 100 mg daily.[8] It is important to remember that in an emergency setting, thiamine is to be administered before glucose replenishment so that the glucose is utilized in ATP generation (which utilizes thiamine as a co-factor), preventing sequestration of the already limited thiamine which may precipitate Wernicke's encephalopathy.

A brief schematic flowchart for management of alcohol intoxication in the emergency setting is presented in Figure 3.

1. *General management*
    a. Maintain airway, breathing, and circulation.
    b. Provide intravenous fluids to counter dehydration and maintain urine output.
    c. Hypoglycemia should be corrected with oral glucose, if conscious level permits, or else with 5% or 10% intravenous (IV) dextrose.
    d. Maintain ambient room temperature, with quiet surroundings and minimal disturbance.
    e. At least one electrocardiogram (ECG) should be obtained for all heavily intoxicated patients and for those with known cardiovascular conditions. "Holiday heart syndrome" characterized by new-onset arrhythmias/atrial fibrillation can occur following alcohol ingestion. Serial ECG monitoring should be done if arrhythmia is detected. As intoxication abates, ECG changes should resolve, but if the changes persist an alternate cause should be considered.
    f. In the case of altered mental status, when a full history cannot be elucidated from the patient, a CT scan of the head can be considered for detecting intracranial pathology contributing to the patients'

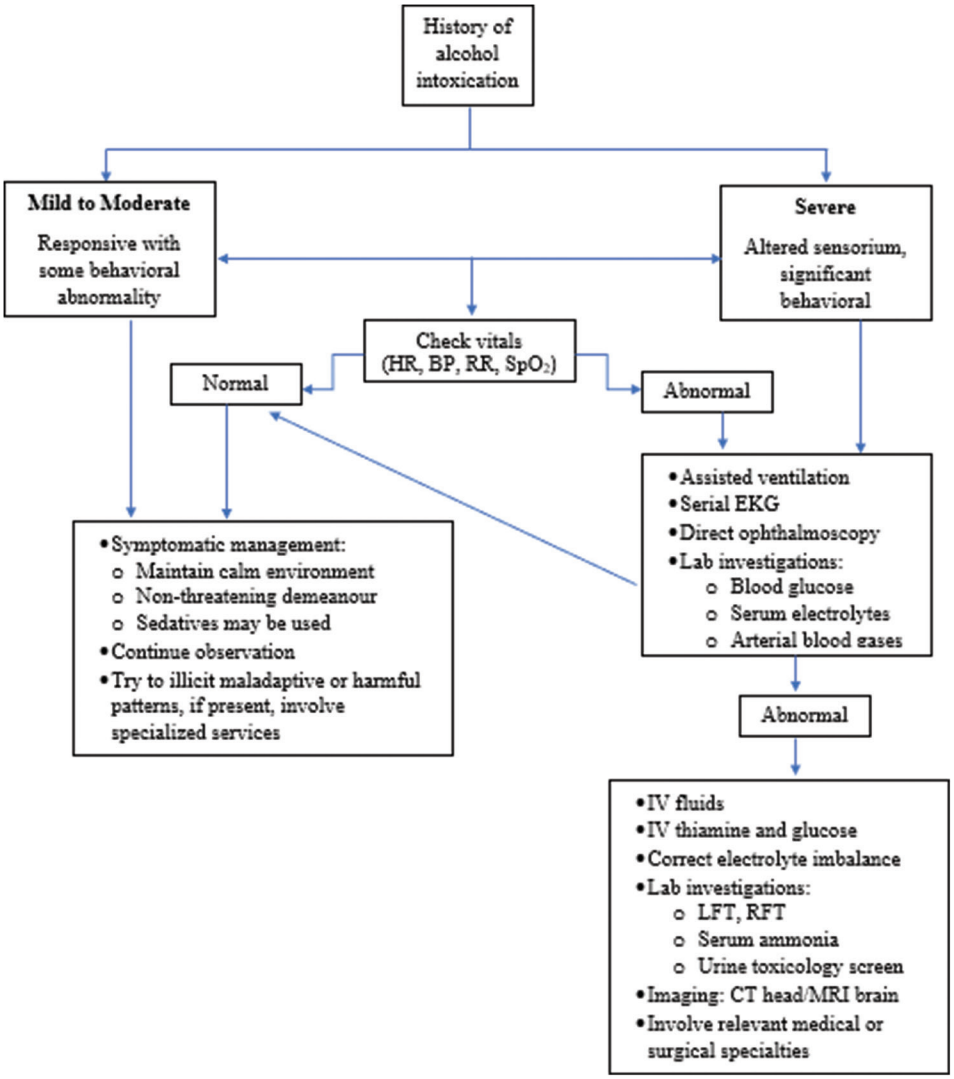

Figure 3: Management of alcohol intoxication in an emergency setting

mental status (e.g., subdural hematoma). MRI can also be considered for select cases.

g. If suicidality is expressed, then psychiatric evaluation should be considered.

2. *Laboratory investigations*
   a. Blood glucose, plasma electrolytes, and blood gases should be measured as frequently as possible in patients with altered sensorium until recovery is assured.
   b. Urine toxicology may be performed, if needed, to check for presence of narcotics and sedatives, if suspected.
   c. Complete blood counts can be done to detect megaloblastic anemia.
   d. Liver function tests should be done when prolonged harmful pattern of alcohol use is suspected.
   e. Renal function tests should be done in cases of altered sensorium, poor urine output, or if behavioral features are out of proportion to the amount of alcohol consumed.
   f. Blood alcohol levels may be required in medicolegal cases when reliable history is not available or when behavioral features are out of proportion to the amount of alcohol consumed.
   g. Whole blood thiamine levels may be measured in patients at risk of or suspected to develop Wernicke's encephalopathy.
3. *Symptomatic management*
   a. Control aggression by adopting a concerned and non-threatening demeanor.
   b. Sedatives should be used judiciously to avoid over-sedation.
   c. Metadoxine (given as a single IV/intramuscular [IM] injection of 300–600 mg) may be used to accelerate the elimination of alcohol in adults leading to faster recovery from intoxication.
   d. In cases of agitation or violence, antipsychotics (haloperidol 5 mg with promethazine 50 mg) should be considered.

In-patient admission of a patient with alcohol intoxication can be considered when there is severe intoxication, medical complications such as Wernicke's encephalopathy, alcoholic hepatitis, dysrhythmias or convulsions, persistent disorientation, continued abnormality in cardiopulmonary parameters, known chronic systemic illnesses that require medical attention independently, prolonged aggressive behavior, or perceptual abnormalities. The specialty under which the patient needs to be admitted can be determined according to the indication for admission.

CANNABIS INTOXICATION IN THE EMERGENCY SETTING

Cannabis is the most common illicit substance of abuse in India. Cannabis intoxication sometimes presents to the emergency setting after consumption (either inhalational or oral) of high amounts of cannabis. It usually presents in those who have never tried cannabis before and experience severe psychiatric or medical manifestation of cannabis consumption. Sometimes, regular cannabis users may also experience symptoms and signs of cannabis intoxication when they are introduced to a cannabis product of higher potency.

Cannabis intoxication manifests with several symptoms as mentioned in Table 3.[9] There can be several physical symptoms of cannabis intoxication. These include tachycardia, tachypnea, increased blood pressure, dry mouth, nystagmus, increased appetite, and, rarely, precipitation of arrhythmias, angina, or myocardial infarction. Rarely, deep inhalation or breath holding may lead to pneumomediastinum or pneumothorax. Marked perceptual and mental status changes can be observed in cases of cannabis intoxication. These can include alteration in perception of time, with the perceived time being faster than clock time. Music is perceived as more engrossing and colors may appear brighter. There may be hallucinations, primarily auditory ones. There can be a sense of depersonalization. One may become more self-conscious, and may manifest paranoid thinking or delusions (persecutory, referential, or grandiose). Cannabis intoxication affects cognition and psychomotor performance as well. There may be motor incoordination and impaired attention and concentration. Judgment may be impaired due to cannabis intoxication.

The cognitive and psychomotor features of intoxication may not be immediately apparent and may manifest up to three hours after consumption of the cannabis product. This may lead novice users to consume higher amounts and experience dysphoria, anxiety, perceptual alterations, and

Table 3: Features of cannabis intoxication

Tachycardia
Increased blood pressure, or rarely, orthostatic hypotension
Conjunctival injection (reddening of eyes)
Dry mouth
Increased appetite
Nystagmus
Increased respiratory rate
Rarely arrhythmias, angina, or myocardial infarction
Rarely pneumomediastinum and pneumothorax caused by deep inhalation or holding the breath
Changes in mood: euphoria, dysphoria or anxiety
Perceptual changes: color and music perception altered
Time perception may be distorted
Distorted spatial perception
Hallucinations
Depersonalization
Delusions or paranoid thinking
Impaired attention and concentration
Slowed reaction time
Impaired motor coordination
Impaired judgement

cognitive changes to a higher than anticipated extent. These features of intoxication may last even for 12 to 24 hours after the consumption of cannabis due to accumulation in the adipose tissue and gradual release afterwards.

Assessment of patients with cannabis intoxication

The assessment of cannabis intoxication is through elaboration of the history and conduct of the examination, supplemented with urine drug screening. Patients presenting to the emergency department with panic attacks or psychotic symptoms after cannabis usage can describe their psychopathology. Attempts should be made to assess the consumption of cannabis products prior to occurrence of such symptoms. Sometimes, friends and family members can provide corollary information. A physical examination that reveals bilateral conjunctival injection without itchiness or pain may indicate cannabis intoxication. A high degree of suspicion may be necessary as the patient may not be forthcoming with proper history, fearing legal or social repercussions.

Urine enzyme-linked immunodorbet assay (ELISA) tests might provide objective information about consumption of cannabis, as cannabis remains in the body and is excreted in the urine for at least three days in infrequent consumers and for an even longer duration for regular users. One has to be cautious about urine false positives for cannabis due to efavirenz and non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen and naproxen.

Differential diagnosis of cannabis intoxication may include intoxication with other substances of use like cocaine, lysergic acid diethylamide (LSD), MDMA (ecstasy), amphetamines, and synthetic cannabinoids. When a patient presents with psychiatric symptoms like hallucinations, delusions, or panic attacks, one should evaluate for the exacerbation of a preexisting psychiatric illness like schizophrenia, acute and transient psychotic disorder, or panic disorder.

Management of cannabis intoxication in the emergency setting

Management of cannabis intoxication in the emergency setting can be initiated with placing the patient in a dimly lit space, reassuring them, and decreasing stimulation. In most cases, the intoxication would fade in a few hours. The patient may be given benzodiazepine orally if the patient is accepting the medication orally. Clonazepam 0.5 mg or lorazepam 1 mg can be given in such a situation.

If the patient is agitated or violent, then appropriate measures should be taken for the management of agitation or violence. This may include use of antipsychotics (like haloperidol 5 mg with promethazine (Phenergan) 25 mg, given intravenously or intramuscularly), or cautious and limited use of restraints.

In cases of chest pain, the patient should be evaluated for cardiac or pulmonary etiological causes. These may focus on myocardial infarction, angina, arrhythmia, pneumothorax, or pneumomediastinum, or evaluation of exacerbation of asthma. ECG or X-rays coupled with referral to cardiologists/pulmonologists or medicine specialists would be useful.

Once the patient recovers from cannabis intoxication, they should be debriefed and offered counseling, providing information about harms associated with cannabis use. If a cannabis use disorder is identified (harmful use or dependence), then the patient should be suitably referred for further treatment of substance use disorder.

OPIOID INTOXICATION IN THE EMERGENCY SETTING

Opioids are highly dependence-producing substances. Opioids used commonly include both pharmaceutical ones (used generally in the form of medications such as methadone, buprenorphine, tramadol, and pentazocine), and non-pharmaceutical ones (generally used for recreational purposes like heroin and raw opium). Intoxication with opioids can be intentional (a patient may be taking increased amounts of opioids to experience a more intense high or as an attempt to harm oneself) or unintentional (a patient may be unable to know the potency of street heroin and hence may inject higher doses of it).

There are several risk factors for opioid intoxication or overdose that have been reported in the literature.[10] These include escalating doses of opioids, combination of opioids and sedative drugs, use of opioids after a period of cessation, and presence of comorbid conditions like HIV, depression, and liver disease.

Opioid intoxication is defined as a condition of transient and clinically significant disturbances in consciousness, perception, behavior, cognition, affect, or coordination that develop during or shortly after the consumption or administration of opioids. Presenting features include somnolence, stupor, psychomotor retardation, slurred speech, mood changes (euphoria followed by dysphoria), respiratory depression, and impaired memory and attention. Pupillary constriction is generally present. The intensity of these symptoms is related to the amount of opioids consumed, and in severe intoxication, coma may occur. These symptoms are not better accounted by the presence of another medical condition or presence of intoxication or withdrawal of another substance. Opioid intoxication can be classified as mild, moderate, or severe on the basis of the level of psychophysiological changes due to the opioids (e.g., impairment in judgement or attention), and impairment of the level of consciousness [Table 4]. Opioid overdose is a related life-threatening condition induced

Table 4: Features of opioid intoxication and opioid overdose

Opioid intoxication
Sedation/somnolence
Psychomotor retardation
Slurred speech
Euphoria, followed by dysphoria
Impaired memory and attention
Respiratory depression
Stupor
Coma
Pupillary constriction (sometimes dilatation due to severe anoxia)
Severity of opioid intoxication
Mild: Changes in psychophysiological functions and responses are apparent, with little/no disturbances in the level of consciousness.
Moderate: Changes in psychophysiological functions and responses are marked, with some changes in the level of consciousness.
Severe: Changes in psychophysiological functions are obvious, with marked changes in the level of consciousness.
Opioid overdose
Coma
Respiratory depression
Pinpoint pupils

by consumption of excess amounts of opioids, which is characterized by pinpoint pupils, unconsciousness, and respiratory depression. The features of opioid intoxication and opioid overdose are presented in Table 4. Severe opioid intoxication and opioid overdose may be clinically indistinguishable, and the clinical label of "opioid overdose" may be more suitable when dealing with patients who present to the emergency unit with respiratory depression, unconsciousness, and pinpoint pupils after recent consumption/administration of large doses of opioids. Furthermore, though generally opioid intoxication presents as euphoria followed by dysphoria, other psychological manifestations of opioid intoxications may be anxiety, agitation, depression, hallucinations, and paranoia. Some of the opioids are known to reduce the seizure threshold (like dextropropoxyphene and tramadol), and the patient may present with an episode of seizure.

Assessment for opioid intoxication

The assessment of patients with opioid intoxication aims at ensuring safety of the patient and prevention of irreversible harm to the patient. In cases of opioid intoxication/overdose, information is generally obtained from friends or family members of the patients. Information on the presence of pills or injection paraphernalia where the patient was found can be a helpful guide to understanding the consumption of opioids by the patient. The onset, duration, and the intensity of the symptoms of intoxication would vary according to the potency of the opioid and the route of administration; for example, the same doses of fentanyl, buprenorphine, and heroin are likely to present differently (symptoms are likely to be more intense for fentanyl and duration of action may be much longer for buprenorphine). Attempts should also be made to discern the use of sedative hypnotics along with opioids for a given patient. Concurrently with the assessment of the patient, emergency measures would need to be instituted for the patient (including attention to the airway, breathing, and circulation).

There are some differential diagnoses that may be considered in patients who present with features of opioid dependence. These include head injury, meningitis or encephalitis, systemic infections, hepatic or other metabolic encephalopathies, diabetic ketoacidosis or hypoglycemia, electrolyte disturbances, and hypoxia/hypercapnia due to preexisting respiratory conditions. Clinical assessment and laboratory investigations, as necessary, should be used to include or rule out other conditions.

Management of opioid intoxication in the emergency setting

Opioid intoxication presents as a medical emergency and can be fatal if the patient is not treated appropriately. The risk of death is primarily due to respiratory depression. The flowchart in Figure 4 describes the usual management of patients with opioid intoxication. It must be remarked that effective treatment options are available for the treatment of opioid intoxication in the emergency setting.[11]

The ABC of management in the emergency setting should be instituted for the patient. Airway should be made patent, and the patient may need to be intubated if they are unable to maintain the airway and saturation. Supplemental oxygen or mechanical ventilation through bag and mask may be required if the patient has low oxygen saturation (<93%) or respiratory rate is less than 8 breaths per minute. Many places have a routine practice of assessing glucose if a patient is unconscious (to detect hypoglycemia) and that may be done as per protocol.

Naloxone is a full opioid antagonist that is an important treatment agent for opioid intoxication. By acting on μ-opioid receptors, it displaces the opioid agonist and reverses the signs and symptoms of opioid intoxication. It has a short duration of action (about 60 to 90 minutes). Generally, it is administered intravenously, but for some patients, when accessing the veins is difficult, it can be administered subcutaneously, intramuscularly, endotracheally, or intranasally. It is administered in doses of 0.2 to 0.4 mg (and higher doses of 1 to 2 mg in cases of patients presenting with apnea or cardiorespiratory arrest). When patients show improvement with naloxone, the improvement occurs within two to three minutes in the form of pupillary dilatation and increase in the respiratory rate. Some patients may require higher doses to show reversal of opioid intoxication. Doses of naloxone can be repeated every two to three minutes to a maximal dose of 10 mg. After reaching reversal, higher doses should be avoided as naloxone may be associated with vomiting.

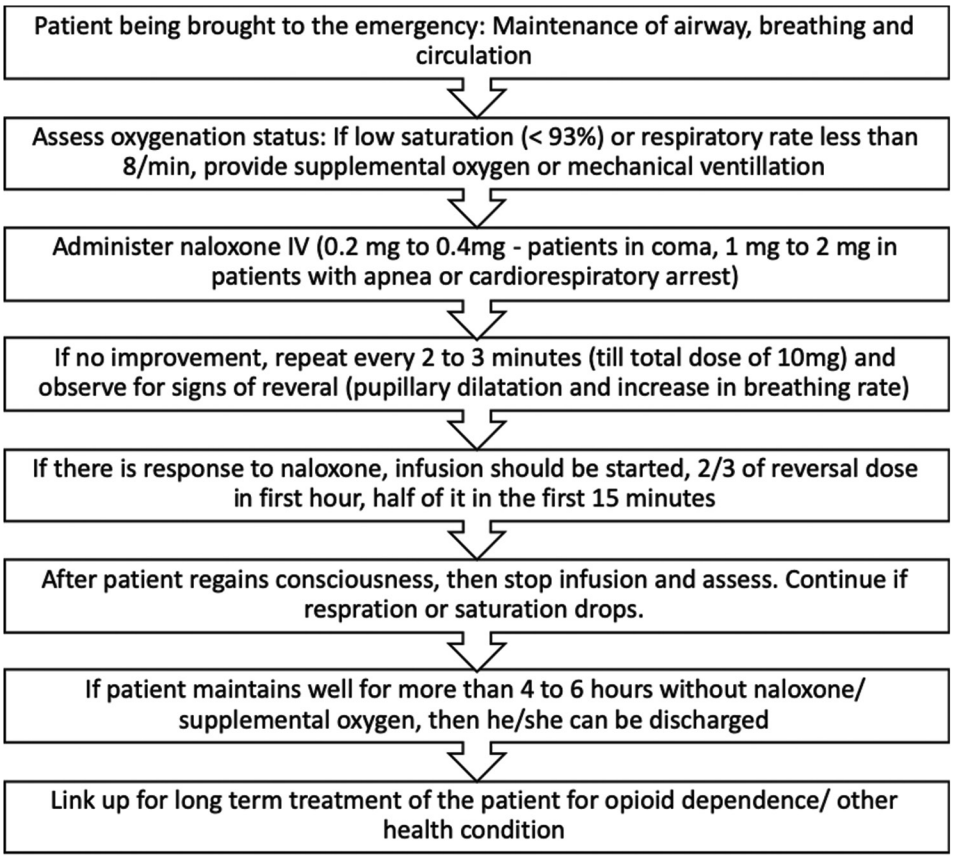

Figure 4: Management of opioid intoxication

In case of response to naloxone, intravenous infusion should be considered in patients with overdose from longer acting opioids (e.g., buprenorphine) because the patient can fall back into coma as the effect of naloxone decreases. For naloxone infusion, two-thirds of the reversal dose should be given hourly. Half of this dose should be administered over the first 15 minutes and the remaining over the next 45 minutes; for example, if the reversal dose was 1.2 mg, then the first hour dose would be 0.8 mg, and 0.4 mg would be administered through infusion in the first 15 minutes. Naloxone can be repeated intramuscularly or subcutaneously if the veins are inaccessible. After reversal and when the patient is clinically better, it is useful to observe the patient for 4 to 6 hours after naloxone infusion is stopped and before the patient is discharged.

There is a high risk of overdose again if a patient has overdosed once. Patients who have overdosed on opioids should be offered pharmacological and non-pharmacological treatment for opioid dependence. It has been seen that opioid substitution treatment with buprenorphine or methadone is associated with lower overdose-related mortality.[12] The reader is referred to the other Indian Psychiatric Society guidelines on the management of opioid dependence in the clinical population.[13]

BENZODIAZEPINE INTOXICATION IN THE EMERGENCY SETTING

Benzodiazepines are commonly prescribed medications in the clinical setting. Drugs in this group are classified as short acting (etizolam, alprazolam, and lorazepam) and long acting (diazepam, nitrazepam, and clonazepam). Benzodiazepines have several clinical applications including treatment of sleep and anxiety disorders. Benzodiazepines have been implicated in 31% of all fatal poisonings reported in the United States over the last two decades.[14] Thus, it is important that emergency care providers learn to identify and manage benzodiazepine overdose, which is defined as ingestion of any drug in the class of benzodiazepines in quantities greater than recommended.

The largest vulnerable groups to present with benzodiazepine intoxication are children, who may ingest it accidentally, and elderly, who commonly complain of insomnia and are prescribed benzodiazepines. Deteriorating metabolism and cognitive functioning may become factors responsible for accidental benzodiazepine overdose. Deliberate overdose with an intent to self-harm may also be a possibility that cannot be ignored.

Clinical features of benzodiazepine intoxication

The clinical features of benzodiazepine intoxication are dose-dependent and wear off spontaneously with small doses of shorter acting agents. Symptoms of benzodiazepine intoxication are presented in Table 5.

Assessment for benzodiazepine intoxication

Many patients with benzodiazepine intoxication are arousable and can provide information regarding their ingestion. In those patients with severe benzodiazepine intoxication who cannot provide an adequate history, a general approach should be undertaken to stabilize the patient. The aims of assessment include definitive identification of benzodiazepine intoxication along with anticipation and prevention of life-threatening risks.

1. *History*
   Elicit details on the use of the drug from family members/friends and the patient, if responsive: name, dose, duration, mode of overdose, and whether the benzodiazepines were mixed with other psychoactive substances like alcohol, cannabis, opioids, barbiturates, tricyclic antidepressants, anticonvulsants, sedating antipsychotics, or antihistamines. Attempts must be made to elicit any prior episodes of benzodiazepine intoxication, in addition to identification of tolerance, craving, withdrawal, salience, and any physical or psychological harms caused by benzodiazepines. Also ask about high-risk behaviors like driving or operating heavy machinery and a history of falls or accidents under intoxication.
2. *Physical Examination*
   Assess vital signs including pulse, respiratory rate, blood pressure, temperature, and oxygen saturation. Assess level of consciousness, preferably using the Glasgow Coma Scale. Ataxia may be present in cases of benzodiazepine intoxication.
3. *Mental status examination*
   1. General behavior: Patients usually appear sedated but responsive. Occasionally, paradoxical reaction may occur, characterized by agitation, anxiety, disinhibition, and aggressiveness.
   2. Slurring of speech, mumbling, or irrelevant talk may be present.
   3. Perceptual and thought abnormalities are rare.
   4. A detailed CNS examination is warranted, especially in elderly patients and those with known liver or renal disease, history of chronic illness, and poor general health condition.

Table 5: Features of intoxication with benzodiazepines

Initial feeling of relaxation, mild euphoria, and sexual enhancement and sedation
Large doses produce impaired judgement, motor incoordination, blurred vision, slurred speech, slowed reflexes, impaired perception of time and space, slowed breathing, and reduced pain sensitivity
Still higher doses cause confusion, unconsciousness, coma, and death

Rule out other causes of acute respiratory depression like head injury, encephalitis, hypoglycemia, hypernatremia, systemic infection, respiratory tract infection, acute cardiac event, and stroke.

Management of benzodiazepine intoxication in the emergency setting

Treatment of benzodiazepine overdose is mainly supportive. Most effects wear off in a few hours for short-acting and in 24–48 hours for long-acting benzodiazepines. However, CNS complication and cardiac and respiratory compromise may contribute to patient mortality unless managed effectively. Hence respiratory distress should be addressed first. Mechanical ventilation may be required to address respiratory compromise. The suggested management here should be considered in conjunction with other Indian Psychiatric Society Clinical Practice Guidelines (IPS CPGs) on the topic.[15]

General management

1. Maintain airway, breathing, and circulation.
2. Measures to prevent aspiration should be instituted (lateral position, suction equipment).
3. An ECG should be considered.
4. Volume expansion may be required for hypotension.
5. Correct hypothermia.
6. Repeated evaluation of neurological status and respiratory functions may be needed.

Investigations

1. Glucose testing may be considered to rule out hypoglycemia.
2. Urine toxicology screening should be carried out for benzodiazepines and other psychoactive substances.
3. Monitoring cardiac activity using ECG may be needed in many cases. ECG- abnormality of QRS or QT_c intervals should suggest co-ingestion of cardiotoxic agents.
4. A chest X-ray may be considered for comatose patients or those with respiratory compromise to rule out aspiration pneumonia.

Prevention of absorption of benzodiazepines

1. Consider gastrointestinal decontamination using a single tablet of activated charcoal via nasogastric tube in cases of heavy ingestion with intended self-harm, co-ingestion with other substances like antidepressants, and if the patient is brought less than one hour after ingestion.
2. Invasive procedures like induced emesis, gastric lavage, and bowel irrigation should be avoided.

Antidote administration

Flumazenil (a benzodiazepine receptor competitive antagonist) can reverse benzodiazepine-induced CNS impairment.[16] The dose of administration is 0.1–0.2 mg/minute intravenously over 30 seconds, which may be repeated as 0.1 mg after one-minute intervals till the patient is alert and respiration is appropriate. A maximum dose of 1–2 mg can be used. Arousal of the patient generally occurs 30–60 seconds after intravenous administration. The effect peaks after 5–10 minutes and lasts for 1–2 hours. Continuous infusion (usually 0.5–2 mg/hour) may be needed to maintain the effect and prevent re-sedation.

Slow injection (0.2 mg over 15 seconds) is recommended to avert the adverse effects associated with sudden arousal, including seizures, cardiac arrhythmias (particularly paroxysmal supraventricular tachycardia), anxiety, palpitations, nausea, and vomiting. Flumazenil is expensive and has limited availability in India and is thus not recommended for routine use. Flumazenil can be safely administered to non-habituated users of benzodiazepines but should be avoided in patients with history of seizure disorders, benzodiazepine dependence, and head injury. Use of flumazenil may be constrained by its availability.

INTOXICATION WITH OTHER SUBSTANCES

Cocaine and other stimulants

Though cocaine and other stimulants have traditionally not been commonly abused in India, their use is gradually rising, especially in bigger cities. Presentation of cocaine intoxication is in the form of euphoric mood, increased psychomotor activity, severe agitation, impaired attention, auditory hallucinations, paranoid ideation, confusion, anxiety, and hypervigilance. Some patients may manifest picking of the skin (formication). Cocaine has sympathomimetic effects and may result in hypertension, tachycardia, hyperthermia, diaphoresis, and mydriasis. Similar actions are also produced by other stimulants (like amphetamine and methamphetamine) and these last till the action of the stimulant subsides. Some patients may exoerience seizures or chest pain due to cardiac ischemic changes. An ECG or troponin T test can be done to find out changes in the cardiac functioning.

Management of cocaine or stimulant intoxication is generally symptomatic.[17] Patients can be placed in a quiet room/area, if possible. Patients can be given benzodiazepines for sympathomimetic symptoms and agitation or seizure. Benzodiazepines like lorazepam 2 mg can be given orally, intramuscularly, or intravenously, and repeated as necessary. For acute agitation and paranoia, the patient may need injectable antipsychotic on a short-term basis (though antipsychotics are not required in the absence of a concurrent psychotic disorder or stimulant/cocaine-induced psychotic disorder). Very rarely, patients may need restraints. Patients may be given IV fluids for dehydration. Aspirin and nitroglycerine are given for chest pain related to cocaine. Patients with cocaine or stimulant intoxication become asymptomatic over a period of hours to within a day. After resolution of the intoxication, the patient may be referred for treatment of the cocaine/stimulant use disorder, if present.

Hallucinogens

Several hallucinogens may cause features of intoxication, and these include LSD and phencyclidine. Symptoms of hallucinogen intoxication includes hallucinations, perceptual changes such as depersonalization and derealization, illusions, synesthesia, affective changes like anxiety or dysphoria, paranoid ideation, impaired judgment, sweating, palpitations, blurred vision, tremors, and lack of coordination. Patients may experience elevated blood pressure, tachycardia, and pupillary dilatation.

Treatment of hallucinogen intoxication is symptomatic.[18] The effects generally wear off within a day or so. Management relies on placing the patient in a quiet room with minimal stimulation. The patient should be reassured. Sometimes, benzodiazepines like clonazepam or lorazepam can be used. If the patient is amenable to oral medications, then these can be used, or else injectable medications can be resorted to. Rarely, injectable antipsychotics and physical restraints would need to be used for such patients. After resolution of the intoxication, the patient should be counseled and advised to seek treatment if hallucinogen-related disorders are identified.

Volatile solvents

There are a variety of volatile solvents that are used by individuals. These include glue, gasoline, spray paints, paint thinners, ink-eraser fluids, nitric oxide, and poppers (alkyl nitrites). Psychiatric effects of poppers are typically temporary and last for minutes. In India, glue, petrol, and ink-eraser fluids are used commonly. Volatile solvents are generally used by children and adolescents, though many adults also consume these substances. The features of volatile solvent intoxication include euphoria, aggression, dizziness, impaired judgment, lethargy and apathy, somnolence, stupor or coma, tremor, slurred speech, incoordination, unsteady gait, psychomotor retardation, and visual disturbance. Patients may experience muscle weakness and diplopia. Volatile solvents may also result in agitation and psychosis (pseudo-hallucinations, hallucinations, and ideas of grandiosity).

Some patients may have arrhythmias after intoxication with inhalants, and hence an ECG may be useful for such patients. Management of patients with inhalant intoxication is largely symptomatic.[18] Monitoring of oxygenation and ventilation is needed, along with maintaining the airway. Supplementary oxygen and intravenous fluids can be used

for some of the patients as needed. Benzodiazepines like lorazepam 1–2 mg can be used for agitation or psychosis. The intoxication generally abates after a short period of time, and the patient improves. Regular users of inhalants should be further referred for treatment.

Polysubstance use

Sometimes healthcare providers working in emergency settings may encounter patients with a history of polysubstance use, which means consumption of more than one drug at once. The substances involved could be illicit, prescription drugs or a combination of both. Alcohol, benzodiazepines, and cannabis are common substances used in combination with other psychoactive substances. Multiple substances are generally mixed together with the aim of enhancing the psychoactive effect, off-setting the adverse effects, and alleviating the withdrawal symptoms.

Risk of intoxication and overdose is heightened when multiple substances are consumed together. This could be either due to mutual potentiation of individual drugs' effects or due to inadvertent consumption of greater amounts of substances in an intoxicated state. Thus, intoxication with multiple substances may sometimes present with a complicated clinical picture and may pose diagnostic challenges.[16]

Common symptoms of polysubstance intoxication can include the following:

1. drowsiness, sleepiness, and inability to wake up
2. chest pain and heart palpitations (especially when multiple stimulants have been mixed)
3. stomach pain, nausea, vomiting, and diarrhea
4. feeling overly hot or cold and having skin that is sweaty or very dry
5. slurred speech and inability to complete normal tasks

Management of intoxication with multiple substances in an emergency setting

There are no fixed guidelines for the treatment of intoxication with multiple substances, and the healthcare professional is required to employ careful observation, thorough assessment, and early intervention in order to prevent complications.[19]

Details of consumed substances, if available, should be elicited from the patient, if responsive, and attendants. It is advisable to refer to medical records, if available, for relevant information on history of substance use and prescription details. Any past episodes of overdose or seizures should be noted. Physical examination may offer clues to substance use; for example, pupil size to detect pin point pupils, characteristic odors emanating from nose or mouth, needle track marks, or any other tell-tale signs that may help identify the substances consumed. Additionally, a complete systemic examination with special attention to CNS and cardiopulmonary systems is often necessary. A drug panel test may be useful to ascertain the substances being used.[20]

Management of polysubstance use in the emergency department aims at preventing and managing life-threatening complications of consumption of multiple psychoactive substances. While definitive management varies from case to case (based on the combination of substances), some standard practices are enumerated as follows:

1. Monitor vital signs and cardiac parameters with serial ECG monitoring.
2. Prevent aspiration by placing the patient in left lateral position.
3. Provide ventilator support when required.
4. Correct hyper- or hypothermia.
5. Intravenous fluids may be required.
6. Definitive management depends on confirmed report of the nature of substances consumed.
7. Sedatives may be used judiciously to avoid worsening respiratory depression.
8. Antidotes like naloxone and flumazenil may be used with caution to avoid unmasking effects of substances with opposing psychoactive effects.
9. Observation for at least 24–48 hours may be advised for any residual effects and detailed assessments.

It is desirable to involve specialized services, such as addiction psychiatry or psychiatry for detailed assessment once the patient is conscious and responsive. This may provide a good opportunity for intervention and long-term engagement with treatment services.

