INVITED ARTICLE

# Poisoning with Drugs of Abuse: Identification and Management

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## Abstract

Substances of abuse include alcohol, nicotine, cannabinoids, opioids, sedatives, volatile solvents, stimulants, and hallucinogens. With the increasing prevalence of drug abuse in India, intensivists are likely to encounter more cases of intentional and accidental poisoning due to drugs of abuse. We aim to sensitize the intensivists to challenges involved in diagnosing and treating poisoning with drugs of abuse. We also aim to provide a hands-on primer that can augment the usual protocols of "approach to life-threatening poisoning". A toxidrome approach along with urine drug testing can help in speedily arriving at a diagnosis and instituting definitive treatment. In this article, we discuss spurious alcohol poisoning (methanol poisoning), benzodiazepine, opioid, and stimulant poisoning in detail and poisoning due to other substances including newer psychoactive substances is discussed briefly.

**Keywords:** Accidental poisoning, Benzodiazepine, Cocaine, Flumazenil, Malignant hyperthermia, Methanol, Naloxone, Opioids, Overdose, Stimulant.

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## Introduction

Poisoning is a common cause of accidental death and injury in India, accounting for 1,61,819 deaths between 2011 and 2015.[1] Pharmaceutical agents are common culprits of poisoning. Pharmaceutical agents illustrate Paracelsus's dictum, the difference between remedy and medicine is the dose; thus, the terms poisoning and overdose are used interchangeably in the literature. In this article, we review drugs of abuse commonly implicated in poisoning with a focus on India.

Drugs of abuse consist of nine classes of substances—alcohol, opioids, cannabinoids, sedative-hypnotics, cocaine, and stimulants including caffeine, hallucinogens, tobacco, and volatile solvents.[2] Based on the dominant effects on the central nervous system (CNS) and autonomic nervous system, we can classify them into depressants, stimulants, and drugs with variable effects (Table 1).

A recent nationwide survey has reported prevalence of current use of various substances—alcohol, 14.6%, cannabis, 2.8%, opioids, 2.1%, sedatives, 1.1%, solvents, 0.9%, amphetamine-type stimulants (ATSs), 0.2%, cocaine, 0.1%, and hallucinogens, 0.1%.[3] While these figures are worrying by themselves, we must note that poisoning with drugs of abuse can as well occur in subjects who do not abuse them. For example, intentional overdose with sedatives led to 3,113 deaths between 2011 and 2015.[1] Therefore, intensivists should have an orientation toward diagnosing and treating poisoning due to drugs of abuse. With the increasing abuse of various groups of drugs, it is likely that such poisoning may present to physicians at various levels of care, who should be able to recognize and stabilize such patients.

There are multiple determinants of the likelihood of poisoning and its severity due to each class of drugs, as shown in Table 2.

Keeping in mind these determinants and relative availability and popularity of each class of drugs in India, we have focused on spurious alcohol, benzodiazepine, opioid, and stimulant poisoning in this article.

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## Approach to a Case of Suspected Poisoning Due to Drugs of Abuse

In addition to the standard approach to suspected poisoning in adults and children, there are some considerations when the poisoning is suspected to be due to drugs of abuse.

### History

Frequently patient may be able to give some indication of types and number of drugs involved. Especially if patients arrive in a conscious and oriented state, every attempt should be made to obtain history before they decompensate. A direct, nonjudgemental, and confidential inquiry by removing the attenders from bedside helps in getting information. Family members can provide vital cues—withdrawn and secretive behavior, change in sleep-wake patterns, weight loss, drug paraphernalia, and earlier episodes of overdose. An astute physician will engage the peers of the patient if available as they may be better informed than family members.

**Table 1:** Classification of drugs of abuse based on predominant effects on central and autonomic nervous system

| *Stimulants* | *Depressants* | *Variable effects* |
|---|---|---|
| Cocaine | Alcohol | Cannabinoids |
| Amphetamine-type stimulants: amphetamine, methamphetamine, methylphenidate, and ephedrine | Benzodiazepines | Classic hallucinogens: lysergic acid diethylamide (LSD), mescaline (peyote), psilocybin (mushrooms), and dimethyltryptamine (DMT) |
| Cathinone: Khat and derivatives | Z-drugs: zolpidem, zaleplon, zopiclone, and eszopiclone | Anticholinergic dissociative: scopolamine |
| Mephedrone and derivatives: "meow-meow" | Barbiturates | Dissociative hallucinogens: phencyclidine, ketamine, and salvinorin |
| Methylenedioxy-methamphetamine (MDMA) and derivatives: ecstasy | Opioids | Synthetic cannabinoids: spice |
| Caffeine and nicotine | Volatile solvents | Designer hallucinogens: *N*-methoxy-benzyl (NBOMe) series |
| Modafinil | Methaqualone | Carisoprodol |

