

# Pharmacological Treatments Protocols of Alcohol and Drugs Abuse



## Purpose of the protocols:

Use and abuse of drugs and alcohol is becoming common and can have serious and harmful consequences on individuals, families, and society. Care with a tailored treatment program and follow-up options can be crucial to success. Treatment should include both medical and mental health services as needed in managing withdrawal symptoms, prevent relapse, and treat co-occurring conditions. Follow-up care may include community- or family-based recovery support systems.

These protocols have been developed to guide medical practitioners and nurses in the use of the most effective available treatments of alcohol and drug abuse in the in-patient and out-patient settings and serve as a framework for clinical decisions and supporting best practices.

Targeted end users:

- Psychiatry and Addiction Medicine Consultants, Specialists and Residents
- Nurses
- Psychiatry clinical pharmacists
- Pharmacists



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## CHAPTER 1 ALCOHOL

### INTRODUCTION

Alcohol is a Central Nervous System (CNS) depressant. Its' psychoactive properties contribute to changes in mood, cognition and behavior. The main psychoactive ingredient in beverage alcohol is ethyl alcohol (ethanol, or C<sub>2</sub>H<sub>5</sub>OH).

### CHRONIC ETHANOL USE IS ASSOCIATED WITH MANY MEDICAL PROBLEMS

#### INCLUDING:

- Osteoporosis
- Electrolyte abnormalities
- Polyneuropathy
- Endocrine disorders
- Dementia
- Alcoholic heart disease
- Cardiac dysrhythmias
- Liver dysfunction
- Suppression of all hematopoietic elements

The elderly and children are more prone to experience ethanol's intoxicating effects. Women experience intoxication effect more than men. Very large doses may be needed for severe withdrawal. Sympatholytic agents should not be used alone in severe withdrawal management.

### ACUTE TOXICITY (INTOXICATION)

It is unusual for persons with alcoholism to present for acute care with intoxication as their only medical problem.

A toxic dose is considered to be 5 g/kg in an adult or 3 g/kg in a child. Chronic drinkers require higher levels to reach similar states of intoxication.

### Signs and Symptoms of Intoxication & Blood Ethanol Concentration in a Non-Alcoholic Dependent Population

ETHANOL CONCENTRATION (MG %)	SIGNS AND SYMPTOMS
<25	Sense of warmth, sense of well-being, talkativeness mild incoordination
25–50	Euphoria, clumsiness decreased judgment and control
50–100	Decreased sensorium, worsened coordination, ataxia, decreased reflexes, increased reaction time emotional lability
100–250	Cerebellar/vestibular dysfunction (ataxia, diplopia, slurred speech, visual impairment, nystagmus) severe emotional lability
250–400	Confusion, stupor nausea, vomiting
250–400	Stupor or coma Little response to stimuli Incontinence Respiratory depression
>400	Respiratory paralysis Loss of protective reflexes Hypothermia Death

\*Correlation between signs and symptoms and blood ethanol levels show wide variability among individuals.



### **Diagnosis of Acute Intoxication**

Alcohol intoxication varies from just perceptible to life-threatening. The differential diagnosis is vast because it involves altered mentation or coma. Conditions that must routinely be considered include:

- Hypoglycemia
- Hypoxia
- Cerebral infection
- Shock
- Encephalopathy
- Seizures
- Uremia

Many medications cause an alteration in mental status including:

- Sedative-hypnotics
- Opioids
- Antidepressants
- Antipsychotics

### **Assessment:**

Alcohol intoxication is a differential diagnosis in patients presenting with abnormal mental states, confusion, ataxia, or coma. It may be complicated by overdose with other drugs, e.g. benzodiazepines, opioids, tricyclic antidepressants, paracetamol, stimulants, and Ecstasy. The person presenting in an intoxicated state may also have other medical or surgical illnesses such as head injury, Wernicke's encephalopathy, hypoglycemia, electrolyte disturbances, hypoxia, hepatic encephalopathy, or intoxication with other alcohols (methanol or ethylene glycol), which are often missed.

### **Assess and monitor:**

- Vital signs—temperature, BP, PR, breathing
- Neurological observations:
  - Glasgow coma scale—hourly
  - Mental state should be monitored for features not consistent with intoxication alone, e.g. confusion, disorientation, anxiety, panic, psychosis, suicidality and neck rigidity
- Breath or blood alcohol levels
- Urine drug screen

### **Management of Acute Intoxication**

Severe alcohol intoxication or alcohol poisoning can be a life-threatening condition, particularly in a non-tolerant individual.

#### **A. Emergency and supportive measures**

##### **Criteria for inpatient treatment:**

- Coma, shallow breathing
- Seizures
- Pregnant women with severe intoxication
- Hypothermia, hypoglycemia with severe dehydration
- Aggressive behavior and suicidality.



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### 1. Acute intoxication

Treatment is mainly supportive.

- a) Protect the airway to prevent aspiration, intubate, and assist ventilation if needed.
- b) Give glucose and thiamine, and treat coma and seizures if they occur. Always give thiamine parenterally before the administration of glucose solutions where there is a suspicion of chronic heavy alcohol use, to avoid precipitating Wernicke's encephalopathy.
- c) Glucagon is not effective for alcohol-induced hypoglycemia.
- d) Correct hypothermia with gradual rewarming.
- e) Most patients will recover within 4–6 hours.

Observe children until their blood alcohol level is below 50 mg/dL and there is no evidence of hypoglycemia.

### 2. Alcoholic ketoacidosis

Treat with volume replacement, thiamine and supplemental glucose. Most patients recover rapidly.

## B. Specific drugs and antidotes

There is no available specific ethanol receptor antagonist, despite anecdotal reports of arousal after administration of naloxone.

## C. Decontamination

### 1. Prehospital

- a. Do not induce vomiting or administer activated charcoal.

### 2. Hospital

- a. Because ethanol is rapidly absorbed, gastric lavage is usually not indicated unless other drug ingestion is suspected.
- b. Consider lavage only if the alcohol ingestion was massive and recent (within 30–45 minutes).
- c. Activated charcoal does not effectively adsorb ethanol but may be given if other toxins were ingested.

## D. Enhanced elimination

- Metabolism of ethanol normally occurs at a fixed rate of approximately 20–30 mg/dL/h.
- Elimination rates are faster in chronic alcoholics and at serum levels above 300 mg/dL.
- Hemodialysis efficiently removes ethanol, but enhanced removal is rarely needed because supportive care is usually sufficient.
- Hemoperfusion and forced diuresis are not effective.

## GLUCOSE

### Dosage and method of administration

As empiric therapy for coma, give 50–100 mL of 50% dextrose (equivalent to 25–50 g glucose) slowly (e.g., about 3 mL/min) via a secure intravenous line.



### **THIAMINE (VITAMIN B1)**

#### **Dosage and method of administration**

- Parenteral, 100 mg (children, 50 mg) slow IV (over 5 minutes) or IM; may repeat every 8 hours at doses of 50–100 mg.

### **ALCOHOL WITHDRAWAL**

The levels of alcohol consumption associated with withdrawal are as follows:

- **Males:** >8 standard drinks (i.e. 80g alcohol daily) for 10 – 20 years OR recent excessive intake of 16 standard drinks (160g alcohol)
- **Females:** >6 standard drinks (i.e. 60g alcohol daily) for 5-10 years, or recent intake of 12 standard drinks (120g alcohol)
- **Adolescents:** lower levels of alcohol consumption than adults may result in alcohol withdrawal in youth, though a withdrawal state is uncommon in this age group
- **Elderly:** as little as two standard drinks daily. Elderly people have less lean body mass and body water than younger people do. They are also more susceptible to alcohol withdrawal and to confusion and disorientation that may result from withdrawal.

#### **Features Of Alcohol Withdrawal Include:**

Symptoms of ethanol withdrawal range from mild anxiety and tremors to seizures, delirium tremens (DTs), and death.

Symptoms start 6 to 8 hours after a significant drop in ethanol level.

#### **Sympathetic symptoms include:**

- Tremors
- Irritability
- Tachycardia
- Hypertension
- Hyperreflexia

#### **Neuropsychiatric symptoms include:**

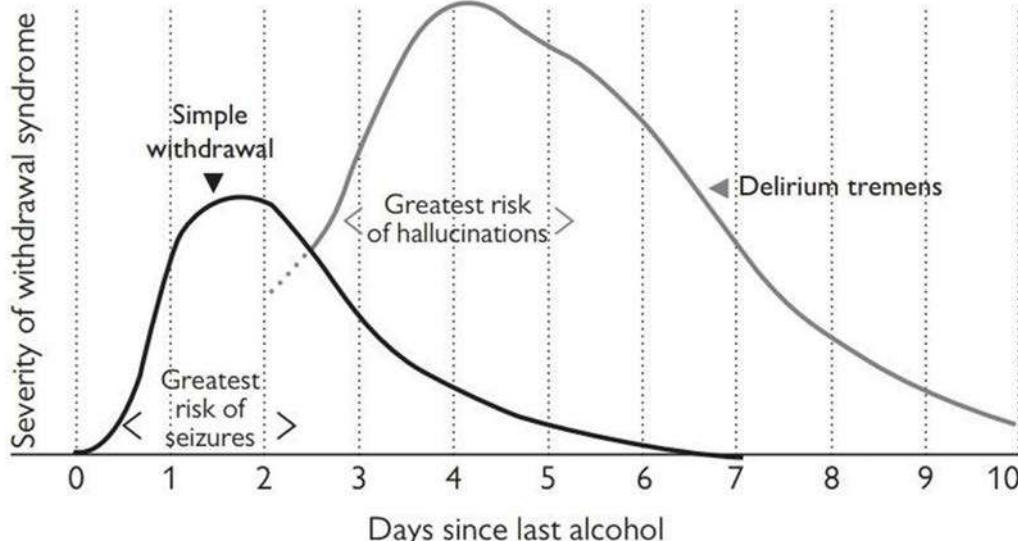
- Anxiety
- Agitation
- Craving for rest
- Hyper alertness
- Inattention
- Easy startling
- Hallucinations in up to 25% of patients
- Insomnia
- Mild disorientation to time with no gross confusion

The absence of significant disorientation, confusion, and autonomic instability differentiates minor withdrawal from the more serious DTs.

#### **Seizures**

Approximately 3% of episodes of alcohol withdrawal are complicated by seizures (convulsions, fits). In 95% of cases they occur within 48 hours of ceasing drinking. Alcoholic withdrawal seizures, or “rum fits,” are generalized and tonic-clonic.

Seizures are unusual after the onset of DTs. Patients who have both withdrawal seizures and DTs typically have the seizures first.



## DELIRIUM TREMENS

Delirium tremens ('the DTs') represents a very severe alcohol withdrawal syndrome (e.g. typically AWS score  $\geq 15$  or CIWA-Ar  $\geq 20$ ). It occurs in about 5% of patients in alcohol withdrawal, often in those who are medically compromised and/or with a long history of dependence. If good screening and treatment policies are implemented, DTs should occur rarely when alcohol withdrawal is adequately treated. DTs is still seen when patients present in a state of advanced withdrawal. Delirium tremens is a potentially life-threatening condition. Before the days of effective sedation and ready access to intravenous fluid replacement, the mortality rate was 35%. Effective diagnosis and management should reduce this in the modern world to under 1%.