Substance intoxication in special populations

Substance use has now emerged as a universal phenomenon with no population group immune to its effects. Certain population groups require unique considerations while managing substance intoxication in emergency settings and in specialized treatment services due to their unique physiological and psychosocial needs. In this section, we will discuss three special groups of such populations: children and adolescents (aged less than 18 years), pregnant women, and elderly (aged 65+ years).

Children and adolescents

Children and adolescents form a special group in the context of substance use due to the fact that physiologically they have smaller body volumes, making a small amount of substance exert significant psychoactive effects, and a developing brain, which may be at risk of serious long-lasting adverse effects when exposed to psychoactive substances.

Experimental substance use is common in this adolescent group; substances commonly consumed out of curiosity are tobacco, alcohol, cannabis, volatile solvents, and opioids.[21] Children and young adolescents may present

with intoxication symptoms similar to those seen in adults with much smaller amounts of substances consumed, posing a higher risk of mortality. The essential principles of treatment are similar to those with adults.[22] Table 6 presents some of the elements to be taken into consideration in the management of children and adolescents with substance intoxication. One can also refer to the IPS CPG related to substance use among children and adolescents.[23]

Pregnant women

Illicit substances, tobacco, alcohol, and prescription drugs are especially harmful during pregnancy due to potential harm to both the mother and the fetus. Physiological changes in pregnancy often lead to unpredictable variations in the pharmacokinetics of drugs, making most medications and psychoactive substances risky. Despite this knowledge, global prevalence of substance use among pregnant women is about 6%, maximal among young pregnant women (18.3% among pregnant women aged 15–17 years). Pregnant women with intoxication present a challenging situation for the emergency department, as both the mother and the fetus are in need of medical attention, and medications need to be used with great caution. General considerations for management of an intoxicated pregnant woman in the emergency setting are presented in Table 7.

Elderly population

The elderly population has some unique risk factors for substance intoxication. They have a lower volume of distribution, leading to increased systemic concentration of consumed psychoactive substances. Often, compromised renal function causes reduced elimination of drugs from the systemic circulation. These factors lead to development of intoxication at relatively lower doses of the substances. Some prescription medications sometimes have a high risk of dependence (opioids and benzodiazepines). One may need to differentiate from symptoms of frailty syndrome, which manifests as memory problems, incontinence, falls, and limitations of functioning. Sometimes, interactions of the medications may also result in features of substance intoxication.[24] A few points to consider while managing elderly patients with substance intoxication in emergency settings are presented in Table 8.

Dual diagnosis

Dual diagnosis refers to the co-occurrence of a substance use disorder along with a psychiatric condition. Studies report that comorbid substance use disorders are substantially related to increased visits to the emergency department across multiple samples of patients with psychiatric disorders (e.g., schizophrenia, depression, anxiety, etc.). Schizophrenia, anxiety, depression, and dementia are common disorders associated with substance use. Presentation to the emergency unit may be required due to accidental overdose or overdose with a desire for self-harm. Pharmacokinetic interaction between substances

Table 6: General considerations in the management of children and adolescents with substance intoxication

Nature of the substance ingested and its dosage per kilo body weight should be identified as accurately as possible.
In cases where substance use is suspected but cannot be confirmed by clinical history, a detailed physical examination including a neurological assessment can be helpful in substance identification.
Administration of emetics, gastric lavage, and activated charcoal should be generally avoided.
Forced diuresis may lead to fluid overload and should be avoided.
There is limited evidence for safety and effectiveness of antidotes to specific substances, and the decision to use them depends on risk-benefit analysis.
A period of at least 24 hours for observation after stabilization of the patient is advised.

Table 7: General considerations for management of an intoxicated pregnant woman in emergency

Monitoring of vital signs is essential for both the mother (heart rate, pulse, blood pressure, SpO_2, temperature) and the fetus (fetal heart rate, non-stress test). In case of signs of fetal distress, close involvement of obstetrician and/or neonatologist may become important.
Reduced fetal movements may indicate fetal sedation and/or hypoxia while increased fetal movements may indicate the fetus experiencing withdrawal symptoms.
Pharmacotherapeutic agents should be avoided as far as possible, and if prescribed, agents with reliable evidence for safety should be given in the lowest possible effective dose.
As intoxication effects wear off, uterine contractions may increase, sometimes precipitating premature rupture of membranes, preterm labor, miscarriage or placental abruption.
In cases of overdose with opioids and benzodiazepines, antidotes may be given after careful risk-benefit assessment. Precipitating withdrawals should be avoided as far as possible.
After stabilization, it is advised that the woman be referred to specialized treatment services for management of harmful patterns of substance use.

Table 8: Considerations for the management of elderly patients with substance intoxication in the emergency setting

Aggressive initial treatment is necessary because the elderly patients are generally more susceptible to life-threatening complications of drug overdose and have lower body reserves to handle health issues.
A pre-existing physical illness can often confuse the clinical picture. Initial examination should focus on the symptoms and physical findings likely to be attributed to the drug involved while attempts should be made to differentiate the symptom etiology based on temporality and presentation.
Essential elements of history include the name and amount of the drug involved, route of exposure, time since exposure, whether the exposure was acute or chronic, symptoms or physical findings, underlying medical or psychiatric illnesses, concurrent medications, and any previously administered medical treatment.
A laboratory analysis of blood or urine may be helpful in confirming a drug-related problem.
Most patients need symptomatic care for intoxication. When specific antidotes are indicated, these should be given in the same doses as those administered to younger patients.
Forced diuresis is risky in patients with congestive heart failure and may lead to fluid overload and pulmonary edema.
Hemodialysis or hemoperfusion may be required at lower plasma drug concentrations of drugs like barbiturates in older patients (though clinical use of barbiturates is very infrequent now).

and psycho-pharmaceutical agents may lead to alterations in metabolism of both and present with symptoms of overdose/intoxication.

Dual diagnosis often complicates the clinical picture in an emergency setting. Detailed history along with access to the patient's medical records with details of the prescription may help to clarify the scenario. Quantitative analyses of intoxicating drugs and medications are helpful in deciding the course of treatment. Specialized psychiatric services along with critical care services, if required, must be referred to in such a scenario at the earliest.

NEW PSYCHOACTIVE SUBSTANCES

The term "new psychoactive substances" (NPS) is used for a broad range of chemical compounds that are consumed for their psychoactive properties but that are not controlled under the United Nations drug control conventions. New psychoactive substances may pose similar risks to those associated with better-known controlled substances and often appear in the same broad classes of drugs (opioids, benzodiazepines, stimulants, etc.). Yet they are chemically different, so the risks they present to health may differ or simply be unknown.

Emergencies associated with NPS may result from trying an unknown agent or a substance with unknown potency or unknown drug interactions. In an emergency associated with NPS use, history becomes of utmost importance. Urine drug screening may not detect these agents and blood assays may not have been developed for them either. While the emergency management procedure remains essentially the same, care must be taken to gather as much information about the NPS as possible for an effective detoxification. Specialized psychiatric services along with critical care services, if required, must be involved.

CONCLUSION

Substance intoxication is often a reason for seeking emergency care. Some substance intoxications (like opioid, alcohol, or benzodiazepine intoxications) can be life-threatening. A certain degree of clinical suspicion is required to identify substance intoxication, especially when the patient is not spontaneously forthcoming with information. Substance intoxication needs to be managed based on the type(s) of substance(s) consumed, current medical and psychiatric status of the patient, history available and examination findings, and available resources. Intoxication may occur in both naïve and regular substance users. The principles of management include ensuring the safety of the patient, managing their vitals (especially if they are in a life-threatening state), letting the symptoms and signs of intoxication abate, handling the concurrent medical or psychiatric condition, and link up to further services as required. For unmotivated individuals, brief interventions may be helpful in the emergency setting as well.[25] Psychiatrists have an important role to play in the management of patients with substance intoxication, and close collaboration with emergency physicians in the care of patients may lead to better patient outcomes.

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Opioid Toxicity

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Continuing Education Activity

Pain is one of the most common reasons a patient seeks medical care. Various modalities may be used to relieve pain, and one of them is the administration of opiates. Opiates and opioids are strong pain relievers derived from the plant *Papaver somniferum*. Conventionally, the term "opiates" refers to natural compounds obtained from the poppy flower base, while "opioids" are synthetic agents with similar effects.

Opiates have been formally approved for analgesia for nearly 70 years, and these drugs have been assumed to be relatively safe despite the potential consequences of overdosing, including central nervous system and respiratory depression resulting in arrest. However, many reports in the last 2 decades have raised concerns about the safety of these drugs. Opiate prescriptions have dramatically increased over this period, with the United States currently experiencing an opioid epidemic with fatal consequences. Overdose and toxicity cases are on the rise and are continually reported in all major cities. Empirical prescription habits by healthcare workers to relieve pain have also led to an epidemic of overdose outside the healthcare setting, with the eruption of clandestine laboratories manufacturing synthetic opioids such as fentanyl and distributing them on the street.

This activity for healthcare professionals is designed to enhance learners' proficiency in evaluating and managing opioid toxicity. Participants gain a deeper understanding of the condition's risk factors, etiology, toxicology, pathophysiology, presentations, and evidence-based diagnostic and therapeutic strategies. The course highlights the use of opioid reversal agents such as naloxone to reduce morbidity and mortality. Emphasis shall be given to the role of healthcare professionals in treating opioid use disorder through medication-assisted and nonpharmacologic approaches to support recovery and abstinence. Greater competence equips clinicians to collaborate effectively within an interprofessional team caring for affected individuals, improving outcomes.

Objectives:

- Apply toxicokinetic data when evaluating the progression of opioid overdose and toxicity.
- Select the appropriate diagnostic tests to differentiate opioid overdose from conditions that can present with similar signs and symptoms.
- Implement individualized combinations of pharmacological and nonpharmacological treatments for managing opioid toxicity.
- Collaborate with the interprofessional team to educate, treat, and monitor patients with opioid toxicity to improve health outcomes.

Access free multiple choice questions on this topic.

Introduction

The term "opiate" refers to natural compounds derived from the base of the *Papaver somniferum* poppy flower, such as opium, morphine, diacetylmorphine (heroin), and codeine.[1] In contrast, opioids are synthesized through chemical processes and include methadone, oxycodone, and fentanyl. Opiates have been used since antiquity to relieve pain and induce euphoria. Today, these agents remain a widely used option for pain relief. Opiates have been formally approved for analgesia for nearly 70 years and have long been assumed to be relatively safe and nonaddictive when used for chronic pain.[2]

In 1995, Dr. James Campbell addressed the American Pain Society, advocating for the evaluation of pain as a vital sign.[3] His intentions were well-meaning, motivated by concerns about the undertreatment of pain. However, over the past 2 decades, numerous reports have raised alarms about the safety of these drugs. Cases of overdose and opiate toxicity are reported regularly across major cities in the United States. Particularly concerning is the dramatic increase in opiate prescriptions over the same period. This widespread prescribing by healthcare providers has contributed to an epidemic of overdoses outside the healthcare setting. Consequently, practicing healthcare professionals should recognize opiate toxicity in patients who present as lethargic or unresponsive without an apparent cause. (CDC, 2017)

Data released by the Drug Enforcement Administration (DEA) and the Centers for Disease Control and Prevention (CDC) indicate that, from 2001 through 2010, the rates of opiate diversion, opiate prescriptions, and opiate-related deaths exponentially increased in the United States. These rates plateaued from 2011 through 2013 but spiked again between 2013 and 2014. Experts in pain management believe that the high number of opiate overdoses is likely unintentional, as patients may have been attempting to manage unrelenting pain. (CDC, 2016)

Prescriptions for opioid-containing medications quadrupled between 1999 and 2010, paralleling a 4-fold increase in overdose deaths due to opioids. The majority of opioid-related deaths are attributed to the use of heroin and synthetic opioids other than methadone.

The issue of poorly treated pain has led medical professionals to use various short- and long-acting opiates. While this approach has significantly improved pain relief, some patients often fail to adhere to proper dosing. When patients increase the dose or duration of opioid use, toxicity becomes a potential complication. Although the annual rates of transition are low, toxicity often occurs when individuals move from the nonmedical use of prescription opioids to heroin.

Opioid overdose occurs when excessive unopposed stimulation of the opiate pathway leads to decreased respiratory effort and, potentially, death. The frequency of opioid overdoses is rapidly increasing. Drug overdose is now the leading cause of accidental death in the United States, with opioids being the most common culprit. According to the CDC, more than 1,000 emergency department visits reported daily are related to opioid misuse, and about 91 opioid overdose deaths are documented every day.

Heroin, priced at about $2 per bag, is up to 10 times cheaper and more readily available than prescription opioid medications purchased on the street, which average around a dollar per milligram. Additionally, heroin is increasingly being mixed with fentanyl and other synthetic opioid compounds, resulting in variable opioid potency and a higher risk of overdose.

Nonpharmaceutical or "street" opioids are often contaminated with other substances. To increase profits, sellers frequently add additional agents to the formula without informing the end user. These additives are pharmacologically active in many cases. Heroin was adulterated with scopolamine 2 decades ago in New York City, causing severe anticholinergic toxicity. Cocaine adulteration is also prevalent.[4][5][6][7]

Prescription Monitoring

Most states have established prescription drug monitoring programs (PDMPs) to counter the liberal prescribing of opiates by healthcare workers. In many states, healthcare professionals must consult the state's online drug database to determine which analgesic drugs may be prescribed to patients. Such state-enacted legislation aims to prevent mass opiate prescriptions by healthcare workers and to help stop the diversion of legitimate opiate prescriptions. (DEA, 2016) Results are mixed, but research suggests that opioid databases have reduced opioid prescribing. [8]

Additionally, with the assistance of the DEA, statewide registries of controlled substances now help healthcare providers track usage patterns among patients to identify people at high risk for opiate diversion or abuse. While the availability of opiates contributes to opioid addiction, no evidence has yet demonstrated a direct link between opiate abuse and the legitimate use of these drugs for pain. (DEA, 2016)

Etiology

Both opioids and opiates act on 3 major classes of opioid receptors: μ, κ, δ, and several minor classes, such as nociceptin and ζ. Simply put, μ-receptors are thought to provide analgesia, respiratory suppression, bradycardia, physical dependence, gastrointestinal dysmotility, and euphoria. Agonism of κ-receptors can lead to hallucinations, miosis, and dysphoria. The δ-receptor likely contributes to pain control and mood modulation, but some suggest that μ agonism is necessary for the δ-receptor to function effectively in analgesia.[9][10] Causes of opioid overdose include substance abuse, unintentional and intentional overdose, and therapeutic drug error.

The risk of opioid overdose increases in the following situations:

- Taking escalating doses
- Returning to use after cessation
- Having severe medical and psychiatric conditions, such as depression, HIV infection, and lung or liver disease
- Combining opioids with sedative medications
- Being male
- Being younger (20 to 40 years)
- Being of White non-Hispanic race [11][12]

More than 1.5 million emergency department visits are related to opioid analgesic use. Opioid overdose is a common cause of death.

Epidemiology

Impact of the Opioid Crisis in the United States

Opiates are frequently prescribed for moderate to severe pain in the United States. These drugs may be prescribed alone or combined with nonsteroidal anti-inflammatory drugs or muscle relaxants. Based on data from the Automation of Reports and Consolidated Orders Systems, the percentage increases in opiate use from 2004 through 2011 were as follows:

- Buprenorphine 2318%
- Fentanyl 35%

- Hydromorphone 140%
- Methadone 37%
- Morphine 64%
- Oxycodone 117%

Meanwhile, the use of codeine decreased by 20%.

Data from the Drug Abuse Warning Network (DAWN) has revealed that abuse of all the above opiates increased, with hydromorphone and buprenorphine leading the way with a 438% and 384% increase, respectively. (SAMHSA, 2014) Other reports from DAWN reveal that nearly 420,000 documented emergency room visits in 2013 were related to opiates. Cases of abuse and diversion of opiates over the past decade have included drugs like hydrocodone, hydromorphone, fentanyl, morphine, oxycodone, and tramadol.

In 2015, United States poison control centers reported a total of 18,425 exposures to pure opiates, which resulted in 68 fatalities and 764 cases of major toxicity. Additionally, 14,632 cases involved exposure to combinations of opiates with alcohol, benzodiazepines, aspirin, acetaminophen, or ibuprofen. The combined exposures resulted in 32 fatalities and 288 cases of severe toxicity. (AAPCC, 2017) The opioid crisis was reported to claim about 128 lives per day in 2018.[13]

Global Consequences of the Opioid Epidemic

The opiate toxicity epidemic is not limited to the United States but is also a worldwide concern. According to the 2014 United Nations Office on Drugs and Crime, at least 0.4% of the population, or nearly 20 million people, regularly use heroin or opium. The highest usage rates are found in Southwest Asia (1.21%), followed by Southeastern and Eastern Europe (0.83%), and Transcaucasia and Central Asia (0.81%).

In Europe, opioid-related deaths have been primarily linked to the illicit use of fentanyl and its analogs. In countries experiencing a heroin shortage, fentanyl and related products have replaced heroin as the illicit drug of choice. In Russia and Ukraine, desomorphine, known as "krokodil" on the street, is inexpensive and easy to produce from codeine. Besides being 10 times more potent than morphine, the unrefined synthesis methods cause skin abscesses, necrosis, and other life- and limb-threatening complications for users.[14]

Pathophysiology

Opioids exert their clinical effects by interacting with the opioid receptor, which has 3 subtypes: μ, κ, and δ. These receptors are all G-protein-linked and are found throughout the human body. Each subtype produces different clinical manifestations when activated.[15]

μ-receptors mediate analgesia, euphoria, sedation, respiratory depression, gastrointestinal dysmotility, and physical dependence. These receptors reduce the medullary response to hypercarbia and decrease the respiratory response to hypoxia, leading to a diminished stimulus to breathe and the development of apnea. μ-receptors are concentrated in the brain, where they regulate analgesia; in the mesolimbic system, which is responsible for euphoria and reward; and in the medulla, which regulates respiration.

κ-receptors mediate analgesia, diuresis, miosis, and dysphoria primarily within the spinal cord. Stimulation of this receptor subtype is not associated with constipation or significant changes in respiration. μ-receptor-specific antagonists do not reverse analgesia provided by κ-receptor stimulation.[16]

δ-receptors mediate analgesia, inhibit dopamine release, and suppress cough. Less is known about the stimulation of this receptor, but it is believed to play a smaller role in behavior reinforcement.

Opioids may be agonists, partial agonists, or agonist-antagonists of opioid receptors, which are located in the brain, spinal cord, and gastrointestinal tract. In overdose, excessive stimulation of the μ-opioid receptors in the brain that regulate respiratory rate leads to respiratory depression and, ultimately, death by respiratory arrest. The typical symptoms of overdose include pinpoint pupils, respiratory depression, and a decreased level of consciousness, which, together, form the "opioid overdose triad."

The roles of the σ- and δ-opioid receptors are less well understood. However, hallucinations, dysphoria, and psychosis may develop when σ-receptors are stimulated. Stimulation of δ-receptors can produce analgesia, euphoria, and seizures. σ-receptors are no longer considered opioids because they are not antagonized by naloxone.

Tolerance occurs rapidly with opioids. In overdose, patients often succumb to respiratory failure. Tolerance to the loss of the hypercarbia drive takes longer to develop than tolerance to other euphoric effects, but opioid-tolerant patients do not develop complete tolerance to the loss of the hypoxic stimulus, leaving them susceptible to death from overdose.[17][18][19]

Toxicokinetics

Opiates may be administered intravenously, topically, inhalationally, intramuscularly, and orally. Peak opiate effects are reached within 5 to 10 minutes following intravenous administration but may take up to 90 minutes if the oral route is used. Drugs like heroin and butorphanol can reach peak levels within 10 to 15 minutes after nasal insufflation and about 30 to 45 minutes following intramuscular injection. Fentanyl, which is the only available topical analgesic agent, often takes 2 to 4 hours to reach peak levels.

Most orally administered opiate is absorbed in the small intestine. Large opiate doses can lead to gastric aperistalsis and a delay in gastric emptying, resulting in increased absorption of the drug. Once in the body, opiates are metabolized by the liver into inactive compounds, which are primarily excreted by the kidneys. Opiates such as buprenorphine and fentanyl are highly lipid-soluble and tend to redistribute into fatty tissues, resulting in a prolonged half-life. Since all opiates are metabolized by the liver, they tend to have a long half-life when consumed in the presence of liver dysfunction (eg, cirrhosis). Opiate toxicity in patients with this condition can occur rapidly, even with small doses, as the drug remains in the body for an extended period.

The hepatic microsomal CYP2D6 enzyme breaks down codeine into the active metabolite morphine. Some individuals carry more than 2 copies of the enzyme, making them ultrarapid metabolizers who quickly convert codeine into morphine. These people may develop morphine toxicity if they take even normal doses of codeine. This same mechanism of ultrarapid breakdown explains why tramadol may also cause opiate toxicity. After being metabolized in the liver, opiate metabolites are excreted in the urine. Individuals with renal dysfunction may experience adverse effects from the accumulation of active metabolites, such as normeperidine. Several studies indicate that long-acting opiates used for noncancer pain may increase the risk of adverse cardiac events compared to tricyclics or anticonvulsants.

Formulas of Opiates and Delivery

In the past, opiates were only available in oral and injectable formulations. Today, dermal, sublingual, and inhaler formulas are also sold in the market. Butorphanol comes in an intranasal form, and fentanyl is available both as a topical and an inhaler.

The transdermal delivery of opiates like fentanyl has become widely accepted in healthcare settings for analgesic relief. This delivery route is preferred because drug levels take 4 to 6 hours to peak, and the elimination half-life is long, making it suitable for patients with chronic, continuous pain. Additionally, this route rarely precipitates toxicity because of the relatively prolonged, slow onset of action. However, the topical formulation of fentanyl can contribute to the toxicity of parenteral and oral opiates.

Dextromethorphan was once widely available in many over-the-counter cough preparations. However, this product is no longer sold without regulation because of diversion. Although dextromethorphan was an over-the-counter preparation, high doses were known to cause sedation and even respiratory depression due to its chemical similarity to codeine. Additionally, using dextromethorphan in combination with monoamine oxidase inhibitors can lead to life-threatening serotonin syndrome, which may result in adverse cardiac events.

Tramadol (Ultram) is classified as a nonopiate analgesic. However, this product has a dual mode of action, acting on both nonopiate and opiate receptors. Tramadol has a comparatively long duration of action, lasting 5 to 6 hours. Naloxone administration is recommended for patients known to have overdosed on tramadol, with most individuals requiring repeated doses or a continuous intravenous infusion.

Many clandestine laboratories have emerged across the nation due to the difficulty of legally obtaining prescription opiates. These laboratories operate under unsterile conditions and use impure substances, resulting in more toxic drugs being sold on the street. Another challenge with illicit drugs produced in clandestine laboratories is that many cannot be detected using standard toxicological screens because of their structural dissimilarities.

Several synthetic fentanyl derivatives, such as α-methylfentanyl, are circulating on the street and are extremely potent. Multiple deaths have been reported, with users found with needles still in their arms. Another synthetic derivative, 3-methylfentanyl, is thousands of times more potent than morphine. Extremely high doses of intravenous naloxone infusions are required for people overdosing on this agent. Deaths from these fentanyl derivatives often occur in clusters, as sellers move from street to street, causing multiple fatalities along the way.

Pentazocine is classified as a partial agonist-antagonist and is used to treat moderate to severe pain. This drug works by stimulating the κ-opiate receptors and inhibiting the μ-opiate receptors. The drug shares many adverse effects common to other opiates. However, a unique feature of pentazocine is its potential to cause nightmares, hallucinations, and delusions. Pentazocine has a high ceiling effect, meaning that a high dose must be reached before further drug administration stops providing additional pain relief, although the risk of side effects still increases. The pharmacological effects of pentazocine may be reversed by naloxone, but extremely high doses (10 to 115 mg) are required.

Propoxyphene is an opiate analgesic once prescribed to manage mild pain and cough. Sporadic cases of poisoning with this drug continued even after it was withdrawn from the American market in 2010 due to concerns about serious adverse cardiac events. Despite the ban, the drug remains available illegally and contributes to a significant number of poisonings each year. Naloxone can reverse the toxicity of propoxyphene but does not address the cardiac arrhythmias caused by the drug. These arrhythmias, resulting from the quinidine-like effects of propoxyphene, are unresponsive to naloxone. Propoxyphene can cause sinus bradycardia, heart block, and ventricular arrhythmias. Immediate treatment involves the administration of sodium bicarbonate.

The combination of diphenoxylate and atropine is commonly used to treat diarrhea. The opioid diphenoxylate acts as an antidiarrheal agent. The anticholinergic atropine is added to deter

deliberate misuse and overdose. Atropine itself has no antidiarrheal activity. High doses of this combination can cause primarily anticholinergic side effects, respiratory depression, and constipation. Cardiac toxicity, including prolongation of the QRS and QTc intervals leading to ventricular arrhythmias, is the main concern with the use of this drug combination.

Body Packers and Stuffers

Transporting illicit drugs in the body has become increasingly common over the past 2 decades. These individuals, often called "drug mules" or "carriers," ingest drugs contained in plastic bags or condoms. The number of packages ingested typically ranges from 1 to 3 dozen. Some may rupture despite being well-packaged, leading to systemic toxicity. Others may develop complications such as bowel obstruction and intestinal perforation, requiring surgery. Additionally, when pursued by law enforcement, these individuals may quickly swallow smaller quantities of drugs to evade arrest. Body stuffers are at a higher risk of adverse effects, as the drugs they transport are often improperly packaged. Symptoms can appear rapidly following ingestion, and aggressive medical intervention is often necessary to prevent overdose and death.

History and Physical

History

Most patients who overdose on opiates are lethargic or comatose. Thus, the history is typically gathered from family, friends, bystanders, or emergency medical service providers. Pills, empty bottles, needles, syringes, and other drug paraphernalia are often found at the scene. Important details to obtain in the history include the amount of drug ingested, congestion, and time of ingestion. In some cases, Emergency Medical Services (EMS) personnel may administer naloxone in the prehospital setting, which can help confirm the diagnosis of opiate overdose.[20][21][22][23]

Physical Examination

Patients with opiate overdose commonly exhibit lethargy or a depressed level of consciousness. Opiate overdose also leads to respiratory depression, generalized central nervous system (CNS) impairment, and miosis. However, healthcare workers must recognize that miosis is not always present in every patient with opiate overdose, and other causes of CNS and respiratory depression should be considered. Additional signs of opiate overdose include euphoria, drowsiness, altered mental status, fresh needle marks, seizures, and conjunctival injection.

Skin evaluation

Examination of the extremities may reveal needle track marks in individuals who abuse intravenous opiates. Many people with substance use disorders also inject morphine and heroin subcutaneously. In some cases, opium oil may be inhaled, and individuals may have patch marks on their bodies from fentanyl use. Most opiates can trigger the release of histamine, leading to itching, skin flushing, and urticaria.

Pulmonary assessment

In some morphine toxicity cases, respiratory distress and hypoxia may present with pupillary dilation. Additionally, drugs such as meperidine, morphine, propoxyphene, and diphenoxylate/atropine can cause midpoint pupils or frank mydriasis. Breathing is typically impaired in patients with morphine overdose. One may observe shallow breathing, hypopnea, and bradypnea, with a respiratory rate of 4 to 6 breaths per minute. Since opiates may also cause bronchoconstriction, some individuals may present with dyspnea, wheezing, and frothy sputum production.

Cardiovascular examination

Most opiates cause peripheral vasodilation, which can lead to moderate-to-severe hypotension. However, this hypotension may be reversed with changes in body position or fluid administration. Other coingestants must be considered if the hypotension is severe and unresponsive to fluids.

Gastrointestinal evaluation

Nausea and vomiting are common in patients with opiate toxicity. These symptoms occur because opiates can induce gastric aperistalsis and slow down intestinal motility.

Psychiatric features

Opiates are generalized CNS depressants. However, these drugs can also cause anxiety, agitation, depression, dysphoria, hallucinations, nightmares, and paranoia.

Neurological assessment

Opiates can lower the seizure threshold, potentially leading to generalized seizures, particularly in young children. This effect is mainly due to the paradoxical excitation of the brain. The opiates most commonly involved in adults experiencing seizures are propoxyphene and meperidine. Hearing loss may occur in rare cases, particularly in individuals who have consumed alcohol with heroin. However, this auditory deficit is usually reversible.

Evaluation

Opiate overdose or toxicity must always be considered in patients presenting with lethargy of an unknown cause. Many individuals who abuse opiates may concurrently use other illicit substances, such as cocaine, or prescription drugs, like antidepressants and benzodiazepines. Suspicion of coingestants should be raised when the usual clinical signs and symptoms of opiate toxicity are absent and the patient does not respond to the opiate antagonist naloxone.[24][25][26][27]

Laboratory Studies

Laboratory studies are often conducted for patients with drug overdoses. Drug screens are widely available but may not significantly affect initial management due to the high potential for false positives and negatives. In patients with opiate toxicity or overdose, the following blood work is usually performed:

- Complete blood cell count
- Comprehensive metabolic panel
- Creatine kinase level
- Arterial blood gas determinations
- Pregnancy testing
- Acetaminophen and salicylate testing

Imaging Studies

A chest x-ray should be obtained if lung injury is suspected. An abdominal x-ray or computed tomography should be obtained if the patient is possibly a body packer.

Electrocardiography

Electrocardiography (ECG) is recommended in all patients with suspected opioid overdose. Coingestants like tricyclics have the potential to cause arrhythmias.

Treatment / Management

Prehospital Management

Often, the first responder at the scene of a suspected opioid overdose is a nonmedical individual, such as a police officer. As of 2016, over 1,214 law enforcement agencies have trained their officers to administer naloxone in the field. This community involvement has led to increased survival rates following overdose incidents in the Midwest United States.[28]

Emergency medical technicians must be aware of prearrival naloxone administration by law enforcement and its effects. In some cases, patients may experience a complete reversal of toxicity and refuse further medical care or transportation to an emergency department. Studies have shown low short-term mortality rates in these cases. However, the potential risks of recurrent toxicity must be explained to these individuals, as well as the associated morbidity and mortality.[29][30]

If EMS are the first responders, priority should be given to assessing airway and hemodynamic stability. Naloxone should be administered in cases of decreased respirations. If the individual has no intravenous access, naloxone may be given intramuscularly, intranasally, intraosseously, or endotracheally via an endotracheal tube.

Data show that the intranasal route is as effective as the intramuscular route in the prehospital setting. However, naloxone may cause agitation and aggression when it reverses the opioid effects. The lowest naloxone dose necessary to reverse respiratory apnea should be administered in individuals with opioid use disorder (OUD). Patients may become combative or violent in the ambulance, and restraints may be needed for the safety of both the patient and EMS personnel. If the patient remains unresponsive to naloxone, endotracheal intubation should be considered to protect the airway.

Emergency Department Care

Immediate assessment of the patient's airway and hemodynamics should be given priority upon evaluation in the emergency department. Additional information from EMS personnel should include the presence of any drugs or paraphernalia, the patient's initial presentation (including vital signs), any potential trauma, and details regarding the timing and specifics of the suspected overdose. EMS personnel at the scene may have already secured the airway by administering naloxone or performing endotracheal intubation in some cases. Emergency physicians should evaluate the patient's airway and breathing upon arrival and determine if further intervention is necessary.

Immobilization should be prioritized if suspicion of occult trauma to the cervical spine arises. A capillary blood glucose level should be checked in any patient presenting with an unknown cause of lethargy or loss of consciousness, even if an overdose is highly suspected.

Initial treatment of overdose starts with supportive care, including assistance with respiration, cardiopulmonary resuscitation (CPR) in the absence of spontaneous circulation, and removal of any opioid agent, such as a patch or infusion. Naloxone should be administered immediately when an opioid overdose is suspected as the cause of respiratory and CNS depression, without delay for laboratory studies.

Naloxone administration

Naloxone is a pure competitive antagonist of opiate receptors and has no agonistic activity. The drug is relatively safe and may be administered intravenously, intramuscularly, subcutaneously, or endotracheally, though research on tracheal absorption has been conducted only in animal models. The Food and Drug Administration (FDA) has approved an intranasal formulation

commonly used by first responders in patients without intravenous access. Intranasal naloxone is also available to the community.[31]

After naloxone administration, the onset of action occurs within minutes, regardless of the route. A second dose may be given every 2 to 3 minutes. With subcutaneous or intramuscular injection, the onset may be delayed by 3 to 10 minutes. The goal of naloxone administration is to restore adequate breathing and ensure a stable airway. Higher doses are required for patients who overdosed on diphenoxylate, methadone, butorphanol, nalbuphine, or pentazocine. A naloxone infusion can be started in patients who need repeated doses to maintain respiration.

Nalmefene is a new agent on the market that can reverse opiate toxicity. This drug has a half-life of 4 to 8 hours. However, routine use of this longer-acting opiate antagonist is not recommended due to concerns about precipitating a prolonged period of opiate withdrawal.

Starting dose of naloxone

The usual starting dose of naloxone for adults ranges from 0.4 to 1 mg. Meanwhile, the starting dose for children is 0.1 mg/kg. The goal of naloxone administration is to reverse respiratory depression, not to "wake up" the individual. Naloxone should be administered slowly in suspected chronic opiate users, with doses of 0.04 to 0.4 mg given intravenously every 1 to 3 minutes. This approach ensures a more controlled reversal of opiate effects and reduces the risk of precipitating withdrawal symptoms.[32] Rapid administration of naloxone in these patients can trigger withdrawal, which is distressing for the patient and potentially places healthcare workers at risk of injury.