**Table 2:** Determinants of poisoning due to drugs of abuse

| *S. no.* | *Determinants* | *Subdeterminants* | *Examples* |
|---|---|---|---|
| 1 | Drug-specific | Narrow therapeutic index | Methanol |
| | | | Barbiturates |
| | | | Opioids |
| | | Synergistic effects | Opioids |
| | | | Alcohol |
| | | | Sedatives |
| | | | Cocaine + alcohol |
| | | Parenteral route of administration | Opioids |
| | | | Benzodiazepines |
| | | | Stimulants |
| 2 | Subject-specific | Extremes of age | All classes of substances |
| | | Loss/absence of tolerance | Opioids |
| | | | Benzodiazepines |
| 3. | Context-specific | Varying potency due to illicit supply | Opioids |
| | | Toxic or synergistic adulterants | Alcohol (methanol) |
| | | | Opioids |
| | | | (benzodiazepines) |
| | | Delayed presentation due to fear of punishment | Alcohol |
| | | | Opioids |
| | | Inadvertent overdose due to body packing and swallowing to avoid detection | Opioids |
| | | | Stimulants |
| | | | Cocaine |

## Urine Drug Testing

Urine is the preferred matrix for detecting drugs of abuse due to longer detection window. Two types of tests can be done—point of care (also known as cassette tests), which gives a qualitative result and confirmatory tests that give exact level of drugs. Confirmatory tests use chromatographic techniques with mass spectrometry and require 6–8 hours. Ideally, if a urine sample is obtained, 10–15 mL should be stored at 4°C for confirmatory analysis.

### *Point of Care Tests*

Multidrug detection kits are available in the country and should be used when possible in a suspected poisoning. A detailed discussion of urine drug testing is beyond the scope of this article, but the following points should be noted:

- Which assay to stock? A test which detects benzodiazepines, opioids, cocaine, and amphetamines is preferred over single-drug detection assays.
- How to read the result? We strongly suggest that if the clinician is using the assay for the first time, they read the package insert. The results are counterintuitive, i.e., absence of the test-line is a positive result.
- False negatives and positives: Since the cost of an erroneous result is high, we recommend that no interpretation should be made without consulting the package insert. For example,

clonazepam, etizolam, clobazam, tramadol, methadone, propoxyphene, buprenorphine, tapentadol, synthetic cannabinoids, and methylphenidate are not detected by the available tests. Similarly, diazepam given for controlling seizures may explain a positive result for benzodiazepine. More so, most drugs are detected for 3–4 days following use, and this may lead the clinician astray. For example, a positive benzodiazepine and opioid test in a comatose patient can indicate co-ingestion or opioid overdose with past use of benzodiazepines or benzodiazepine overdose with past opioid use; presence of miosis and respiratory depression should prompt naloxone treatment rather than watchful waiting for benzodiazepine metabolism.

- Performance of test: The performance of these tests in the presence of frank hematuria, myoglobinuria, and casts is not known.

### Toxidrome-based Approach

Flowchart 1 describes a heuristic framework to evaluate suspected poisoning due to drugs of abuse.

### Polysubstance Poisoning

In a case of polysubstance poisoning, or when the substance cannot be reliably identified, an "ABCDE" approach can be used.

"A"—Airway protection with early intubation, giving naloxone trial in all stuporous patients. Rocuronium instead of succinylcholine should be used in view of high risk of rhabdomyolysis.

"B"—Breathing, a low threshold for invasive mechanical ventilation should be used. Relatively high-minute ventilation is preferable to decrease acidosis.

"C"—Characteristic electrocardiogram (ECG) changes like QRS widening and QT prolongation should be promptly managed.