### Delirium tremens (DT) (i.e. severe alcohol withdrawal):

- Onset: 48–72 hours after the last drink (may occur up to 5 days after)
- Duration: 3–10 days
  - Generally preceded by other signs of alcohol withdrawal
  - Seizures may herald the onset of delirium tremens.
- Clinical features: As per severe alcohol withdrawal:
- Autonomic hyperactivity: tachycardia, sweating, tremor, hypertension, &/or fever
- Severe anxiety: marked agitation
- Dehydration: electrolyte imbalances may be present.
- Plus:
- Clouding of consciousness/delirium (disorientation and confusion, fluctuating mental state); symptoms often emerge at night-time
- Hallucinations: typically, visual or tactile
- Paranoid delusions
- Cardiovascular collapse may occur.



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Mortality likely is relatively low in patients with DTs who have received adequate doses of benzodiazepines and appropriate nursing care. Death during DTs is usually related to patients' underlying medical conditions including:

- Pancreatitis
- Infection
- Subarachnoid hemorrhage
- Dehydration
- Gastrointestinal hemorrhage
- Seizure disorders
- Severe electrolyte abnormalities
- Cardiac rhythm disturbances
- Liver disease

### **INVESTIGATIONS FOR THE ALCOHOL WITHDRAWAL SYNDROME:**

Investigations are directed to:

- exclude metabolic imbalances
- assess recent alcohol use
- assess evidence of any co-morbid or complicating medical conditions
- detect conditions which may mimic or exacerbate withdrawal, or be precipitated by withdrawal.

Tests which are of particular importance in assessment and management of alcohol withdrawal are:

- FBC: e.g.:
  - Low Hb (anemia, recent bleed)
  - Leucocytosis (occult infection)
- INR: liver function; if INR is increased and albumin reduced, this may influence the choice of sedatives, e.g. oxazepam may be preferred
- Biochemistry:
  - EUC to detect dehydration, hypokalemia, or hyponatremia
  - Serum magnesium levels (hypomagnesaemia)
  - Blood glucose—hypoglycemia or hyperglycemia
  - LFTs : low albumin (chronic liver disease)
  - AST/ALT ratio >1.5 (acute alcoholic hepatitis)
- Blood Alcohol Concentration (BAC) —if withdrawal signs and symptoms are present with relatively high BAC, withdrawal is likely to worsen as BAC falls
- Urine drug screens—if suspicion of other drug use, e.g. stimulant or benzodiazepine use
- If clinically indicated, tests to exclude other pathology, e.g.: • brain CT or MRI— head injury, subdural hematoma.

### **MONITORING ALCOHOL WITHDRAWAL**

If the patient requests detoxification from alcohol, or his/her history or presentation suggests a possibility of alcohol withdrawal, the patient should be commenced on the Alcohol Withdrawal Scale (AWS) or the Clinical Institute Withdrawal Scale for Alcohol - Revised Version (CIWA-Ar).



**CIWA-AR, withdrawal assessment for alcohol**

Patient: ..... Date: .....

Time: .....

Pulse or heart rate, taken for one minute: .....

Blood pressure: ...../..... Rater's initials: .....

Nausea and vomiting (0–7)	
Tremor (0–7)	
Paroxysmal sweats (0–7)	
Anxiety (0–7)	
Agitation (0–7)	
Tactile disturbances (0–7)	
Auditory disturbances (0–7)	
Visual disturbances (0–7)	
Headaches, fullness in head (0–7)	
Orientation and clouding of sensorium (0–4)	
Total (maximum possible is 67)	

**Clinical Institute withdrawal for alcohol scale (CIWA-AR)**

<u><i>Nausea and vomiting</i></u>		<u><i>Tremor</i></u>	
Ask "Do you feel sick to your stomach? Have you vomited?" and observe.		Observe patient's arms extended and fingers spread apart	
<b>0</b>	No nausea and no vomiting	<b>0</b>	No tremor
<b>1</b>	Mild nausea with no vomiting	<b>1</b>	Not visible, but can be felt fingertip to fingertip
<b>2</b>		<b>2</b>	
<b>3</b>		<b>3</b>	
<b>4</b>	Intermittent nausea with dry heaves	<b>4</b>	Moderate, with patient's arms extended
<b>5</b>		<b>5</b>	
<b>6</b>		<b>6</b>	
<b>7</b>	Constant nausea, frequent dry heaves and vomiting	<b>7</b>	Severe, even with arms not extended
<u><i>Paroxysmal sweats</i></u>		<u><i>Anxiety</i></u>	
<b>0</b>	No sweat visible	<b>0</b>	No anxiety, at ease
<b>1</b>	Barely perceptible sweating, palms moist	<b>1</b>	Mildly anxious
<b>2</b>		<b>2</b>	
<b>3</b>		<b>3</b>	
<b>4</b>	Beads of sweat obvious on forehead	<b>4</b>	Moderately anxious, or guarded, so anxiety is inferred
<b>5</b>		<b>5</b>	
<b>6</b>		<b>6</b>	
<b>7</b>	Drenching sweats	<b>7</b>	Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions



<u><i>Agitation</i></u>		<u><i>Tactile disturbances</i></u>	
Ask "Have you any itching, pins and needles sensations, any burning, any numbness or do you feel bugs crawling on or under your skin?"			
0	Normal activity	0	None
1	Somewhat more than normal activity	1	Very mild itching, pins and needles, burning or numbness
2		2	Mild itching, pins and needles, burning or numbness
3		3	Moderate itching, pins and needles, burning or numbness
4	Moderately fidgety and restless	4	Moderately severe hallucinations
5		5	Severe hallucinations
6		6	Extremely severe hallucinations
7	Paces back and forth during most of the interview, or constantly thrashes about	7	Continuous hallucinations
<u><i>Auditory disturbances</i></u>		<u><i>Visual disturbances</i></u>	
Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?", and observe.		Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?", and observe.	
0	Not present	0	Not present
1	Very mild harshness or ability to frighten	1	Very mild sensitivity
2	Mild harshness or ability to frighten	2	Mild sensitivity
3	Moderate harshness or ability to frighten	3	Moderate sensitivity
4	Moderately severe hallucinations	4	Moderately severe hallucinations
5	Severe hallucinations	5	Severe hallucinations
6	Extremely severe hallucinations	6	Extremely severe hallucinations
7	Continuous hallucinations	7	Continuous hallucinations



Headaches, fullness in head		Orientation and clouding of sensorium	
Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.		Ask "What day is this? Where are you? Who am I?"	
0	Not present	0	Orientated and can do serial additions
1	Very mild	1	Cannot do serial additions or is uncertain about date
2	Mild	2	Disorientated for date by no more than 2 calendar days
3	Moderate	3	Disorientated for date by more than 2 calendar days
4	Moderately severe	4	Disorientated for place and/or person
5	Severe		
6	Very severe		
7	Extremely severe		

#### Alcohol withdrawal scale (AWS)

Patient: .....

Date:..... Time: .....

Pulse or heart rate, taken for one minute: .....

Blood pressure: ...../..... Rater's initials: .....

Perspiration (0–4)	
Tremor (0–3)	
Anxiety (0–4)	
Agitation (0–4)	
Axilla temperature (0–4)	
Hallucinations (0–4)	
Orientation (0–4)	
Total (maximum possible is 27)	

Perspiration		Tremor	
0	No abnormal sweating	0	No tremor
1	Moist skin		
2	Localized beads of sweat, e.g. on face, chest	1	Slight tremor
3	Whole body wet from perspiration	2	Constant slight tremor of upper extremities
4	Profuse maximal sweating— clothes, linen are wet	3	Constant marked tremor of upper extremities

Anxiety		Agitation	
0	No apprehension or anxiety	0	Rests normally during day, no signs of agitation
1	Slight apprehension	1	Slight restlessness, cannot sit or lie still Awake when others asleep
2	Apprehension or understandable fear (eg, of withdrawal symptoms)	2	Moves constantly, looks tense Wants to get out of bed but obeys requests to stay in bed
3	Anxiety occasionally accentuated to a state of panic	3	Constantly restless Gets out of bed for no obvious reason
4	Constant panic like anxiety are wet	4	Maximally restless, aggressive Ignores requests to stay in bed extremities

Axilla temperature		Hallucinations (sight, sound, taste <u>or</u> touch)	
0	Temperature of 37.0°C	0	No evidence of hallucinations
1	Temperature of 37.1°C	1	Distortions of real objects, aware that these are not real if this is pointed out
2	Temperature of 37.6–38.0°C	2	Appearance of totally new objects or perceptions, aware that these are not real if this is pointed out
3	Temperature of 38.1–38.5°C	3	Believes the hallucinations are real but still orientated in place and person
4	Temperature above 38.5°C	4	Believes himself to be in a totally nonexistent environment, preoccupied and cannot be diverted or reassured

Orientation	
0	The patient is fully orientated in time, place and person
1	The patient is fully orientated in person but is not sure where he is or what time it is
2	Orientated in person but disorientated in time and place
3	Doubtful personal orientation, disorientated in time and place; there may be short periods of lucidity
4	Disorientated in time, place and person; no meaningful contact can be obtained.

#### INTERPRETATION

Severity	AWS Score	CIWA-Ar Score
Mild	1-4	< 10
Moderate/Severe	5-14	10-20
Very Severe	> 15	> 20

## ALCOHOL DETOXIFICATION PROTOCOLS

### Assessing Suitability for Home Detoxification

1. Not severely dependent
2. No previous complicated withdrawal
3. No concomitant illness, injury or recent surgery
4. No significant use of other psychotropic drugs that could aggravate withdrawal
5. The patient is motivated to achieve abstinence
6. A reliable career is available
7. The patient has a stable home environment for home detoxification

### Assessing Suitability for Inpatient Hospital / Specialist Unit Detoxification

1. Moderate to severe dependence is demonstrated so that medical management is likely
2. Previous complicated withdrawal (e.g. seizures or DTs)
3. May have signs of withdrawal as judged clinically and/or supported by a rating scale (e.g. AWS > 3 or CIWA-Ar > 10)
4. Concomitant physical or psychiatric illness, injury or recent surgery
5. No reliable career is available and has no stable home environment
6. Alcohol or drug use in pregnancy or in mothers with babies who have no supportive environment
7. May have had repeated unsuccessful attempts to detoxify at home, particularly relevant for admission to a specialist detoxification unit, less so for a general hospital

**Benzodiazepines are the mainstay of therapy of alcohol withdrawal.**

**Benzodiazepines, Because of:**

- Their Cross-tolerance with alcohol.
- Their Wide margin of safety.

They are very effective and the drugs of choice for the treatment of the alcohol withdrawal syndrome.

Although there is a potential for physical dependence, the rate is low if they are used in the short term, as is recommended in these protocols.