Before naloxone administration, the patient should receive 100% fraction of inspired oxygen assisted by bag-valve ventilation until they become more alert and cooperative or until naloxone is administered. The onset of naloxone’s action is immediate, with peak response occurring within 3 to 8 minutes. A repeat dose may be indicated if the patient continues to show signs of opiate toxicity.

Starting with a low dose of naloxone is important, typically 0.05 to 0.1 mg intravenously, gradually titrating upward to minimize the risk of withdrawal symptoms, such as nausea, vomiting, agitation, pain, and aspiration. This careful dosing is especially crucial in patients suspected of ingesting opiates combined with other CNS depressants such as alcohol, tricyclic antidepressants, and benzodiazepines. Peripheral intravenous access may be difficult in some patients with opiate overdose and long-term OUD. In such cases, 2 mg of naloxone may be administered intramuscularly or intranasally. Even with this route, opiate toxicity is reversed within 5 to 10 minutes.

The half-life of naloxone is about 30 to 45 minutes, with a duration of action ranging from 90 to 180 minutes. These variations depend on the route of administration and dose. Patients should be monitored for any recurrence of opioid toxicity, as the initial drug effect may last longer than naloxone’s duration of action. An infusion may be started in patients requiring multiple bolus doses. The naloxone infusion dose is 3/4 of the amount required to reverse respiratory depression.[33]

Much higher doses of naloxone are usually needed to reverse toxicity in patients who have taken large doses of propoxyphene, methadone, diphenoxylate/atropine, or fentanyl. Repeat doses of 2 mg may be required every 3 to 4 minutes for a total of 10 mg. The diagnosis of opioid toxicity should be reconsidered in patients who fail to respond to 10 mg of naloxone. Many street opiate preparations are adulterated, and the response to naloxone may not always be complete. A steady naloxone infusion is generally preferred over intermittent dosing for treating large overdoses. However, a naloxone infusion should not be administered if intubation is necessary.[34][35][36] Clinicians must be ready to intubate if the patient remains in respiratory distress.

Role of activated charcoal

Activated charcoal may be used to decontaminate the gastrointestinal tract in cases of oral opiate overdose, such as with body stuffers, if the patient is alert at the time of admission. Activated charcoal is typically effective only if administered within 1 hour of drug ingestion. However, opiates slow gastric motility, allowing activated charcoal to be given up to 2 to 3 hours after ingestion. Activated charcoal should be considered for all patients with opiate overdose in the absence of contraindications, such as vomiting and decreased mental status.

Activated charcoal should not be administered to patients with depressed mental status or any individual with airway concerns. Patients should not be intubated solely to administer activated charcoal.

Bowel irrigation

Whole bowel irrigation may be considered for individuals who have ingested drug packets containing opiates, as in the case of a body packer. However, no controlled studies confirm that this treatment offers any benefits or improves outcomes. Whole bowel irrigation is not recommended for patients showing signs of ileus, bowel obstruction, peritonitis, hemodynamic instability, or an unprotected airway.

Additional measures

Some patients with opiate toxicity may not respond to high-dose naloxone treatment. Anecdotal reports suggest that buprenorphine may be beneficial if the cause is determined to be an opiate and the patient is in respiratory arrest.

Intranasal administration of naloxone

Naloxone is highly effective when administered promptly, but its use has traditionally been limited to physicians and paramedics. With the rise in opioid overdoses, intranasal medication administration by bystanders is currently being advocated. Evidence supporting the efficacy of out-of-hospital naloxone administration is promising. The bioavailability of concentrated naloxone nasal spray has been shown to be around 25%. Fifty percent absorption occurs within 6 to 8 minutes, with maximum blood concentration reached at 20 minutes, making it a viable option for community and prehospital use.

A retrospective study of Basic Life Support (BLS) crews administering prehospital intranasal naloxone over 6 years found that 95% of patients who received treatment showed clinical benefits before arrival. Less than 10% of patients required additional doses in the emergency department, and 70% were eventually discharged.

Opioid poisoning in children

The dose of naloxone for children who are younger than 5 or weigh less than 20 kg is 0.1 mg/kg. For children who are older than 5 or weigh more than 20 kg, the dose ranges from 0.1 to 0.2 mg/kg. Repeat dosing may be required every 3 to 4 minutes, up to a maximum cumulative dose of 10 mg of naloxone. Repeat dosing is often necessary when the child has ingested longer-acting opiates like methadone. A continuous naloxone infusion may be started, but caution must be taken to avoid overhydration, which could lead to pulmonary edema. The pharmacy may assist with determining the correct concentration of fluid and naloxone for safe administration, but repeat bolus dosing may be safer if a concentrated infusion is unavailable.

Use of combined buprenorphine and naloxone

Buprenorphine, in combination with naloxone, is widely available and used to treat OUD in the outpatient setting. Buprenorphine acts as a partial agonist and antagonist at the opioid receptor.

Anecdotal data indicate that the risk of overdose is lower with buprenorphine/naloxone compared to methadone. Naloxone has no oral bioavailability and is included in the formulation to deter intravenous use. Unfortunately, the sublingual preparation of buprenorphine and naloxone may also be easily abused.

Naloxone adverse effects

Naloxone has demonstrated a very safe side effect profile. Studies on opioid-naive patients who received large doses of the drug showed no significant effects. However, naloxone can trigger acute opioid withdrawal symptoms in opioid-tolerant patients. These symptoms may include sudden aggression, agitation, restlessness, diaphoresis, tachycardia, and gastrointestinal effects such as nausea and vomiting, which occur in approximately 30% of patients. Most symptoms are mild and short-lived, with fewer than 1% of patients requiring admission. Acute withdrawal is more likely with higher doses of naloxone.

A rare but potential side effect of naloxone is noncardiogenic pulmonary edema, which is thought to result from a sudden catecholamine surge, typically following the administration of high doses of naloxone. Treatment involves positive pressure ventilation, starting with bilevel positive airway pressure (BiPAP) and escalating to endotracheal intubation if necessary.[37]

Inpatient Care

Most patients who overdose on opiates and experience a reversal with naloxone are admitted for observation for at least 12 to 24 hours. Naloxone's duration of action is approximately 1 hour, and long-acting opiates may continue to cause sedation and respiratory depression. These patients are best monitored on a specialized floor. The majority of patients on heroin overdose are admitted due to the risk of acute lung injury, which often presents early. Individuals who are asymptomatic after a heroin overdose may not require 24-hour monitoring but still need 6 to 12 hours of observation before discharge, provided their vital signs remain stable.

Admission is also recommended for patients requiring multiple doses or prolonged intravenous infusions of naloxone to maintain respiratory function. Admission is the safest course of action if the patient’s clinical stability is in question.

Outpatient Care

Given the association of opiate use with sudden respiratory difficulty, many healthcare professionals now advocate for take-home naloxone. Having naloxone at home is particularly beneficial for individuals at high risk of narcotic overdose.

Mainstreaming Addiction Treatment Act

The Mainstreaming Addiction Treatment (MAT) Act updates federal guidelines to expand access to evidence-based treatments for the opioid epidemic. This act enables all healthcare providers with a standard controlled substance license to prescribe buprenorphine for OUD, similar to how they prescribe other essential medications. The MAT Act aims to reduce the stigma surrounding OUD treatment and promote its integration into general healthcare settings.

The MAT Act has eliminated the DATA-Waiver (X-Waiver) program as of December 2022. DEA-registered practitioners with Schedule III authority are now permitted to prescribe buprenorphine for OUD within their practice, provided it aligns with applicable state laws. The Substance Abuse and Mental Health Services Administration (SAMHSA) encourages providers to take advantage of this change. Practitioners previously registered under the DATA-Waiver program automatically receive updated DEA registration certificates reflecting this change, with no action required on their part.

Practitioners are no longer limited in the number of patients with OUD they may treat with buprenorphine. Additionally, separately tracking patients treated with buprenorphine or the number of prescriptions written is not required.

Pharmacy staff can now fill buprenorphine prescriptions using the prescriber's DEA number without requiring a DATA 2000 waiver. However, depending on the pharmacy, dispensing software may still prompt for X-Waiver information to proceed. Practitioners must also adhere to any applicable state regulations regarding the treatment of patients with OUD. Contact information for State Opioid Treatment Authorities can be found here: https://www.samhsa.gov/medicationassisted-treatment/sota.

Differential Diagnosis

The differential diagnosis of opioid poisoning includes conditions presenting with sudden-onset respiratory or CNS depression, as follows:

- Barbiturate toxicity
- Benzodiazepine toxicity
- Carbon monoxide toxicity
- Clonidine toxicity
- Cyanide toxicity
- Diabetic ketoacidosis
- Ethanol toxicity
- Ethylene glycol toxicity
- γ-Hydroxybutyrate toxicity
- Hypercalcemia
- Hypernatremia
- Hypothermia
- Hypoglycemia
- Meningitis/encephalitis
- Neuroleptic agent toxicity
- Traumatic brain injury
- Valproic acid toxicity

Efficient and thorough evaluation of these alternative diagnoses ensures timely intervention and better outcomes.

Prognosis

Mortality and Morbidity

Death from opioid overdose is on the rise. One study found that deaths from opioid-only overdose increased by 384% between 1999 and 2018. Polysubstance overdose deaths increased by 760% over the same period in adolescents and young adults.[38] According to the CDC, nearly 108,000 individuals succumbed to opioid overdose in 2022. The COVID-19 pandemic response also led to an increase in mortality, as it limited access to treatment services.

The primary cause of morbidity and mortality following an opiate overdose is respiratory arrest. Seizures, acute lung injury, and adverse cardiac events may also occur but are less common. Individuals with preexisting lung pathology who overdose on opiates face a significantly higher risk of respiratory distress and death compared to the general population. Another factor contributing to opiate toxicity is the presence of coingestants, with the eventual toxicity depending on the type of substance involved. A Canadian study found that the risk of fatal opiate toxicity doubled when opiates were taken with gabapentin, which is also known to depress respiration. Additionally, morbidity and mortality are influenced by the intent behind the opiate ingestion. Individuals attempting suicide often consume multiple drugs simultaneously, substantially increasing the risk of death.

Prognosis

If the patient does arrest in the setting of a pure opiate overdose, the cause in most cases is severe hypotension, hypoxia, and poor brain perfusion. The outcome for these individuals is poor.

Complications

Opiate toxicity can also produce complications beyond the typical respiratory and CNS adverse effects.[39][40][41] The most common ones are discussed in this section.

Acute Lung Injury

Acute lung injury is a well-known complication of heroin overdose. However, this condition may also occur after overdoses involving methadone and propoxyphene and is almost universally observed in patients who succumb to high doses of opiates. The exact mechanism by which opiates cause lung injury remains unclear, but the outcome is hypoventilation and hypoxia caused by noncardiogenic pulmonary edema.

Clinically, heroin-induced lung injury presents with sudden onset of dyspnea, frothy sputum production, cyanosis, tachypnea, and rales—symptoms consistent with pulmonary edema. Acute lung injury has also been reported in children who ingest high doses of opiates. The presentation is very similar to acute respiratory distress syndrome (ARDS), and most cases resolve with aggressive airway management and oxygen therapy, including positive pressure ventilation. Standard medications for pulmonary edema are typically avoided, as diuretics may worsen hypotension.[42]

Infection

Complications of intravenous opioid use include abscesses, cellulitis, and endocarditis. Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus,* are the most common organisms involved. If these bacteria enter the systemic circulation, the risk of additional complications like epidural abscess and vertebral osteomyelitis increases. These conditions often present with symptoms such as fever and persistent back pain.

Some individuals who inject drugs directly into the neck risk developing jugular vein thrombophlebitis, Horner syndrome, and pseudoaneurysms of the carotid artery. Both peripheral and pulmonary emboli have been reported in people who inject opioids. Accidental injection into nerves may also cause permanent neuropathy.

Endocarditis is a serious complication of intravenous drug use, often resulting from injecting illicit drug mixtures with contaminated needles. Diagnosing infectious endocarditis can be challenging due to the initially vague symptoms. While right-sided heart valves are most commonly affected, left-sided valves may also be involved in some cases. The tricuspid valve is the valve most frequently affected in individuals who use intravenous

drugs. Endocarditis often presents with fever, malaise, and a new murmur. In some patients, recurrent septic pulmonary embolism may be the only presenting feature.

The organism most commonly involved in right-sided endocarditis is *Staphylococcus aureus*. In contrast, left-sided endocarditis may be polymicrobial, involving organisms such as *Streptococcus*, *E. coli*, *Pseudomonas*, and *Klebsiella*. Symptoms and signs tend to be more pronounced in left-sided endocarditis compared to right-sided cases.

Other infectious manifestations of opioid abuse include recurrent pneumonia, with aspiration pneumonia occurring in some unconscious individuals. Necrotizing fasciitis, another life-threatening complication, often presents with severe pain, fever, and dark, dusky skin with crepitus. The individual may show signs of septic shock. Aggressive resuscitation and immediate surgical debridement can be life-saving.

Musculoskeletal and Neurologic Sequelae

Rhabdomyolysis is a relatively common complication of opioid overdose that may occur even without compartment syndrome. Opioids are likewise known to increase the risk of seizures, particularly drugs like propoxyphene, meperidine, pentazocine, intravenous fentanyl, and heroin. The individual may present with a prolonged seizure, which may result from CNS hypoperfusion and hypoxia or from intracranial injury due to a fall.

Narcotic Bowel Syndrome

Narcotic bowel syndrome is a type of opiate-induced bowel pathology characterized by frequent episodes of moderate-to-severe abdominal pain that worsens with escalating or continued opiate doses. This syndrome typically occurs in individuals without prior bowel pathology and represents a maladaptive response. Narcotic bowel syndrome may also be associated with intermittent vomiting, abdominal distension, and constipation. Eating tends to aggravate the symptoms, which can last for days or weeks. Anorexia may result in weight loss, and delayed gastric emptying and intestinal transit are delayed.

The syndrome is often mistaken for bowel obstruction. The key to diagnosis lies in recognizing that continued and escalating opiate doses worsen abdominal pain rather than provide relief. Treatment for narcotic bowel syndrome involves psychotherapy, as well as tapering or discontinuing the opioid. Successful treatment depends on developing a strong patient-physician relationship and trust, gradually withdrawing the narcotic, and using nonpharmacological treatments to manage pain.

Withdrawal Reaction

Withdrawal symptoms following cessation of opiates are common, but they are often vague and less severe than those observed with alcohol or benzodiazepine discontinuation. The onset of symptoms depends on the drug ingested, typically occurring within 2 to 4 days after methadone cessation and 8 to 10 hours after meperidine withdrawal. Autonomic symptoms may include excessive lacrimation, sweating, piloerection, rhinorrhea, repeated yawning, myalgia, nasal congestion, diarrhea, and abdominal cramps. Symptoms usually peak between 36 and 48 hours and gradually subside within 72 hours.

Symptoms may last 7 to 14 days in chronic drug addicts. Treatment for withdrawal symptoms is supportive, and the use of additional opiates to counter withdrawal symptoms is not recommended. Clonidine may be used in severe withdrawal cases, especially when methadone is inappropriate or unavailable. After acute treatment, the patient should be referred to a long-term drug rehabilitation program to help prevent relapse.

Deterrence and Patient Education

In early 2015, the U.S. Department of Health and Human Services acknowledged the expanded use of naloxone among healthcare professionals to counter opiate overdoses nationwide. Now, pharmacists, EMS personnel, and physicians can all play an active role in preventing opiate overdoses. Current recommendations also suggest coprescribing naloxone to patients taking opiates. Several studies show that patients who receive naloxone alongside an opiate prescription have fewer opiate-related emergency room visits than those who do not. Today, some healthcare workers have started prescribing naloxone to patients on high doses of opiates.

Recently, the U.S. Food and Drug Administration approved the use of a handheld autoinjector that can be prescribed to caregivers or family members for managing suspected opiate overdoses. Additionally, numerous naloxone organizations have emerged across the country to fight the opiate overdose epidemic, including efforts to involve nonmedical professionals like law enforcement officers.

Enhancing Healthcare Team Outcomes

With the drastic increase in opioid abuse and overdose-related deaths, much attention has focused on this so-called "opioid epidemic." All healthcare workers, including nurse practitioners who prescribe controlled substances, have a role in reducing the opioid epidemic and should be equipped to identify and treat those experiencing toxicity and overdose.

New research focuses on finding effective interventions and identifying risk factors for overdose. Some of these efforts include treatment programs, take-home intranasal naloxone, and monitored injection facilities. A review of research exploring overdose education and naloxone distribution suggests reduced fatality rates for patients who receive counseling and prescriptions for home naloxone.

Naloxone has been shown to have a very safe side effect profile. Several studies on opiate-naive patients who received large doses of the drug showed no significant effects. However, acute opioid withdrawal symptoms may develop when this agent is administered to opioid-tolerant patients. Individuals given naloxone in the setting of opioid overdose may experience sudden withdrawal syndrome, manifesting as aggression, agitation, restlessness, diaphoresis, and tachycardia. Gastrointestinal symptoms such as nausea and vomiting also occur in about 30% of patients. Most symptoms are not severe or sustained, and less than 1% of patients require admission. Acute withdrawal symptoms are more likely with larger doses of naloxone. Despite the risk of precipitated withdrawal, naloxone should not be withheld in cases of acute opioid overdose with respiratory depression.[43][44]

An interprofessional approach should involve physicians, nurses, and substance abuse counselors. The goal of the collaborative efforts of this group is to reduce morbidity and mortality associated with OUD.

Review Questions

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REVIEW

Managing intoxications with nicotine-containing e-liquids

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ABSTRACT

Introduction: Nicotine is an addictive and poisonous agent. The recent development of e-cigarettes has caused a new demand for highly concentrated nicotine-containing solutions. These concentrated nicotine solutions have also increased the risk of nicotine overdoses.

Areas covered: Essential factors for nicotine exposure are the concentration of the nicotine-containing e-liquid solution and its pharmacokinetics. Liquid nicotine refills contain nicotine in varying concentrations, which vary widely between and within products. The pharmacokinetics of nicotine are dependent on the route of administration, renal/hepatic clearance and urinary pH. The dose is another essential determinant of nicotine exposure. There is a considerable discrepancy between the generally accepted lethal dose and symptoms reported in case studies. Ingested doses correlate poorly to clinical symptoms. Symptoms of liquid nicotine toxicity vary from mild to severe between patients and are the result of overstimulation of nicotinic acetylcholine receptors, which may lead to fatal respiratory failure and cardiovascular collapse.

Expert opinion: The literature on nicotine-containing e-liquid intoxications originating from vaping device refills are mainly case reports. Based on these case reports, we propose a treatment plan which is primarily symptomatic. Research should focus on providing insight on its toxicity, based on oral and transdermal pharmacokinetics and on toxicodynamics.

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E-cigarettes; intoxications; nicotine-containing e-liquid; treatment plan

1. Introduction

Nicotine is an addictive and toxic compound that has been known to man for a long time. Until the recent introduction of e-cigarettes, nicotine was never smoked or ingested as a single compound, but always as part of smoking or ingesting tobacco. The tobacco plant, *nicotiana tabacum* was named after Jean Nicot de Villemain after the introduction of nicotine leaves and seeds for medicinal purposes in 1560. The first isolation of nicotine from tobacco took place in 1828 by the German chemists Posselt and Reimann [1]. Not long after this introduction, researchers discovered the neurotoxic action of nicotine. Therefore, nicotine was used as a potent pesticide in agriculture as well. The amount of nicotine used as an insecticide was over 2500 tons worldwide from World War II until the 1980s [2]. However, because of fatal intoxications as a result of inhalation, ingestion or skin contact, the use and production of nicotine decreased drastically over the last decades [3].

Nicotine originating from tobacco is estimated to be the second most widely used drug in the world after caffeine from coffee and tea. Nicotine is consumed regularly across all cultures, countries and almost all religions [4]. In the last 40 years, smokers have been under increasing pressure to quit smoking. This pressure has been increasing because of the many carcinogens and oxidizing chemicals that are present in tobacco smoke and the increased risk of diseases, including cancer, cardiovascular disease and COPD [5,6]. Based on the high use of nicotine and the rich history of the compound, a considerable amount of knowledge on smoking prevalence is available [7].

Since e-cigarettes are advertised to contain fewer carcinogens, they quickly gained popularity among smokers. Additionally, e-cigarettes have also been marketed as supporting in the cessation of smoking, as well as providing additional health benefits over cigarettes [8]. The appearance of e-cigarettes has generated a whole new market for nicotine, however. E-cigarettes use nicotine in a highly concentrated solution (nicotine-containing e-liquid) to release nicotine. The generation of this market has resulted in unprecedented access to potentially toxic doses of nicotine in the home environment [9]. There are several reports of accidental nicotine intoxications in young children [10] but also reports of suicide attempts by adults using nicotine-containing e-liquids and of accidental transdermal absorption during handling of the liquid nicotine [11]. One study using the National Poison Data System (NPDS) for nicotine and tobacco product exposures among children younger than 6 years showed that between January 2012 through April 2015, the child exposure to e-cigarette products increased ~1500% [12]. Children exposed to e-cigarettes had a higher chance of

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Article highlights

- E-cigarettes contain nicotine in a highly concentrated solution. The generation and increasing popularity of the e-cigarette market has resulted in unprecedented access to potentially toxic doses of nicotine in the home environment.
- Nicotine pharmacokinetics are crucial in predicting nicotine exposure and blood plasma concentrations. Researchers have performed many studies into the absorption, distribution, metabolism and excretion of nicotine in the last few decades.
- Nicotine and cotinine serum or saliva concentrations may be useful for confirming nicotine-containing e-liquid intoxications, but are not useful for guiding therapy due to the rapid onset of symptoms.
- Nicotine is estimated to have a human oral LD_{50} of 6.5–13 mg/kg.
- The symptoms of nicotine toxicity are not dose-dependent and resemble the cholinergic toxidrome. Symptoms of severe toxicity typically occur within 4 hours and consist of lethargy, convulsions, and coma and finally respiratory paralysis.
- Treatment for nicotine-containing e-liquid intoxications is mostly supportive and symptomatic. Most life-threatening aspects of nicotine poisoning are respiratory muscle weakness and respiratory arrest. Monitoring of respiratory function and consideration of intubation if indicated is the most important aspect of care. In the case of dermal exposure, however, exposed skin should be washed thoroughly with water and soap to avoid continued absorption of nicotine.

This box summarizes key points contained in the article.

hospitalization and a higher chance of a severe outcome. The authors attributed this rise in e-cigarette exposure by the increased use of the products. A retrospective study between 2012 and 2018 showed 5277 exposures, of which 3033 involved combustible cigarettes, 1489 involved e-cigarettes and 818 involved other nicotine containing devices in California (e.g. nicotine patches) in California [13].

Evidence-based treatment protocols for acute nicotine poisoning from liquid formulations are currently lacking. Therefore, this study's main objective is to provide a summary of the literature on the toxicity and propose a treatment plan for intoxications with nicotine-containing e-liquids.

2. Methods

Relevant literature was obtained using literature databases PubMed, Web of Science and Google Scholar in the period of December 2019 to May 2020. The main search terms used included 'liquid nicotine' and 'intoxications.' These search terms were supplemented with combinations of 'electronic nicotine delivery systems,' 'ENDs,' 'pharmacokinetics,' 'pharmacodynamics,' 'lethality,' 'lethal dose,' 'symptoms,' 'plasma concentration,' 'case,' 'case report' either alone or combined. The results were evaluated on quality and fit with the main objective. Also, cross-references were used.

3. Electronic nicotine delivery systems

E-cigarettes, or better, electronic nicotine delivery systems (ENDS) are the largest source for liquid nicotine exposure in the home environment. In the context of this review, the term ENDS will be used as a carrier device for liquid nicotine. ENDS are handheld devices that produce an aerosol from a solution which the smoker inhales. The aerosol typically contains nicotine, chemicals for flavor and carrier solvents. Examples of carrier solvents found in ENDS are propylene glycol and vegetable glycerin (glycerol) [14]. Although the components of the aerosol are more or less similar, wide variations exist in terminology, design and engineering of ENDS.

Some ENDS have an illuminating diode, simulating the burning end of a traditional cigarette. Newer ENDS, however, are designed to resemble other everyday objects like pens or flashlights. In 2014, more than 460 different brands of ENDS were on the market [15,16]. All these different brands vary substantially in quality and price. The ENDS are sold in various places like gas stations, online stores or specialized stores called 'vape shops.' They can be disposable or reusable. Recent case reports have identified several serious pulmonary diseases among people who have reported the use of nicotine or cannabis extracts in e-cigarettes [17]. Documented case reports described several severe pulmonary diseases among people who reported nicotine together with cannabis extracts being used in e-cigarettes [17]. It is suspected that this pulmonary disease is due to the presence of vitamin E acetate, which is utilized as a diluent in illegal cannabis vapes [18].

Despite the variations in terminology and design, ENDS products generally have various components in common. These components include an aerosol generator, flow sensor, solution storage area and battery [19]. ENDS can be of disposable or reusable nature that contain either an open or a closed system. When a user inhales the aerosol (or vapes) from the device, the flow sensor identifies a change in pressure and triggers the aerosol generator. This generator draws the nicotine solution from the storage area. In the storage area, the nicotine solution is heated or dispersed, generating the aerosol [20].

In open delivery systems, nicotine is supplied in the form of containers (canisters) with a concentrated solution of nicotine (liquid nicotine refills). Closed ENDS do not allow refilling. The liquid nicotine refills are available in different concentrations ranging from 0.5 mg/ml to a maximum of 100 mg/ml [21,22]. Nicotine-containing e-liquid refills are generally small and can contain up to 10 ml of this solution. According to the EU Tobacco Product Directive, such a refill can contain up to 200 mg. Due to a recent change in policies of the EU Tobacco Product Directive [23], significant advances have been made in for example child-resistant packaging and tamper-proof vials. However, the products did not completely comply to the policies yet [24]. Manufacturers in the United States are prohibited from making false health claims, though manufacturers of e-cigarette refills are subject to fewer restrictions [25]. The variable nicotine concentrations allow users to adjust the nicotine exposure to fit their needs [26]. However, there may be a large discrepancy between the stated nicotine concentration on the label and the actual concentration. For example, a study of 35 liquid refills showed that the actual nicotine concentration was substantially different from the label statement in up to 89% of the cases [21,24,27]. The

measured nicotine concentrations in the ENDS solution ranged from 0 to 36 mg/mL in the different sized cartridges. Concentration differences between the label and actual nicotine content ranged from 1% to 31% for different batches of the same brand of e-cigarettes [28,29]. In comparison, the amount of nicotine in the tobacco in a traditional cigarette varies between 10 and 30 mg [30], and the actual exposure to nicotine for a smoker by smoking a cigarette is estimated between 0.05 and 3 mg per cigarette [31,32]. Besides the dose, the users' actual exposure to nicotine is also determined by nicotine pharmacokinetics.

4. Nicotine pharmacokinetics & pharmacodynamics

Nicotine pharmacokinetics are crucial in predicting nicotine exposure and blood plasma concentrations. Researchers have performed many studies into the absorption, distribution, metabolism and excretion of nicotine in the last few decades.

Nicotine absorption through biological membranes is pH dependent. Since nicotine is a weak base (pKa = 8.0), it is present in its ionized form under acidic conditions, and it does not cross membranes very easily [33]. Therefore, manufacturers increase the pH to facilitate the absorption of nicotine through the cell membrane. The newer nicotine salt liquids have a lower pH (as low as 5) to facilitate inhalation and allow for effective dosing of high nicotine concentrations in small aerosol volumes [34]. Data on the absorption of nicotine-containing e-liquids is scarce. The bioavailability of nicotine via the oral mucosa is 20–45% [35,36], and this is based on a study with nicotine replacement therapy (nicotine gum, for example). The skin absorbs the nicotine as a base dependent on the pH of the liquid, which may, therefore, be a potential risk for nicotine intoxications [37]. This concept was proved by Maina et al. [38]. The authors filled chambers of a Franz diffusion system, a model for percutaneous absorption, with liquid nicotine and donated skin cells for 24 hours. The nicotine was detectable after 2 hours and the absorbed amount gradually increased.

After absorption, nicotine enters the systemic circulation. At pH 7.4, nicotine is about 69% ionized and 31% unionized. Less than 5% of the nicotine in the bloodstream binds to albumin [39]. The body distributes nicotine extensively to tissues with a steady-state volume of distribution averaging 2.6 L/kg. The highest affinity for nicotine is found in the liver, kidney, lung and spleen. The lowest affinity for nicotine is found in adipose tissue, based on human autopsy samples from smokers [40]. Nicotine accumulates in gastric juice and saliva. Most essential for nicotine intoxications is the accumulation of nicotine in the brain, which accounts for the addictive effects. The time course of nicotine accumulation in the brain is highly dependent on route and rate of dosing. For example, after a single cigarette puff, nicotine enters the brain in 10–20 s. The intake of nicotine during smoking depends on the length of the puff, depth of inhalation, degree of dilution with room air and the rate and strength of the puffing [35].

The quantitative aspects of human nicotine metabolism are well known. Nicotine is primarily metabolized by the liver and undergoes extensive metabolism [36]. Therefore, enterohepatic recirculation is unlikely. There are six primary metabolites of nicotine identified so far, which are inactive. The lactam derivative cotinine is the most important metabolite, which accounts for nearly 90% of a systemic dose of nicotine in urine [35]. Other nicotine metabolites in urine include nicotine N′–oxide (4–7% of a nicotine dose) and nicotine glucuronide (3–5%). The liver metabolizes 70–80% of the ingested nicotine to cotinine via a mechanism involving cytochrome P450 isoform 2A6 (CYP2A6). Cotinine can be excreted unchanged in the urine (10–15% of the nicotine) but can also be further metabolized by the liver. Cotinine metabolites found in urine include trans–3′–hydroxycotinine glucuronide (7–9%), cotinine glucuronide (12–17%) and trans–3′–hydroxycotinine (33–40%). The plasma half-life (t1/2) of nicotine averages between 100 and 150 min [36]. Metabolism of nicotine can be influenced by various characteristics, including gender, age, food intake and medication use [41].

Glomerular filtration and tubular secretion by the kidney are the main excretion routes for unmetabolized nicotine [36]. The renal clearance of unmetabolized nicotine varies between 17–600 ml/min [42] and is dependent on urine pH and urinary flow. In acidic urine, the nicotine is mostly ionized, thereby minimalizing tubular reabsorption. For example, when the urinary pH is 4.4, renal clearance of nicotine can increase up to 600 ml/min. In alkaline urine, however, renal clearance can become as low as 17 ml/min due to tubular reabsorption.

Elimination of cotinine is mainly through metabolism to 3-hydroxy-cotinine [33,41]. The cotinine metabolites are excreted unchanged in the urine. Extreme urinary acidification increases the glomerular filtration of cotinine up to 50%. Cotinine is less alkaline and therefore less sensitive for physiological pH changes. The urinary flow rate influences the excretion of cotinine, as is the case with nicotine [43].

In summary, nicotine pharmacokinetics depend on the route of administration, renal/hepatic clearance and urinary pH. As with every other drug, total nicotine exposure and plasma concentrations depend on the dose and pharmacokinetics.

Pharmacodynamic effects of nicotine are mediated via nicotinic acetylcholine receptors (nAChRs). nAChRs are located on the cell membrane of cells in the central nervous system, autonomic ganglia (sympathetic and parasympathetic nervous system), and neuromuscular junctions. Similar to acetylcholine, binding of nicotine to the postsynaptic nAChRs results in the opening of the cation (Ca^{2+}, Na^{+} and K^{+}) permeable ion channels, resulting in the rapid depolarization of target cells. Depolarization subsequently opens voltage-dependent calcium channels. In contrast to acetylcholine, nicotine is not readily deactivated by acetylcholinesterase resulting in prolonged activation of the nAChRs. Persistent activation of nAChRs by nicotine may lead to receptor desensitization and depolarization blockade. In summary, exposure to nicotine may initially result in a stimulation of the nAChRs, followed by a blockade. In addition to its effects on nAChRs, chronic nicotine exposure may also change the expression of muscarinic AChRs [44].

5. Toxicity of nicotine

5.1. Intoxication

There is a weak relation between the dose of nicotine and the clinical symptoms of nicotine-containing e-liquid intoxications. Therefore, differentiation between mild and severe intoxications is based on clinical symptoms.

In low doses, comparable to cigarette smoking, nicotine exposure produces an increase in heart rate, blood pressure and respiratory rate. Besides cardiovascular effects, a low nicotine dose induces a slight tremor, cutaneous vasoconstriction, nausea and increased gastrointestinal motility [45]. In the central nervous system, stimulation of nicotinic receptors causes increased alertness and euphoria.

With mild intoxication and in the early phase of moderate/severe intoxication, symptoms such as headache, dizziness, confusion, agitation, anxiety, restlessness, sweating and tremors may occur. Also, tachycardia, pallor (due to vasoconstriction) and hypertension may develop [44,46,47]. Since nicotine is quickly metabolized, mild symptoms are likely to disappear within 4 to 6 hours. Patients with symptoms of nicotine toxicity after transdermal nicotine patch application are an important exception to this rule, as a drug reservoir may remain in the skin after patch removal and may serve as a source of continuing absorption [45].

In moderate/severe intoxication, the stimulation phase will be followed by depression of organ functions. Early-stage symptoms, such as headache, dizziness, confusion, agitation, anxiety, restlessness, and tremors, may be followed by lethargy, convulsions, and coma. Weakness, fasciculations, hypotonia, and hyporeflexia can result in paralysis, including respiratory paralysis.