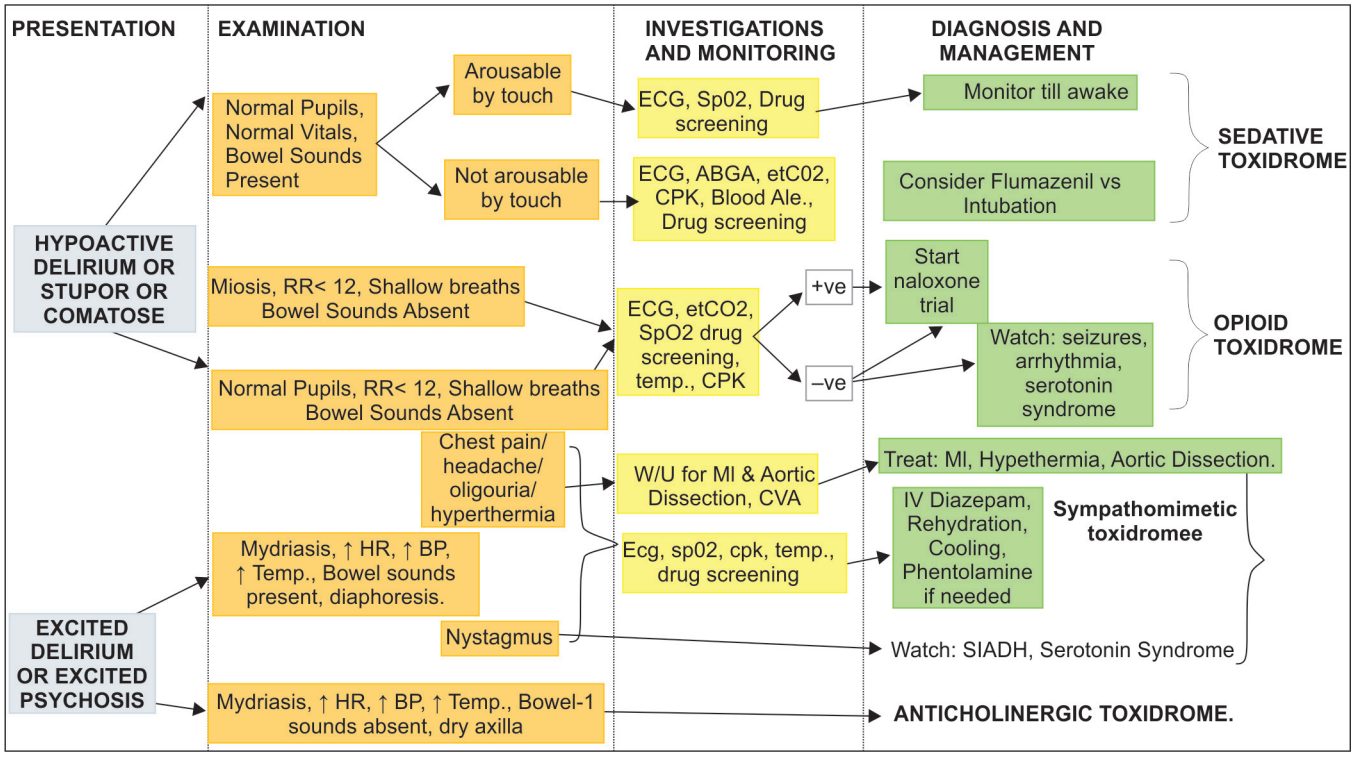
"D"—Disability and neurological stabilization. Naloxone should be used empirically in comatose patients. Seizures due to sodium channel blockade indicated by QRS widening should be treated with sodium bicarbonate and diazepam. Phenytoin should be avoided and propofol may be used as a second-line agent.

"E"—Exposure and elimination. Hyperthermia is associated with stimulant overdose and should be promptly managed with cooling, sedation, and fluid resuscitation. Hypothermia is associated with opioids and reverses slowly with naloxone. Further loss of body heat should be prevented. Gastric decontamination should not be attempted till airway is secure and even then the risk of aspiration mostly outweighs the benefits.

## Spurious Alcohol Poisoning

In 2015, a report in the British Medical Journal had estimated that at least 700 patients died in hooch tragedies in the preceding 15 years.[4] In 2016, several reports from the state of Bihar which enforced a complete prohibition of alcohol use indicated at least 100 deaths. Most recently, hooch tragedies in Assam and Uttarakhand claimed 150 and 104 lives. Therefore, spurious alcohol poisoning represents the most prevalent alcohol-related poisoning in the country.