There are four important aspects of the clinical management of patients undergoing alcohol detoxification.

They are summarized as:

1. **Sedation**
  - Alcohol 1 (A1) Protocol – Diazepam as required
  - Alcohol 2 (A2) Protocol – Regular diazepam regime
  - Alcohol 3 (A3) Protocol – Loading dose diazepam regime
  - Alcohol 4 (A4) Protocol – Intravenous diazepam regime
2. **Symptomatic relief**
3. **Supplements**
4. **Supportive environment**

### **SEDATION**

It is a corner stone in treatment of withdrawal of alcohol.



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### PRECAUTIONS

Special precautions need to be taken before sedating patients who have any of the problems listed below:

#### a. Chronic Liver Disease

- Major diagnostic and management problems can arise in patients with chronic liver disease, especially if they have cirrhosis and/or signs of hepatic decompensation.
- It is essential to determine that the patient has alcohol withdrawal and not hepatic encephalopathy. The two may easily be confused. Consult specialist physician if there is doubt.
- If the patient with known or suspected chronic liver disease is confirmed as having a withdrawal state, give 50% of the usual dose of sedative.
- If the patient has signs of hepatic decompensation (such as marked jaundice, ascites, and hepatic encephalopathy) or has experienced a recent variceal hemorrhage, do not sedate without a specialist assessment.

#### b. Midazolam is an alternative benzodiazepine for intravenous use.

### ALCOHOL 1 (A1) PROTOCOL (DIAZEPAM AS REQUIRED)

This is an “as required” diazepam regime. The scores on the Alcohol Withdrawal Scale taken second or fourth hourly determine whether diazepam is required, and at what dosage. It assumes regular monitoring of the withdrawal syndrome using an approved rating scale such as AWS or CIWA-Ar.

The regime is set out in table:

AWS SCORE	CIWA -Ar SCORE	DIAZEPAM DOSE
0	0	Nil
1-4	1-9	Nil
5-9	10-14	5-10mg
10-14	15-20	10mg or switch to A3
> 15	> 20	switch to A3

### ALCOHOL 2 (A2) PROTOCOL (REGULAR DIAZEPAM)

This is a regular diazepam regime which is designed for hospital wards. It is appropriate for elective detoxification where patients are being monitored for withdrawal and for the management of existing alcohol withdrawal syndromes of moderate severity, or where prophylactic sedation is considered necessary.

### ALCOHOL 3 (A3) PROTOCOL (LOADING DOSE DIAZEPAM REGIME)

This protocol is indicated in severe withdrawal symptoms, CIWA >20 and ASW>15. It's optionally indicated in CIWA 15-20 and ASW10-14.



1. Give 20mg diazepam orally every 2 hours until sedation achieved.
2. At this point the patient will be in a state resembling light sleep, from which the pt. can be easily roused.
3. During the loading regime, ensure review by medical officer after 4 hours.
4. **No more** than 120mg diazepam should be given by the loading regime in the first 12 hours. If the patient is still not sedated consult the specialist on call.
5. After sedation is achieved, switch to the Alcohol 2 protocol (commencing at the Day 1 point).

#### **ALCOHOL 4 (A4) PROTOCOL (INTRAVENOUS DIAZEPAM REGIME)**

This is an intravenous sedative regime which is prescribed for patients with the most severe alcohol withdrawal syndromes (i.e. delirium tremens). In this situation rapid control of the withdrawal state is paramount. Patients receiving this regime must be managed in **an intensive care unit** or high dependency unit where facilities for resuscitation and ventilation support are present

- Give intravenous injection of 10mg diazepam over 5 minutes, repeated up to three times if necessary in the first 30 minutes. **Note there is a danger of apnea in the first 2-3 minutes after administration.**
- Continue with 10mg diazepam intravenously every 2 hours, until sedation is achieved or switch to the Alcohol 3 protocol if the patient is able to take oral medication.
- After sedation is achieved, switch to the Alcohol 2 protocol (commencing at the Day 1 point).

The dosage may need to be modified depending on severity of withdrawal, weight and presence of any physical disease.

	6 am	12 Mid-day	6 pm	12 mid- night
Day 1	10mg	10mg	10mg	10mg
Day 2	10mg	10mg	10mg	10mg
Day 3	5mg	5mg	5mg	10mg
Day 4	5mg	5mg	5mg	10mg
Day 5	Nil	5mg	Nil	5mg

For patients with severe alcohol withdrawal, especially when hallucinations are evident, it is advisable to supplement the diazepam regime with a major tranquilizer, such as haloperidol.

Give 2.5-5mg intramuscularly initially, repeat up to three times over the next hour, then every six hours as required, and then commence a regular dose of 2.5-5mg every six hours. Review the need for continued haloperidol after 48 hours.

For extra-pyramidal side-effects from the haloperidol, benztrapine 0.5-2mg is given IM or orally twice daily as required.

As an alternative to oral haloperidol, the atypical anti-psychotic risperidone 2mg twice daily or olanzapine 5- 10mg daily may be used which has fewer extra-pyramidal side- effects.



### **SYMPTOMATIC RELIEF**

- Antiemetics: Use reducing doses over 3 to 7 days (e.g. metoclopramide 10 mg 3 times a day)
- Antidiarrheal agents: These may be useful during the first two to three days.
- Antispasmodic agents: May help severe abdominal cramps. Hyoscine butylbromide 10 mg three times daily as needed. (up to 7 days).
- Non-steroidal anti-inflammatory drugs (NSAIDs) for muscle and joint pains. e.g. Ibuprofen 200-400 mg three times daily with food, or Paracetamol 1g 6/24 hour.
- Small doses of clonidine or propranolol may be useful in patients with uncontrolled hypertension
- Exclude, and treat, concurrent medical and/or psychiatric conditions

### **SUPPLEMENTS**

- Fluids and electrolytes: correct dehydration and fluid and electrolyte imbalance particularly hypokalaemia (e.g. with potassium supplements 80–240 mmol/day). In patients with little food intake prior to withdrawal, consider risk of refeeding syndrome.
- If there have been periods of prolonged immobility, which may cause rhabdomyolysis and acute kidney injury, check CPK; rehydrate and monitor fluid balance, turn regularly.
- Correct hypomagnesaemia
  - Magnesium is an essential co factor in thiamine-dependent enzyme systems and low magnesium levels may result in failure to respond to thiamine therapy.
  - Magnesium is contraindicated in renal failure.

### **AFTER CARE**

Pharmacotherapies aim to prevent relapse or lapse and/or to maintain abstinence from alcohol. They may do this through reducing craving and the internal drive to drink or by reducing the reward of drinking.

### **NALTREXONE**

It is one of two anti-craving drugs that have been shown to increase the likelihood of maintaining abstinence and reducing relapse following detoxification. Naltrexone has been reported to:

- Reduce craving for alcohol
- Increase time to first drink or 'lapse'
- Reduce volume and frequency of alcohol consumed
- Improve abstinence rates as compared to controls

Naltrexone is an opioid antagonist and therefore is not suitable if the patient is being prescribed opioids (e.g. for chronic pain) or is a recreational user of opiates.

If a patient has an impaired liver function (e.g. LFT's higher than three times normal range), care must be taken when prescribing naltrexone. It is advisable to repeat LFT's at seven days then as indicated. It should be avoided during pregnancy.

At least two days of abstinence from alcohol is recommended before initiating naltrexone.

Usually, 25mg is administered as an initial dose, with 50mg administered on subsequent days as a single daily dose. Compliance with naltrexone is improved with education, supervision and the care giver is encouraged to become involved with the naltrexone regime and after-care arrangements.

The optimum duration of treatment is unclear, however most studies recommend a minimum of three months. For many patients treatment for 12 months is appropriate.

### ACAMPROSATE

Acamprosate is an anti-craving drug that has similar beneficial effects to naltrexone, but acts in a very different way to this drug. It suppresses activity of the glutamate excitatory neurotransmitter system by inhibiting NMDA receptors. It also restores activity levels of GABA (inhibitory transmitter).

Acamprosate has been shown in several controlled trials to:

- increase abstinence rates when compared to controls at 12 months
- reduce relapse into heavy drinking
- reduce overall alcohol intake

Acamprosate is reported to have no sedative properties and unlike naltrexone, has no interaction with opiates.

Its most common side effect is diarrhea, vomiting and pruritus.

As the liver does not detoxify acamprosate, liver disease is not considered a contra-indication for treatment with acamprosate.

The recommended dose of acamprosate is two tablets (exact dose is required) three times daily for persons weighing in excess of 60kgs. For patients who weigh less than 60kgs, four tablets divided into three daily doses is recommended. The recommended duration of treatment is one year, and as is the case with naltrexone, acamprosate may be best administered in conjunction with CBT or other supportive counseling.

### TOPIRAMATE

This anticonvulsant has shown promise in decreasing alcohol intake, but side effects may be a barrier. It may reduce glutamatergic function and enhance GABA receptor activity or modulate impulsivity. Dose: titrate up to 150 mg twice daily, with a starting dose of 25 mg twice daily. Side effects: sedation, unsteadiness, paraesthesia, headache, dizziness, depression, anxiety, cognitive impairment, glaucoma. Topiramate may lead to weight loss, which may be of advantage to some obese patients. It is contraindicated in pregnancy.

## NEUROPSYCHIATRIC COMPLICATIONS

### Wernicke's Encephalopathy

Wernicke's encephalopathy is an acute reversible neuropsychiatric condition which occurs as a result of thiamine deficiency. It occurs mainly but not exclusively in individuals with alcohol use disorders who are malnourished and in those with malabsorption or repeated vomiting and diarrhea. Thiamine is an essential co-factor for many enzymes in the glycolytic and pentose phosphate pathways, and thiamine deficiency is due to low thiamine intake, impaired thiamine absorption, or impaired thiamine utilization. Wernicke's encephalopathy can present during the course of alcohol withdrawal or DTs, or while the individual is still drinking.

- It is characterized by one or more symptoms/signs from the classical triad: Oculomotor abnormalities:
  - Nystagmus
  - Ophthalmoplegia: paralysis or weakness, most common affecting lateral or upward gaze, often with diplopia  
(i.e. effects on external recti, e.g. sixth nerve palsy)
- Cerebellar dysfunction (ataxia)
- Confusion of recent onset (disorientation, inattention, poor responsiveness).

However, the full triad of symptoms is seen in only 16–20% of cases and the diagnosis is often missed. Patients with Wernicke's encephalopathy may present with nausea, vomiting and confusion, and rarely, hypothermia, hypotension, and coma. Autopsy studies show that Wernicke's pathology is 20 times more common than the classical triad, and is seen in 12.5% of people who misuse alcohol and in 0.4–2.8% of the general population. Wernicke's encephalopathy is difficult to differentiate from, and often coexists with, other causes of confusion/delirium. It is therefore commonly underdiagnosed, untreated, or inadequately treated. Wernicke's encephalopathy constitutes a medical emergency with an estimated mortality of 10–20% if untreated. It is easily reversible with the timely administration of adequate doses of parenteral thiamine. Most patients who do not recover promptly within the first 48–72 hours develop.