In cases of severe nicotine poisoning, early symptoms are due to nicotinic cholinergic excess. This excess can cause an increase in salivation, nausea, vomiting and diarrhea. These symptoms can occur within minutes after systemic absorption [45]. Vasoconstriction is also a sign of early, severe nicotine poisoning, causing hypertension and pallor. Besides vasoconstriction, tachycardia is another cardiovascular symptom of severe nicotine poisoning in early stages. Nicotinergic stimulation can cause mild sinus tachycardia and a variety of cardiac dysrhythmias. These dysrhythmias can vary from somewhat innocent supraventricular tachycardia to severe electrophysiological toxicity with AV blocks and ventricular arrhythmias. Studies show a dose-dependent arrhythmogenicity of nicotine in dogs. Intravenous administration of nicotine induced supraventricular arrhythmias, atrioventricular junctional arrhythmias, and ventricular arrhythmias. In these studies, supraventricular bradycardia was found in 30 (83%) experiments, supraventricular arrhythmia in 30 (83%), sinus arrest in 18 (50%;), atrial ectopics in 24 (67%), and atrial tachycardia in 98 experiments (25%;) [48]. Case reports support this data in humans [49,50]. Neurologically, nicotine causes headache, dizziness, confusion, ataxia and perceptual distortion [45].

In moderate and severe intoxications, the nicotinic stimulation phase will be followed by depression of organ functions due to persistent blockage of the receptor. Symptoms during this second phase of a severe nicotine intoxication are potentially fatal. Lethargy, convulsions, and coma thus follow early-stage symptoms. Weakness, fasciculations, hypotonia, and hyporeflexia can result in paralysis, including respiratory paralysis. These symptoms of toxicity typically occur within 4 hours after exposure [10].

Additionally, nicotine is an irritant when ingested. Therefore, ingesting a high dose of nicotine-containing e-liquid can cause contraction of the throat muscles and burning in the mouth [45].

5.2. Lethal nicotine dose

Established by Mayer in 2014, there is a disagreement between the generally accepted lethal dose and documented cases of nicotine intoxications [51]. The typical databases and textbooks consistently indicate that the lethal ingested dose for adults is around 30 to 60 milligrams. However, this number is based on a textbook written by Rudolf Kolbert in 1906 who estimated the lethal nicotine dose of 60 mg as a result of dubious self-experiments [51]. This amount corresponds to five cigarettes or 10 ml of a diluted nicotine-containing e-liquid solution.

Later experiments showed that the value from Kolbert is not accurate and that the LD_{50} value of nicotine varies considerably between species. For example, the LD_{50} of nicotine is 3.3 mg/kg in mice, whereas the LD_{50} value of nicotine is 50 mg/kg in rats [52]. The (controversial) postulated fatal dose of 60 mg dose in humans corresponds to an LD_{50} of 0.8 mg/kg, which is much lower. This low LD_{50} indicates that nicotine is a highly toxic and potentially lethal compound in e-liquids and patches [53,54]. However, fatal nicotine intoxications are relatively uncommon. Additionally, other nicotine overdose reports are barely compatible with the standard lethal dose of 60 mg or lower with a maximum nicotine intake of 20 mg [55–57].

Solarino et al. reviewed literature reports on fatal nicotine intoxications. This review of post-mortal findings indicates that nicotine concentrations of 2 mg/L or higher are lethal [47]. Reports from fatal intoxications showed plasma concentrations up to 4 mg/L, which would require a 500 mg of oral nicotine, according to Mayer [51]. Taken all this together, nicotine is estimated to have a human oral LD_{50} of 6.5–13 mg/kg. A case report that also presents an overview of more recent nicotine intoxication cases supports this statement [58].

6. Diagnosis

Plasma concentrations of nicotine and its metabolite cotinine are not convenient markers to confirm the exposure and estimate the expected degree of toxicity. Given the rapidity of nicotine toxicity, the time required for laboratory analysis precludes their use in treating an acutely poisoned patient. The main use for these concentrations is for forensic purposes and for use in tobacco regulations.

In the case studies on nicotine-containing e-liquid intoxications, various methods are used for the analysis of nicotine and metabolites. Examples of these techniques are gas chromatography, high-performance liquid chromatography, gas chromatography-mass spectrometry or liquid chromatography with mass spectrometry. All these techniques have their advantages and disadvantages like complexity the sample work-up and analysis, and time to result. A useful review of these techniques is described in detail by Rentsch et al. [59].

The metabolite cotinine might be a better biomarker for forensic purposes than nicotine in case of accidental ingestion. The half-life of cotinine is considerably longer (13–19 hours) than that of nicotine (100–150 minutes), resulting in higher serum concentrations. Secondly, cotinine is an important metabolite eliminated in the urine, facilitating its analysis. Because of this, clinicians often use cotinine as a biomarker for nicotine exposure [60]. In nicotine-containing e-liquid intoxications, however, the survival rates and clinical patterns do not always correlate with cotinine concentrations [61]. A possible explanation for this inconsistency could be that the metabolism rate of nicotine might differ between individuals. Another explanation could be that liver damage interrupts the metabolism of nicotine to cotinine. However, these explanations are not studied.

Additionally, cotinine levels may be relatively low early in the ingestion due to ongoing formation. Whereas later in the ingestion, cotinine levels may remain high while the nicotine has been fully metabolized.

To overcome the problem of diagnostic time, newer test are being developed. One suggestion is a point-of-care saliva test for nicotine [62]. This test reacts with metabolites of nicotine, including cotinine. Due to the nature of the test, it can only distinguish between exposed to nicotine or not exposed to nicotine in accidental exposures, and is thus only useful for confirmation and not for quantification. Therefore, this test may be useful for proving nicotine exposure but not for clinical guidance. In conclusion, nicotine and cotinine serum or saliva concentrations may be useful for confirming nicotine-containing e-liquid intoxications but are not useful for guiding therapy due to the rapid onset of symptoms. Its major limitations are the necessary time to perform the analysis and that the test is only useful if the patient is a nonsmoker. Treatment should, therefore, be based on the evaluation of the patient's symptoms and medical history.

7. Treatment

Age is an essential consideration in treating nicotine-containing e-liquid intoxications. Adult exposures are frequently caused by suicide attempts resulting in severe intoxication symptoms [63–66] In children, however, exposures are mainly accidental [67–69].

Treatment for nicotine-containing e-liquid intoxications is mostly supportive and symptomatic. In the case of dermal exposure, however, exposed skin should be washed thoroughly with water and soap to avoid continued absorption of nicotine.

For both adults and children, treatment options consist of activated charcoal, atropine for bradycardia and benzodiazepines. In two case reports, activated charcoal was administered to the patients. In one case, the patients showed an improvement of consciousness in combination with atropine [61], and in the other case, there were no other adverse effects established [70]. Children that ingested small amounts of nicotine-containing e-liquid or only show minor symptoms should be observed and monitored until the symptoms have disappeared. Discharge is generally safe after 4 to 6 hours of observation since severe intoxication syndromes occur within 4 hours [9,19,71]. When a severe intoxication is suspected, the child should be brought to the hospital. Activated charcoal should only be administered if the child is still asymptomatic, alert, cooperative, and can be administrated within one hour after ingestion [22,71]. After this timeframe or when more severe symptoms are already present, charcoal should not be given because of the risk of aspiration [71]. One case describing the intoxication of an 18-month old child that ingested nicotine-containing e-liquid showed a decrease of symptoms after 6 hours of observation and supportive care [71]. The child was intoxicated with a 1 mg/kg dose. A fatal case was reported in a child swallowing 4 mg/kg. Despite symptomatic treatment, the child developed fatal hypoxic brain damage [68]. In adults, activated charcoal is always the treatment of choice, together with careful monitoring of cardiovascular and respiratory functions. The preferable dose for both children and adults is 1 g/kg without sorbitol since sorbitol can induce spontaneous vomiting [71].

In both adults and children, respiratory problems and bradycardia should be treated with 0.5–1.0 mg atropine in 5–10-minute intervals [61]. Other cardiac arrythmias should be treated according to clinical observations and the European resuscitation guideline [72]. Although atropine is a muscarinic cholinergic receptor antagonist and therefore may not block nicotine actions, it is still indicated for severe bradycardia as stated in the bradycardia algorithm from the European resuscitation guidelines [72]. Seizures should be treated by administering benzodiazepines [56]. In adults, hypotension is initially treated with fluid resuscitation and if refractory, expanded with vasopressors (dopamine or norepinephrine) [42,56]. Monitoring of heart and respiratory function combined with intubation are the most crucial aspects of care in nicotine-containing e-liquid intoxications.

8. Conclusion

The main objective of this review was to provide an outline of the literature on toxicity and propose a treatment for nicotine-containing e-liquid intoxications. Nicotine overdose is an increasing problem due to the widespread availability of e-cigarettes and nicotine-containing e-liquid. The symptoms of nicotine toxicity are not dose-dependent and resemble the cholinergic toxidrome. Analysis of nicotine and cotinine serum concentrations may be helpful in some circumstances, but are time-consuming and therefore of limited value in acute overdose settings concerning the short onset of the overdose symptoms. The treatment of nicotine-containing e-liquid intoxications is mainly symptomatic, and we

propose activated charcoal, atropine and benzodiazepines and fluid resuscitation when systemic symptoms arise. Cardiac and respiratory function should be monitored closely.

9. Expert opinion

The upcoming market of the e-cigarette has allowed for easy access to high doses of nicotine. This creates potential health risk in case of accidental ingestions, especially by children, or suicide attempts by adults. Additionally, spilling of the refill containers could lead to accidental transdermal absorption in both adults and children.

Currently, the research in the field on the toxicity and treatment of nicotine intoxications is limited and new research should focus on providing insight in its toxicity, based on oral and transdermal pharmacokinetics and on toxicodynamics. The refills should contain warnings regarding the maximum content based on the results from safety studies and case reports. The liquid nicotine containers should be provided with a proper list of ingredients and nicotine concentrations, volume and total dose. Also, the option of adding flavors and appealing packages should be limited to prevent attention of children as much as possible. Lastly, the design of the refills should be such, that accidental opening and swallowing by children is not possible. Regulations regarding these issues should be strengthened to limit the risk of accidental intoxications.

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SYNOPSIS
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Synopsis of the Clinical Practice Guidelines on Substance Use Disorders

INDIAN PSYCHIATRIC SOCIETY
SPECIALTY SECTION ON SUBSTANCE USE DISORDERS
2015

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PREFACE

It gives me great pleasure to write the Preface of the book "Synopsis of Clinical Practice Guidelines on Substance Use Disorders", published by the Indian Psychiatric Society.

The problem of substance use disorders is too well known to be described in detail. A global problem, it has reached epidemic proportions in India as well, taking its toll on the economic, social and human fabric of our civilization. Although a multi-disciplinary and multi-sectoral issue, substance use disorders are essentially a group of psychiatric disorders, for which expert psychiatric management is needed.

Last year, the IPS Specialty Section on Substance Use Disorders had brought out an entirely new set of comprehensive Clinical Practice Guidelines (CPGs) on the assessment and management of common substance use disorders. The set of eight CPGs (assessment, alcohol, opioids, cannabis, sedative-hypnotics, tobacco, inhalants and dual diagnosis) is a rich and updated source of knowledge and skills. The authors had rigorously collected the evidence, organized and rated them, and combining the evidence with the local situation and context, came up with their recommendations. The book was comprehensive in its width as well as depth of coverage.

However, a need was felt to produce an evidence-based synopsis of the previous exhaustive reference book. This is targeted directly for the practitioners and students, for an easy checking and implementation. This brief "Synopsis" can be seen as a handy companion to the more detailed previous book. Together, these complement each other as a set of resources that should prove useful to all concerned.

I congratulate the IPS Specialty Section on Substance Use Disorders on this well accomplished task. I also thank the Publication Committee of IPS for publishing this useful book with great care. I wish that IPS should come up with more such volumes on various important psychiatric topics in future, setting a healthy and helpful tradition.

Dr. T.V. Asokan
President, Indian Psychiatric Society
January, 2015

MESSAGE FROM HONORARY GENERAL SECRETARY, INDIAN PSYCHIATRIC SOCIETY

It is a matter of pleasure to know that Indian Psychiatric Society is bringing out a useful book on Substance Use Disorders.

Drug addiction is an important psychosocial problem from time immemorial and is found amongst all cultures and civilizations across the world thorough out history. Drug addiction causes immense human distress and unfortunately there is no part of the world that is free from it. Millions of people all over the world are leading very miserable and pathetic lives. The drug abuse is a complex phenomenon with involvement of social, cultural, biological, geographical, historical and economic aspects.

All of us know that there are innumerable varieties of drugs which are abused but most commonly used include alcohol, nicotine, cannabis, inhalants, psychotropics, benzodiazepines and opium related drugs. The availability along with policies is helping the enhanced use in the society. What starts as novelty seeking behavior soon gets converted into unavoidable vice. The unforeseen and unpredictable psychological and social outcomes are devastating.

Alcohol dependence has been showing a rising trend thanks to rapid change in lifestyle behavior. The resulting physical complications are a major concern for health policy planners. Early onset of alcohol use is associated with motor vehicle accidents and long term medical complications. The research indicates that earlier people begin to drink; the more likely they are to experience alcohol dependence within ten years of drinking onset. Earlier drinkers are also more likely to experience chronic relapsing dependence characterized by more and longer episodes. Early onset is also related to antisocial behavior, major depression, and family history of alcoholism. (Hingson R. et al Pediatrics 2001; 108: 739-746).

It is unfortunate that the management of substance abuse is the most challenging in psychiatry. The prevention of relapses is very daunting and requires a multi specialty approach. There are no two opinions with regard to the fact that psychiatrists play a major role in planning and implementation of any program on drug use. It is fittest of things that the experts who have worked all their professional lives in the betterment of drug use victims have come forward to share their experiences.

Indian Psychiatric Society is happy to involve in bringing out the latest developments in the field of substance use disorders and I am sure the handbook will be very useful to experienced clinicians, young post graduates and serious researchers. I thank Dr. P.K. Dalal, Dr. Debasish Basu, Dr. Gautam Saha and Dr. Sandeep Shah in addition to all authors for completing such a daunting task. Of course such a dream would not have been reality but for the support extended by Dr. T.V. Asokan and the EC members.

Long live IPS!

Dr. N.N. Raju
Hony. General Secretary, IPS

FROM THE DESK OF IPS PUBLICATION COMMITTEE

Dear Member,

The landscape of medical education has changed rapidly in recent years and will continue to do so into the future. In addition, the composition of our continuing medical education will continue to change, with increasing numbers and shares of the population coming from communities of color. In this publication we use experimental clinical projection techniques to capture the impact of these changes on the size and ethnic composition of medical education to the members of each state, each zone, and nationally the Indian Psychiatric Society as a whole.

A number of individuals were instrumental in the preparation of this publication. First and foremost among them were authors who played critical roles at several steps along the way to publication. Special thanks to Dr. P.K. Dalal and Dr. Debasish Basu who designed and produced the layout and graphics; who edited the text and helped proof the data; who built the interactive tool providing readers with customizable data and graphics for our Society; and we also like to design in the web environment for the online version of the publication.

We would also like to thank those individuals who gave of their time and expertise in serving on the technicalities over the past few months. Finally, our thanks go to all the senior members for their generous support of the preparation, publication, and dissemination of this edition.

IPS Publication Committee prepares the white paper that formed the foundation of the methodology review component of this work. In short, we hope the future is a brighter one than what we experience here – for all members.

All the authors earn our sincere gratitude for their efforts on this publication.

We thank our President Dr. TV Asokan, Vice-President Dr. Vidyadhar Watve, Hony General Secretary Dr. N.N. Raju, Hony Treasurer Dr. Vinay Kumar, Hony Editor Dr. T.S.S. Rao, and grateful to all Council Members for helping and cooperating us to run the Publication Committee at ease.

Long live I.P.S.

Dr. Gautam Saha
Chairperson, Publication Committee
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INDIAN PSYCHIATRIC SOCIETY – SPECIALTY SECTION ON SUBSTANCE USE DISORDERS (IPS-SS-SUD)

SYNOPSIS OF CLINICAL PRACTICE GUIDELINES ON SUBSTANCE USE DISORDERS

CONTENTS

Synopsis of the Clinical Practice Guidelines on Substance Use Disorders: An Overview

P.K. Dalal
Debasish Basu
On behalf of the IPS-SS-SUD

2015

A book was released at the Inauguration Ceremony of the 66th Annual National Conference of the Indian Psychiatric Society (ANCIPS) held in Pune in January 2014. It was an official publication of the Indian Psychiatric Society (IPS), brought out by its Specialty Section on Substance Use Disorders (IPS-SS-SUD). It was named "Clinical Practice Guidelines for the Assessment and Management of Substance Use Disorders" (referred hereafter as the "CPG-SUD book"). The following areas were covered in the CPG-SUD book: assessment of substance use disorders in general; alcohol use disorders; opioid use disorders; cannabis use disorders; sedative-hypnotic use disorders; tobacco use disorders; inhalant use disorders; and dual diagnosis.

The CPG-SUD book was the culmination of intensive year-long efforts of a group of dedicated psychiatrists working in the field of substance use disorders in various reputed academic medical institutes of India. The development, refinement and finalization of these Clinical Practice Guidelines (CPGs) was the result of an arduous, long-drawn and rigorous process following a pre-defined iterative strategy involving progressively widening circles of peer review. The pre-defined strategy for the process of development, refinement and finalization of these CPGs has been mentioned in details in the "Overview" chapter of the CPG-SUD book. To recapitulate briefly, the development of the CPGs were guided by: (a) an extensive review of the relevant literature, including Indian data wherever available in published and retrievable form; (b) pre-existing recent guidelines in this area; (c) an awareness of the local needs and priorities whenever applicable (e.g., the need to focus on smokeless tobacco use in India); (d) need to balance the rigor and extensiveness of data coverage with the pragmatic considerations of condensing and filtering the data for practical use by clinicians; (e) need to rate the category of evidence and the strength of recommendations as per internationally accepted norms; and (f) the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) instrument. The CPGs thus developed were finalized through an iterative process of progressively widening circles of peer review. Ethical issues and potential conflicts of interest were also taken care of, and mentioned explicitly in the "Overview" chapter of the CPG-SUD book.

Since its publication in 2014, the CPG-SUD book has been well received by clinical practitioners, researchers, academicians, and psychiatric students, i.e., by all the target groups this book was meant for. It provided the clinicians with updated and evidence-based guidelines for assessment and management of substance use disorders, and others with a comprehensive compendium of updated knowledge that can be a rich resource for academic purposes of teaching, learning, and research. For wide dissemination, the CPG-SUD book was priced at a no-profit-no-loss low price, often distributed free of cost at conferences, and – by the time this book is released – should be available in a freely downloadable Portable Document Format (PDF) from the IPS website as well.

So far, so good. However, it became quickly apparent that there was a need for a more concise, practice-oriented, easy-to-follow "Synopsis" of the comprehensive CPG-SUD book as well. The CPG-SUD book is 531 pages long, with more than 500 text pages, and literally thousands of references (e.g., the chapter on alcohol use disorders cite 209 references, the chapter on inhalant use disorders cite 171, and the one on opioid use disorders cite 295 references!). There are many issues covered and discussed in that book, which, while extremely valuable for providing a comprehensive coverage of the subject matter, may not be needed immediately for a busy practitioner or a psychiatric student looking for quick tips. Thus, a need was felt for a set of compact, precise, yet evidence- and expertise-based guidelines.

This is the genesis point for this current volume. Easy-to-carry in a pocketbook sized format, and easy-to-use with clear tables, panels, boxes and algorithms, it is a perfect supplementary companion of the comprehensive CPG-SUD book. It synthesizes all the practice-relevant information necessary for the assessment and management of common substance use disorders and dual diagnosis. In order to maintain comparability and consistency with the CPG-SUD book, it contains the same chapters in the same order: assessment of substance use disorders in general; alcohol use disorders; opioid use disorders; cannabis use disorders; sedative-hypnotic use disorders; tobacco use disorders; inhalant use disorders; and dual diagnosis. In keeping with the purported aim and scope of this book, the text of the chapters does not cite any reference (with rare exceptions), but a short list of key references/further reading is provided at the end of each chapter.

Before we conclude this overview, a very important caveat needs to be re-emphasized. As mentioned in the CPG-SUD book, "Like any CPG, along with their potential utility as outlined above, their scope and limitations need to be kept in mind so as to avoid their misuse, and encourage their correct use.... please remember that CPGs are "guidelines", not "mandates" or obligatory "standards" required by law or by an institute (though mandates and standards may later be derived from them as a policy matter). CPGs are meant to inform, assist and "guide" the clinician, not ask them to sacrifice their autonomy of clinical judgment, nor to be oblivious of the individual patient's clinical situation and psychosocial context." (Emphasis added). This caveat is all the more important to keep in mind while using this "Synopsis". Management of SUDs is a complex, multifaceted business involving often difficult decision balancing in the face of different needs and context of the individual patient and after weighing the pros and cons of several competing options. If followed blindly, individual decision making may take a back seat, encouraging blind copy-pasting of general recommendations in a mindless manner that might help the individual patient in question in a blank-shot-in-the-air manner, or, in a worse case scenario, be of no benefit, or, in the worst case scenario, even be harmful. We do not intend this "Synopsis" to

degenerate into an "Easy Recipe Cook Book" or a "Learn-French-in-seven-days" booklet!

With this disclaimer and caveat, however, we believe that this "Synopsis", when properly used along with clinical training in addiction psychiatry, can be a very useful and handy companion to the students, clinicians and even teachers in their day-to-day practice. For the seeker, the CPG-SUD book is always there!

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Synopsis of the Clinical Practice Guidelines on Assessment of Substance Use Disorders

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2015

1. INTRODUCTION

1.1 NEED FOR ASSESSMENT

- Substance use and related disorders are highly prevalent worldwide.
- Meta analysis of studies indicate overall substance use prevalence of 6.9/1000 in Indian population.
- Prevalence is greater in people with mental illness.
- Despite high prevalence it remains under diagnosed.
- Early intervention and management is of paramount importance to reduce associated significant morbidity and mortality.

1.2 PURPOSE OF ASSESSMENT

Assessment needs to be done because

- To screen people for substance use disorders and early intervention.
- For diagnosing substance use disorders and to assess severity and associated co morbidity.
- For assessing motivation, support and available resources so that appropriate intervention can be planned.

1.3 COMMONLY USED SUBSTANCE

ICD 10 encompasses 10 different classes of drugs in substance related disorders and these includes alcohol, opioids, cannabinoids, sedative or hypnotics, cocaine, other stimulants including caffeine, hallucinogens, tobacco, volatile substance and other psychoactive substance. DSM 5 includes similar drugs except that these drugs have been categorized differently. DSM 5 includes similar drugs except that these drugs have been categorized differently.

ICD 10 describes

Harmful use - Pattern of psychoactive substance use that is causes actual physical or mental damage to health

Dependence - A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. For a definite diagnosis 3 or more of following is required in last one year

- Craving
- Loss of control
- Withdrawal symptoms in the absence of use
- Tolerance

- Salience
- Persistent use despite harm

DSM 5 gives criteria's of substance use disorders

A problematic pattern of substance use leading to significant impairment or distress as manifested by at least two of the followings, occurring within a 12 month period-

- Substance is often taken in larger amounts or over a longer period of time than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- A great deal of time is spent in activities necessary to obtain substance, use substance or recover from its effects.
- Craving, or a strong desire or urge to use substance.
- Recurrent substance use resulting in failure to fulfill major role obligations at work, school or home.
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of substance.
- Important social, occupational or recreational activities are given up or reduced because of substance use.
- Recurrent substance use in situations which are physically hazardous.
- Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance.
- Tolerance
- Withdrawal symptoms in absence of use

2. TYPES OF ASSESSMENT

Clinical assessment remains the mainstay of assessment.

Laboratory tests and assessment instruments are useful to complement clinical assessment.

2.1 CLINICAL ASSESSMENT

2.1.1 Detailed history

Socio demographic details and details of informants

- Chief complaints should be enumerated in chronological order. Onset of symptoms, precipitating factor and course of illness should be assessed. A

systematic inquiry into current and past substance use evaluating various environmental and contextual factors leading to initiation and maintenance of substance. Using DSM 5 and ICD 10 assess whether person fulfills criteria of dependence. Past abstinence attempts with history of past treatment response should be noted in detail. Current motivation for quitting substance should be assessed as per accordance with Prochaska and Diclemente stages. Assess for marital, social, financial, legal and occupational consequences secondary to substance abuse. Screen for co morbid physical illness and psychiatric illness secondary to or independent of substance use. High risk behavior needs special attention in personal history in such patients. Externalizing traits and internalizing traits act as contributing or susceptibility factors in initiation and/or maintenance of substance use and should be explored carefully.

2.1.2 Physical Examination

Certain specific features which aid in the diagnosis are

Sl. No.	Condition	Signs and symptoms
1.	**Alcohol withdrawal**	Anxiety, tremors, nausea, vomiting, agitation, paroxysmal sweats, tactile disturbances, visual disturbances, auditory disturbances, clouding of consciousness, headache
2.	**Opioid withdrawal**	Muscle aches, lacrimation, sweating, rhinorrhoea, nausea, vomiting, diarrhea, increased blood pressure, tachycardia, yawning, insomnia or anxiety, restlessness or irritability, piloerection, increased sensitivity to pain and craving for opioids.
3.	**Myriad systemic effects of excessive alcohol use**	Delirium, seizures, signs of liver enlargement or failure, ascites, anemia, thrombocytopenia, bleeding, myopathy, cardiomyopathy, nystagmus, lateral nerve palsy, peripheral neuritis and dermatitis.
4.	**Effects of marijuana or cocaine smoking.**	Thrombosed veins and track marks due to repeated injectable drug use and chronic sinus/nasal problems, worsening of bronchitis
5.	**Other Systemic infections**	Cellulites, sexually transmitted disease (ex HIV, hepatitis B and C), tuberculosis, bacterial endocarditis.

2.1.3 Mental status examination

Various components which should be assessed are

Sl. No.	Condition	Signs and symptoms
1.	**General appearance and behaviour**	Level of consciousness and orientation – Provides valuable clue regarding substance withdrawal/intoxication General demeanour, Eye to eye contact Abnormal movements ex tremers can be seen in substance withdrawal
2.	**Psychomotor activity**	Can be affected in substance related delirium (ex hypoactive or hyperactive) or substance related mood disorder etc
3.	**Speech**	Spontaneity, tone, tempo and volume of speech, relevance, coherence, reaction time and prosody
4.	**Thought**	In **form and stream** Assess for circumstantiality, tangentiality, thought block, incoherence, verbigeration, word salad, neologism and perseveration **Content** Referential/Persecutory/Grandiose/Hypochondrical ideation/delusions,depressive cognitions, death wishes and suicidal ideation. **Possession** Assess for thought alienation, obsession and compulsions.
5.	**Mood**	Subjective and objective component, range, reactivity, congruence to thought process and appropriateness to environment
6.	**Perception**	**Sensory distortions** - under substance intoxication **Sensory deceptions** - can occur under both substance intoxication and withdrawal.
7.	**Cognitive function assessment**	Includes assessment of orientation, attention and concentration, memory, judgment and abstraction. It is of paramount importance especially when substance related cognitive impairment is suspected ex during intoxication, Korskoff psychosis or substance induced dementia

As per Prochaska and DiClemente's classification the stages of motivation are precontemplation, contemplation, preparation, action and relapse.

Patient's motivation can also be assessed as

Sl. No.	Condition	Signs and symptoms
1.	**Poor**	Failure to perceive any problems with substance use and/or denying any substance-related functional impairment and/or refusing professional help
2.	**Superficial**	Admits that there are substance problem but ascribes it to external or rationalizing internal problem
3.	**Fair/good**	Having an insight about the basic nature of the problem as 'dependence' and/or appreciating the extent and severity of substance related complications and ability to link them with substance as the causative factor, and/or feeling the need of treatment for the dependence itself.

- A direct, empathic, non judgmental and compassionate attitude is the key to keep patient in treatment loop and improve overall treatment outcome.

2.2 LABORATORY ASSESSMENT

- Is not mandatory for diagnosing patients with substance use and related disorders
- It can complement clinical assessment in diagnosis and to assess effects of substance on patient's body

2.2.1 Breath alcohol concentration

- Easy, non invasive method for quantifying alcohol concentration using breath analyser in end expiratory air.
- It provides good insight into acute body burden of alcohol.
- Is insensitive to differentiate between acute or chronic consumption of alcohol, binge drinking or long term alcohol abuse.

2.2.2 Liver function test

- Deranged liver function tests are neither specific nor sensitive to alcohol abuse
- However are commonly affected during heavy drinking and is a pertinent factor determining treatment options.

- Enzyme gamma glutamyl transferase - a non specific indicator of liver damage as it is also found in blood and brain. Its level in blood rises before elevation in liver enzymes. It has a half life of 14 – 26 days.
- Carbohydrate deficiency transferrin (CDT) levels are related specifically to amount of alcohol consumed and alcohol metabolism. CDT has half life of approx 15 days.
- Combination of CDT with enzyme gamma glutamyl transferase may further increase sensitivity without reducing specificity.

2.2.3 Mean Corpuscular Volume (MCV)

- It is one of the indirect biomarker of alcohol use like liver function test and detects the effects of alcohol on organ system or body biochemistry.
- It takes 2 to 4 months to normalize.

2.2.4 Carbon monoxide (CO)

- The most convenient and economical measure of nicotine intake
- With a relative short half life of 4 – 5 hours, for the most accurate readings its levels are best measured during end of the day.

2.2.5 Nicotine and Cotinine

- Nicotine levels are measured in plasma about 6 – 7 hours after smoking when it tends to plateau.
- Cotinine has t1/2 is generally a preferred measure of nicotine exposure.
- Salivary cotinine is the most accurate index of nicotine but is expensive and involves complicated laboratory assessment.

2.2.6 Urine analysis

- Detects the presence or absence of drugs and its specific metabolites.
- May not indicate dosage or time of drug administration or extent of any drug effect on the body.
- Through semi quantitative urine analysis concentration of substance in urine can be monitored over time.

2.3 INSTRUMENT BASED ASSESSMENT

- It has the advantage of being non invasive and non expensive.
- Some of these can be rapidly applied and are self administered or require minimal to no special training for administration.
- Limiting factor being that information in such questionnaires can be easily feigned and depends on coherent thought process and overall mental status and intact insight.

Various assessment questionnaires for alcohol, nicotine and other drugs are mentioned below

2.3.1 Assessment of alcohol use

Sl. No.	Condition	Brief description
1.	**AUDIT** (Alcohol Use Disorders Identification Test)	Comprehensive 10 item brief screening instrument. Provides information on alcohol hazardous, harmful use, abuse and dependence.
2.	**MAST** (Michigan Alcoholism Screening Test)	24 item screening instrument designed to identify and access alcohol abuse and dependence. Shortened 13 item and 10 item versions are available
3.	**CAGE**	4 item screening instrument. Particularly useful in geriatric population and can be easily used in primary health settings
4.	**T-ACE**	Screening instrument developed to identify at risk drinking in pregnant women
5.	**TWEAK**	Screening instrument developed to identify at risk drinking in pregnant women
6.	**SADQ – C** (Severity of Alcohol Dependence Questionnaire)	20 item scale designed to measure severity of alcohol dependence. Has five subscales.
7.	**SADD** (Short Alcohol Dependence Data Questionnaire)	15 item self report questionnaire used to measure the severity of alcohol dependence.
8.	**ADS** (Alcohol Dependence Scale)	25 item self-report questionnaire useful to measure severity of alcohol dependence It is also a useful instrument to measure alcohol dependence in women
9.	**ASI** (Addiction Severity Index)	155-item multidimensional structured interview for assessing alcohol and drug dependence. Assesses frequency of use without addressing quantity of use. Useful instrument to assess alcohol abuse Vs dependence in women also.
10.	**CDP** (Comprehensive Drinker Profile)	88 item structured instrument useful for the assessment and treatment of alcohol problems

2.3.2 Assessment of nicotine use

Sl. No.	Condition	Brief description
1.	**RTQ** (Revised Fagerström Tolerance Questionnaire)	10 item questionnaire designed to measure the severity of nicotine dependence.
2.	**FTND** (Fagerström Test for Nicotine Dependence)	Consists of six items from the RTQ. It assesses the severity of nicotine dependence, tolerance and withdrawal

2.3.3 Assessment of other drug use

Sl. No.	Condition	Brief description
1.	**DAST** (Drug Abuse Screening Test)	20 item screening instrument designed to identify individuals with drug abuse problems excluding alcohol) in past 12 months.
2.	**OTI** (Opiate Treatment Index)	Structured instrument which provides comprehensive measure of drug misuse. It measures outcome in six domains
3.	**SODQ** (Severity of Opiate Dependence Scale)	5 section questionnaire which assesses opiate dependence. It is useful to assess pattern and quantity of drug use and various other aspects of dependence.
4.	**BDEPQ** (Benzodiazepine Dependence Questionnaire)	30 item questionnaire for measuring dependence on benzodiazepines, sedatives and hypnotics.
5.	**LDQ** (Leeds Dependence Questionnaire)	10-item, multiple choice self completion questionnaire which is used most sensitive to detect psychological dependence.
6.	**SDS** (Severity of Dependence Scale)	5 item questionnaires used to measure the degree of dependence on a variety of drugs. It focuses on psychological aspects of dependence.
7.	**SDSS** (Substance Dependence Severity Scale)	Semi-structured clinical interview designed to assess dependence on a variety of substances over past one month
7.	**SDSS** (Substance Dependence Severity Scale)	Semi-structured clinical interview designed to assess dependence on a variety of substances over past one month

3. SPECIAL GROUP – CHILDREN AND ADOLESCENT

- Average age at first use is around 12 to 14 years

- Tobacco, alcohol, cannabis and inhalants are commonly used substances in adolescents.
- Although adolescents typically drink less than adults, they tend to engage more in binge drinking behavior and hence are more likely to experience acute effects of alcohol in the form of intoxication and hangover rather than more chronic effects.
- Physiological dependence symptoms, e.g. withdrawal and tolerance are less likely to be present in adolescents.
- AUDIT has been shown to be superior to other instruments for assessing alcohol problems in adolescents.