**Flowchart 1:** Toxidromic approach to poisoning due to drugs of abuse[a,b,c]. [a]Airway protection, breathing, and circulatory support (ABC) should be ensured in all cases and is not indicated in the figure. [b]Serum electrolytes, random blood sugar, renal function tests, liver function tests, and hemogram should be checked in all cases and are not indicated in the figure. [c]Abbreviations: RR, respiratory rate; ECG, electrocardiogram; ABGA, arterial blood gas analysis; $etCO_2$, end-tidal carbon dioxide; CPK, creatine phosphokinase; MI, myocardial infarction; IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone



### Pathophysiology

Methanol is metabolized by alcohol dehydrogenase to formic acid, which accumulates, causing a high anion gap and a high osmolar gap acidosis. Formate is directly responsible for optic nerve damage. Ensuing acidosis in addition to methanol and ethanol is responsible for CNS, respiratory depression, and cardiac depression. Ethanol competes with methanol for alcohol dehydrogenase metabolism, thus delaying and decreasing acidosis. Formate metabolism depends on tetrahydrofolate availability and can be increased marginally with folate supplementation.

### Typical Scenarios and Presentation

Several patients from lower social strata presenting in a short duration with typical symptoms and smelling of alcohol are a strong clue to an unfolding hooch tragedy. Interested readers are referred to Bennett et al.'s detailed account of clinical presentation of methanol poisoning.[5] Although the presentation can vary substantially, all patients with acidosis invariably have dehydration and eye signs like afferent pupillary defect, floaters, scotomas, and if examined, disk hemorrhage or hyperemia. Importantly, even patients in advanced acidosis may not have Kussmaul's breathing and hypotension. In advanced cases, obtundation followed by coma and seizures heralds the terminal apnoea.

### Investigations, Diagnosis, and Management (Flowchart 2)

Confirmatory diagnosis by detecting methanol in blood using gas chromatography and mass spectrometry (GCMS) does not give timely results and is not required. Most patients in an intensive setting will require frequent electrolyte, renal functions, and ECG monitoring.

With regards to treatment, alcohol dehydrogenase inhibitor fomepizole, which is a specific antidote, is not available in India. As an alternative, parenteral ethanol dosing is a well-studied option;[6] however, it will have to be usually locally compounded, which is difficult in emergencies. Both fomepizole and ethanol prolong the excretion of methanol, and thus, worsening sensorium should be expected.

Ethanol can be administered per oral or through a nasogastric tube as a last resort. To achieve a serum ethanol concentration of 100 mg/dL, approximately 1.8 mL/kg of 42.8% liquor will be required for loading and 0.83 mL/kg/hour for maintenance. For a 70-kg male, 126 mL liquor preferably diluted with fruit juice should be given initially followed by 58 mL per hour.[7] In addition to hypoglycemia, dehydration, and sedation, there is an increased risk of vomiting, and thus, airway protection is necessary.

The definitive treatment for methanol poisoning remains hemodialysis. Early hemodialysis for all acidotic cases prevents blindness and other complications.[7]