Korsakoff's syndrome with irreversible memory loss. There should be a high index of suspicion of Wernicke's encephalopathy/Wernicke Korsakoff syndrome (WE/KS) in patients with alcohol use disorders. Consider a diagnosis of Wernicke's encephalopathy in any confused patient with an alcohol use disorder until proven otherwise. Investigations for Wernicke's encephalopathy Where Wernicke's encephalopathy is clinically suspected, treatment with high-dose intravenous thiamine should commence before any investigations are carried out.

Treatment is generally safe and inexpensive and the consequences of delaying treatment can be lifelong disability.

Guidelines for the treatment of patients with suspected or established Wernicke's encephalopathy

- At least 500 mg thiamine IV (or IM), three times daily, for 5 days:
- Administer IV thiamine in 100 mL normal saline over 30 minutes.
- If no response to therapy is observed after this time, discontinue.
- If a response is observed, continue with 250–300 mg thiamine daily (oral or injectable as before?) for another 5 days, or longer if improvement continues.
- Follow with oral thiamine (dose is required?) and multivitamin supplementation thereafter and as an out-patient.

NB: for patients with enduring ataxia, polyneuritis or memory disturbance, high-potency vitamins should be given for as long as improvement continues

#### **Fetal Alcohol Syndrome (FAS)**

Women who drink alcohol during pregnancy can give birth to babies with fetal alcohol spectrum disorders, (FASDs). FASD is the umbrella term for a range of disorders. Fetal alcohol syndrome (FAS)

- partial fetal alcohol syndrome
- alcohol-related birth defects
- alcohol-related neurodevelopment disorder
- neurobehavioral disorder associated with prenatal alcohol exposure

FAS is a severe form of the condition. People with FAS may have problems with their vision, hearing, memory, attention span, and abilities to learn and communicate. While the defects vary from one person to another, the damage is often permanent.



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When a pregnant woman drinks alcohol, some of that alcohol easily passes across the placenta to the fetus. The body of a developing fetus doesn't process alcohol the same way as an adult does. The alcohol is more concentrated in the fetus, and it can prevent enough nutrition and oxygen from getting to the fetus's vital organs.

Damage can be done in the first few weeks of pregnancy when a woman might not yet know that she is pregnant. The risk increases if the mother is a heavy drinker. According to many studies, alcohol use appears to be most harmful during the first three months of pregnancy. However, consumption of alcohol any time during pregnancy can be harmful, according to guidelines from the American Academy of Pediatrics.

### Fetal Alcohol Syndrome Covers A Wide Range Of Problems:

- A smooth ridge between the upper lip and nose, small and wide-set eyes, a very thin upper lip, or other abnormal facial features small head
- Below average height and weight
- Hyperactivity
- Lack of focus
- Poor coordination
- Delayed development and problems in thinking, speech, movement, and social skills
- Poor judgment
- Problems seeing or hearing
- Learning disabilities
- Intellectual disability
- Heart problems
- Kidney defects and abnormalities
- Deformed limbs or fingers
- Mood swings

What are the treatments for fetal alcohol syndrome?

While FAS is incurable, there are treatments for some symptoms. The importance of mentioning this disorder in this protocol is to put emphasis on treating pregnant women who have alcohol related disorders and coordinate services between addiction therapist and obstetrician

## CHAPTER 2 BENZODIAZEPINES

### INTRODUCTION

Benzodiazepines are CNS depressants which act predominantly on gamma- aminobutyric acid (GABA) A receptor, the main inhibitory system in the brain. The benzodiazepines first introduced into clinical practice in the 1960s. Prior to the introduction of benzodiazepines, the most commonly available sedative-hypnotics were the barbiturates and non- barbiturate drugs, such as methaqualone and chloral hydrate. Benzodiazepines, because they are a much safer alternative to barbiturates, are now one of the most prescribed drugs on the market.

In Western societies, it is estimated that around 10% of adults regularly take benzodiazepines. Although in the past decade there has been a reduction of prescription benzodiazepines for day- time use in anxiety treatment, hypnotic use remains quite stable. Self- medication with benzodiazepines is common, particularly by those who are alcohol or opioid dependent, or who misuse psychostimulants.(1)

### BENZODIAZEPINE INTOXICATION

The patient with benzodiazepines intoxication may present with the followings:

- Inappropriate sexual or aggressive behavior.
- Mood lability
- Impaired judgment
- Slurred speech
- Incoordination
- Unsteady gait
- Nystagmus
- Impairment in cognition (e.g., attention, memory)
- Stupor or coma.
- Respiratory depression (Reduced respiratory rate (<10/min) or oxygen saturation (<90%)), is rare with oral benzodiazepine therapy but is possible when the IV route is used.
- In case of respiratory depression, give oxygen, raise legs, and ensure patient is not lying face down.
- Give flumazenil (a specific benzodiazepine antagonist) if benzodiazepine-induced respiratory depression suspected.
- Flumazenil has a much shorter half- life than diazepam, making close observation of the patient essential for several hours after administration.



**Box 7.13 Guidelines for the use of flumazenil**

<b>Indication for use</b>	If, after the administration of lorazepam, midazolam or diazepam, respiratory rate falls below 10/minute.
<b>Contraindications</b>	Patients with epilepsy who have been receiving long-term benzodiazepines.
<b>Caution</b>	Dose should be carefully titrated in hepatic impairment.
<b>Dose and route of administration</b>	<b>Initial:</b> 200 µg <b>intravenously</b> over 15 seconds – if required level of consciousness not achieved after 60 seconds, then, <b>subsequent dose:</b> 100 µg over 10 seconds.
<b>Time before dose can be repeated</b>	60 seconds.
<b>Maximum dose</b>	1 mg in 24 hours (one initial dose and eight subsequent doses).
<b>Side-effects</b>	Patients may become agitated, anxious or fearful on awakening. Seizures may occur in regular benzodiazepine users.
<b>Management</b>	Side-effects usually subside.
<b>Monitoring</b>	Respiratory rate
<b>What to monitor?</b>	Continuously until respiratory rate returns to baseline level.
<b>How often?</b>	Flumazenil has a short half-life (much shorter than diazepam) and respiratory function may recover and then deteriorate again. <b>Note:</b> If respiratory rate does not return to normal or patient is not alert after initial doses given, assume that sedation is due to some other cause.

Robert S., Mary A., Howland A., Lewis S., Lewis R. (2014). *Goldfrank's Toxicologic Emergencies*. 10<sup>th</sup> Edition, United States of America: The McGraw-Hill Education/Medical.

### **BENZODIAZEPINE WITHDRAWAL SYNDROME**

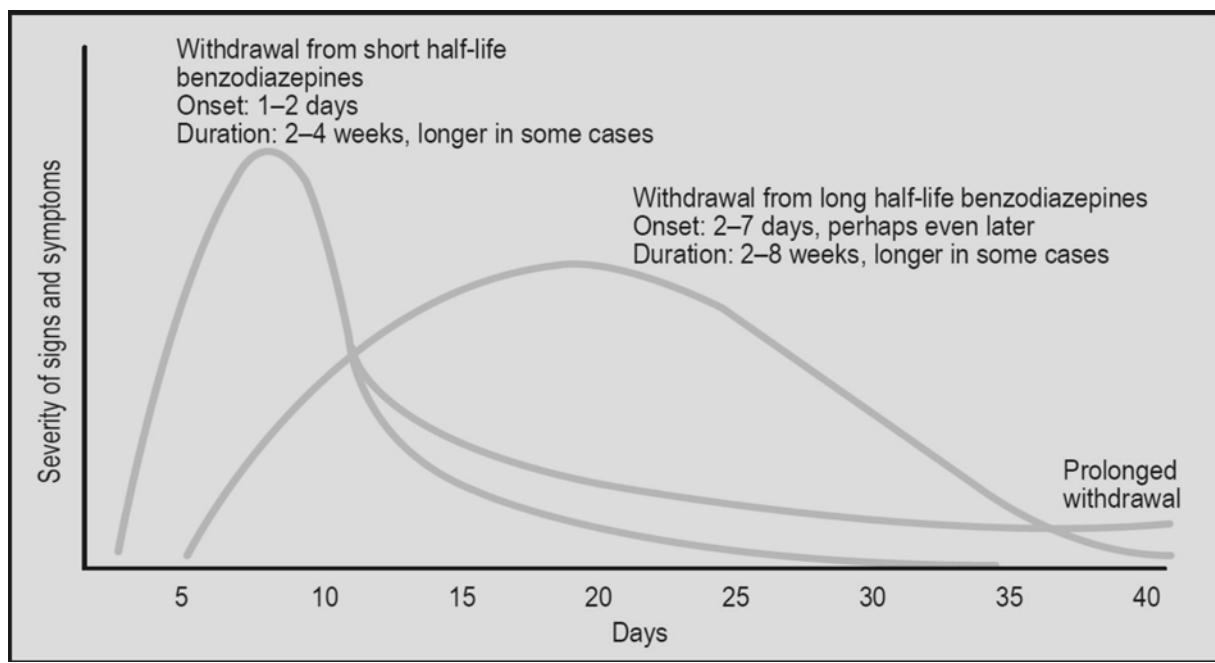
- The withdrawal syndrome for mono-dependent benzodiazepine users can vary from relatively mild to complex and high risk.
- In some cases, particularly those involving chronic use of high doses of short acting benzodiazepines, complications may be similar to those seen in complex alcohol withdrawal, including confusion or seizures.
- The risks of polydrug use should be considered in benzodiazepine withdrawal assessment and planning.
- The onset of benzodiazepine withdrawal is variable and dependent on factors such as dose, duration of use, individual susceptibility and half-life of drug.
- Onset of symptoms in short-acting benzodiazepines (e.g. alprazolam) may occur within 24 hours of last dose, while withdrawal may be occurring gradually and take from several days to weeks with long acting benzodiazepines such as diazepam or clonazepam.
- Severity of benzodiazepine withdrawal is also affected by multiple factors but is often worse with short half-life drugs such as alprazolam.
- In many cases of benzodiazepine withdrawal there are protracted low grade symptoms that may require care over a number of weeks or months.
- Benzodiazepine withdrawal symptoms may include:
  - Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm).
  - Hand tremor
  - Nausea or vomiting



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- Anxiety, irritability, insomnia and restlessness
- Abdominal discomfort
- Muscle aches
- Dysphoria, poor concentration and memory
- Less commonly, perceptual disturbances (like: Transient visual, tactile, or auditory hallucinations or illusions) and panic attacks
- Occasionally, seizures and symptoms of psychosis or confusion
- As shown in the figure below, the symptoms and duration of a benzodiazepine withdrawal vary.
- The amount and frequency of dose reduction is the most important factor affecting severity of the withdrawal syndrome.
- Additional contributing factors include:
  - Other drug dependence
  - History of seizures
  - Background of documented anxiety disorder, depression or trauma
  - Marked fluctuations in benzodiazepine doses used (e.g. due to prescription Shopping/illegal purchase)



Robert S., Mary A., Howland A., Lewis S., Lewis R. (2014). Goldfrank's Toxicologic Emergencies. 10th Edition, United States of America: The McGraw-Hill Education/Medical.