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Synopsis of the Clinical Practice Guidelines on Management of Alcohol Use Disorders

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2015

INTRODUCTION

- Globally alcohol dependence ranks 5th and 3rd in the list of preventable cause of morbidity and mortality

EPIDEMIOLOGY

- Alcohol use disorders show an increased trend in developing countries like India
- National Household survey: Alcohol (21.4%) was the primary substance use apart from tobacco. Among them 17-26% of alcohol users qualified to ICD-10 diagnosis of dependence translating into an average prevalence of about 4%
- In India currently the most important and significant changes seen in alcohol use is
  - Decrease in age of initiation into alcohol,
  - Increase in female alcohol use and
  - Signature pattern of alcohol intake - take alcohol regularly (mostly solitarily) and heavily to the point of intoxication.

CONSEQUENCES OF ALCOHOL DEPENDENCE SYNDROME

- Medical
- Vocational
- Legal
- Financial
- Family (including Marital)
- Social

MAJOR CONCERNS FOR CURRENT MANAGEMENT OF ALCOHOL USE DISORDERS IN INDIA

- Low awareness level
- Beliefs about alcoholism
- Lack of trained personnel
- Lack of community resources
- Inadequate access to health care

REVIEW OF TREATMENT MODALITIES

GENERAL ISSUES

- Alcohol Dependence Syndrome (ADS) is a chronic relapsing and recurring condition - requires a continuous and prolonged comprehensive multipronged care over long period of time.
- An integrated Bio-psychosocial approach to care is needed to address several aspects of treatment

- An active collaboration with the family while planning and delivering treatment is required.
- Management of ADS should be sensitive to the needs and empirically titrated to the patient's response and progress.

TREATMENT AIMS/GOALS

The goals of treatment vary according to time frame, across individual patients and can be revised from time to time.Main goal of treatment is to maintain abstinence and if not possible decrease the frequency and severity of relapses and maximize functioning in between.

- Promote complete abstinence
- Stabilize acute medical and psychiatric conditions as needed
- Increase motivation for recovery
- Initiate treatment for chronic medical and psychiatric conditions as needed
- Enhance coping and relapse prevention skills
- Improve occupational functioning, social support and assist in integrating to society as needed
- Promote maintenance of recovery through ongoing participation in structured treatment or self-help groups

SHORT TERM GOALS	LONG TERM GOALS
1. Manage Intoxication	1. Relapse Prevention
2. Manage withdrawal	2. Maintain Abstinence
3. Motivation Enhancement	3. Occupational rehabilitation
4. Treat acute medical sequel	4. Social reintegration
5. Crisis Intervention	5. Improve Quality of Life

- **ASSESSMENT OF ALCOHOL USE DISORDERS**
- Assessment will help in diagnosing, establishing rapport, motivating the person and in formulating the plan of the management.
- The goal of assessment also varies in different phases of the treatment.
  - During the first contact it is to establish rapport, diagnosis and plan of management
  - During intervention it is monitoring the progress and assessing abstinence.
- The goal also depends on the context, motivation of the client and cooperativeness of the client.
  - If the client is uncooperative the aim of assessment is to retain the client in the treatment. During this time the information can be collected in pieces and information can be added when patient is co-operative.

CLINICAL HISTORY	PHYSICAL EXAMINATION	INSTRUMENTS	INVESTIGATIONS
Substance related factors - age of initiation, frequency, amount, tolerance, craving, withdrawal symptoms, salience, last dose, motivation, consequences of substance use etc., History of other substance use, *Physical and psychiatric co-morbidity* if any, *Abstinent related factors* - past abstinence, duration, reasons for relapse, past treatment/s, methods used for controlling craving etc., *High risk behaviours*, Presence of any externalizing disorders, *Family history* of substance abuse, and psychiatric illness, *Assessing social support*, current living arrangements and *reasons for current visit*	Look for signs of intoxication, withdrawal signs, evidence of physical damage, assess for psychopathology	CAGE, ASSIST, CIWA - Ar etc.	Confirmation of alcohol, LFT, Hemogram, GGT, Serum B12, USG Abdomen, HIV, VDRL (high risk cases) ECG (> 40yrs) Neuropsychological test

MANAGEMENT OF ALCOHOL INTOXICATION		
GOAL To relieve patient's discomfort, and prevent the occurrence of more serious symptoms		
	ETHANOL TOXICITY	**METHANOL TOXICITY**
DIAGNOSIS	• Diagnosis as per ICD-10 or DSM 5 • The signs and symptoms include slurred speech, lack of coordination, unsteadiness of gait, impairment in attention and concentration and • In severe cases coma and stupor.	• **Common symptoms are visual disturbances and abdominal pain** • **Neurological abnormalities, Kussmaul breathing, impaired cardiac function and hypotension**
ASSESSMENT	Clinical Assessment which includes general assessment along with physical status, mental status, substance use history and associated consequences	

	ETHANOL TOXICITY	METHANOL TOXICITY
TREATMENT	◆ If breath analysers are available the BAC can be measured ◆ Acute effects - generally subside with time and do not warrant any specific treatment ◆ Pharmacological treatment - when presented with respiratory depression and recent use of other substance/s ◆ General measures like reassurance, and maintain in a safe and monitored environment to decrease external stimulation and to provide orientation as necessary ◆ Maintain adequate hydration and nutrition ◆ Monitor withdrawal state - past history of complicated withdrawal, and prolonged heavy drinking	◆ Gastric lavage, induced emesis or use of activated Charcoal within 30-60 min of intake ◆ Fomepizole (not available in India) ◆ Ethanol (never approved) ◆ Dialysis if necessary ◆ Giving ethylene glycol

MANAGEMENT OF ALCOHOL WITHDRAWAL AND DETOXIFICATION

WITHDRAWAL STATE

The factors which predict the severity of a withdrawal syndrome

- Time elapsed since last use
- Concomitant use of other substance use
- The presence or absence of concurrent general medical or psychiatric disorders, and
- Past complicated withdrawal syndromes

SIMPLE WITHDRAWAL	COMPLICATED WITHDRAWAL
◆ Starts after 6-48 hrs after cessation or reduction in alcohol use ◆ Symptoms suggestive of GI distress, anxiety, irritability, elevated blood pressure, tachycardia and autonomic hyperactivity ◆ Symptoms intensify in initial period and diminish over 24-48 hrs ◆ Symptoms would be normally abating over duration of 5-7 days.	**WITHDRAWAL SEIZURES (RUM FITS)** ◆ Starts within 12-72 hrs of cessation of prolonged ingestion of alcohol ◆ mostly generalized tonic clonic seizure ◆ majority (60%) have multiple seizure but only 3% progress to status epilepticus ◆ Around 30-40% progress to **DELIRIUM TREMENS**

COMPLICATED WITHDRAWAL (DELIRIUM TREMENS)

- Medical emergency : occurs in 5% of Alcohol dependent syndrome patients
- Begins after 2-5 days of sudden reduction or stoppage of alcohol
- May also triggered by infection, illness, head injury
- Clinical Features: Usual withdrawal symptoms PLUS
  - Coarse tremors of the limbs and whole body
  - Reduced level of consciousness, disorientation, impaired recent memory, disruption in sleep wake cycle, transient hallucinations or delusions, with severe agitation
  - Fluctuation and evening worsening of symptoms
  - In addition: ataxia, mild pyrexia, autonomic disturbance
- No specific clinical findings are diagnostic .
- Mortality: 20-50% without treatment and 5-10% with treatment
- Complications include dehydration, arrhythmias, hypotension, renal failure and pneumonia

TREATMENT GOALS FOR WITHDRAWAL STATE

- To relieve patient's discomfort, prevent the occurrence of more serious symptoms, and forestall cumulative effects that might worsen future withdrawal.
- To utilise the withdrawal treatment opportunity to engage patients in long-term management.

TREATMENT REGIMENS FOR ALCOHOL WITHDRAWAL

- Pharmacological agents are treatment of choice in alcohol withdrawal
- Pharmacological agents are directed towards reducing CNS hyper excitability and restore homeostasis
- The ideal pharmacological agent should be effective in relieving the symptoms of alcohol withdrawal and also should prevent alcohol withdrawal seizures and delirium
- It should be safe in overdose with benign side effect profile, less drug-drug interaction, tolerability and suppress drinking during and after alcohol withdrawal

TREATMENT SETTINGS

- Majority in outpatient settings
- Inpatient care is needed in
  1. Confusion or has hallucination
  2. Previous H/O complicated withdrawal
  3. Epilepsy/ H/o fits

4. Malnourished
5. Severe vomiting/ diarrhoea
6. Suicidal risk
7. Severe dependence coupled with unwillingness to be seen daily
8. Previous failed home assisted withdrawal
9. Has acute physical or psychiatric illness
10. Has multiple substance misuse
11. Unsupportive home environment

MANAGEMENT OF SIMPLE WITHDRAWAL

ASSESSMENT

Routine assessment with particular emphasis placed on

- Time elapsed since last use,
- Concomitant use of other substance use,
- The presence or absence of concurrent general medical or psychiatric disorders
- Past complicated withdrawal syndromes.

BENZODIAZEPINES (BZD)

- Used in withdrawal syndrome due to cross tolerance with alcohol
- Several meta-analyses and systematic reviews have consistently shown that BZD are better than placebo in reducing the severity of withdrawal, prevention of delirium and withdrawal seizures and thereby leading on to higher success rate of detoxification and entering into long term programmes
- All BZD (short and long acting) are equally effective in management of the simple alcohol withdrawal state
- Both short acting and long acting Benzodiazepines are effective in primary and secondary seizure prevention
- Long acting BZD are better in prevention of seizures and delirium tremens
- Short acting BZD (Oxazepam and Lorazepam) are preferred in liver damage, elderly and in cognitive impairment
- Dosing pattern - fixed dose regimens for BZD are recommended for routine use with symptom-triggered dosing reserved for use only with adequate monitoring.

ANTICONVULSANTS

- Used as they reduce glutamate overactivity and risk of brain toxicity
- Insufficient evidence for use of anticonvulsants
- Anticonvulsants have limited side effects and they are effective for some symptoms such as seizures

- Prophylactic use of anticonvulsants is not recommended except in cases of co-occurring seizure disorder and alcohol use

BACLOFEN

- Selective GABA-B agonist
- Evidence is insufficient for its use in alcohol withdrawal

ACAMPROSATE

- NMDA antagonist and GABA-A agonist
- The evidence for the use of acamprosate in alcohol withdrawal is confusing. Some trials have shown that when given along with Benzodiazepines during withdrawal they improved outcome, whereas some trials have shown that they indeed worsen the outcome when given during the beginning of detoxification

OTHERS

- Propranolol - bblocker
- Clonidine - a2 agonist
- Supplementation on D-Phenyl-alanine, L glutamine, L-5 hydroxytryptophan
- Limited evidence in withdrawal stage

MANAGEMENT OF COMPLICATED WITHDRAWAL

ALCOHOL WITHDRAWAL SEIZURES

- Benzodiazepines reduce withdrawal severity and the incidence of seizures and delirum
- Both short acting (Lorazepam) and Long acting Benzodiazepines (Diazepam). Long acting Benzodiazepines are effective when compared to short acting Benzodiazepines
- Carbamazepine (insufficient evidence)

MANAGEMENT OF DELIRIUM TREMENS

- **GENERAL MEASURES**
  - In patient care for all patients
  - Maintain water and electrolyte balance
  - Correct metabolic disturbance, nutritional supplement
  - Close supervision
  - Appropriate medications
  - Safe and protective environment
- **SPECIFIC MEASURES**
  - Benzodiazepines are more effective than neuroleptics in reducing mortality in alcohol withdrawal delirium

- Heavy doses of benzodiazepines are required
- Insufficient evidence - for use of Baclofen, Ethyl alcohol, Lamotrigine and magnesium

ALCOHOL RELATED BRAIN DISORDERS

WERNICKE'S ENCEPHALOPATHY (WE)

- Acute neuropsychiatric condition due to insufficient supply of Thiamine to the brain
- Diagnosis - dietary deficiency + 2 of the classic triad (Ophthalmoplegia, Ataxia, & Confusion)
- Presumptive diagnosis - if ophthalmoplegia, ataxia, acute confusion, memory disturbance, unexplained hypotension, hypothermia, coma, or unconsciousness in ADS
- High risk cases (suspicion needed) - using > 15 units /day for a month or more, evidence of recent weight loss/ vomiting / diarrhoea / malnutrition / peripheral neuropathy/chronic ill health

MANAGEMENT

- Medical emergency
- For all suspected and high risk individuals – parental thiamine 100 mg i.m or oral thiamine before glucose.
- In India –
  - All suspected and high risk cases parental thiamine to be given for 2 weeks + oral thiamine of 100-200 mg /day for a minimum period of 3 months
  - All cases of ADS it is recommended to start oral thiamine for minimum of three months.

KORSAKOFF'S SYNDROME

- Undiagnosed or inadequately treated Wernicke's Encephalopathy proceed to Korsakoff's syndrome
- Diagnosis - Severe anterograde amnesia, retrograde amnesia and cognitive deficits

MANAGEMENT

- Best treatment is timely recognition of WE & appropriate intervention and treatment
- 200 mg thrice daily thiamine before carbohydrate in high risk cases
- Once cognitive impairment or Korsakoff's syndrome is evident (after thiamine replacement) - No additional pharmacotherapy to ameliorate cognitive impairment has been shown to be effective

MANAGEMENT OF ALCOHOL DEPENDENCE

PHARMACOLOGICAL MANAGEMENT

GOALS

- Maintain complete abstinence
- If not possible:
  - Decrease the frequency and severity of relapses
  - Maximize functioning in between
  - Improve the quality of life

DISULFIRAM

- First pharmacological agent to be approved by FDA in 1951
- Aversive agent. Only drug used for complete abstinence from alcohol dependence
- Irreversible inhibitor of Aldehyde dehydogenase - causes ↑ in the level of acetaldehyde if alcohol is consumed resulting in nausea, sensation of heat in head and neck, hypotension, flushing and palpitations. This deters people from drinking along with disulfiram
- Causes increase in the level of dopamine and decrease in the level of nor adrenaline in brain by blocking dopamine β hydroxylase
- Supervised' disulfiram use was found to better than placebo, naltrexone, acamprosate, lengthening time to relapse and maintaining abstinence on short term abstinence rate. There are several studies that shows that supervised disulfiram is effective in Indian populations
- Patients who are motivated, have less impulsivity, intelligent, and whose craving is dependent on internal and external cues are better candidates for disulfiram
- Dose: 250 mg/day for 1 year. Started when the body is alcohol free for at least 24 hrs
- Common side effects are drowsiness and gastric irritation
- No evidence to guide how long to prescribe - guiding principle to stop disulfiram is when patient and therapist mutually agree and patient is confident of remaining abstinence

NALTREXONE

- Naltrexone is one of the most widely studied medications with a strong efficacy base
- Opiate receptor antagonist - decrease in euphoric and rewarding effects of alcohol, and decrease in alcohol induced dopamine release which causes reduction in rewarding and decrease in craving

- Reduces return to heavy drinking by reducing lapse to relapse, but does not improve the abstinence rate. Long acting Injectable form of Naltrexone has been used to overcome poor adherence.
- Useful in people with family history of alcohol dependence and type A alcoholism (Babor classification)
- Oral dose: 50 mg/day (can be given also while using alcohol)
- Injectable (not yet formally approved for use in India): 190 mg and 380 mg/month in people with poor adherence
- Mild and transient side effects –
  - Most common adverse effect is nausea and sedation
  - CNS: headache, dysphoria, fatigue
  - GI: nausea, abdominal pain, vomiting, and liver toxicity
- Longer duration of use (6 months) had better outcomes compared to shorter duration (3 months) - benefits also observed to last for 3-12 months after stopping

ACAMPROSATE (calcium acetyl homotaurinate)

- Synthetic molecule which is hypothesized as a functional glutaminergic NMDA antagonist and reduces hyperglutamatergic state and reestablishes the homeostasis.
- Acamprosate better than placebo in maintaining abstinence and in preventing relapse; Acamprosate reduces heavy drinking in patients who have relapsed.
- Dosage: Available in 333 mg pill & dose of 999 mg to 1998 mg/day based of weight of the patient
- Adverse effects: GI disturbance most common
- Not metabolized in the liver and excreted unchanged in kidney – contraindicated in severe liver and renal impairment
- To be used for a year - benefits also observed to last for 3-12 months after stopping

BACLOFEN

- Stereo selective gamma aminobutyric acid B receptor (GABA) agonist - inhibit the release of neurotransmitters such as Dopamine, 5HT, NA, Glutamate
- Baclofen has a higher rate of abstinence and decreases anxiety. Baclofen holds promise and should be first line of management in patients with moderate to severe cirrhotic liver disease.
- Dose: 30-60 mg/day
- First line of management in the presence of moderate to severe cirrhosis

TOPIRAMATE

- Reduces mesolimbic activity of dopamine by Facilitates GABA transmission, decrease in AMPA (Glutamate excitation)

- Reduces the percentage of heavy drinking days, maintain abstinence, harmful drinking consequences, physical health and quality of life.
- Dose: 150-300 mg/day
- Adverse effects: Paraesthesia, Anorexia, Insomnia, difficulty in concentration

SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI)

- SSRIs are generally used for patients with comorbid depression, effectiveness is less consistent in non depressed patients
- SSRIs worsen outcome in early onset, family history of alcoholism

GAMMA HYDROXYBUTYRIC ACID (GHB)

- GABA-B agonist
- To prevent relapse and decrease in craving in patients during 3 months follow up
- Because of the risk of addiction drug should be used only under strict medical surveillance

ONDANSETRON

- 5-HT3 antagonist
- May be effective in early onset users

ANTIPSYCHOTICS

- Aripiprazole, Quetiapine, Olananzapine, Amisulpride, Flupenthixol, Haloperidol and Clozapine – only case reports which state that they improve drinking outcome
- Not recommended for general use

MANAGEMENT OF ALCOHOL DEPENDENCE

PSYCHOSOCIAL INTERVENTIONS

- Psychosocial therapies differing widely in conceptual framework, intensity, duration, and location
- Structured specific therapies have better outcome compared to less defined supportive counselling
- No particular psychotherapy has been found consistently to be better than others

GOALS:

- Enhance efficacy of Pharmacotherapy
- Achieving sustained drug free status
- Change in life style and

- Improve quality of life

MOTIVATION ENHANCEMENT THERAPY

- Maximize patient's intrinsic desire to change substance use using motivational interviewing techniques
- Empathic, non-judgemental and supportive approach to examine patient's ambivalence about changing substance use behaviours

BRIEF INTERVENTIONS

- Also used for motivation enhancement
- Consists of FRAMES: Feedback, Personal Responsibility, Advice, Menu , Empathy and Self efficacy
- Lesser time and carried out in primary health care setting, cost effective
- Motivation Enhancement Therapy (MET) / Motivation Interviewing and Brief intervention (BI) have been found to be effective - They can be given in different setup by different professionals. A brief MET of 4 sessions has been found to be as effective as or better than other therapies for alcohol dependence. The effects have been improved when combining with medications.

COGNITIVE BEHAVIOUR THERAPY

- Based on social learning theories aimed at improving self control and social skills
- Along with medications they have found to be effective in relapse prevention & decrease in alcohol use

RELAPSE PREVENTION COUNSELLING

- Uses CBT techniques to develop greater self control over alcohol use behaviours to avoid relapse
- People who have better coping strategy for internal and external stressors, learn from previous lapses and have mastery over self control measures have better outcome

BEHAVIOURAL THERAPIES

- Based on learning theories and positive reinforcements for target behaviours
- Community reinforcement approach is effective

GROUP THERAPIES

- Helps in making efficient use of therapist time
- Encourage people to discuss problems and reduction in stigma
- Group therapies involving assertive techniques, social skill training, family focussed

therapy and motivation enhancement has been shown to be effective

FAMILY THERAPY

- To address dysfunctional families and those with high expressed emotions that leads to substance abuse and plays an important role in Indian context
- Family therapies along with medication have found to be better in reduction of alcohol, relapses and this has also been found effective in Indian setup

SELF HELP GROUP APPROACH AND 12 STEP ORIENTED PROGRAMME

- 12 steps approach – steps used in Alcoholics Anonymous (AA)
- Offers emotional support and a model of abstinence for people recovering from alcohol dependence
- AA or other 12 step approaches have been found to be effective method for management but was not found to better than other treatments in reducing alcohol use and achieving abstinence

COMPARISON OF DIFFERENT THERAPIES

- Have minimal long-term difference between inpatient/residential treatment and outpatient counselling approaches
- Equivalent outcomes with both brief, non-intensive treatments and intensive treatments for moderately severe alcohol dependence

COMBINED PHARMACOLOGICAL AND NON PHARMACOLOGICAL APPROACH HAS BETTER EFFECTIVENESS

- Several well conducted studies have consistently shown that utility of pharmacological therapies can be enhanced when combined with psychosocial interventions

MANAGEMENT OF ALCOHOL DEPENDENCE IN SPECIAL POPULATIONS

PREGNANCY AND LACTATION

- Adverse effect on mother, baby and course of pregnancy
- Fetal alcohol spectrum disorder
- Typical facies, growth and mental retardation

MANAGEMENT

- Stop alcohol use
- Treat medical and psychological co-morbidities
- Monitor pregnancy closely

- Non-pharmacological treatments should be treatment of choice
- When needed drugs can be used after discussing about pros and cons and taking an informed decisions and close monitoring of the pregnancy

YOUNG AGE GROUPS

- Associated disorder: Conduct disorder, ADHD, Major Depression, Anxiety/ Bipolar disorder

MANAGEMENT

- Young people with problems of alcohol use have shown that school based interventions, family based interventions and multipronged interventions have found to effective in medium and long term
- Young children should also be assessed for psychiatric comorbidity and managed accordingly

PROBLEMATIC ALCOHOL USER

- Refers to any user who has problem with alcohol use which may be physical, psychological, social consequences etc.
- Includes hazardous use of alcohol, harmful use of alcohol and alcohol dependence
- Hazardous use: term given by WHO to pattern of substance use which carries with it a risk of harmful consequences (physical/mental/social) to the substance users or others
- Harmful use of alcohol as per ICD-10 refers to use of alcohol leading to physical and psychological harm to the individual
- 50% of Indian regular users contribute to the category of hazardous drinking

MANAGEMENT

- Screening for alcohol use and Brief Intervention decrease considerable morbidity and mortality.
- Screening for alcohol use and Brief intervention (BI) has been found to decrease alcohol use in different settings and with different person providing intervention

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Synopsis of the Clinical Practice Guidelines on Management of Opioid Use Disorders

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2015

1. INTRODUCTION

- Substance use is a complex problem having multiple medical and social ramifications.
- Opioid dependence is a chronic, relapsing disorder amenable to medical treatment.

1.1 History

- In India, Opioids have been used for centuries as medicines as well as for recreational purpose.
- In recent years, the problem of opioid use – particularly through the injecting route – has assumed an entirely new dimension in India.

1.2 Epidemiology

- Worldwide, some 12 to 21 million people use opiates (0.5-0.8%).
- In India, prevalence of opiates use range from 0.7% to 1.4% in the general adult male population. A pattern of shift from using natural opioids to newer and prescription opioids such as buprenorphine, codeine and dextropropoxyphene is apparent in the country.
- Though prevalence is low among general population, it is substantial among treatment seekers (41 to 43%).

1.3 Consequences of opioid use

- Opioid dependence imposes a significant economic burden on society.
- Opioid dependence also has an effect on productivity, due to unemployment, absenteeism, and premature mortality.
- Injecting drug use (IDU) is strongly associated with HIV, hepatitis C and other blood borne infectious diseases. In India, opioids are the drugs most commonly injected by IDUs.

Box 1: Pharmacology

- In the clinical context, opioid may be classified on the basis of their action on the opioid receptor as:
  - Opioid agonists,
  - Opioid antagonists and
  - Partial agonists
- **Opioid receptors**: μ, δ, κ and OFQ/N (ORL-1)
- **Opioids effects**: include analgesia, euphoria, respiratory depression, miosis, changes in mood, indifference to anticipated distress, drowsiness, decreased ability to concentrate, changes in endocrine and other functions regulated by the hypothalamus, and increased tone of smooth muscle in the gastrointestinal (GI) tract.

1.4 Opioid Use Disorders

- It encompasses harmful / hazardous use, dependence, intoxication, withdrawal, and psychiatric syndromes and disorders that result from substance use.

1.5 Course and outcome of opioid use disorders

- A chronic, relapsing course; around 10-40% opioid user remain abstinent in follow up.
- **Factors associated with maintaining abstinence**: Contact with treatment team, personal motivation, spirituality, family and employment.
- **Measures of treatment outcome**: drug use / abstinence, legitimate work, crime, family relationships, psychological adjustment.

2. ASSESSMENT

2.1 Clinical History

- Focus upon: mode of onset, quantity, frequency, and duration of substance use; the escalation of use over time; history of withdrawal symptoms, the motivation for use; the specific circumstances of the individual's substance use; the desired effect of the substance used; the most recent dose of each substance used; last dose of each substance used. Additionally consequences of substance use in health (physical and mental), occupational, social, financial, legal spheres of life.
- History of any prior treatment / abstinence, family and social history, Individual preferences, motivations, and barriers for treatment.

2.2 Clinical examination

- A comprehensive general medical and psychiatric examination, including mental status and physical. Assessment for intoxication and withdrawal symptoms.

2.3 Investigations

- NONE ESSENTIAL FOR THE PURPOSE OF DIAGNOSIS and planning the core treatment for opioid use disorders, but it is a good practice to document the 'baseline' status. Recommended investigations: urine screening for substances of abuse, routine hematological and biochemical tests, screening for infectious and other diseases (HIV, tuberculosis, hepatitis)

2.4 Instruments

- Screening and diagnostic.
- Instruments have high sensitivity so that they can be used for screening purpose. Instruments with high degrees of specificity confirm the diagnosis of substance use disorder. Role largely confined to research settings and not in the routine clinical care.

3. GOALS OF TREATMENT

- Abstinence from using opioids.
- Retention in treatment.
- Reduction in the frequency and severity of substance use episodes.
- Improvement in psychological, social, and adaptive functioning.
- Harm reduction: Reduction of harms associated with drug use without reduction in drug use per use.

Box 2: Concept of Harm Reduction

- Defined as '*policies, programmes and practices that aim primarily to reduce the adverse health, social and economic and legal consequences of the use of legal and illegal psychoactive drugs without necessarily reducing drug consumption*'.
- Aim of harm reduction strategies: is to keep drug users alive, well and productive until treatment works or they grow out of their drug use and can be reintegrated into society.
- Harm reduction approach is endorsed in the National policies and used for Injecting Drug Users (IDUs) to reduce risk of HIV infection through sharing and reuse of unsafe injecting equipment.
- **Strategies for harm reduction**
  - Outreach programs and peer education
  - Needle and syringe programs.
  - Drug substitution / Agonist maintenance programs

4. TREATMENT SETTINGS

4.1 Factors affecting choice of treatment setting

- Capacity and willingness to cooperate with treatment, ability for self-care, social environment, management of co-morbidity, preferences.

4.2 Types of setting

- Hospitals, Partial hospitalization programs and intensive outpatient programs, Residential treatment, Therapeutic communities, Community residential facilities, Aftercare, Outpatient settings, Prison as treatment setting, Employee assistance programs.

MOST PATIENTS CAN BE MANAGED IN OUTPATIENT CLINICS. SOME MAY REQUIRE INPATIENT SETTINGS LARGELY FOR THE TREATMENT OF ACUTE WITHDRAWAL SYMPTOMS.

5. MANAGEMENT OF OPIOID USE DISORDERS

5.1 General Principles

- Motivation Enhancement, Establishing and maintaining a therapeutic framework and alliance, Assessing safety and clinical status, Pharmacological management.

5.2 Pharmacological management

5.2.1 Managing intoxication / Overdose: (Refer to figure 1)

- **Classic triad** of severe opioid intoxication / overdose includes (i) Coma / Unconsciousness, (ii) Severely depressed respiration, and (iii) Pinpoint pupils.
- **Management**:
  - Ensuring clear airways and breathing, and other supportive measures.
  - **Naloxone** is the specific antidote (0.8mg i.v./subcutaneous initially and may require repeat administration).

5.2.2 Withdrawal Management (detoxification)

- **Criteria for determining suitability**: a relatively short history of opioid use, younger age, good motivation, good social support, no maintenance treatment program is available locally, or the patient desires to not be restricted by the requirements of agonist maintenance medication.

5.2.2.1 Agonist agents

- Treatment of choice for Withdrawal Management is an agonist medication with long duration of action.

5.2.2.1.1 Buprenorphine

- Buprenorphine sublingual tablets are strongly recommended agent in India.
- Adequate dose and duration should be guided by withdrawal status of the patient.
- Most patients stable on Buprenorphine 6 mg per day - tapered off within next 7-10 days inpatient setting.
- Outpatient setting: Dose reductions should occur gradually over a period of 10–14 days.
- The dose can be decreased in increments of 0.4 to 2 mg/day over several days. Because buprenorphine has a long duration of action, minimal withdrawal symptoms are seen during the dose reduction.

5.2.2.1.2 Methadone

- Inpatient setting: patient is stabilized on a daily methadone dose that is determined by the patient's response based on objective withdrawal sign. Once the stabilization dose is determined (usually 40–60 mg/day and sometimes less), methadone can be tapered by 5 mg/day.
- Withdrawal management using Methadone should be avoided in the outpatient settings.

5.2.2.2 Alpha-2 adrenergic agonists (Clonidine)

- Clonidine is a centrally acting á2-adrenergic antihypertensive medication which decreases the noradrenergic hyperactivity associated with opioid withdrawal.
- Reduces withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating.
- However not effective for other – more distressing – withdrawal symptoms such as pains, muscle aches, insomnia, distress, and drug craving.
- Does not produce opioid-like tolerance or dependence.
- Requires careful monitoring of side effects (particularly hypotension).

5.2.2.3 Use of other medications

- Some other medications may also reduce some of the symptoms of opioid withdrawal
- Sedative hypnotics or anxiolytics for insomnia and/or anxiety, antiemetics for nausea and vomiting, NSAIDs for muscle cramps, and antispasmodics for gastrointestinal cramping.
- Agonist is treatment of choice for detoxification.
- In cases where agonists cannot be used, clonidine treatment can be recommended, but only in the inpatient settings with careful monitoring of side effects (particularly hypotension)
- The phase of detoxification should be utilized for preparing the patients for a longer term treatment which is aimed at prevention of relapse and rehabilitation.
- Ultra rapid detoxification is not recommended owing to unnecessary expenses, risks involved and no extra benefits.

5.2.3 Long term pharmacotherapy

5.2.3.1 Agonist maintenance treatment / Opioid Substitution Treatment:

- **Criteria for determining suitability for OST**: long-duration opioid users with severe dependence, with high risk of relapse and for those who are willing to comply with the requirements.
- **The specific objectives of agonist maintenance treatment are**
  - to reduce illegal and other harmful drug use,
  - improve the patient's health and well-being,
  - reduce the risk of transmission of blood-borne infectious diseases,
  - reduce death and other medical morbidities associated with drug use,

- reduce crime committed by patients,
- facilitate an improvement in the patient's occupational and social functioning,
- improve the economic status of patients and their families

5.2.3.2 Methadone

5.2.3.2.1 Introduction

- Methadone is a synthetic narcotic analgesic compound, a typical mreceptor agonist and produces euphoria, analgesia, and other typical morphine-like effects.
- Properties of methadone makes very useful maintenance agent:
  - its reliable absorption and bioavailability after oral administration
  - The delay of peak plasma levels until 2 to 6 hours after ingestion.
  - The binding to tissues that creates a large reservoir of methadone in the body contributing to long duration of action (and hence requires administration just once a day).

5.2.3.2.2 Treatment outcome

- Methadone treatment reduces mortality, and decreases illicit drug use, criminal activity, Reduces HIV infection healthcare cost, unemployment and accidental overdoses among opioid dependent individuals.
- Socially productive behaviour as measured by employment, schooling or home making also improve with length of time in treatment.
- Overall methadone maintenance is cost-beneficial.

5.2.3.2.3 Dosing and Duration

- Minimum effective dose found in the western studies is 60 mg / day. A dose below 50 mg enhances the risk of patient drop-out. Higher doses on the other hand lead to longer retention and greater reduction in illicit opioid use.
- In general longer the duration of treatment and retention in treatment, better the outcome.
- **Preparation of methadone**: usual formulations are 5mg/ml of liquid and 5 mg / 10 mg / 20 mg tablets.
- **Induction**: administering lower doses in the beginning (10 to 20 mg per day on first three days) and subsequent dose increments of about 5 mg every third day (owing to accumulation of methadone in the body).
- Stabilization dose of methadone for Indian patients between 40 and 80 mg per day.

- Methadone offers the advantage of being a pure agonist and consequently better subjective experience for patients.
- The process of **slow induction of dose of methadone coupled with its relatively higher risk of overdose poses a challenge**.

5.2.3.2.4 Adverse effects

- **Common side effects**: sedation, constipation, sweating, nausea, dizziness, and hypotension.
- Methadone in moderate to high doses can impair cardiac conduction, prolong the QT interval, and, in rare instances, lead to torsades de pointes.

Box 3: The optimum dose of Methadone (or any other agonist for maintenance treatment) is achieved when:

- the patient evidences **no withdrawal** signs or symptoms throughout the 24-hour dosing period,
- the patient reports an **absence of craving** for opioids,
- adequate cross tolerance is obtained such that the patient experiences little or **no reinforcement** from use of other opioids.