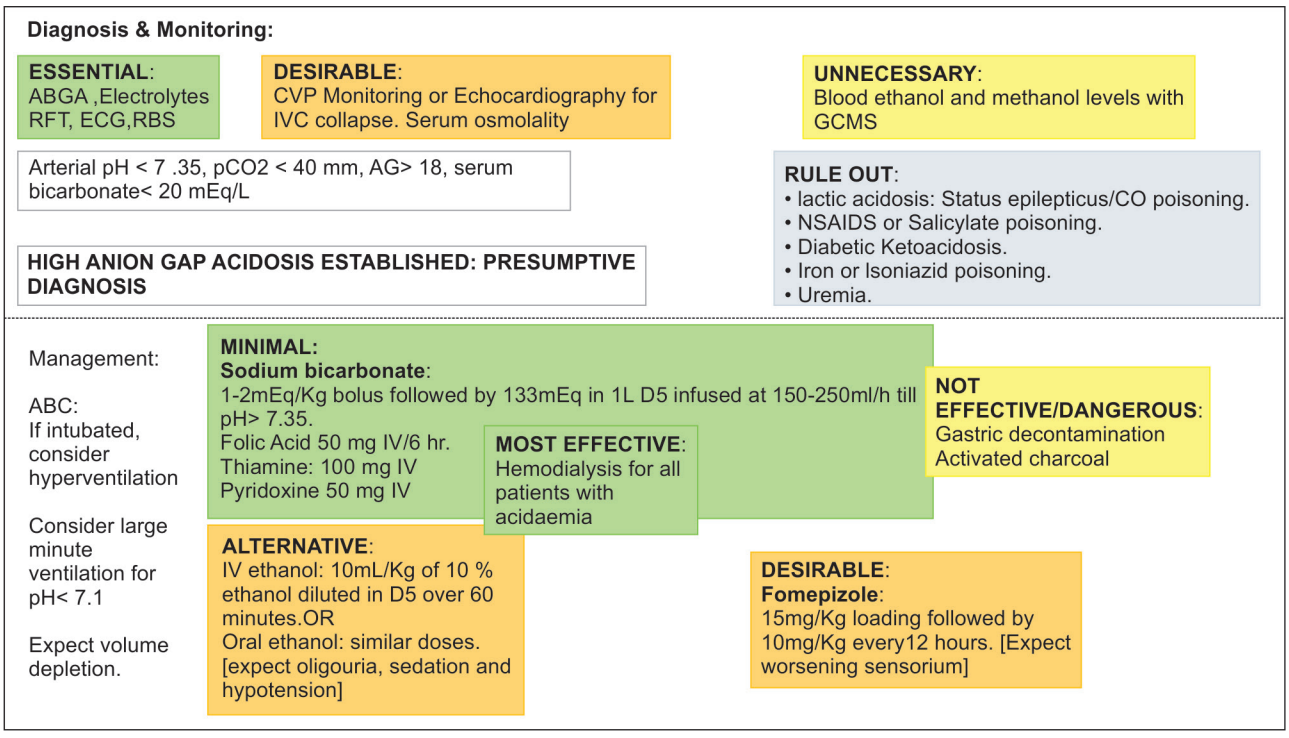
## Sedatives-hypnotics

Benzodiazepines are frequently implicated in intentional overdose and can prove fatal.

### Pathophysiology

Benzodiazepines potentiate GABA-A transmission causing CNS depression but do not have a direct GABA agonistic action. Since brain stem has a low density of GABA-A receptors with benzodiazepine binding sites, isolated oral overdose rarely causes respiratory depression or cardiovascular instability. However, IV bolus or benzodiazepine use along with ethanol, barbiturates, or

**Flowchart 2:** Diagnosis and management of methanol poisoning[a]. [a]RAPD, relative afferent pupillary defect; RFT, renal function tests; ECG, electrocardiogram; RBS, random blood sugar; CVP, central venous pressure; IVC, inferior vena cava; CO, carbon monoxide; $pCO_2$, partial pressure carbon dioxide; AG, anion gap; IV, intravenous



opioids can cause respiratory depression, alveolar hypoventilation, and type II respiratory failure.

### Typical Scenarios and Presentation

A history of mental health problems, using "sleeping pills," or recovery of empty strips will indicate an intentional overdose. Frequently, the patient can give history if kept awake by tactile stimuli. Coma with normal vital signs is the hallmark of benzodiazepine overdose. Nonresponse to noxious stimuli, hypotension, and respiratory depression indicates co-ingestion of other substances. The duration of stupor depends on half-life of the agent and alprazolam may have particularly serious toxicity.[8]

### Investigations, Diagnosis, and Management (Flowchart 3)

For uncomplicated cases, a definitive diagnosis with history, urine drug screening, and monitoring until the patient is out of sedation is sufficient. For cases that have hemodynamic instability or co-ingestion of other substances, it is essential to ascertain the identity of substances ingested and history of benzodiazepine abuse.

Although flumazenil is a specific antidote of benzodiazepines, its use in noniatrogenic scenarios is controversial. First, it is not established if flumazenil reverses the respiratory depression with the same efficacy as it reverses sedation.[9] Second, in habituated users, it can precipitate seizures more so in the presence of other proconvulsant drugs.[10,11] Keeping this in mind, a clinical decision should be made for each overdose case. Stabilization with mechanical ventilation until the clearance of benzodiazepines is a viable alternative.

## Opioid Poisoning

The recent National Drug Use Survey has reported the prevalence of opioid use, including injection drug use higher than expected. Opioids are notorious for high overdose mortality as currently playing out in the United States. Although there is no systematic data from India about opioid overdose, we must expect increasing number of patients will require intensive care for this condition in the coming years.