### Withdrawal Care:

- Benzodiazepine-dependent clients may experience mild, moderate or severe withdrawal.
- Clinical assessment and review of response to treatment will inform dosing and reduction regimens. For example, in cases of protracted uncomfortable withdrawal, doses of benzodiazepine may need to be maintained at a fixed level until the person



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feels able to continue reduction. Conversely, drowsiness during treatment may be reason to progress reduction of benzodiazepine more rapidly.

- All benzodiazepine withdrawal care involves ongoing regular monitoring in the initial stages of a client's presentation, with the frequency of reviews modified based on client response and stability. Biochemical testing through urine drug assays is often useful in management of benzodiazepine dependence.
- Level of dependence on benzodiazepines is affected by factors including duration of use and dose. For example, clients who consume large quantities of benzodiazepines within a short period of time (such as over 5-10 days for management of alcohol or other drug withdrawal) generally do not require a slow tapering benzodiazepine regimen as part of withdrawal care, and those on long term therapy of very small doses of benzodiazepines may cease without significant symptoms.
- While benzodiazepine conversion tables are a useful guide, most are based on mono dependent benzodiazepine users on near therapeutic doses of benzodiazepines.
- Conversion tables may not be as directly useful in clients with multiple drug use histories (including those on alcohol and/or prescribed drugs) or those using very high doses of benzodiazepines (see below).

### *Outpatient dosing regimen for therapeutic benzodiazepine users*

Client type/ setting	Withdrawal goal	Recommended regimen
Therapeutic users (regular dose of a long-acting benzodiazepine) in outpatient withdrawal	Reduction or stabilisation	<p>Tapered withdrawal</p> <ul style="list-style-type: none"> <li>• Convert the patient to diazepam and reduce by 10% every 1–2 weeks</li> <li>• When dose is at around 5 mg, reduce by 1 mg</li> <li>• Provide ongoing review, support and reassurance</li> <li>• Manage therapeutic issues underlying the benzodiazepine dependence</li> <li>• Supervised pick-up of doses should be based on a management plan in conjunction with a community prescribing doctor</li> </ul>

Source: Key informant interviews; CEAG

### *Conversion table for benzodiazepine/diazepam transfer*

Benzodiazepine (brand name)	Approximate equivalent to 5 mg diazepam
Alprazolam (Xanax, Kalma)	0.5 mg
Oxazepam (Serepax, Murelax)	30 mg
Clonazepam (Rivotril)	0.5 mg
Nitrazepam (Mogadon, Aldorm)	5 mg
Flunitrazepam (Hypnodorm)	1 mg
Lorazepam (Ativan)	0.5 mg

Source: Adapted from Ashton (2005)



**Benzodiazepine Withdrawal Scales:**

- Withdrawal symptoms from benzodiazepines are often “soft” and subjective and difficult to rate.
- In some cases, scales may be used.
- The Clinical Institute Withdrawal Assessment Scale-Benzodiazepines (CIWA-B) is a 22-item instrument designed to assess and monitor the type and severity of symptoms of benzodiazepine withdrawal (6).
- Note: Withdrawal scales should never be solely relied upon to monitor complex withdrawal as they may lack the sensitivity to detect progression to serious illness.
- Withdrawal monitoring should always include close clinical observation and judgment.

**Benzodiazepine withdrawal scale (CIWA-B)**

UR:									
Name:									
Address:									
DOB:									
Last Benzodiazepine use: Date: / /		Time: _____		AM/PM					
Amount last 24 hours: Name: _____				Dose: _____					
Date: _____									
Time: _____									
BLOOD PRESSURE									
PULSE									
TEMPERATURE per axilla									
RESPIRATIONS									
LEVEL OF CONSCIOUSNESS  1 Alert, obeys, oriented 2 Confused, responds to speech 3 Stuporous, responds to pain 4 Semi-comatose 5 Comatose									
PUPILS + reacts - no reaction B brisk S sluggish	SIZE (in mm)								
	REACTION								
MEDICATION GIVEN?									
NURSE INITIALS									
1 2 3 4 5 6 7 8		SCALE IN MM							

Person Report:						
For each of the following items, circle the number that best describes how you feel.						
Do you feel irritable?	0 Not at all	1	2	3	4 Very much so	
Do you feel fatigued?	0 Not at all	1	2	3	4 Unable to function	
Do you feel tense?	0 Not at all	1	2	3	4 Very much so	
Do you have difficulties concentrating?	0 Not at all	1	2	3	4 Unable to concentrate	
Do you have any loss of appetite?	0 Not at all	1	2	3	4 No appetite, unable to eat	
Have you any numbness or burning on your face, hands or feet?	0 No numbness	1	2	3	4 Intense burning/numbness	
Do you feel your heart racing? (palpitations)	0 No disturbance	1	2	3	4 Constant racing	
Does your head feel full or achy?	0 Not at all	1	2	3	4 Severe headache	
Do you feel muscle aches or stiffness?	0 Not at all	1	2	3	4 Severe stiffness or pain	
Do you feel anxious, nervous or jittery?	0 Not at all	1	2	3	4 Very much so	
Do you feel upset?	0 Not at all	1	2	3	4 Very much so	
How restful was your sleep last night?	0 Very restful	1	2	3	4 Not at all	
Do you feel weak?	0 Not at all	1	2	3	4 Very much so	
Do you think you didn't have enough sleep last night?	0 Very much so	1	2	3	4 Not at all	
Do you have any visual disturbances? (sensitivity to light, blurred vision)	0 Not at all	1	2	3	4 Very sensitive to light, blurred vision	
Are you fearful?	0 Not at all	1	2	3	4 Very much so	
Have you been worrying about possible misfortunes lately?	0 Not at all	1	2	3	4 Very much so	

**Clinician observations:**

Observe behaviour for restlessness and agitation	0 none, normal activity	1	2 restless	3	4 paces back and forth, unable to sit still
Observe tremor	0 No tremor	1 Not visible, can be felt in fingers	2 visible but mild	3 Moderate with arms extended	4 severe, with arms not extended
Observe for sweating – feel palms	0 no sweating visible	1 barely perceptible sweating, palms moist	2 palms and forehead moist, reports armpit sweating		

**Interpretation of scores:**

1–20 = mild withdrawal

21–40 = moderate withdrawal

41–60 = severe withdrawal

61–80 = very severe withdrawal

Ref: Bustos, U.E., Sykora, K. & Sellers, E.M. (1989). A clinical scale to assess benzodiazepine withdrawal. *Journal of Clinical Psychopharmacology*, 9 (6), 412–416.

## CHAPTER 3 OPIOIDS

### INTRODUCTION

Opium, one of the oldest known pharmacologic agents, is derived from the poppy Papaver somniferum. In general, a drug classified as an opiate or opioid elicits the same overall physiological effects as morphine.

### Common Opioid Substance, With Details of Approximately Equivalent Doses

Generic name	Approximate dose (mg)	Duration of analgesia (hours)	Half-life (hours)
Buprenorphine hydrochloride	0.3	4-8	20-73
Codeine phosphate	30-60	3-4	2-4
Diacetylmorphine	(converts to morphine)	4-5	2
Fentanyl citrate	0.1	1-1.5	3-4
Methadone 4-5hydrochloride	10	4-6	15-60
Morphine sulfate	10	4-5	2
Oxycodone hydrochloride	4.5	3-4	6.5

### **CLINICAL EFFECTS OF OPIOIDS:**

<i>Cardiovascular</i>	Peripheral vasodilation Orthostatic hypotension Bradycardia
<i>Dermatologic</i>	Flushing (histamine). Pruritus
<i>Endocrine</i>	Reduced ADH release, Reduced gonadotrophin release
<i>Gastrointestinal</i>	Reduced motility Reduced gastric acid secretion Increased biliary tract pressure Increased anal sphincter tone
<i>Neurologic</i>	Sedation, coma Analgesia Euphoria, Seizures (meperidine, propoxyphene), Antitussive
<i>Ophthalmic</i>	Miosis
<i>Pulmonary</i>	Respiratory depression Bronchospasm (histamine) Acute lung injury

### MANAGEMENT AND INTERVENTION STRATEGIES

There are three treatment pathways available for dependent Opioid users:

1. Intoxication management
2. Withdrawal management
3. Maintenance therapy



Drugs which bind to Opioid receptors is:

1. Agonist as methadone, morphine
2. Antagonist as naloxone
3. Partial agonist as buprenorphine

### **OPIOID INTOXICATION AND OVERDOSE**

Identified by a combination of three signs and symptoms known as Opioid overdose triad:

- Pinpoint pupils
- Unconsciousness
- Respiratory depression

#### **Management of Opioid Intoxication:**

- Hypoglycemia, hypoxia, and hypothermia are common clinical presentations that share features with opioid poisoning and may exist concomitantly.
- Each may be rapidly diagnosed with routinely available, real-time testing, but the proof of their existence does not exclude opioid toxicity.
- In such patients, however, clinical evidence is usually available to assist in diagnosis.

#### **Medication For Intoxication Management**

##### **Naloxone:**

- In the absence of a confirmatory history or diagnostic clinical findings, the cautious empiric administration of naloxone may be both diagnostic and therapeutic.
- Administration of naloxone to opioid-dependent patients may result in adverse effects; obviously, precipitation of an acute withdrawal syndrome should be anticipated. Additionally, emesis, a common.

Feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration (e.g., concomitant ethanol or sedative hypnotic exposure). This raises the risk for the pulmonary aspiration of vomitus if the airway is unprotected.

The decision to discharge a patient who awakens appropriately following naloxone administration is based on practical considerations, those patients manifesting only moderate signs of poisoning who remain normal for at least several hours following parenteral naloxone, and who have no other clinical concerns (e.g., suicide risk) are likely safe to discharge.

##### **Dose of Naloxone**

A dose of naloxone of 0.4 mg IV reverses the respiratory depressant effects of most opioids and is an appropriate starting dose in the non-opioid dependent patient. However, this dose usually produces withdrawal in an opioid-tolerant patient.

The goal is to reverse respiratory depression without inducing withdrawal. Consequently, 0.05 mg is a practical starting dose in most patients, increasing to 0.4 mg, then to 2 mg, and finally to 10 mg as needed. If there is no response to 10 mg, then an opioid is unlikely to be responsible for the respiratory depression.

Evaluation of the return of respiratory depression should be monitored continuously and intoxication symptoms should be treated with either repeated doses of the antagonist or, if necessary, with another bolus followed by a continuous infusion.

If intravenous access is unavailable, the intramuscular or subcutaneous route may be used, but the onset of action is delayed by 5–15 minutes after a 1mg dose.



### OPIOD WITHDRAWAL

Heroin is a relatively short-acting drug. Symptoms of withdrawal of heroin usually commence 6–24 hours after the last dose, reach a peak at 24–48 hours, and resolve after 5–10 days.