5.2.3.3 Buprenorphine

5.2.3.3.1 Introduction

- Buprenorphine is a partial μagonist and k antagonist, long acting, highly lipophilic opiate and 25-50 times more potent than morphine (in analgesic action).
- Bioavailability: oral route - 15%; sublingual – 50-60%.
- Elimination half-life: I.V. Buprenorphine is 3.21 hours and for sublingual Buprenorphine is 27.2 hours.
- Should be the **preferred agent due to safety profile, evidence-base and experience in India**

5.2.3.3.2 Treatment outcome

- Cochrane meta-analysis: Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but is not more effective than methadone at adequate doses.
- Buprenorphine treatment reduces mortality, and decreases illicit drug use, blood borne infections, criminal activity, healthcare cost, unemployment among opioid dependent individuals.

5.2.3.3.3 Dosing

- Optimal maintenance dose among Indian patients is 6-10 mg per day.
- Alternate day dosing and twice weekly dosing are also feasible options
- Induction: Buprenorphine induction involves administering the first dose in the relative opioid-free state (i.e. when patient is in mild withdrawals) and observation of the patient for 2 hours. Repeat if withdrawal symptoms persist.
- The first day's dose is usually 4-6 mg.
- Dose can be titrated upwards or downward based on clinical parameters.
- **Optimum dose**: no withdrawals, no craving, and no reinforcement on taking illicit opioids.
- Maintenance treatment should be supervised and observed to prevent diversion and abuse.
- Buprenorphine-naloxone combination is a relatively safer option and can be dispensed as 'take-home' treatment.

5.2.3.3.4 Adverse effects

- No specific adverse effects. Most of the observed effects include effects of either a lower dose (Generalized weakness, muscle aches, yawning, lacrimation, craving, anxiety, sleeplessness) or a higher dose (sense of high, relief from pain, constipation).
- Buprenorphine as maintenance treatment: Indian Experience
- India has vast clinical and research experience in using buprenorphine.
- Improvements have been observed in relation to needle sharing, unsafe sex, incidents of detention, and a range of quality of life measures.

5.2.3.4 Buprenorphine- naloxone combination

5.2.3.4.1 Introduction

- Combination of sublingual buprenorphine-naloxone addresses the problem of diversion: have a minimum risk of being injected.
- Rationale: Naloxone has poor sublingual bioavailability. By sublingual route the effect of Buprenorphine is predominant. Injected tablet will result in a predominant naloxone effect.
- Ratio of Buprenorphine and Naloxone: 4:1

5.2.3.4.2 Treatment outcome

- Direct buprenorphine/naloxone induction is a safe and effective strategy for maintenance treatment of opioid dependence; buprenorphine/naloxone combination is less likely to be diverted and injected than buprenorphine alone.

5.2.3.4.3 Dosing

- Buprenorphine-Naloxone combination is available in 2 mg/0.5 mg and 8 mg/2 mg dosages.

5.2.3.5 LAAM (levo-alpha-acetyl-methadol)

- LAAM, a mopioid agonist is a synthetic congener of methadone with the half-life of 48-96 hours
- Usual starting dose is 20-40 mg/day with supplemental methadone 5-20 mg/day and weekend dose of 80-90 mg.
- Due to Prolongation of the QT interval it is recommended that LAAM be reserved for use as a second-line agent for the treatment of opioid dependence.
- Not available in India, as yet.

5.2.3.6 Slow release oral morphine (SROM)

- Slow release oral morphine (SROM), a natural derivative of opium and a mu receptor agonist. has the advantage of single dosage, decreased sleep disturbance and increased medication compliance.
- SROM has been used as a maintenance agent in methadone intolerant individuals.
- Usual dose: 60 mg/day, some patient need dose up to 180mg -240mg.
- Indian Experience: evidence of decrease in heroin consumption, improved functioning and a decrease in illegal activities.

5.2.3.7 OST: General issues

- Outcome of OST is determined by (i) optimum dose, (ii) adequate duration of treatment and (iii) retention in treatment.
- Switching to use of another substance such as alcohol or cannabis (substitute dependence) remains a possibility in opioid dependent patients undergoing long-term treatment.
- Psychosocial treatment is an essential part of package of agonist maintenance treatment
- All agonist medications are liable to be diverted and abused. Thus, observing the operational procedures is critically important for service providers.

5.2.3.8 Antagonist treatment:

- Criteria for suitability of antagonist treatment: relatively shorter duration of opioid use, less severe dependence, high motivation, better social and occupational status, and good social support.

5.2.3.9. Naltrexone (Refer to figure No.4)

5.2.3.9.1 Introduction

- Naltrexone is a non-specific opiate antagonist that binds to all three opiate receptors sites.
- The plasma half-life of naltrexone is 4 hours, but the duration of opioid receptor blockade is much higher.

5.2.3.9.2 Treatment outcome

- Patients involved in meaningful relationships, employed full time, or attending school and living with family members are most likely to benefit from naltrexone treatment.

5.2.3.9.3 Dosing

- **Available in 50 mg tablet, daily dose is 50 mg per day.**
- Induction with naltrexone requires a totally opioid free state
- Three days of confirmed abstinence from short acting opioids, determined clinically. (Optional: Naloxone challenge test for confirming abstinence)
- Initiated in the dose of 25mg and if no withdrawals occur after 1 hour then another dose of 25 mg is given.
- Maintenance dose of oral naltrexone is 50 mg per day. Owing to its long duration of action, it can also be administered, 100 mg every alternate day or 150 mg every third day.
- Involving family members for supervising naltrexone administration is a good practice.
- Liver function tests should be monitored at baseline and during the course of therapy (every three months).
- Confirming abstinence- from family members, urine screening.

5.2.3.9.4 Adverse effects

- Gastrointestinal distress (nausea, vomiting, diarrhoea, and abdominal pain), anxiety, restlessness, dysphoria, mild hypertension, headache and insomnia.
- Hepatotoxicity at high doses

Fig.1 Algorithm for management of Opioid dependence & Opioid intoxication

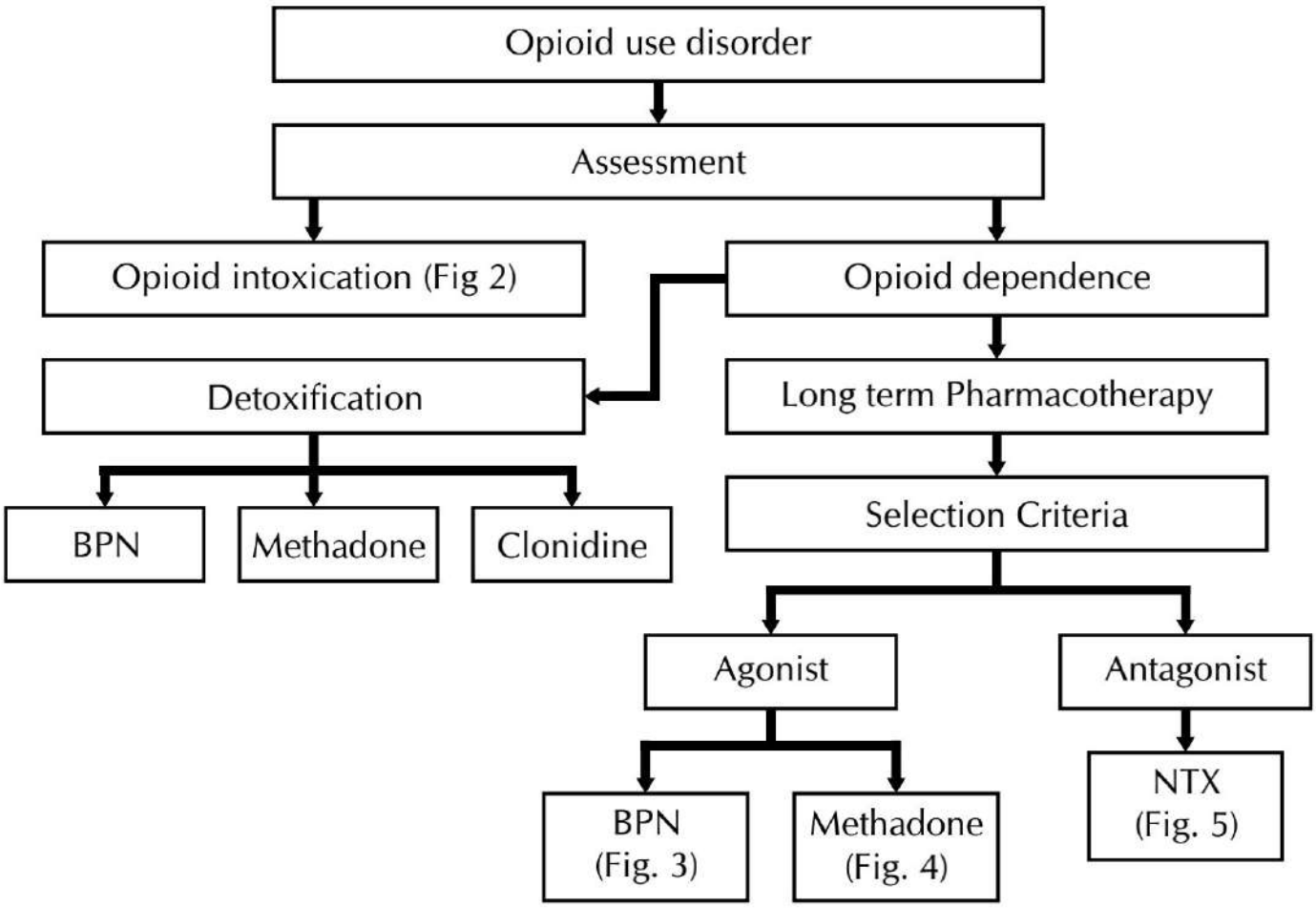
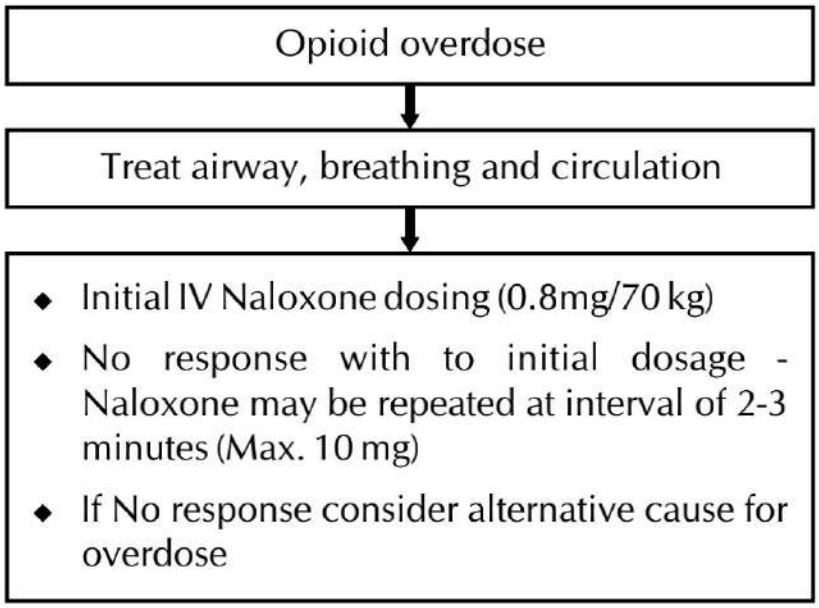


Fig. 2 Management of Opioid Overdose



Box 4 : Naloxone testing for residual dependence (Naloxone Challenge test)

- A positive test indicative of residual opioids would consist of typical signs and symptoms of opiate withdrawal. These include yawning, abdominal cramps, irritability, anxiety, chills etc.

Intravenous:

- Inject 0.2 mg naloxone.
- Observe for 30 seconds for signs or symptoms of withdrawal.
- If no evidence of withdrawal, inject 0.6 mg of naloxone.
- Observe for an additional 20 minutes.

Subcutaneous:

- Administer 0.8 mg naloxone.
- Observe for 20 minutes for signs or symptoms of withdrawal.

5.3 Psychosocial Interventions

- Task of therapist to tailor them according to the needs of particular patient.
- Essential psycho social interventions: Motivation Enhancement / Motivation Interview, Psycho-education and Relapse Prevention.

Box 5 : Special Population Groups

- **Women in pregnancy and lactation**: Agonist maintenance treatment is the preferred treatment option during pregnancy and lactation.
- **Adolescents and minors**: most guidelines discourage agonist maintenance treatment; there is growing evidence that this treatment approach can be effective and safe for adolescents as well.
- **HIV positive individuals**: agonist maintenance treatment with methadone or Buprenorphine improve outcome of ART.
- **Prison inmates**: Agonist maintenance treatment has been found to be effective.
- The help-seeking behaviour of **chronic pain patients** can be easily misconstrued as addiction.

Fig. 3 Treatment algorithm for Buprenorphine maintenance

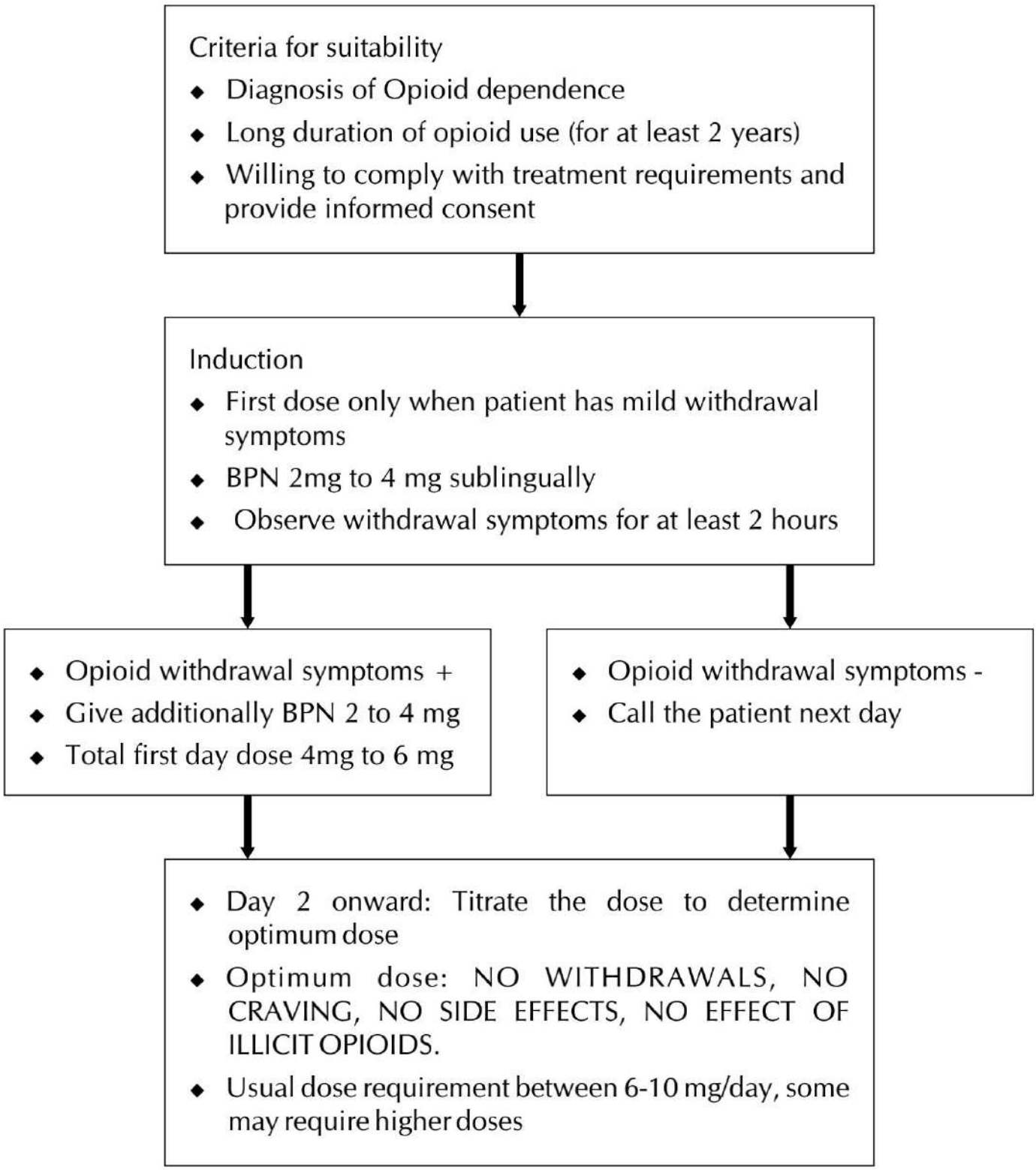


Fig. 4 Treatment algorithm for Methadone maintenance

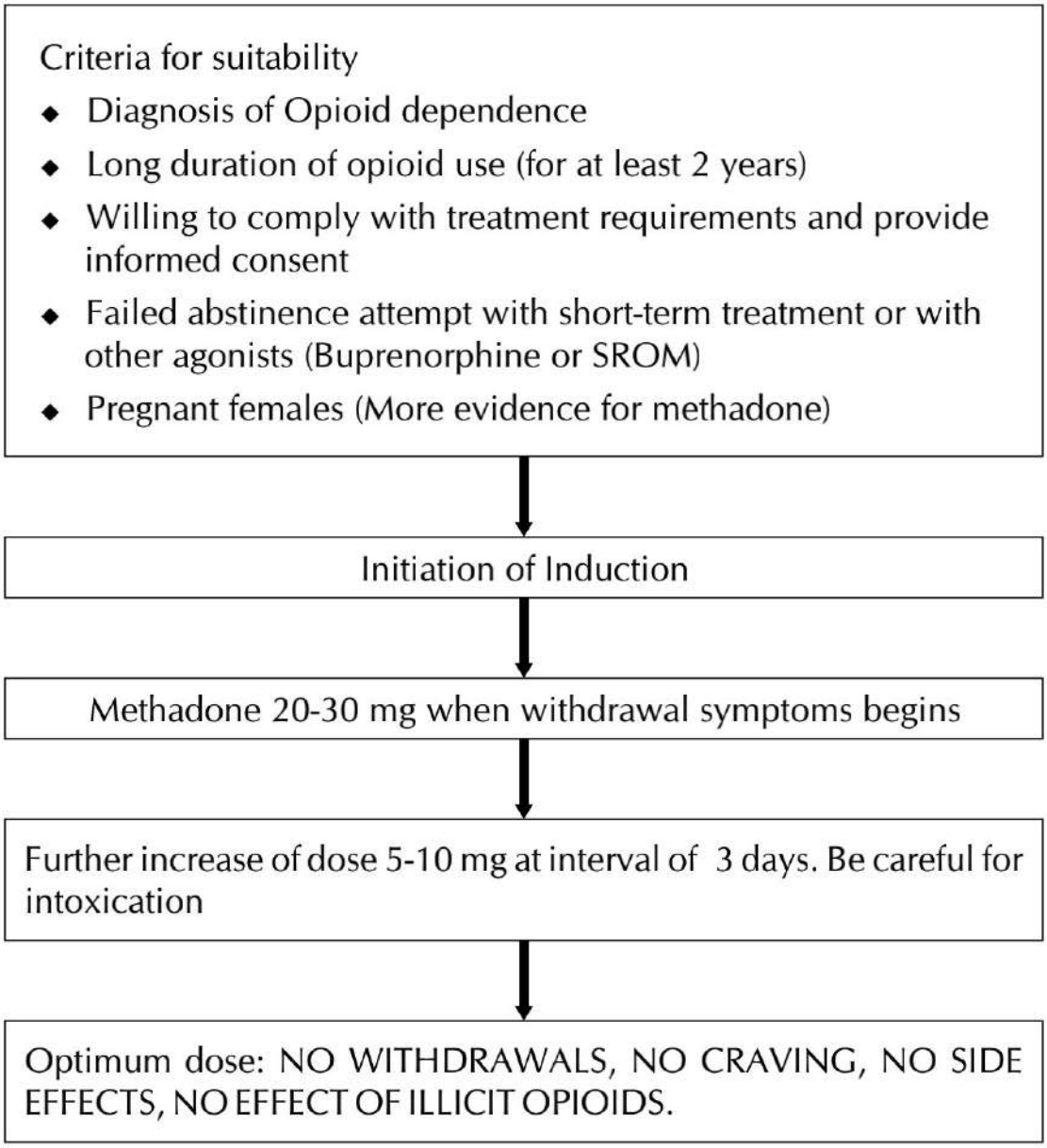
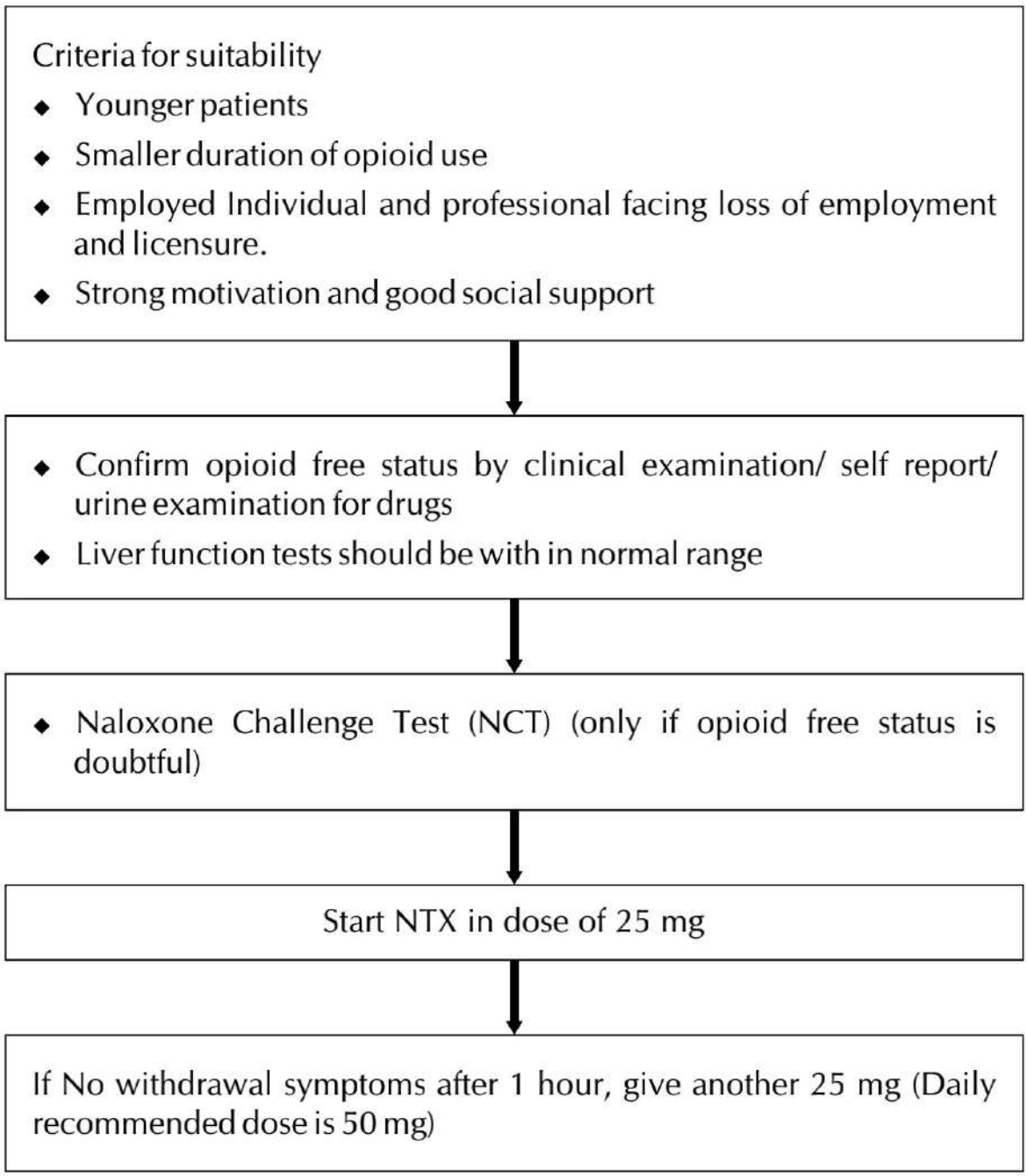


Fig 5 Treatment algorithm for Naltrexone maintenance



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Synopsis of the Clinical Practice Guidelines on Management of Cannabis Use Disorders

Shubh Mohan Singh
Abhishek Ghosh
On behalf of the IPS-SS-SUD

2015

1. CANNABIS USE DISORDERS

Cannabis and cannabis use disorders

- Source of cannabis: various parts of the female Cannabis plant
- Major psychoactive compound: Delta-9- tetrahydrocannabinol (THC)
- Concentration of THC varies across different parts of the plants: leaves ('Bhang') contain 1-3%, female flowering top ('Ganja') has a concentration of 3-5% and resinous extract ('Charas') contains 5-10% of THC
- Cannabis preparations can be smoked or ingested orally
- When smoked, effects usually last for 3-4 hours; effects may last longer up to 48-72 hours when ingested orally
- Nature and severity of cannabis use disorders depend on: the amount, frequency, duration, form and route of administration of cannabis; individual susceptibility
- Cannabis use disorders:
  - Cannabis intoxication
  - Cannabis withdrawal syndrome
  - Cannabis dependence
  - Cannabis induced psychiatric disorders
- Association between cannabis use and psychosis is well known

Some caveats to consider

- Clinical manifestations of cannabis use disorders especially cannabis intoxication and withdrawal are mostly self-limiting and nonspecific
- Treatment of these conditions is symptom directed
- Level of evidence base for proposed guidelines for the treatment of cannabis intoxication and withdrawal are speculative; therefore there is no 'recommended' treatment for these disorders
- Drug treatment for the maintenance of cannabis abstinence is also preliminary and they fall in the category of either 'suggested' or 'might be considered' level of evidence
- Only psychosocial interventions have reasonable evidence base and are recommended for the treatment of cannabis dependence
- The proposed guideline is based on the extrapolated evidence obtained from developed countries

2. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

Treatment setting

Owing to the transitory and self-limiting nature of most cannabis use disorders, Outpatient treatment is sufficient for most patients

Inpatient treatment is warranted for those who develop:

- Severe anxiety or paranoia with cannabis intoxication
- Cannabis induced psychosis that is unmanageable in the outpatient setting
- Serious comorbid psychiatric disorders (like Schizophrenia)which merits hospital admission
- Comorbid substance use disorder with an independent indication for inpatient treatment

General assessment

- Clinical history: Form, relative potency and the amount of the cannabis consumed, route of administration, duration and frequency of intake, last intake, history of previous adverse reactions
- Determination of the diagnosis of cannabis use disorders: based on the nature and severity of presenting complaints (cannabis intoxication/ withdrawal)
- Assessment for co-morbid substance use disorders/psychiatric disorders/general medical or neurological conditions
- Laboratory tests: urine qualitative immunoassay for the presence of cannabinoids in urine; not diagnostic of any disorders but indicates recent use of cannabis

3. MANAGEMENT OF SPECIFIC SYNDROMES RELATED TO CANNABIS USE

Treatment of cannabis intoxication

- Diagnosis is likely when:
  There is a close temporal relation with some form of cannabis intake
  and
  Presence of symptoms like conjunctival injection, increased appetite, dry mouth, tachycardia, anxiety, perceptual disturbances
- Symptoms are mostly transient, mild and self-limiting
- Reassurance and supportive care are usually sufficient
- Pharmacological treatment is necessary in patients with:
  - Severe and distressing anxiety symptoms
  - Unmanageable and disruptive psychotic symptoms
- 'Suggested' treatment: Benzodiazepine (preferably short acting) and antipsychotics (preferably second generation) are drugs of choice for symptomatic relief
- 'Might be considered' treatment: Propranolol 60-120 mg/day
- Duration of treatment: 1-2 days

Treatment of cannabis withdrawal syndrome

- Diagnosis is likely when:
  Following cessation of heavy and prolonged cannabis use
  and
  Presence of symptoms like irritability, anger, depressed mood, restlessness, insomnia, tremors, decreased appetite
- Symptoms are mostly transient, mild and self-limiting
- Reassurance and supportive care are usually sufficient
- Pharmacological treatment is necessary in patients with severe and distressing withdrawal symptoms
- 'Suggested' treatment: Benzodiazepines, based on clinical experience
- 'Might be considered' treatment: Dronabinol (20-60 mg/day), Baclofen 40 mg/day
- Duration of treatment: around 7 days

Treatment of cannabis dependence

- Maintaining complete abstinence is the goal of treatment
- Psychosocial interventions are the mainstay of treatment
- Evidence for drug treatment is still preliminary
- Pharmacological treatment:
  - Should ideally be used in combination with psychosocial interventions
  - 'Suggested' treatment: Buspirone (up to 60 mg/day)
  - 'Might be considered' treatment: Baclofen (40-60 mg/day), Fluoxetine (20-40 mg/day), N-acetyl-cysteine (1200 mg/day), Entacapone (200 mg/day)
  - Duration of treatment: 3-12 months
- Psychosocial interventions: all are 'recommended' for the treatment of cannabis dependence
  - Motivation enhancement therapy (MET)
  - Cognitive behavioral therapy (CBT)
  - Combined MET & CBT
  - Contingency management (CM) in conjunction with either MET/CBT
  - Family Systems therapy
  - Number of sessions for psychosocial intervention: 2-14 depending on the type and setting of psychosocial intervention
  - Frequency of sessions: once in a week to once in 2 weeks
  - Either individual or group sessions

Psychosocial interventions for cannabis dependence

Motivation enhancement therapy (MET)

- Non-directive
- Resolve ambivalence for quitting cannabis and strengthen the motivation to change
- Individual session duration:45-60 minutes session
- Number of sessions: 1-4 sessions
- Tested across various age groups and treatment settings

Cognitive behavior therapy (CBT)

- Teaching of coping skills to quit cannabis
- Problem solving skill training
- Life style management
- Conducted through interactive exercises, practical assignments and role playing
- Individual session duration:45-60 minutes
- Number of sessions: 6-14
- Has synergistic effect when combined with MET

Contingency management (CM)

- Reinforcing or punishing consequences in order to achieve therapeutic goal
- Primarily aims at abstinence reinforcement
- Also intends to facilitate retention in treatment, adherence to medications or therapy sessions
- Reinforcement is mostly through payment of token vouchers
- Should always be used in conjunction with other forms of psychosocial interventions

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Synopsis of the Clinical Practice Guidelines on Management of Sedative-Hypnotics Use Disorders

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2015

1. INTRODUCTION

- Sedatives and hypnotics are used to treat a wide variety of disorders, including sleep disorders, anxiety disorders, epilepsy, manic episodes, depression, symptoms of alcohol withdrawal, and rapid tranquilisation
- Medications included in the category of sedatives and hypnotics are of 3 types: barbiturates, benzodiazepines and others which include the "Z-drugs" (zolpidem, zopiclone, zaleplon)

APPROXIMATE THERAPEUTIC EQUIVALENT DOSES OF BENZODIAZEPINES

Benzodiazepines	Common therapeutic use	Approximately equivalent dosage (mg)	Elimination half life (active metabolite) in hrs
Alprazolam	Antianxiety	0.5	6-12
Chlordiazepoxide	Antianxiety	25	5-30 (36-200)
Clonazepam	Anticonvulsant	0.5	18-50
Diazepam	Antianxiety	10	20-100 (36-200)
Flunitrazepam	Hypnotic	1	18-26 (36-200)
Flurazepam	Hypnotic	15-30	40-250
Loprazolam	Antianxiety	1	6-12
Lorazepam	Antianxiety	1	10-20
Lormetazepam	Hypnotic	1	10-12
Nitrazepam	Hypnotic	10	15-38
Oxazepam	Antianxiety	20	4-15
Temazepam	Hypnotic	20	8-22

2. MANAGEMENT OF BENZODIAZEPINE USE DISORDERS

2.1 Management Of Benzodiazepine Intoxication

- The benzodiazepines in contrast to the barbiturates and the barbiturate like substances have a large margin of safety when taken in overdoses
- The ratio of lethal to effective doses is approximately 200 to 1 or higher
- Flurazepam, had the highest fatal toxicity index of any benzodiazepine (15.0), followed by temazepam (11.9), vs. benzodiazepines overall (5.9) taken with or without alcohol

STEPS FOR MANAGEMENT OF BENZODIAZEPINE INTOXICATION

Gastric lavage	**Not recommended** but **might be considered** if the presence of a lethal co-ingestant is suspected and the patient presents within 1 hour of ingestion
Assisted ventilation	**Might be considered** in case of respiratory depression
Flumazenil	Flumazenil is a competitive benzodiazepine receptor antagonist. Barring mixed overdoses and benzodiazepine dependent patients, use of Flumazenil **is suggested** in acute intoxication with benzodiazepines Dose: Intravenous injection of 0.1 mg to 0.3 mg over a period of 30 seconds is the most effective and safe mode to elicit optimal arousal, but additional boluses are usually required until consciousness is adequately established or a predetermined maximal dose (2 to 5 mg) is reached

2.2 Management Of Benzodiazepine Dependence

Three overlapping types of benzodiazepine dependent populations exist:

- **Therapeutic dose dependence**: The 'therapeutic dose' users include patients who have been prescribed benzodiazepines usually on a long-term basis for a disorder such as anxiety or insomnia but who do not abuse their prescription
- **Prescribed high-dose dependence**: A minority of patients who start on prescribed benzodiazepines escalate their dosage excessively.
- **Recreational benzodiazepine use**: These are the patients who misuse their prescription and/or use illicit benzodiazepines, often in high doses. This may include benzodiazepines purchased via the internet

2.2.1 Management of benzodiazepine dependence in 'therapeutic dose' users

- A stepped approach **might be considered**, moving through minimal interventions to gradual dose reduction and then additional therapies aimed at specific symptoms

MANAGEMENT OF BENZODIAZEPINE DEPENDENCE IN 'THERAPEUTIC DOSE' USERS

Minimal interventions such as advisory letters or General Practitioner advice	**Recommended** in early/mild dependence
Gradual dose reduction of prescribed benzodiazepine	**Recommended** where dependence is established
Switching to a long half-life benzodiazepine from a short half-life benzodiazepine before gradual taper	**Might be considered** for patients having problematic withdrawal symptoms on reduction
Additional psychological therapies e.g. group Cognitive Behavior Therapy (CBT)	**Suggested** for patients with insomnia and panic disorder
Additional pharmacotherapy e.g. antidepressants, melatonin, valproate, and flumazenil	**Might be considered** on an individual basis

2.2.2 Management of benzodiazepine dependence in high-dose and/or illicit drug users

- Little evidence to guide practitioners in the management of this often difficult-to-treat population
- Patients should be assessed to determine why they are using benzodiazepines
- The presence of alcohol or other illicit drug abuse or dependence should be determined
- Existing evidence do not support maintenance prescription of benzodiazepines in illicit drug users, although it may reduce illicit benzodiazepine use in some patients
- Reduction schedules should be negotiated at the outset and doses greater than 30 mg diazepam equivalent per day should rarely be prescribed
- In high-dose users, reducing to a 'therapeutic' benzodiazepine dose level **is recommended**, because of the high relapse or drop-out rates with detoxification
- Carbamazepine **might be considered** instead of benzodiazepines to control withdrawal symptoms

WITHDRAWAL FROM HIGH DOSE (6mg) ALPRAZOLAM WITH DIAZEPAM SUBSTITUTION (6mg alprazolam is approximately equivalent to 120mg diazepam)

	Morning	Midday/Afternoon	Evening/Night	Daily Diazepam Equivalent
Starting dosage	alprazolam 2mg	alprazolam 2mg	alprazolam 2mg	120mg
Stage 1 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1.5mg diazepam 10mg	120mg
Stage 2 (one week)	alprazolam 2mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 3 (one week)	alprazolam 1.5mg diazepam 10mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 4 (one week)	alprazolam 1mg diazepam 20mg	alprazolam 2mg	alprazolam 1mg diazepam 20mg	120mg
Stage 5 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 1mg diazepam 20mg	110mg
Stage 6 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	alprazolam 0.5mg diazepam 20mg	100mg
Stage 7 (1-2 weeks)	alprazolam 1mg diazepam 20mg	alprazolam 1mg diazepam 10mg	Stop alprazolam diazepam 20mg	90mg
Stage 8 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 1mg diazepam 10mg	diazepam 20mg	80mg
Stage 9 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	alprazolam 0.5mg diazepam 10mg	diazepam 20mg	80mg
Stage 10 (1-2 weeks)	alprazolam 0.5mg diazepam 20mg	Stop alprazolam diazepam 10mg	diazepam 20mg	60mg
Stage 11 (1-2 weeks)	Stop alprazolam diazepam 20mg	diazepam 10mg	diazepam 20mg	50mg
Stage 12 (1-2 weeks)	diazepam 25mg	Stop midday dose; divert 5mg each to morning and night doses	diazepam 25mg	50mg
Stage 13 (1-2 weeks)	diazepam 20mg	–	diazepam 25mg	45mg
Stage 14 (1-2 weeks)	diazepam 20mg	–	diazepam 20mg	40mg

[Courtesy - The Ashton Manual: Slow withdrawal schedules]

2.3 Management of Benzodiazepine Withdrawal State

- Long term use of benzodiazepines or other sedative hypnotics at dosage above the therapeutic dose range produces physical dependence and all drugs have similar withdrawal symptoms that may be severe and life threatening
- Therapeutic doses of benzodiazepines taken daily for months to years may also produce physiological dependence and consequently withdrawal

CHARACTERISTICS OF SYNDROMES RELATED TO BENZODIAZEPINE WITHDRAWAL

Syndrome	Signs and symptoms	Time course	Response to reinstitution of benzodiazepine
High-dose withdrawal	Anxiety, insomnia, nightmares, major motor seizures, psychosis, hyper pyrexia, death	Begins 1 -2 days after a short acting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Symptom rebound	Same symptoms that were present before treatment	Begins 1 -2 days after a short acting benzodiazepine is stopped; 3-8 days after a long-acting benzodiazepine is stopped; lasts for 7-17 days	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Protracted, low dose withdrawal	Anxiety, agitation, tachycardia, palpitations, anorexia, blurred vision, muscle spasms, psychosis, increased sensitivity to sounds and light, paresthesia	Signs and symptoms emerge 1 -7 days after a benzodiazepine is reduced to below the usual therapeutic dose	Signs and symptoms reverse 2-6 hours after a hypnotic dose of a benzodiazepine
Symptom reemergence	Recurrence of the same symptoms that were present before taking a benzodiazepine (e.g., anxiety, insomnia)	Symptoms emerge when benzodiazepine is stopped and continue unabated with time	Signs and symptoms reverse 2-6 hours after usual therapeutic dose of a benzodiazepine

- Benzodiazepine withdrawal can be treated by gradually decreasing the dosage of the agent of dependence, substituting the short acting benzodiazepine with a long acting one (e.g. diazepam or chlordiazepoxide), or with Phenobarbital substitution – a three day fixed-dose phenobarbital taper for benzodiazepine dependence was found to be safe and effective where no fall, seizures or injuries were reported and hence **might be considered**
- Flumazenil **might be considered** in the treatment of benzodiazepine withdrawal
- Valproate and carbamazepine **might be considered** in the management of benzodiazepine withdrawal seizure

2.4 Management of Benzodiazpine Dependence in Special Population

2.4.1 Pregnancy and lactation

- Benzodiazepines and metabolites freely cross the placenta and accumulate in fetal circulation.
- It is advisable to avoid use in the first trimester because of risks of teratogenicity (association with incidence of cleft palate)
- High doses or prolonged use by the mother in the third trimester may precipitate fetal benzodiazepine syndrome including floppy infant syndrome, impaired temperature regulation and withdrawal symptoms in the newborn
- Benzodiazepines are excreted in breast milk in levels sufficient to produce effects in the newborn, including sedation, lethargy, and poor temperature regulation

POINTS TO REMEMBER

Diazepam	Safe during pregnancy but not during lactation because it can cause lethargy, sedation, and weight loss in infants
Chlordiazepoxide	Use during pregnancy and lactation seems to be safe
Alprazolam	Avoid during pregnancy and lactation
Benzodiazepine as monotherapy might be considered at the lowest effective dosage for the shortest possible duration during pregnancy and lactation	

2.4.2 Older adults

- Benzodiazepine use has been associated with increased risk of falls, cognitive decline, fractures, and mortality in older adults
- It is **recommended** that therapeutic dose benzodiazepine users should be

offered minimal interventions or graded discontinuation along with psychological interventions depending on the clinical picture

2.4.3 Children and adolescents

- In children maintenance prescribing is not recommended and detoxification with diazepam **might be considered**

3. MANAGEMENT OF BARBITURATE USE DISORDERS

- During 1930s and 1940s medical use of the barbiturate derivatives grew dramatically as a hypnotic worldwide extending its arms as an anticonvulsant and anesthetic agent.
- Misuse of barbiturates and fatal overdoses became widespread globally for its strong dependent potential and narrow therapeutic window with therapeutic to lethal dose ratio varies from 1:3 to 1:30 (average 1:10), whereas approximately 1:200 for benzodiazepines.
- Therapeutic use and misuse of barbiturates began to decline with the discovery of chlordiazepoxide after 1960 and because of greater supply of another 'downer' drug, heroin by mid 1980.
- Data regarding management of barbiturate overdose/intoxication, dependence and withdrawal state are sparse. Data are mostly in the form of retrospective chart review, comparative studies, case reports and case series.

COMMONLY USED BARBITURATES

Barbiturates compounds	Route of administration	Elimination half life (in hours)	Withdrawal equivalency to 30 mg of Phenobarbital	Common therapeutic use
Amobarbital	IM, IV	10-40 (short acting)	100	Insomnia, preoperative sedation, emergency management of seizures
Butabarbital	Oral	35-50 (short acting)	100	Insomnia, preoperative sedation
Butalbital	Oral	35-88 (medium acting)	100	Marketed in combination with analgesics
Mephobarbital	Oral	10-70 (long acting)	NA	Seizure disorders, daytime sedation

Barbiturates compounds	Route of administration	Elimination half life (in hours)	Withdrawal equivalency to 30 mg of Phenobarbital	Common therapeutic use
Methohexital	IV	3-5 (ultra-short acting)	NA	Induction and maintenance of anesthesia
Pentobarbital	Oral, IM, IV, Rectal	15-50 (short acting)	100	Insomnia, preoperative sedation, emergency management of seizures
Phenobarbital	Oral, IM, IV	80-120 (long acting)	30	Seizure disorders, status epilepticus, daytime sedation
Secobarbital	Oral	15-40 (short acting)	100	Insomnia, preoperative sedation
Thiopental	IV	8 -10 (ultra-short acting)	NA	Induction and maintenance of anesthesia, preoperative sedation, emergency management of seizures

Pattern and recent trends of barbiturate abuse

- Individuals with emotional inadequacy, comorbid psychiatric illness, personality disorders or psycho-social maladjustment are at risk of barbiturate dependence
- Analgesics (e.g. Fiorinal, Sedapap etc.) marketed in combination with barbiturate are source of iatrogenic dependence
- Used in "mixed addiction" to counteract the troublesome effects of the primary substances (e.g. alcohol, heroin, methamphetamine, cocaine etc.)
- Short acting intravenous barbiturates (e.g. secobarbital, pentobarbital) are common drugs of abuse because of the immediate 'high' they produce
- Purchasing online is now a common trend

CLINICAL FEATURES

Barbiturate intoxication / overdose	Sign of CNS depression (e.g. stages of coma with flabby body parts), cardiovascular collapse (e.g. shallow and failing respirations, fall of blood pressure), renal shutdown and bullous eruptions Exhibition of 'automatism' phenomenon may leads to fatal overdose
Barbiturate abuse / dependence	**Neurological symptoms**: fatigue, dizziness, lightheadedness, lethargy, sluggishness, nystagmus, diplopia, strabismus, ataxic gait, hypotonia, diminished superficial reflexes, incoordination and positive Romberg's sign **Behavioural symptoms**: difficulty in thinking, poor memory, slowness in speech and comprehension, faulty judgment, hostility, argumentativeness, moroseness, paranoid ideas, disinhibition of sexual and aggressive impulses and suicidal ideation
Barbiturate withdrawal	Uneasiness, postural hypotension, dizziness, anorexia, vomiting, anxiety, insomnia, muscle weakness and twitching, coarse tremor, myoclonic jerks, EEG changes

3.1 Management of Barbiturate Intoxication

- No specific antidote. Use of analeptics or CNS stimulants should be avoided
- Patients with barbiturate intoxication should be hospitalized immediately with monitoring of vitals and CNS signs
- Airway, breathing and circulation (ABC) must be maintained. Use of intravenous fluid and vasopressor may be helpful to maintain vitals
- Routine gastric lavage with activated charcoal and forced alkaline diuresis with mannitol and sodium bicarbonate is **recommended** for all patients
- Hemodialysis and hemoperfusion is helpful for both long and short acting agents

3.2 Management of Barbiturate Dependence

- Decide treatment setting – inpatient or outpatient

INPATIENT MANAGEMENT IS INDICATED FOR:
- Patients taking more than 0.4 g/d of secobarbital or an equivalent dose for > 90 days or 0.6 g/d or an equivalent dose for > 30 days - Had withdrawal seizures or delirium - Phenobarbital loading has been planned - Using several drugs including opioids - Uncontrolled use - Failed outpatient treatment - With active medical complications - With serious psychiatric morbidity - Poor social support - Willingness to undergo detoxification in hospital

3.2.1 Pharmacological intervention: There are three basic strategies to treat physical dependence of barbiturates

<table>
<tr><th colspan="3">Pharmacological strategies for barbiturate dependence</th></tr>
<tr><td colspan="3">STRATEGY 1: Decrease the dose of barbiturate gradually; appropriate for dependence with low dose and long-acting agents</td></tr>
<tr><td colspan="3">STRATEGY 2: Substitute long-acting one for the existing barbiturate of use and then gradually withdraw the long-acting agent</td></tr>
<tr><th>STRATEGY 2: METHOD 1</th><th>STRATEGY 2: METHOD 2</th><th>STRATEGY 2: METHOD 3</th></tr>
<tr><td>Assess the level of tolerance</td><td rowspan="2">Calculate the estimated dose of phenobarbital or equivalent on the basis of patient's reporting</td><td rowspan="2">Titration of a loading dose of phenobarbital hourly till signs of mild intoxication starts or withdrawal symptoms disappears</td></tr>
<tr><td>Let the signs of barbiturate intoxication to go (if present) and withdrawal symptoms just to start</td></tr>
<tr><td>Start an intermediate or long acting barbiturate to stabilize the withdrawal symptoms</td><td rowspan="2">Continue the estimated dose for next 2-3 days then taper off (dose reduction of 30-60 mg of phenobarbitone or equivalent in every 2-3 days)</td><td rowspan="2">Monitor clinical signs of intoxications and/or blood concentration of phenobarbital</td></tr>
<tr><td>Continue the stabilized dose for next 2-3 days then taper off (around 10% daily dose reduction)</td></tr>
<tr><td colspan="3">STRATEGY 3: Substitution with an anticonvulsant, appropriate for comorbid seizure disorder</td></tr>
</table>

3.2.2 Psychological intervention

- In uncomplicated withdrawal, during and after detoxification with pharmacological treatment, cognitive restructuring, implementation of adaptive coping strategies, systematic desensitization, problem solving, individually or in groups **might be considered**.

4. MANAGEMENT OF Z-GROUP AND OTHER NEWER SEDATIVE-HYPNOTIC DRUGS USE DISORDERS

Z-GROUP AND OTHER NEWER SEDATIVE-HYPNOTIC DRUGS

Active ingredient	International/ National Brands	Initial doses		Half-life (hrs)
		Adults	Older adults	
Zolpidem (Extended release)	Ambient, Stilnoct, Sove-IT	10 (12.5) mg	5 (6.25) mg	2.2 (2.8)
Zaleplon	Sonata	10 mg	5 mg	1
Zopiclone	Imovane	7.5 mg	3.75 mg	5-6
Eszopiclone	Lunesta, Fulnite, Bexomer	2-3 mg	1-2 mg	6
Ramelteon	Rozerem, Ramitax	8 mg	8 mg	1.36

- There is no standard management protocol for this group itself
- Treatment is usually in the line of other sedative-hypnotic drugs

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Synopsis of the Clinical Practice Guidelines on Management of Tobacco Use Disorders

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2015

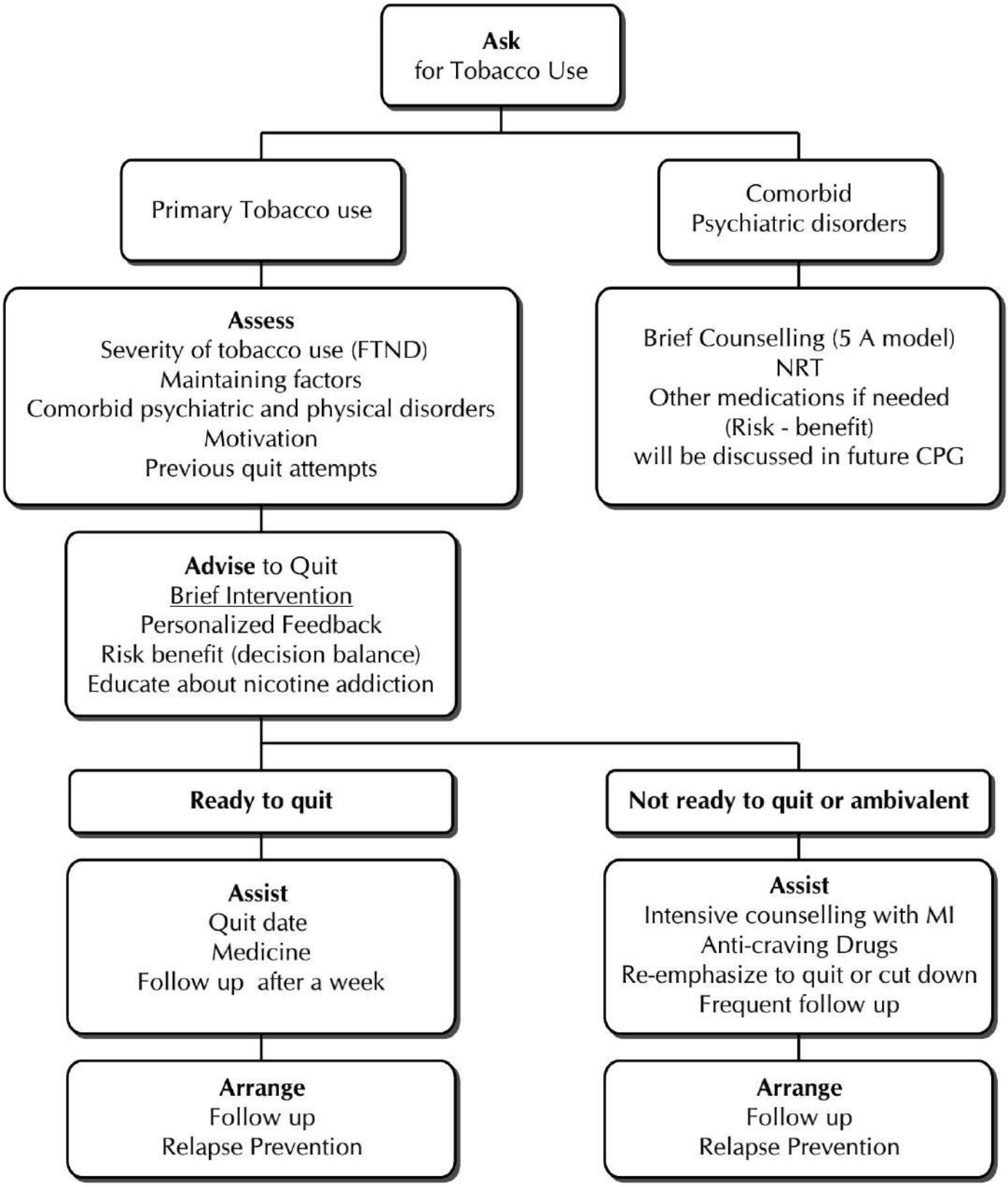
1. TOBACCO ADDICTION: FACTS

- Tobacco use is a major cause of preventable death and disease in India. Thirty five percent of adults in India use some form of tobacco. Smokeless tobacco use is more common than smoking, both in male and females.
- Nicotine, the addictive component of tobacco, binds to brain nicotine cholinergic receptors and releases a surge of dopamine.
- Dopamine, a neurotransmitter in the reward pathway, is responsible for the reinforcing effect of nicotine.
- Delivery of Nicotine from tobacco plays a significant role in its repeated use. Immediately following inhalation, smoking delivers a bolus of nicotine in the cerebral arterial circulation. Use of smokeless tobacco produces slower delivery of nicotine.
- Regular use of nicotine leads to addiction. This is clinically recognised as nicotine dependence, characterised by craving, tolerance, withdrawal symptoms, use despite harm etc.
- Much of the "relaxation and pleasure" associated with nicotine use may simply be a brief interruption of withdrawal symptoms, including restlessness, anxiety, depression, irritability, impatience, difficulty concentrating, insomnia, and increased appetite.
- Nicotine dependence is a chronic relapsing medical disorder, just like ulcerative colitis or diabetes.
- While all physicians need to manage and provide brief advice, they should network with experts who can effectively help in the management of dependence which is often associated with multiple relapses. Psychiatrists are experts who can effectively help patients in tobacco cessation.

2. NON-PHARMACOLOGICAL INTERVENTIONS

- Extremely important
- Several modalities, starting from the 5-A Model (Figure 1)
- Stage Specific interventions

Figure 1.Treatment Outline (5-A Model: Ask, Assess, Advise, Assist, Arrange)



FTND: Fagerstrom's test for Nicotine dependence (smoking and smokeless) is useful to assess the severity of nicotine dependence

2.1 MI: Motivational Interviewing (Developing discrepancy, Decision balance, self-efficacy, etc.) is a useful technique to engage the dependent tobacco user in initiating cessation

2.2 Brief Intervention

- Very effective in the practice of tobacco cessation.
- Easy to deliver by any health professional, preferably the treating doctor irrespective of the settings.
- Lasts 3-5 minutes, yet increases overall abstinence rates.
- Brief intervention should be provided to all tobacco users.

- *Advise all current tobacco users to quit*
- *Educate about tobacco addiction (a small self-help booklet useful)*
- *Link the current problem with Tobacco*
- *Provide Brief Counseling & Feedback*
- *Offer Medications to help in quitting*
- *Encourage follow-up*

2.3 Intensive Counseling

- Needs multiple sessions and ideally to be provided by trained personnel.
- The intervention depends on the motivational stage of the person.
- Objective is to increase the tobacco user's motivation either to quit or decrease tobacco use (Table 1) and prevent relapse (Table 2).

Table 1. Enhancing Motivation

Stage of motivation	What will help	What psychiatrist can do
Pre-contemplation • *Person does not want to stop using tobacco*	• Providing information about tobacco use and the benefit of quitting (Educational booklet). • Helping the person to speak about tobacco use and also its impact to the people around including himself.	• Avoid confrontation. • Educate about tobacco and other substance use (in case this is present). • Focus on rapport building. • Encourage and appreciate any expression of desire to quit tobacco (even in future).
Contemplation • *Acknowledges that there is a problem.* • *Actively considering costs and benefits of tobacco use.*	• Assessing the client's feelings and thoughts about his/her tobacco use behaviour.	• Facilitate (also provide further inputs) the analysis of pros and cons. • Help in realistic appraisal of the good and bad things about continued use of tobacco.

Stage of motivation	What will help	What psychiatrist can do
Determination/ Preparation ◆ *Feeling the need to do something about tobacco use and Making the decision to quit something to it.*	◆ Choosing to give up tobacco and committing to specific goals.	◆ Reaffirm person's ability to make the change (self-efficacy).
Action ◆ *Taking action to stop using tobacco*	◆ Achieving the goals by taking concrete steps.	◆ Help the tobacco user lay a definite plan of action for quitting

Table 2. Preventing Relapse

Techniques	Examples
Identify the high risk relapse situations	◆ Mood state, peer pressure, i.e. being around other tobacco users, risk states e.g. drinking alcohol
Learn to manage craving	◆ Identify craving, using distraction, deep breathing, drinking a glass of water, using chewing gum or cinnamon, urge surfing (Experiencing the changing nature and impermanence of urges)
Increase in problem solving ability and coping skills	◆ Learning cognitive strategies and behavioral interventions to reduce cues ◆ Anticipate negative or trigger situations and work accordingly
Make Life style changes	◆ Time management to reduce stress, improve quality of life ◆ Keeping oneself busy ◆ Staying in non-smoking locations
Learn Cognitive ways to motivate and change self	◆ Increase self-efficacy i.e. 'I can do it' ◆ Encourage self-visualisation as a non-tobacco user ◆ Understand the addictive nature of tobacco use disorders and develop confidence to overcome the addiction ◆ Encourage to take credit and feel good for not using tobacco

3. PHARMACOTHERAPY (MEDICATIONS, INCLUDING NRT)

- Interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to minimal intervention or usual care.
- Pharmacotherapy for tobacco dependence treatment is safe and effective and significantly increases the chance for long-term smoking abstinence compared with quit attempts unaided by pharmacotherapy.

3.1 Nicotine Replacement Therapy (NRT)

- NRT (Gum, Patch, Pastilles/Lozenge, Spray, Inhaler) is a safe and effective treatment for dependence on both forms of tobacco. The first three are available in India.
- Dose is dependent on the severity of tobacco use e.g. the amount of tobacco and how early one uses in the morning.
- Adequate dosage and duration of NRT is associated with better outcome.
- Can be initiated while person is not fully decided on quitting tobacco.
- Optimal duration of treatment is three months.
- The likelihood of tobacco abstinence with NRT in case of smoking is one and half time than placebo.
- Combination of NRTs can be tried in refractory cases. (Table 3)

Table 3: Nicotine Replacement Therapy

Preparation	Dosage	Administration	Adverse effects	Advantage
Nicotine Gum/ Lozenge ***2mg, 4mg***	*< 25 cig = 2mg every 1-2 hrly* *> 25 cig = 4mg every 1-2 hrly* (maximum: 24 gums/day) Duration: 12 wks Wk 1-6:1 piece every 1-2 h Wk 7-9: 1 piece every 2-4 h Wk 10-12: 1 piece every 4-8 h	*Chew and Park Method* (chew until a tingling/peppery taste is obtained and park in the gap between gum and inner cheek. Continue till the sensation stops i.e. around 30 min) No drink 30 minute before or after the gum. Gum can be kept more than one hour in mouth before spitting out. Lozenge gets absorbed completely.	Usually Safe Mouth Irritation, Jaw fatigue, Dyspepsia hiccup	Effective in controlling withdrawal symptoms. Concomitant use of tobacco does not cause any significant problem. Can be initiated without complete stoppage of tobacco use. User can control nicotine dose.

Preparation	Dosage	Administration	Adverse effects	Advantage
Nicotine Patch ***21mg, 14mg, 7 mg***	*> 10 cigarettes/day d: 21 mg/day* *< 10 cigarettes per d: 14 mg per d* Duration : 10-12 wk Wk 1-6:21 mg/day or 14mg/day Wk 7-9: 14 mg/day or 7mg/day Wk 10-12: 7mg/day	Apply in clean, dry and non-hairy part of the body. Press the patch over the skin and press down on the margin. One patch per day. Do not stop using patch abruptly.	Local skin reactions (erythema, pruritus, burning), headache, sleep problem (insomnia/dreams)	Easy, as once per day use. Provides steady nicotine level.
Nicotine Inhaler 10-mg cartridge delivers 4 mg of nicotine per spray	*Usual: 6-16 cartridges per day Initially: 1 cartridge every 1-2 h* Duration: 12-24wk Taper in last 6-12 wk	Inhaled through the mouth. Patient should inhale into back of throat or puff in short breaths. Open cartridge retains potency for 24 h. No food or beverages 5 min before or during use.	Mouth and throat irritation	Delivers nicotine rapidly. Mimics the *"hand to mouth"* ritual of a cigarette user. Controls the nicotine delivery.
Nicotine Nasal spray	*1 spray (1 mg nicotine) in each nostril* Initial treatment is 1–2 doses per h, as needed. Typical dosing is 8–40 doses/d. Duration : 12-24wk	Nasal administration	Nasal irritation	Very fast delivery of nicotine. Most rapid delivery of nicotine.

There is lack of literature on pharmacological treatment of Bidi users. The above intervention should be effective among Bidi users also.

3.2 Non Nicotine Pharmacotherapy

Options for non-nicotine pharmacotherapy include varenicline, bupropion, nortriptyline and cytisine. The first three are available in India. Choice of drug may be determined by the presence of co-morbidity and affordability.

- Varenicline is the most effective agent for smoking cessation (one and half time more than bupropion and twice that of NRTs)
- Varenicline use has been associated with neuropsychiatric and behavioral change and thus it must be regularly monitored.

- Varenicline can be used in patients with stable psychiatric disorder under close monitoring.
- Nortriptyline, clonidine and cytisine are the low-cost treatment options.

Table 4. Dosing of Commonly Used Non-Nicotine Pharmacotherapy

Drugs	Dosage	What psychiatrist can do
Varenicline	1st to 3rd day: 0.5 mg morning OD 4th to 6th day: 0.5 mg BID 8th day to 12th week: 1mg BD Start 1 week before quit date	Well tolerated Nausea, Insomnia
Bupropion	150 mg/d for 3days, then 150 mg twice a day, Start 1 wk before quit date	Increases seizure risk in higher doses

3.3 Smokeless Tobacco

- Most research is on "Snus" (a smokeless tobacco) and there are hardly any studies on pharmacotherapy for chewing tobacco.
- Varenicline and NRT are shown to be effective.
- NRT increases short-term abstinence but only varenicline seems effective in longer term abstinence.
- Bupropion has not been significantly associated with increased tobacco abstinence
- Behavioural counseling and long term follow up increases the abstinence rate in chewing tobacco.

Suggested Reading

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Synopsis of the Clinical Practice Guidelines on Management of Inhalant Use Disorders

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1. BACKGROUND INFORMATION

- Inhalants are breathable chemical vapors or gases abused for their psychoactive effects.
- Use mostly reported by children or adolescents. These are usually among the first drugs used by young people.
- These are available as cheap household or commercial products. Toluene is one of common constituent in many abused products.
- Inhalants can be classified into four broad types, as follows:
  (a) Volatile solvents are liquids that vaporize at room temperature if left in unsealed containers. Paint thinner, gasoline, correction fluid, nail polish remover and glue are some of examples
  (b) Aerosols are sprays that contain propellants and solvents e.g. paint, deodorant etc.
  (c) Gases e.g. refrigerants and medical anesthetics
  (d) Nitrites.
- Commonly abused inhalants in India are: ink eraser fluid/correction fluid, petrol and adhesive glue
- Inhalants can be used by various modes of administration:
  - huffing (soaking a rag and placing it on the mouth to inhale) – most common
  - sniffing/snorting (inhaling through the nose),
  - bagging (inhaling from a bag that contains the substance),
  - dusting (spraying directly into the mouth or nose).
- Acute effects of inhalants resemble that of other CNS depressants e.g. alcohol. They comprise of stimulation, disinhibition and euphoria. It may be followed by hallucinations and then a general depression including slurred speech and disturbed gait, dizziness, disorientation, and drowsiness or sleep within seconds to minutes.
- Intoxication occurs rapidly and is relatively short-lived (average elimination half-life for toluene from breath is 25 minutes). Some users may self-administer inhalants repeatedly or continuously to maintain intoxication.
- Risk factors associated with inhalant use include
  - economically underprivileged, marginalized (e.g. street children)
  - dropping out of school, delinquency
  - conduct disorder/anti-social personality.
  - drug-using /delinquent peers

- psychiatric co-morbidity
- child abuse, low parental supervision, family instability
- family history of substance dependence

◆ Most inhalant users appear to discontinue inhalants eventually, but early onset of inhalant use is associated with an increased risk of heroin use, injecting drug use, other drug use and antisocial behavior.

2. MANAGEMENT

2.1 General principles

2.1.1 *Ethical considerations*

◆ Physician must take special care to ensure that the patient's rights are not violated at any stage of treatment, more so, because patients are generally minors.

◆ If an adolescent seeks consultation on his/her own, effort must be made to approach and engage the parents (or guardians) after patient's approval.

◆ Admission must proceed only after a valid consent from the parents (or legal guardians), and if they are willing to accompany with the patient throughout the ward stay.

◆ An adolescent who is unwilling to get admitted for inhalant use must not be admitted, even if parental consent is present.

◆ Any private or personal information disclosed in confidence to the treating professional should not be disclosed to parents (unless there is a genuine threat to safety).

2.1.2 *Levels of care*

The patients using inhalants may receive various levels of care, ranging on a continuum of service intensity from

- Early intervention services, which comprise brief intervention in a health care or community settings (opportunistic)
- Outpatient treatment services, with periodic follow-up visits (weekly)
- Intensive outpatient, in which adolescents attend treatment or day-care facility during the daytime (daily basis)
- Residential/ in-patient treatment services (few weeks to few months)
- Medically-managed intensive inpatient, which is most appropriate for adolescents with substance use, medical, and/or psychiatric problems warranting intensive, supervised care.

A critical issue in treatment of inhalant use is whether inpatient or outpatient

treatment is the more appropriate. Certain clinical considerations may facilitate the decision (refer box 1 and 2).

Box 1: Clinical considerations: Outpatient treatment

Out-patient treatment is particularly suitable for patients:

(a) If the use is occasional or less frequent
(b) If the use is of shorter duration (few months)
(c) If there is mild or moderate dependence
(d) If the treatment is being sought for first time, no prior failed attempts
(e) If there is no significant health damage
(f) If there is no concurrent abuse/dependence on other substances
(g) If the functioning at school or home is relatively preserved
(h) If there is a good social support system
(i) If patient stays in close proximity of treatment services

Box 2: Clinical considerations: In-patient treatment

In-patient treatment is more appropriate:

(a) If there is a severe dependence
(b) If the patient is using inhalants for a prolonged duration (few years)
(c) If there are multiple failed abstinent attempts in the past
(d) If there are significant health complications
(e) If there is a concurrent use of multiple other substances
(f) If there is severe dysfunction at home or school
(g) If the family support is absent/minimal, and/or presence of familial psychopathology interfering with treatment and care
(h) Geographical distance from treatment centre

2.1.3 Treatment goals

The goal of treatment in case of inhalant users is complete abstinence in view of severe and life-threatening health risks.

- Immediate goals may be establishment of rapport, detoxification and intervention for a psychosocial and medical crisis.
- Short-term goals may include management of co-morbid conditions and re-integration with family.
- Long-term goals consist of relapse prevention, vocational skills acquisition or an improvement in overall quality of life.

However, it is also acknowledged that inhalant users are one of most elusive, and difficult groups to retain in treatment.

Therefore, while working for an ultimate goal of abstinence, these users must also be provided with the necessary health education aimed at harm minimization (refer Box 3). Although not considered as a mainstream treatment approach in the context of inhalant use, it has been used to reduce the risks associated with inhalant use.