Withdrawal from a long-acting opioid such as methadone usually commences 36–48 hours after the last dose. The peak severity of withdrawal tends to be lower than for heroin withdrawal, but withdrawal may be more prolonged, lasting 3–6 weeks. The symptoms and signs of withdrawal from buprenorphine are similar to those found in withdrawal from other opioids, but withdrawal from buprenorphine is generally milder than withdrawal from methadone or heroin because of its slow dissociation from the  $\mu$ -receptor.

Symptoms commence generally within 3–5 days of the last dose and can last for several weeks. Following acute withdrawal, protracted, low-grade symptoms of discomfort (psychological and physical) may last many months.

#### Signs and symptoms of opioid withdrawal

SIGNS	SYMPTOMS
<input type="checkbox"/> RESTLESSNESS	<input type="checkbox"/> Anorexia and nausea
<input type="checkbox"/> YAWNING PERSPIRATION	<input type="checkbox"/> Abdominal pain
<input type="checkbox"/> RHINORRHOEA DILATED	<input type="checkbox"/> Hot and cold flushes
<input type="checkbox"/> PUPILS PILOERCTION	<input type="checkbox"/> Bone, joint and muscle pain
<input type="checkbox"/> MUSCLE TWITCHING (PARTICULARLY RESTLESS LEGS WHILE LYING DOWN)	<input type="checkbox"/> Insomnia and disturbed sleep
<input type="checkbox"/> VOMITING	<input type="checkbox"/> Cramps
<input type="checkbox"/> DIARRHEA	<input type="checkbox"/> Intense craving for opioids

#### Factors impacting severity of withdrawal

##### **Opioid Type:**

Withdrawal from longer acting opioids (e.g. methadone) is typically slower in onset and lasts longer (weeks to months). Withdrawal from partial agonists (e.g. buprenorphine) appears to be less severe.

##### **Opioid Dose:**

Higher doses are generally associated with greater withdrawal severity.

##### Duration of regular opioid use

A short history of regular use (e.g. < 6 months) is generally associated with a milder withdrawal syndrome.



### Common symptoms and time frames of heroin withdrawal

#### **Complications Associated With Heroin Use:**

Time since last heroin use	Common symptoms
6 to 12 hours	Runny eyes and nose, sneezing, yawning, sweating
12 to 24 hours	Agitation and irritability piloerection (goose bumps) sweating, hot and cold flushes loss of appetite
more than 24 hours	Strong urges (cravings) to use heroin stomach cramps, diarrhea, poor appetite, nausea, vomiting back pain, pain in joints, legs or arms, headache, poor sleep, lethargy, fatigue, restlessness, irritability, agitation, poor concentration hot and cold flushes, increased sweating
2nd to 4th day	Symptoms reach their peak
5th to 7th day	Most physical symptoms begin to settle down. Appetite returns
second week	'Physical' discomfort subsiding. May have ongoing problems with poor sleep, tiredness, irritability, cravings
weeks to months	Return of normal sleep, levels of activity and mood. Improvement in general health, and cravings reduce

#### **Overdose:**

Estimated mortality rate (from all causes) for heroin users is approximately 1–2% per year.

#### **Harms Related to Injecting**

Trauma and/or infection of injection sites: scarring, thrombosis, thrombophlebitis (injection marks), cellulites, Intra-arterial injection.

Systemic bacterial or fungal infections: septicemia, infective endocarditis (tricuspid valve involvement is the most common), pneumonia, osteomyelitis, and renal complications (glomerulonephritis).

Blood borne viruses (HIV, HCV and HBV).

#### **Assessment Of Opiate Withdrawal:**

By using Subjective Opiate Withdrawal Scale ( SOWS ). The SOWS is the person's assessment of their withdrawal symptoms, i.e. a person self-evaluation.

Persons are asked if they have suffered the symptoms in the last 24 hours and to rate each symptom according to severity.



Each item is rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Item	Score
<input type="checkbox"/> Do you have nausea or are you vomiting? <input type="checkbox"/> Do you have stomach cramps? <input type="checkbox"/> Do you have leg cramps &/or restless legs? <input type="checkbox"/> Are you having hot or cold flushes or shivering? <input type="checkbox"/> Is your heart pounding? <input type="checkbox"/> Do you have muscle tension? <input type="checkbox"/> Do you have aches and pains? <input type="checkbox"/> Are you yawning often? <input type="checkbox"/> Do you have a runny nose &/or weepy eyes? <input type="checkbox"/> Did you have sleeping problems last night?	
Total	

As this is a person self-evaluation the clinician's role is to assist the person to complete the task, not do it for them or interpret their symptomatology.

A suggested interpretation of the SOWS Scores:

Severity	SOWS Scores
Mild	1 – 10
Moderate	11 – 20
Severe	21 – 30

## MANAGEMENT OF WITHDRAWAL (DETOXIFICATION)

### Medication for Withdrawal Management

#### 1. Clonidine

Clonidine ( $\alpha$ -adrenergic agonist) effective in reducing 'autonomic' features (diarrhea, nausea, abdominal cramps, sweating, rhinorrhea); but less effective for sleep disturbances, aches, cravings. Clonidine is used in doses up to 300ug (2 tablets) 8th hourly (maximum dose is 6 tablets per day).

Clonidine helps control agitation and restlessness. However, the dose which can be employed is limited by side effects. Most patients will become somewhat hypotensive, and should be warned of this risk. It is generally safest to start with a dose of 150ug (1 tablet) every 6 hours, monitoring the symptomatic response and the patient's blood pressure.

Clonidine should be withheld if the systolic blood pressure falls below 90 or patients complain of lightheadedness.

#### 2. Symptomatic medications for opioid withdrawal

**Benzodiazepines:** for sleep, anxiety. Diazepam 10 mg to 30 mg per day (to maximum 40 mg / day), in 2 or 3 divided doses; or Midazolam 10 to 30 mg is given into divided doses, no longer than 10 days.

**Antiemetics:** Use reducing doses over 3 to 7 days (e.g. metoclopramide 10 mg three times daily).

**Antidiarrhoeal agents:** These may be useful during the first two to three days.

**Antispasmodic agents:** May help severe abdominal cramps. Hyoscine butylbromide 10 mg three times daily as needed (up to 7 days).

**NSAIDs:** For muscle and joint pains. Ibuprofen 200-400 mg three times daily as needed with food.

### 3. Treatment of Withdrawal by Buprenorphine or Methadone

#### Use of Buprenorphine in Opioid dependence

Buprenorphine is the principal treatment option for managing opioid withdrawal. It relieves symptom severity in opioid withdrawal so that other symptomatic medication is not usually required.

Buprenorphine can precipitate withdrawal in someone who has recently used heroin (in the previous 12 hours) or methadone (in the previous 48 hours).

Buprenorphine is registered as an analgesic (low dose sublingual tablets), and for the management of opioid dependence (high dose sublingual tablets). Buprenorphine is a partial opioid agonist (i.e. low activity)

**Contraindications to the use of buprenorphine include:**

- pregnancy, intolerance or allergy to buprenorphine or severe medical or psychiatric illness.

**Relative contraindications include:**

- respiratory deficiency, urethral obstruction, diabetes and poly drug use.

**The use of buprenorphine as one of two options:**

- i. Buprenorphine monotherapy.
- ii. Buprenorphine / naloxone combination treatment (Suboxone).

**Also two protocols in therapy:**

- i. Detoxification.
- ii. Maintenance Treatment.
- iii. A range of post-withdrawal treatment options available, including
  - a. transfer to maintenance buprenorphine
  - b. naltrexone treatment or
  - c. 'drug-free' rehabilitation.

#### BUPRENORPHINE MONOTHERAPY

The standard regime for opioid detoxification is based on the use of buprenorphine alone. Give 4-6 mg of buprenorphine as the first dose. Review the patient 3-4 hours after the first dose. If the patient is experiencing no increase in withdrawal severity and is still reporting withdrawal, give another 2-4 mg of buprenorphine.

Buprenorphine is more effective than symptomatic medications in reducing withdrawal symptoms and more effective in retaining patients through the withdrawal episode and beyond into post-withdrawal treatment.

This protocol is used for home or ambulatory heroin detoxification using buprenorphine as a substitution pharmacotherapy. It is included for reference and for use in settings where once daily dosing is necessary.

The recommended duration of treatment with buprenorphine for the management of heroin withdrawal is 4 – 8 days.

This short regime ensures the treatment covers the time when heroin withdrawal symptoms are most severe (typically up to 4 or 5 days), and then is promptly discontinued thereby minimizing rebound withdrawal phenomena and limiting the duration of withdrawal discomfort.

Some flexibility is allowable in doses to accommodate a range of factors, such as amount of heroin use and psychological condition, impacting on the person's individual dosing requirements and withdrawal severity.

Combined use of other sedative substances (e.g., benzodiazepines, opioids, alcohol, and tricyclic antidepressants) with buprenorphine can be extremely dangerous and may result in respiratory depression, coma and death.

Buprenorphine S/L	Proposed regime	Recommended lower and upper limits
Day 1	6mg	4 to 8mg
Day 2	8mg	4 to 12mg
Day 3	10mg	4 to 16mg
Day 4	6mg	2 to 12mg
Day 5	4mg	0 to 8mg
Day 6		0 to 4mg
Day 7		0 to 2mg
Day 8		0 to 1mg

### Buprenorphine prolonged-release solution for injection

#### Dosing forms:

Weekly dosing: 8 mg, 16 mg, 24 mg and 32 mg prolonged-release solution for injection

Monthly dosing: 64 mg, 96 mg and 128 mg prolonged-release solution for injection

#### Therapeutic indications:

Treatment of opioid dependence within a framework of medical, social and psychological treatment, the treatment is intended for use in adults and adolescents aged 16 years or over.

#### Posology and method of administration:

Administration of Buprenorphine prolonged-release solution for injection is restricted to healthcare professionals. Appropriate precautions, such as to conduct patient follow-up visits with clinical monitoring according to the patient's needs, should be taken when prescribing and dispensing buprenorphine. Take-home use or self-administration of the product by patients is not allowed.

#### Precautions to be taken before initiation of treatment:

To avoid precipitating symptoms of withdrawal, treatment with Buprenorphine prolonged-release solution for injection should be started when objective and clear signs of mild to moderate withdrawal are evident. Consideration should be given to the types of opioid used (that is long- or short-acting opioid), time since last opioid use and the degree of opioid dependence.

- For patients using heroin or short-acting opioids, the initial dose of Buprenorphine prolonged-release solution for injection must not be administered until at least 6 hours after the patient last used opioids.
- For patients receiving methadone, the methadone dose should be reduced to a maximum of 30 mg/day before starting treatment with Buprenorphine prolonged-release solution for

injection which should not be administered until at least 24 hours after the patient last received a methadone dose. Buprenorphine prolonged-release solution for injection may trigger withdrawal symptoms in methadone-dependent patients.

#### Posology

Initiation of treatment in patients not already receiving buprenorphine; Patients not previously exposed to buprenorphine should receive a sublingual buprenorphine 4 mg dose and be observed for an hour before the first administration of weekly Buprenorphine prolonged-release solution for injection to confirm tolerability to buprenorphine.