Box 3: Harm minimization

- Do not use inhalants with a bag on the head (bagging) to avoid suffocation
- Avoid using inhalants when alone or in secretive, enclosed spaces e.g. cupboards
- Avoid use of inhalants when you are smoking or near a lit cigarette or lighter
- Do not drive (for the next several hours) after using inhalants
- Avoid concomitant use of other drugs to prevent overdose
- Use inhalants from small bottles with small surface areas to minimize exposure
- Do not use inhalants immediately before exercise or physical exertion to reduce risk of arrhythmias and sudden death
- If someone is using inhalants, do not unnecessarily alarm or chase them, to reduce risk of sudden death which is more common if heart rate is elevated
- Call emergency medical services if the person shows unusual symptoms or behavior, e.g., agitation, seizure, disorientation or loss of consciousness.

2.1.4 Phases of treatment

(1) In the *early phase of management* of inhalant users, two issues that require particular attention are

(i). ***Medical management for health damage***, if any: Depending on severity of inhalant use, there may be complications in a number of body systems, including the brain, heart, lungs, kidneys, liver, and blood, which need a thorough assessment, management and multiple referrals.

(ii). ***Management of withdrawals ('detoxification')***: There may also be some withdrawal symptoms which are generally non-specific, although craving may be prominent, and require supportive care. Inhalants are lipophilic and can stay in fatty tissue of the body for weeks; therefore detoxification periods could

extend for a month or even more. Unless the patient is comfortable, it will be difficult to engage him/her in the therapeutic aspects of treatment Patient may also have some mistrust, resistance and dilemmas for treatment in the initial phase, which need to be resolved. Therefore, in the initial phase, emphasis should be on

- building a therapeutic alliance (rapport)
- basic supportive care (rest, nutrition, calm environment etc)
- use of analgesics and sedatives, if required,
- general counseling
- involvement of family
- provision of education to patient (and families)

(2) *Long term psychosocial treatment* can be initiated once the patient is comfortable and more receptive, and may need to be continued for a prolonged duration.

2.2 Assessment and diagnosis

2.2.1 *Screening*

Many a times, the diagnosis of inhalant abuse relies almost entirely on a high index of suspicion. (Box 4).

Box 4: Clinical pointers for suspected inhalant use

- Any discernible or unusual odor or stains on fingernails, body parts or clothes
- Presence of sniffer's rash around nose and mouth, rhinorrhea, injected sclera
- Appears to be under influence of a drug (e.g. drowsiness, incoordination)
- Deterioration in physical appearance
- A recent change in child' behavior
- Drop in school performance/ frequent absenteeism
- Impairments in attention, memory or other cognitive functions
- Secretive behavior regarding actions and possessions
- Unusual borrowing/stealing of money from home or friends

2.2.2 *Thorough history and examination*

Besides the immediate reasons for presentation, a thorough history should cover following aspects:

- nature, type, frequency, duration, mode of administration of inhalants and/or co-occurring substance use

- reasons for initiation/continuation
- acute effects, withdrawals (if any), tolerance, craving
- time spent on drug use, neglect of alternate activities, drug-using peer group (if any)
- consequences of drug use (physical, psychological, familial, school, social, legal),
- abstinence attempts
- co morbid psychiatric disorders, if any (e.g. depression, psychosis, conduct disorder, attention deficit disorder, learning disorders, borderline intelligence etc)
- family history, personal history (including educational/vocational and sexual history) and pre-morbid temperament/ personality.
- assessment of family dynamics, inter-personal relationships and communication styles is required for child/adolescent inhalant users seeking treatment.
- general physical and systemic examination should be conducted diligently in all users and any discernible abnormality recorded.
- mental state examination should be conducted routinely in all inhalant users covering aspects of alertness and orientation, behavior, speech, affect/mood, thought, perception, and higher cognitive functions (attention and concentration, memory, intelligence, abstraction, judgment, insight.

The sexual history, including high-risk sexual behaviors, should be taken from all patients. If indicated, laboratory investigations to rule out sexually transmitted infections (including HIV-ELISA) may be considered. Possibility of sexual abuse should be considered in vulnerable users e.g. street children using inhalants and other substances.

2.2.3 *Assessment of health damage*

- Various health complications related to use of inhalants have been shown in Box 5. A comprehensive clinical assessment must be performed.
- Neurological toxicity is the most recognized adverse effect of chronic inhalant abuse.
- Laboratory tests and imaging studies (including MRI brain) and neuropsychological examination should be performed, if indicated. Specialist referral and consultation must be sought for a medical complication.

2.2.4 *Diagnosis*

- The diagnostic criteria in current classificatory systems (ICD 10 and DSM 5) for inhalants are essentially the same as for rest of the substances.

- Unlike ICD-10, however, the DSM-5 diagnostic criteria do not acknowledge the presence of withdrawals for inhalant use disorder.

Organ system	Complications
Neurological	Encephalopathy (acute/chronic), cerebellar ataxia, cranial and peripheral neuropathies, parkinsonism, tremor, visual loss/optic neuropathy, white matter degeneration/atrophy
Neuropsychiatric & neuropsychological	Apathy, dementia, depression, psychosis Memory deficits, deficits in attention and executive functions, reduced speed of information processing
Cardiovascular	Dysrhythmias, hypoxic-induced heart block, myocardial fibrosis Sudden sniffing death syndrome (due to sudden release of catecholamines resulting in ventricular fibrillation)
Respiratory	Cough, wheezing, dyspnoea, emphysema, pneumonitis, Goodpasture's syndrome
Abdominal	Hepatotoxicity, nausea and vomiting
Renal	Acid-base disturbance, acute renal failure, renal tubular acidosis, Fanconi's syndrome
Haematological	Aplastic anemia, bone marrow suppression, leukaemia
Dermatologic	Burns, contact dermatitis, peri-oral eczema
Reproductive/ Fetal exposure	Low fertility, Increased risk of abortion, possible neonatal withdrawals, low birth weight and craniofacial abnormalities, growth retardation and cognitive/speech/motor deficits in later life

2.3 Management of Inhalant Intoxication

The treatment recommendations for inhalant intoxication (Box 6) have been summarized below:

- Basic supportive case; Ensure safety
- Careful monitoring of the intoxicated patient, on following parameters:
  - blood pressure, pulse rate , respiratory rate
  - temperature
  - oxygen saturation
  - orientation to time, place, person
  - level of consciousness
  - changes in mood and behavior

Box 6: DSM-5: Inhalant Intoxication

A. Recent intentional use or short-term, high-dose exposure to volatile inhalants.

B. Clinically significant maladaptive behavioral or psychological changes that developed during or shortly after inhalant use or exposure.

C. Two (or more) of the following signs, developing during, or shortly after, inhalant use or exposure: dizziness, nystagmus, incoordination, slurred speech, unsteady gait, lethargy, depressed reflexes, psychomotor retardation, tremor, generalized muscle weakness, blurred vision or diplopia, stupor or coma, euphoria.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

- Environment should be calm, quiet and reassuring, with minimal stimulation (to reduce the risk of cardiac arrhythmias and arrest which may be precipitated by undue alarm)
- Speak in a calm, non-threatening voice
- Physical restraints should not be used
- Use of sedatives should be avoided
- Complications, if any, resulting from inhalant use (e.g. metabolic acidosis) must be treated by specific treatment measures after appropriate referral/consultation
- Emergency medical care should be arranged or provided immediately if there are any danger signs e.g. breathing difficulty, circulatory failure, loss of consciousness.
- Patient can be discharged from medical care (under supervision of a guardian) when the symptoms have fully recovered (usually < 4-6 hours if uncomplicated)
- Advise the family member or caregiver to keep monitoring the patient for at least 24 hours

2.4 Management for Inhalant Withdrawals

Inhalant withdrawals are experienced by regular users of inhalants, usually within 24 hours of cessation. Often, the withdrawal symptoms are mild, and may last from 2-5 days. Craving for inhalants may, however, last for a few weeks.

Inhalant withdrawal symptoms can be managed by basic supportive care and symptomatic medical management. Treatment recommendations are summarized below:

- Ensure a quiet and supportive environment
- Ensure hydration, by means of adequate oral fluids; and regular meals.
- Pharmacological treatment should be on symptomatic basis only, with close monitoring.
- Analgesics (e.g. paracetamol, ibuprofen) can be given for headache or somatic pain/s.
- Benzodiazepines (e.g. lorazepam) may be used to manage the anxiety, agitation and sleep disturbances for a short period. Gradual taper is advised to minimize the discomfort to patient.
- Monitor for any sudden change in patient's state, which may need immediate medical assessment and referral.
- No evidence, apart from a case series, on any specific pharmacotherapy to manage inhalant withdrawals

3. PSYCHOSOCIAL INTERVENTIONS

Psychosocial treatment should be offered to all inhalant users.

3.1 *General considerations*

- Ideally, patients using inhalants should receive multi-disciplinary care (psychiatrists, psychologists, social workers, trained nurses).
- It is important to have a network of referral sources such as the school counselors, welfare organizations, law enforcement officials, homeless shelters etc which can refer the patient for help.
- Psychological interventions for inhalant users should be kept as brief (e.g., 20-minute sessions) in the initial few months. This is because the attention span and other cognitive functions are often impaired to a varying degree.
- Extensive involvement of the family is required, in view of younger age of patients.
- It is important for this purpose to identify one or more key family members who can be educated about the nature of the disorder, the treatment process and recovery.
- When dealing with underprivileged children living on the streets who constitute a substantial percentage of inhalant users, family members are often absent and NGOs may play the role of surrogate guardians
- Deviant or drug using peers have a powerful influence on adolescent drug use. It is often necessary to work towards building an alternate group of non-drug using friends in the course of therapy.
- Emphasis should be placed on retry into school and school re-adjustment issues

- Vocational skills training for older inhalant abusers to promote self-sufficiency should be part of the management.
- The management should also focus on imparting life skills training e.g. how to handle money, personal affairs and handle problematic situations efficiently
- Extensive aftercare and follow-up period, extending as many as 2 years, is advisable.

3.2 *Specific therapies*

3.2.1 *Brief Intervention*

- Brief Intervention, using motivational interviewing, should be provided, as and when, there is an opportunity and contact with health professionals.
- Motivational interviewing is a non-confrontational, client-centered approach, which is employed. There are six elements critical to a brief intervention , summarized as the acronym FRAMES:
  - Feedback is given about personal risk or impairment (using information gained from questionnaire scores or blood investigations)
  - Responsibility for change is placed on the patient.
  - Advice to change is given in clear terms
  - Menu of alternative treatment options is offered
  - Empathic style is followed
  - Self-efficacy is encouraged

3.2.2 *Targeted education*

It must be provided to all inhalant users and their families aimed at

- provision of information about the harmful effects of inhalants
- harm minimization (Box 3)
- management of intoxication, and
- resources to get more information

3.2.3 *Cognitive-behavioral therapy (CBT) based approaches*

Both individual and group CBT has been shown to be effective in treating adolescent substance use disorders. CBT-based approaches should have certain common features, as follows:

- Employing motivation-enhancing techniques to establish a strong treatment alliance and improve treatment engagement and retention
- Performing a functional analysis to identify patterns of inhalant use, skills deficits, and dysfunctional attitudes and thoughts

- Enhancing coping strategies to effectively deal with craving and negative moods
- Strengthening problem-solving and communication skills and the ability to anticipate and avoid high risk situations; and
- Identifying enjoyable activities incompatible with drug use/alternate recreational pursuits.
- New skills and coping strategies are initially taught and practiced during therapy sessions, then applied to the patient's daily life in 'homework' assignments, with a review of successes and setbacks the following week.
- Typically, the sessions are delivered on a weekly basis, ranging between 5-16 sessions

CBT-based brief interventions, typically between 1-4 sessions, have also been used.

3.2.4 *Supportive psychotherapy*

There is some role for supportive psychotherapy, particularly among the patients in whom CBT is not feasible. Issues focused in such therapy include:

- positive and negative life events in family
- expectations and disappointments about family
- information about substance abuse
- educational levels and expectations from education
- communication styles in interpersonal relationships
- positive and negative life events in interpersonal relationships
- evaluation of problem solving skills and its restructuring
- expectations from the future
- creating alternatives about what can be done in the future.

3.2.5 *Narrative therapy*

- An informal approach that can be of assistance for adolescents showing resistance to traditional psychotherapies.
- It involves an informal interactive conversation through the use of stories.
- It explores how the adolescent forms and links these stories to make meaningful conclusions.
- In an intervention developed in India for out-of-school/street children with inhalant use (Box 7), story-telling method in one of sessions, proceed as follows:

Children are shown six pictures based on which they are expected to build a story. The six scenes depict the child

(1) with the family

(2) on the railway station (running away from home)

(3) with his new peer group

(4) using inhalants

(5) depicting problems due to drug use –social, legal or health related and lastly,

(6) a blank picture that has to be filled up by the child depicting what should happen to change the outcome to a more desirable one.

The last blank card facilitates processing.

Box 7: Intervention for out-of-school/street children with Inhalant use developed in India

The six sessions of the intervention are delivered in groups of 5-10 children over five half days (or 2-3 full days). Intervention uses role play, forum theatre, story-telling and other innovative and engaging methods to deliver the sessions.

The themes of the sessions are as follows:

1. Functional analysis of pro-social activities and substance use behaviour
2. Motivation enhancement and harm reduction
3. Life skill Training (drug refusal skills and enhancing self-esteem)
4. Health management and knowledge of harms or perceived benefits of inhalant use
5. Money management and healthy recreational pursuits
6. Relapse Prevention and role of networks and family in preventing relapse

3.2.6 *Contingency management*

- Adolescents often enter treatment because their parents, school, or the judicial system require it.
- In this scenario, contingenecy interventions may offer clear incentives and positive reinforcers for quitting.
- Such interventions could be effective additions or alternatives to clinic-based treatments of adolescent substance users.

3.2.7 *Person-centered general counseling*

- Non-directive approach to psychotherapy
- It is based on premise that person may be able to understand the cause of their problems after reflecting on their thoughts and feelings.
- This form of therapy does not recommend any particular course of action to the patient and instead, assists him/her to take responsibility for themselves.

3.2.8 *Family based approaches*

The role of family in adolescent inhalant users is much more important than adult substance users.

- Parents are taught about the monitoring skills and basic behavioral management principles, together with strategies to improve overall family functioning and sustain the gains of treatment.
- Even when structured family therapy is not feasible, an attempt must still be made to engage and involve the family in treatment process.
- A range of family interventions should be used in routine clinical care of adolescents , including family education (including information on harm minimization) and family counseling.
- The aims of family-inclusive clinical practice is:
  - provision of information to family members and caregivers
  - ensure their involvement in treatment process and care
  - seek their help to enforce behavioral strategies at home
  - minimize expressed emotions
  - make the family environment and relationships conducive to recovery of inhalant users

3.2.9 *Activity and engagement based approaches*

- Use of recreation or activity-based strategies (e.g. arts training, cultural evening, outdoor excursions etc where meals were also provided) to engage children in therapeutic relationships.
- These may be especially useful for homeless street children. Participation in at least 3-5 sessions was found to be optimal.

3.2.10 *Life Skills based approaches*

- Life skills are abilities for adaptive and positive behavior, that enable the individual to deal with problems and challenges of life.
- As inhalants are usually started early in life, the basic life skills are often deficient in inhalant using children.

- Several treatment approaches have used various life skills as one of the components of a multi-modal intervention.
- For example, activities aimed at money management, designed to allow the children to reflect on various alternate/healthy ways of spending money and thus, increase options of spending money. It may be especially useful for street children who often do not have concept of managing money and end up using all day's income on using inhalants and other drugs.

3.2.11 *Residential rehabilitation*

- Suitable only for chronic, heavy users of inhalants (with or without multiple substance use) for whom other treatment options have shown multiple failures.
- Multi-modal programs, which incorporate a range of components such as counseling, education and life skills.
- An extended 6-12 month residential treatment program utilizes a modified therapeutic community for adolescents with inhalant use and related problems.

4. LONG TERM PHARMACOTHERAPY

- Available literature on pharmacological treatment of inhalant use disorders is almost non-existent, except for a few case reports.
- There is an insufficient evidence for using a pharmacological agent for long term treatment.

5. MANAGEMENT OF CO MORBID CONDITIONS, IF ANY

- Careful history and mental state examination (especially for attention deficit/hyperactivity disorders, learning disorders, oppositional defiant disorder, conduct disorder, etc).
- Inhalant-induced psychiatric disorders are likely to subside with supportive treatment and maintenance of abstinence. Specific psychotropic medications are not warranted, unless the symptoms are severe, risky or life-threatening.
- Inhalant users are more likely to have underlying neurological damage, and consequently, may be more susceptible to develop adverse effects. May avoid typical antipsychotics.
- Medication, if needed, must be started at low dose and increased very gradually (start low, go slow) with close monitoring.

To conclude, Inhalant users continue to remain a largely hidden population, with very few treatment seekers. The absence of requisite expertise, child-friendly services or specific pharmacotherapies makes it difficult to retain patients.

Nonetheless, efforts must be made to engage the patient and families, if available, using a wide range of psychosocial interventions and supportive care. Treatment must be continued for long term.

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Synopsis of the Clinical Practice Guidelines on Management of Dual Diagnosis

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2015

1. DUAL DIAGNOSIS – BASIC ISSUES

- Dual Diagnosis: Co-occurrence of a substance use disorder with a non-substance psychiatric disorder, e.g., cannabis dependence with schizophrenia, alcohol dependence with bipolar disorder, benzodiazepine dependence with agoraphobia, etc.
- Other equivalent terms:
  - chemical abuse and mental illness (CAMI)
  - substance abusing mentally ill (SAMI)
  - mentally ill chemical abusers (MICA)
  - mentally ill substance abusers (MISA)
  - co-occurring substance use and mental disorders (COD)
- Associated with poorer prognosis than either substance use or psychiatric disorder in terms of:
  - Longer hospital stay
  - Early recurrence of illness
  - Greater risk of comorbid medical illness
  - Greater risk of violence
  - Greater risk of suicide
- Relevant, as service delivery of substance use disorders and other psychiatric disorders vary
- Substance use disorders combine in various ways with different psychiatric disorders to produce a range of dual diagnosis

Representative psychiatric disorder	Substance of use	Substance use disorder
Schizophrenia	Alcohol	Harmful use
Schizoaffective disorder	Tobacco	Dependence
Bipolar disorder	Opiates	Intoxication
Major depression	Cannabis	Withdrawal
PTSD	Cocaine	Substance induced psychosis
Panic disorder	Volatile solvents	Substance induced amnesic state
Generalized anxiety disorder	Sedative hypnotic	Residual and late onset psychosis
Somatization disorder	Stimulants	
Personality disorders	Hallucinogens	

1.1 Epidemiology

- Co-occurrence of substance use disorder and other psychiatric disorder more frequent than by chance

- Association borne out by large scale epidemiological studies: ECA, NCS, NESARC
- Other clinic based/ disorder focused studies also support the same

1.2 Specific difficulties faced while managing dual diagnosis patients

- Poor motivation for treatment and non-engagement to treatment process
- Which disorder to tackle first (substance use or psychiatric)?
- Where to manage: de-addiction facility or general psychiatry?
- Whether to provide substance use treatment during involuntary admission for psychiatric disorder?
- Some patients use substances to self-medicate psychiatric symptoms
- Medical co-morbidities may require attention
- Drug-interactions between substance of use and pharmacological agents for treatment of psychiatric condition
- Rehabilitation requirement for associated social problems like poor social supports, homelessness etc.

1.3 Four-quadrant Model

Severity of substance use disorder and psychiatric illness need to be assessed, as in four quadrant model, which determines the aims and goals of management:

High mental illness severity High substance use severity	High mental illness severity Low substance use severity
Low mental illness severity High substance use severity	Low mental illness severity Low substance use severity

2. AIMS AND GOALS OF MANAGEMENT

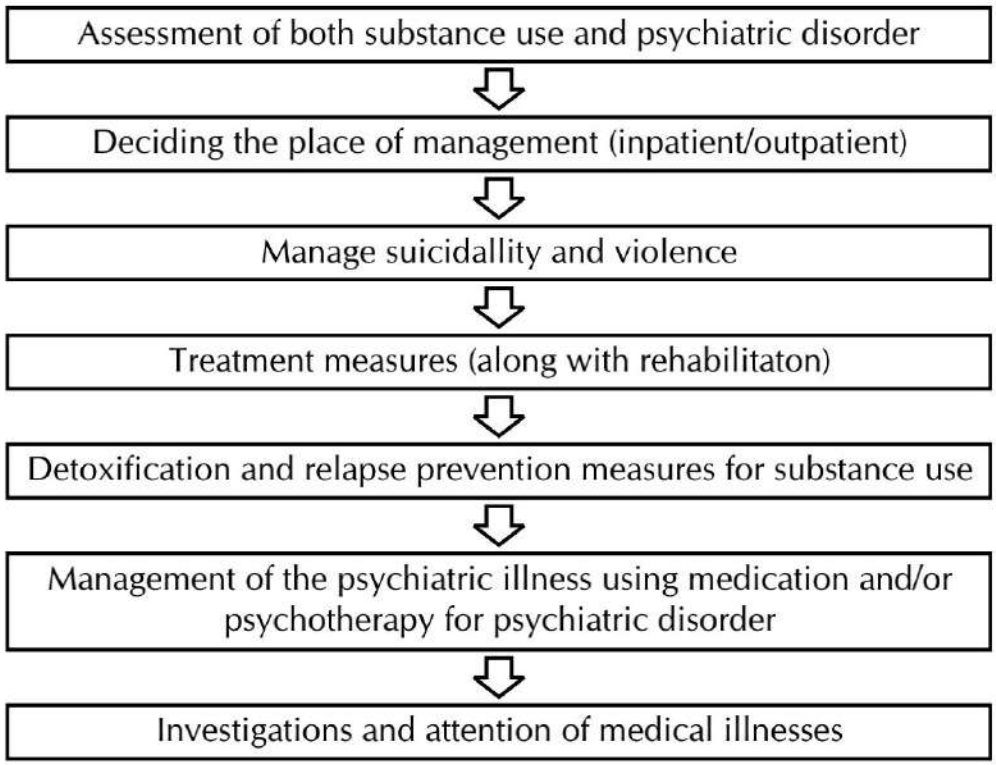
- Address acute and life threatening conditions (substance intoxication and withdrawal, psychiatric symptoms like suicidality, medical illness)
- Promote abstinence from substance of use
- Control the symptoms of psychiatric disorder
- Address the comorbid medical illnesses if any
- Increase motivation for recovery
- Enhance coping and teach relapse prevention skills
- Improve socio-occupational functioning
- Promote maintenance of recovery through continued treatment and/or participation in self-help groups

Goals of treatment vary according to individual patient and can be modified / revised from time to time.

The decision about treatment setting (inpatient or outpatient) needs to take care into account:

- Acute psychiatric symptoms in the form of suicidality and active psychotic symptoms
- Violent behavior of the patient
- Severity of withdrawal symptoms/ intoxication
- Associated medical illnesses
- Severity of substance dependence
- Prior abstinence attempts
- Motivation status of the patient
- Presence of social supports
- Patient and physician preference

3. PATIENT TREATMENT FLOWCHART



ASSESSMENT

- Clinical history:
  - substance use disorder – types of substances used, onset, progression, complications, abstinence attempts, relapses

- psychiatric illness – onset, clinical features, course, threat to self and others, dysfunction due to illness, past treatment and response to medications

- Physical examination
- Look for effects of substances
- Withdrawal signs
- Assessing risk: For both violence and suicide
- Scales and instruments: For psychiatric illness (e.g. PANSS, BPRS, YMRS) and substance use disorder (Drug Abuse Screening Test, ASSIST)
- Investigations: Based upon type of substances being used. e.g. Hemogram, liver functions, ultrasound abdomen for alcohol use disorders; Hepatitis B & C, HIV for intra-venous drug users; dual diagnosis patients are more likely to have additional medical comorbidities
- Assessment also gives an opportunity for motivation enhancement for patients who are poorly motivated for the treatment of their substance use disorder.

For convenience, dual diagnosis can be broadly classified into: Psychotic dual diagnosis and Non-psychotic dual diagnosis.

4. PSYCHOTIC DUAL DIAGNOSIS

- Mainstay of pharmacological treatment of psychotic illness: Antipsychotics - typical or atypical
  - Selection of drug based upon side effect profile, previous treatment response, patient preferences
  - Dual diagnosis patients are at increased risk of developing extrapyramidal side effects
  - Evidence has accumulated about the use of: olanzapine, risperidone, quetiapine, clozapine, aripiprazole, flupenthixol, zuclopenthixol
  - Some antipsychotics may reduce craving for substances (aripiprazole may reduce cocaine craving)
  - Attention should be paid towards drug interactions: drug for psychotic illness and drug for substance abuse treatment; drug for psychotic illness and substance itself
- Add-on treatment: Sedative hypnotics (diazepam, clonazepam), mood stabilizers (lithium, valproate) and antidepressants (fluoxetine or imipramine) might be used in select cases
- For substance use disorder:
  - Detoxification treatment should be begun along with the treatment of substance use disorder.

- Bupropion and varenicline are effective for smoking cessation in patients with schizophrenia and nicotine dependence.
- Nicotine replacement therapy efficacious in patients with tobacco dependence and psychosis
- Naltrexone beneficial in patients with schizophrenia and alcohol use disorder
- Caution about risk of exacerbation of schizophrenia with disulfiram and baclofen, though some patients with schizophrenia have received disulfiram without worsening of psychosis
- Opioid substitution therapy can be safely used in patients with schizophrenia and opiate dependence

- Non-pharmacological measures
  - CBT has been shown to be effective
  - CBT can be coupled with motivational interviewing, family intervention
  - CBT can also be provided in group format for substance users with psychotic illnesses
  - Contingency management useful for reducing tobacco usage in this population
  - Family intervention and family psychoeducational programs helpful

5. OTHER (NON-PSYCHOTIC) DUAL DIAGNOSIS

- Includes major depression, bipolar disorder, anxiety spectrum disorders etc.
- Antidepressants shown to be effective in patients with depression or dysthymia and alcohol use disorders
- SSRIs and TCAs act equally well in depression with alcohol dependence
- Antidepressants may not be effective in patients with depression and opioid use disorder
- Escitalopram monotherapy as effective as in combination (with buproprion or mirtazapine) in patients with depression and substance use disorder
- Venlafaxine effective in patients with depression and cocaine use
- Nefazodone may reduce symptoms of depression and cocaine craving
- Among bipolar disorder patients, lithium and valproate shown to improve outcomes for bipolar disorder as well as substance use disorder
- Add-on quetiapine does not offer superior outcomes in patients with bipolar disorder in terms of measures of substance use
- ADHD: Atomoxetine, pemoline effective for control of ADHD symptoms, but

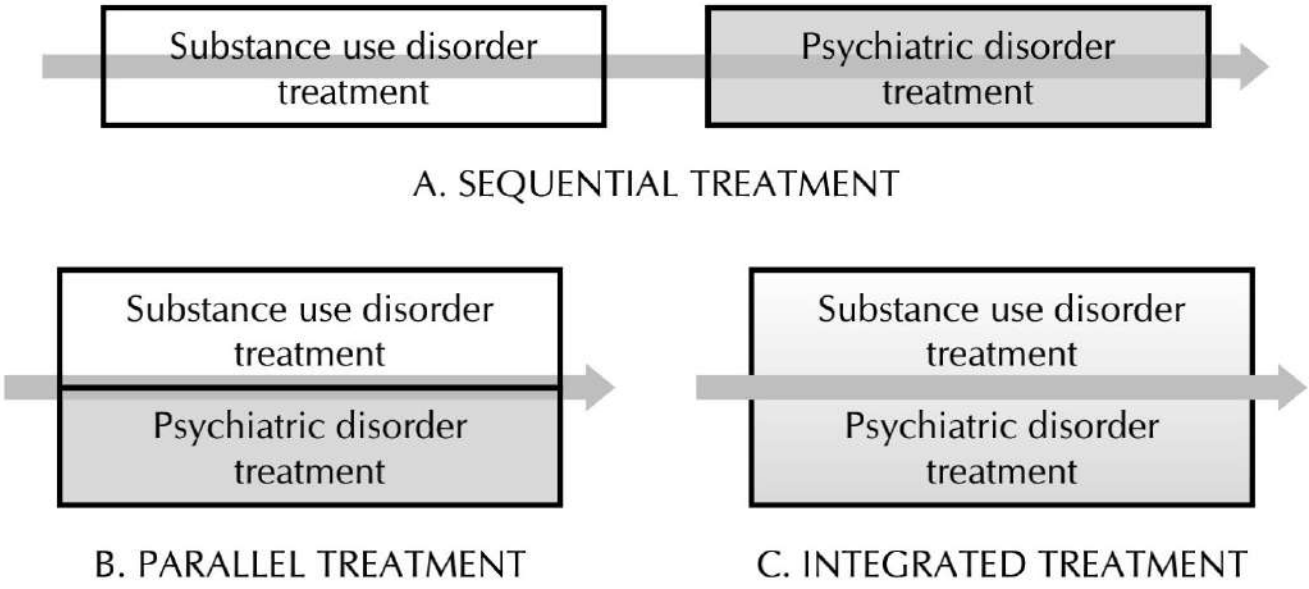
not for substance use; methylphenidate which had potential for abuse, not significantly better than placebo in reducing substance use.

- Social anxiety disorder with alcohol use disorder: paroxetine has demonstrated benefits in reducing anxiety symptoms as well drinking habits
- Avoid benzodiazepines in patients with substance use and anxiety/ depression as they have a higher propensity for dependence
- Withdrawal symptoms (e.g. of alcohol dependence) may be confused with symptoms of anxiety disorder: in such situations, better to wait for detoxification to be over before establishing a diagnosis of anxiety disorder
- Treatment of alcohol use disorder using acamprosate, naltrexone, disulfiram or baclofen
- In patients with PTSD, naltrexone, disulfiram and combination of two more effective than placebo
- Psychotherapy
  - Integrated treatment for substance use disorder and psychiatric illness, 'dual focused therapy': e.g. integrated CBT, focusing on both the disorders
  - Variants of CBT: Integrated Cognitive Behavioral Therapy, Behavioral Therapy for Depression in Drug Dependence, Trans-diagnostic Cognitive Behavior Therapy
  - Twelve Step Facilitation approaches useful
  - Motivational interviewing important component of treatment
  - Dialectical behavior therapy for substance use disorder and personality disorder
  - Group based treatment can be utilized
  - Contingency management and vocational rehabilitation improve substance use and socio-occupational outcomes
  - Therapeutic community helpful for patients with dual diagnosis

6. SERVICE DELIVERY

- Treatment service delivery can be: sequential (one disorder after the other), parallel (both the disorders simultaneously but by different experts) or integrated (both the disorders simultaneously by same expert)
- Integrated treatment is the best approach among the three
- Assertive Community Treatment (ACT) extends the integrated treatment to the community, is associated with better outcomes than standard case management

Figure: Service delivery formats



- High service intensity associated with better outcomes
- Treatment of dual diagnosis patients in the therapeutic community/ ACT may be high, but expenses are offset by the indirect benefits as a result of the treatment
- Training of the treatment providers is associated with improved staff self-efficacy and knowledge about dual diagnosis, though increased knowledge of staff however may not translate into better patient outcomes

7. SPECIAL POPULATIONS

- Prison population
  - A large proportion of prison population may have substance use disorder along with psychiatric disorder
  - Interventions inside the prison targeting substance use disorder resulted in lower chance of relapse after
  - Diversion of patients with acute psychiatric symptoms for treatment services may result in immediate benefit to the patient without risk to the community
- Homeless population
  - Contingency management results in less substance using behaviors
  - Therapeutic community for homeless dual diagnosis patients resulted in less psychiatric symptoms and substance use over follow up

Suggested Reading

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Synopsis of the Clinical Practice Guidelines on

Substance Use Disorders

The book titled "Clinical Practice Guidelines for the Assessment and Management of Substance Use Disorders" (CPG-SUD) was published by the Indian Psychiatric Society Specialty Section on Substance Use Disorders in January 2014. It was the culmination of intensive year-long efforts of a group of dedicated psychiatrists working in the field of substance use disorders in various reputed academic medical institutes of India. Since its publication in 2014, the CPG-SUD book has been well received by clinical practitioners, researchers, academicians, and psychiatric students, i.e., by all the target groups that book was meant for.

However, it became quickly apparent that there was a need for a more concise, practice-oriented, easy-to-follow "Synopsis" of the comprehensive CPG-SUD book as well. A need was felt for a set of compact, precise, yet evidence- and expertise-based guidelines.

This is the genesis point for this current slim volume. Easy-to-carry in a pocketbook sized format, and easy-to-use with clear tables, panels, boxes and algorithms, it is a perfect supplementary companion of the comprehensive CPG-SUD book. It synthesizes all the practice-relevant information necessary for the assessment and management of common substance use disorders and dual diagnosis. In order to maintain comparability and consistency with the CPG-SUD book, it contains the same chapters in the same order: assessment of substance use disorders in general; alcohol use disorders; opioid use disorders; cannabis use disorders; sedative-hypnotic use disorders; tobacco use disorders; inhalant use disorders; and dual diagnosis. A short list of key references/further reading is provided at the end of each chapter.

CPGs are meant to inform, assist and "guide" the clinician, not to ask them to sacrifice their autonomy of clinical judgment, nor to be oblivious of the individual patient's clinical situation and psychosocial context. With this disclaimer and caveat, however, we believe that this "Synopsis", when properly used along with clinical training in addiction psychiatry, can be a very useful and handy companion to the students, clinicians and even teachers in their day-to-day practice.

P.K. Dalal, Debasish Basu (Editors)

Indian Psychiatric Society
Specialty Section on Substance Use Disorders