The recommended starting dose of Buprenorphine prolonged-release solution for injection is 16 mg, with one or two additional 8 mg doses at least 1 day apart, to a target dose of 24 mg or 32 mg during the first treatment week. The recommended dose for the second treatment week is the total dose administered during the week of initiation.

Treatment with monthly Buprenorphine prolonged-release solution for injection can be started after treatment initiation with weekly Buprenorphine prolonged-release solution for injection, in accordance with the dose conversion in Table 2 and once patients have been stabilized on weekly treatment (four weeks or more, where practical).

Switching from sublingual buprenorphine products to Buprenorphine prolonged-release solution for injection; Patients treated with sublingual buprenorphine may be switched directly to weekly or monthly Buprenorphine prolonged-release solution for injection, starting on the day after the last daily buprenorphine sublingual treatment dose in accordance with the dosing recommendations in Table 1. Closer monitoring of patients is recommended during the dosing period after the switch.

**Table 1. Conventional sublingual buprenorphine daily treatment doses and recommended corresponding doses of weekly and monthly Buvidal**

Dose of daily sublingual buprenorphine	Dose of weekly Buvidal	Dose of monthly Buvidal
2-6 mg	8 mg	
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

The dose of buprenorphine in mg can differ between sublingual products, which needs to be taken into consideration on a product-by-product basis.

#### Maintenance treatment and dose adjustments

Buprenorphine prolonged-release solution for injection can be administered weekly or monthly. Doses may be increased or decreased, and patients can be switched between weekly and monthly products according to individual patient's needs and treating physician's clinical judgement as per recommendations in Table 2. Following switching, patients may need closer monitoring. Assessment of long-term treatment is based on 48-week data.

**Table 2. Recommended dose conversion when switching from weekly to monthly dosing or from monthly to weekly dosing**

Weekly dose of Buvidal	Monthly dose of Buvidal
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg



#### Supplemental dosing

A maximum of one supplemental Buprenorphine prolonged-release solution for injection 8 mg dose may be administered at an unscheduled visit between regular weekly and monthly doses, based on individual patient's temporary needs. The maximum dose per week for patients who are on weekly Buprenorphine prolonged-release solution for injection treatment is 32 mg with an additional 8 mg dose. The maximum dose per month for patients who are on monthly Buprenorphine prolonged-release solution for injection treatment is 128 mg with an additional 8 mg dose.

#### Missed doses

To avoid missed doses, the weekly dose may be administered up to 2 days before or after the weekly time point, and the monthly dose may be administered up to 1 week before or after the monthly time point.

If a dose is missed, the next dose should be administered as soon as practically possible.

#### Termination of treatment

If Buprenorphine prolonged-release solution for injection treatment is discontinued, its prolonged-release characteristics and any withdrawal symptoms experienced by the patient must be considered. If the patient is switched to treatment with sublingual buprenorphine, this should be done one week after the last weekly dose or one month after the last monthly dose of Buprenorphine prolonged-release solution for injection according to the recommendations in Table 1.

#### BUPRENORPHINE/NALOXONE (SUBOXONE)

Before initiating buprenorphine induction, patients should have discontinued the use of illicit opioids and should be exhibiting the early symptoms of withdrawal.

#### Induction Phase

An initial 4/1 mg dose of buprenorphine/ naloxone is recommended. This dose can be followed in 2–4 hours with a second dose of 4/1 mg, if indicated.

Over the next 2 days, the dose of buprenorphine/naloxone should be increased to 12/3–16/4 mg per day.

#### Dose Reduction Phase (one of three):

##### A. Long-Period Reduction

- a. Use of buprenorphine for gradual detoxification over long periods is probably more effective than its use for rapid detoxification over short or moderate periods.
- b. Patients who are unwilling or unable to engage actively in rehabilitation services without agonist support may benefit from long-term detoxification (or, even more so, from maintenance treatment).

##### B. Moderate-Period Reduction

- a. Patient can be detoxified over a 10- to 14-day (or longer) period by gradually decreasing the initial stabilization dose of buprenorphine (usually 8–16 mg per day) by 2 mg every 2–3 days.
- b. It is extremely important that patients engage in rehabilitation programs during the detoxification period.



### C. Short-Period Reduction

- a. Patients with a compelling reason to achieve an opioid-free state quickly (e.g., impending incarceration, foreign travel, job requirement) may have their buprenorphine dose reduced over 3 days and then discontinued.

When compared to clonidine for the treatment of short-term opioid withdrawal, buprenorphine is better accepted by patients and more effective in relieving withdrawal symptoms.

## **MAINTENANCE THERAPY**

### **Substitution with Buprenorphine**

Treatments pass in three steps:

1. Induction
2. stabilization, and
3. maintenance.

#### **Induction Phase**

**Duration:** approximately 1 week.

**Goal:** find the minimum dose of buprenorphine at which:

1. Experiences no withdrawal symptoms
2. Minimal or no side effects.
3. No uncontrollable cravings for drugs of abuse. In pregnancy give monotherapy, not Suboxone.

#### **Day 1:**

A minimum of 12–24 hours should have elapsed since the last use of opioids.

**Dose:** initial dose of Suboxone is 4/1 mg and, if withdrawal symptoms relieved, so Day 1 dose established.

But if not relieved after 2 hours, a second dose of 4/1 mg can be administered.

The total amount of buprenorphine administered in the first day should not exceed 8 mg.

If patient withdrawal controlled over this Day 1, daily dose established equal to total Suboxone administered (4/1 or 8/2mg), this is maintained over next 6 days.

If withdrawal symptoms are still not relieved on Day 1, symptomatic relief with non- opioid medications should be provided and the patient asked to return the following day for dose management.

#### **Day 2:**

Day 2 give patient 4/1 mg Suboxone and if withdrawal is not controlled the induction dose would be 12/3mg followed over rest of the week.

If not controlled after 2 hours, give another 4/1 mg (maximum 16/4 mg total on Day 2)

On subsequent induction days, if the patient returns experiencing withdrawal symptoms, continue dose increases as per the schedule shown above, up to a maximum of 32/8mg Suboxone per day.

#### **Stabilization Phase**

The induction phase is completed and the stabilization phase (usual duration approximately 1 to 2 months).

Doses of buprenorphine/naloxone may be increased in 2/0.5–4/1 mg increments per week until stabilization is achieved.



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Nearly all patients will stabilize on daily doses of 16/4–24/6 mg; some, however, may require up to 32/8 mg daily.

### Maintenance Phase

The longest period that a patient is on buprenorphine is the period of maintenance. This period may be indefinite.

### Issues that will need continual monitoring are:

1. Attention to the psychosocial and family issues.
2. Cravings control and preventing relapse.

### Substitution With Methadone

Is a long-acting synthetic opioid which can be used for both withdrawal and maintenance treatment.

#### Issues include:

Opioid-like side effects (usually mild and tolerable) are common during first few days.

An authorized medical practitioner requires a permit to prescribe methadone, and it is dispensed under supervision at an authorized pharmacy.

Withdrawal discomfort generally increases as the patient reduces their methadone dose, with greatest discomfort experienced when/soon after the patient ceases their methadone, and can continue for several days. This limits the use of methadone in inpatient settings.

Other medications for opioid withdrawal are not routinely required until the patient has reduced their methadone dose. Caution about using other sedating drugs (benzodiazepines, alcohol).

Methadone can be used in short regimes (e.g. 7 to 14 days), or longer regimes with gradual reduction over weeks. Commence with doses between 20 and 30 mg. Dose is reduced according to proposed duration of regime (e.g. start 25 mg, reduce by 2.5 mg per day for 10-day regime).

## CHAPTER 4 PSYCOSTIMULANTS

### INTRODUCTION

Psychostimulants are substances that increase CNS arousal and are typically sympathomimetics, acting like noradrenaline to increase cardiovascular tone and activity. The term psychostimulants refer to both naturally occurring substances and the many synthesized drugs whose primary actions are CNS stimulation.

Naturally occurring psychostimulants have been used by human beings for thousands of years. They include:

- Caffeine (a constituent of coffee and tea)
- Cocaine (coca leaves)
- Ephedra
- Khat.

In addition to plant- based psychostimulants, there are numerous synthetic products, such as amphetamine- type stimulants (AT S) and their derivatives (e.g. Fenethylline- Captagon).

### Management Stimulant Intoxication

- Up to three-quarters of stimulant users report paranoia or psychotic symptoms associated with their use, although the contribution of acute versus chronic stimulant exposure is often unclear.
- Patients with stimulant-induced psychoses may closely resemble those with acute schizophrenia.
- Very severe stimulant intoxication may produce an excited delirium or organic brain syndrome that can be fatal.
- Patients should be evaluated promptly for an acute neurologic lesion (e.g., intracranial bleeding) or a pre-existing neuropsychiatric condition and be treated aggressively.
- Drug overdose must be managed in the ER of a general Hospital or a center equipped to receive such cases with an internal medicine team on place.

### Management of Psychological and Behavioral Effects of Stimulant Intoxication:

- A thorough drug use history with drug toxicology.
- As the patient's condition permits, further evaluation should rule out other
  - ✓ Potential medical (hyperthyroidism, hypoglycemia)
  - ✓ Neuropsychiatric (panic or bipolar affective disorder) conditions.

#### a) Non-pharmacological Approach:

All procedures should be explained to the patient before initiation. The "ART" Approach:

- ✓ **Acceptance** of the patient's immediate needs (such as pain relief or use of the bathroom).
- ✓ **Reassurance** that the condition is due to the drug and likely will dissipate within a few hours.
- ✓ "**Talk down**": to provide reality orientation and avoid hostility.
- ✓ The use of physical restraints to control agitation or violent behavior should be avoided unless absolutely necessary.



The use of restraints can increase the risk of hyperthermia and rhabdomyolysis, with resulting severe medical complications.

b) Pharmacological Approach

- If medication is needed, most experts prefer Benzodiazepines (such as diazepam [10 to 30 mg PO or 2 to 10 mg IM or IV] or lorazepam [2 to 4 mg PO or 1 to 2 IM or IV]) to control severe agitation, anxiety, or psychotic symptoms.
- Parenteral benzodiazepine dosing may be repeated every 5 to 10 minutes until light sedation is achieved.
- If an antipsychotic is needed to control psychosis, a high-potency agent such as haloperidol (5 to 10 mg PO, IM, or IV), or risperidone (2 to 4 mg PO) is preferred because of its minimal anticholinergic activity.
- Anticholinergic activity should be avoided because it may contribute to delirium and hyperthermia (by impairing heat dissipation from sweating).
- A psychotic or agitated patient who has not responded to initial treatment should be hospitalized until the episode has resolved.
- Transient psychotic symptoms during periods of abstinence ("flashbacks") have been reported among methamphetamine users

c) Management of Medical Effects of Stimulant Intoxication

- Maintenance of basic life support functions. Vital signs, hydration status, and neurologic status should be monitored closely.
- Activated charcoal or gastric lavage with isotonic saline. Activated charcoal (50 to 100 g orally) may be just as effective as gastric lavage and minimizes the risk of aspiration.
- Basic laboratory investigations with drug toxicology screen and HIV testing and screening for hepatitis.
- Severe hypertension (e.g., diastolic blood pressure > 120) that lasts more than 15 minutes should be treated promptly to avoid CNS hemorrhage
- Benzodiazepines in sedative doses are the initial treatment of choice for both acute cardiovascular and CNS toxicities from stimulants.
  - Hypertension or tachycardia that does not respond to sedation alone may be treated with an alpha-adrenergic blocker such as phentolamine (2 to 10 mg IV over 10 minutes).
  - If alpha-adrenergic blockade is ineffective, direct vasodilation with sodium nitroprusside infusion (0.25 to 10 µg/kg/min) or nitroglycerin (5 to 100 µg IV) can be used

**1. Treatment of cocaine-induced cardiac tachyarrhythmia**

It begins with correction of any exacerbating conditions such as myocardial ischemia, hypoxia, electrolyte abnormalities, or acid-base disturbance.

- ✓ Arrhythmias occurring several hours after cocaine use are usually secondary to myocardial ischemia. Standard arrhythmia management is usually appropriate, including use of lidocaine.
- ✓ Arrhythmias occurring immediately after cocaine use are usually from the sodium channel blocking action of cocaine. These may respond to sodium bicarbonate.

**2. The treatment of stimulant-associated acute coronary syndrome**

- ✓ Largely resembles that for the non-drug-associated syndrome
- ✓ Avoiding use of beta-adrenergic blockers and labetalol
- ✓ Angioplasty may be preferable to fibrinolysis because of the increased risk of intracranial hemorrhage in cocaine users

**3. Elevated body temperature (> 38.5 C orally)**

- ✓ It is a marker for poor prognosis and should be managed aggressively to avert **hyper thermic crisis** (as by cold water sponging, cooling blankets, ice packs, ice water gastric lavage, or cold peritoneal lavage).
- ✓ Untreated hyperthermia may result in rhabdomyolysis and renal failure.

**4. Seizures**

- ✓ Intravenous benzodiazepines (diazepam 5 to 10 mg or lorazepam 1 to 2 mg over 2 minutes, repeated as needed) are recommended to control seizures stemming from stimulant intoxication.
- ✓ Phenobarbital (15 to 20 mg/kg over 20 minutes) also can be used.

**Management of Stimulant Withdrawal**

- Symptoms of stimulant withdrawal are best treated supportively with rest, exercise, and a healthy diet.
- Short-acting benzodiazepines such as lorazepam may be helpful in selected patients who develop agitation or sleep disturbance.
- Severe (suicidal ideation) or persistent (>2 to 3 weeks) **depression** may require antidepressant treatment and psychiatric admission.

## CHAPTER 5

## CANNABIS

### INTRODUCTION

Cannabis is the most commonly used illicit drug worldwide. Cannabis is the general name used for the products of the plant Cannabis sativa. A dry, shredded green/brown mix of flowers, stems, seeds, and leaves of the hemp plant Cannabis sativa is called marijuana. As a more concentrated, resinous form it is called hashish and, as a sticky black liquid, hash oil. Marijuana smoke has a pungent and distinctive, usually sweet-and sour odor. There are countless street terms for marijuana including herb, grass, and hash.

Cannabis sativa contains over 400 chemical substances, about 60 are responsible for its unique effects. The principal psychoactive ingredient is delta-9-tetrahydrocannabinol (THC). THC content varies greatly (from 0.5–12%), depending on genetic and environmental factors and the method of preparation.

THC is lipophilic and rapidly taken up by fatty tissue. This results in a slow elimination of metabolites. Psychotropic effects of cannabis are maximal at 20 minutes and last for 2–4 hours.

### Toxicity

Overall, toxicity arising from cannabinoid use is mild. Even when large doses are used, the effects are not usually prolonged or life threatening.

### Clinical Presentation

- Subjective effects after smoking a marijuana cigarette include euphoria, palpitations, heightened sensory awareness, and altered time perception followed after about 30 minutes by sedation. More severe intoxication may result in impaired short-term memory, depersonalization, visual hallucinations, and acute paranoid psychosis. Occasionally, even with low doses of THC, subjective effects may precipitate a panic reaction.
- Physical findings may include tachycardia, orthostatic hypotension, conjunctival injection, incoordination, slurred speech, and ataxia. Stupor with pallor has been observed in children after they have eaten marijuana cookies.
- Other health problems include salmonellosis and pulmonary aspergillosis from use of contaminated marijuana. Marijuana may be contaminated by paraquat, but the latter is destroyed by pyrolysis and there have been no reports of paraquat toxicity from smoking marijuana.
- Intravenous use of marijuana extract or hash oil may cause dyspnea, abdominal pain, fever, shock, disseminated intravascular coagulation, acute renal failure, and death.

### Psychological and Neurologic Effects

Marijuana's effects on central nervous system functions such as:

- Behavior
- Cognition
- Perception
- Performance
- Increased appetite
- General difficulty in concentration
- Short-term memory loss



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Individuals who consume low to moderate quantities generally report a feeling of well-being and pleasant relaxation, euphoria, a dreamlike state, alteration of time and space perception, and a heightening of their senses.

Smoking a **large quantity** of marijuana can produce a range of effects including:

- Mild anxiety
- Paranoid behavior
- Acute psychosis
- Problems in dealing with reality
- Fine tremor
- Ataxia
- Obsessional thought content
- Delusions, hallucinations, illusions, and bizarre behavior

Uncommon cannabinoid-induced symptoms may include severe panic and anxiety states, paranoia, depression, personality changes, confusional states, and psychoses, which are indistinguishable from primary psychiatric syndromes unless the drug-induced etiology is known.

### Respiratory Effects

Inhalation of marijuana smoke is associated with

- Rhinitis
- Pharyngitis
- Laryngitis
- Cough
- Hoarseness
- Bronchitis
- Bronchodilatation in both normal and asthmatic patients
- Chronic bronchitis

Uncommon adverse effects include

- Pneumothorax
- Pneumomediastinum from the Valsalva maneuver that marijuana users frequently employ in an attempt to increase THC absorption by the lung.
- Compared to tobacco smoke, marijuana smoke contains threefold more tar and results in fivefold higher carbon monoxide concentrations.
- Marijuana smoke has also revealed high concentrations of carcinogenic hydrocarbons.

### Cardiovascular Effects

- Sinus tachycardia
- Orthostatic hypotension
- ECG changes in intoxicated individuals include
  - nonspecific ST-T changes
  - Premature ventricular contractions
- Atrial fibrillation is rare
- Increase Risk of myocardial infarction

These effect associate with dose and No long-term cardiovascular effects have been described



### **Reproductive Effects**

- No definitive evidence shows that marijuana use alters reproductive function in either gender to such an extent that reproduction is compromised.
- Even when lower testosterone levels have been noted, the levels have been within normal limits.
- Whether long-term use of marijuana might result in persistently depressed levels of serum testosterone is unknown.
- An increased incidence of gynecomastia and elevated estrogen levels have been noted in some men who use marijuana chronically.
- Studies of the semen of male long-term users found abnormalities in count, motility, and structural characteristics of the sperm examined.

### **Treatment**

- I. **Emergency and supportive measures**
  - a. Most psychological disturbances may be managed by simple reassurance, possibly with adjunctive use of lorazepam, diazepam, or midazolam
  - b. Sinus tachycardia usually does not require treatment but if necessary may be controlled with beta blockers.
  - c. Orthostatic hypotension responds to head-down position and intravenous fluids.
- II. **Specific drugs and antidotes.**
  - a. There is no specific antidote.
- III. **Decontamination**
  - a. Only after ingestion
- IV. **Enhanced elimination**
  - a. These procedures are not effective owing to the large volume of distribution of cannabinoids.

### **WITHDRAWAL**

#### **Onset and duration of cannabis withdrawal:**

Most symptoms commence on day 1, peaking at day 2–3, returning to baseline after a week or two. However, there is temporal variation in the profile of specific symptoms, with the late onset of aggression (day 4) and anger (day 6) being particularly significant, with the former often peaking after 2 weeks of abstinence.

#### **Symptoms of cannabis withdrawal**

Clinical studies suggest that 50%–75% of dependent cannabis users will experience four or more symptoms, with sleep disturbance, reduced appetite, irritability, anger and aggressiveness occurring in at least 40%.

#### **Symptoms of cannabis withdrawal**

Common symptoms	Less common Symptoms
Anger or aggression	Chills
Decreased appetite or weight loss	Depressed mood
Irritability	Stomach pain
Nervousness/anxiety	Shakiness
Restlessness	Sweating
Sleep difficulties, including strange dreams	



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### Cannabis withdrawal chart

Patient MRN label here:

DATE:							
TIME:							
SCORES: 0 – not at all, 1 – mild, 2 – moderate, 3 – severe							
SYMPTOM							
Craving for marijuana							
Decreased appetite							
Sleep difficulty							
Increased aggression							
Increased anger							
Irritability							
Strange dreams							
Restlessness							
Chills							
Feverish feeling							
Stuffy nose							
Nausea							
Diarrhea							
Hot flashes							
Dizziness							
Sweating							
Hiccups							
Yawning							
Headaches							
Shakiness							
Muscle spasms							
Stomach pains							
Fatigue							
Depressed mood							
Difficulty concentrating							
Nervousness							
Violent outbursts							
<b>TOTAL SCORE</b>							
Person completing assessment (INITIAL)							

### CANNABIS DETOXIFICATION

#### Pharmacotherapies

There are no specific pharmacotherapies that have proven utility in managing cannabis withdrawal or maintaining abstinence.

Users should refrain from caffeinated drinks during the withdrawal period, as they may increase restlessness, irritation and insomnia.

#### Medications to consider for different symptom clusters in cannabis withdrawal

Symptom	Medication
Sleep problems	benzodiazepines, zolpidem, promethazine
Restlessness, anxiety, irritability	Diazepam
Stomach pains	hyoscine (Buscopan), atrobel
Physical pain, headaches	paracetamol, non-steroidal anti-inflammatory agents
Nausea	promethazine, metoclopramide

#### Symptomatic relief by symptom cluster

Given the wide interpersonal variability in the response to cannabis withdrawal, dosages and prescribing schedules for symptomatic relief will most effectively be decided upon only after thoroughly exploring the individual patient's symptom profile and circumstances.

#### Outpatient (Oral medications) regimens might be:

7 days of diazepam 5 mg four times daily, NSAIDs/buscopan as needed; or 7 days of zolpidem 7.5 mg at night.

Inpatient regimens should not use other medication types, but there may be a need to use higher doses of selected pharmacotherapies, administered for a longer period.

Regular patient contact and monitoring, either via clinic visits or telephone, can be useful in adjusting drug selection and dose.

Monitoring should continue when withdrawal is complete and medication ceases, to identify any psychiatric symptoms that were previously masked or latent.

Routine outpatient follow-up during the first 2–4 weeks should be offered.

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