### Pathophysiology

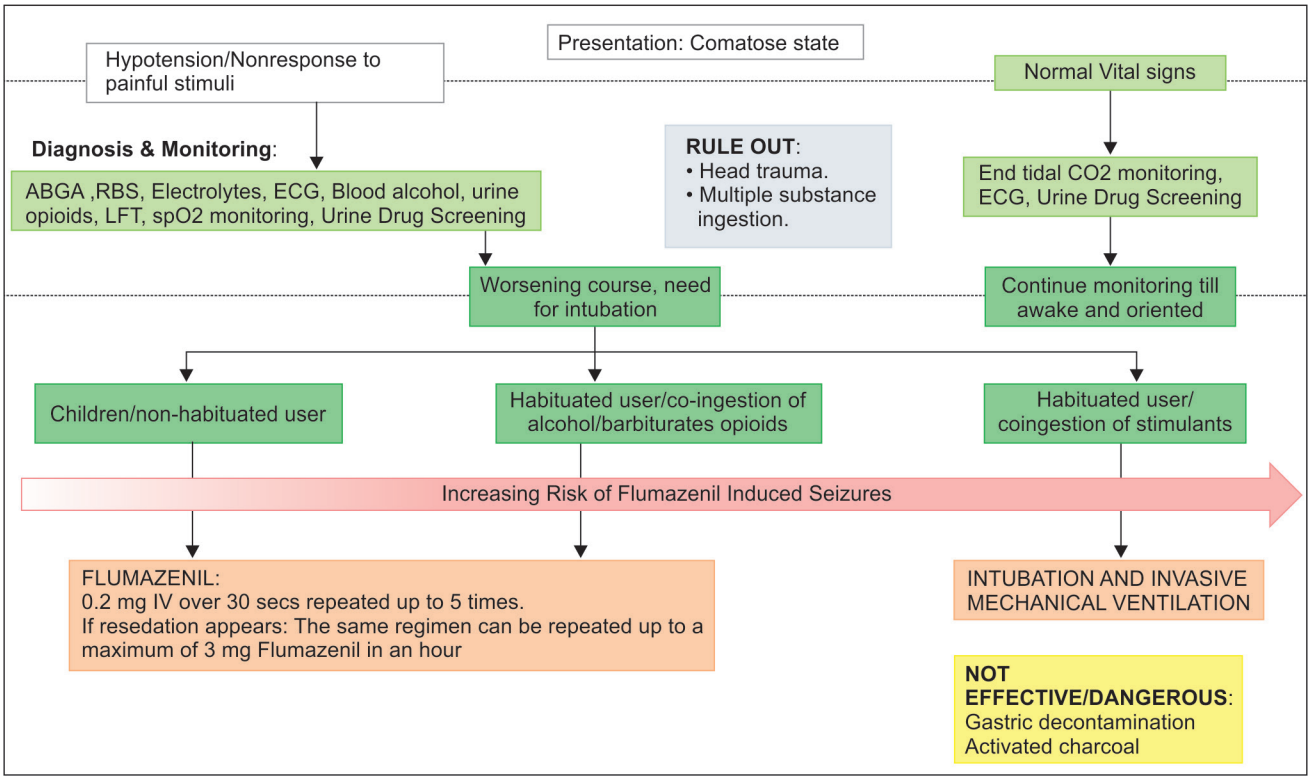
All opioids are capable of respiratory depression with different potencies. Respiratory depression causing type II respiratory failure is the most life-threatening pathophysiology in opioid poisoning. Some agents can cause seizures (tramadol and meperidine) or arrhythmias due to specific action on ion channels. The severity and duration of toxidrome depend on the individual agent. For example, potent agonists with long-terminal half-life like methadone cause more profound and longer respiratory depression than propoxyphene.

### Typical Scenarios and Presentation

Unintentional opioid poisoning is seen in three distinct scenarios:

- Inadvertent poisoning when a child consumes opioid medications meant for adults.
- Inadvertent poisoning when opioid users misjudge the dose-tolerance dynamic. For example, patients who have recently undergone detoxification or have been incarcerated and have lost tolerance. A similar situation occurs when preparation is tampered to achieve a high like crushing an extended-release

**Flowchart 3:** Diagnosis and management of benzodiazepine poisoning[a]. [a]ABGA, arterial blood gas analysis; RBS, random blood sugar; ECG, electrocardiogram; LFT, liver function tests; $SpO_2$, oxygen saturation



preparation, swallowing fentanyl patch, or injecting oral preparations.
- Inadvertent poisoning due to synergistic effects of other CNS depressants or contaminants of opioid preparations.

Clues to the diagnosis include linear track marks indicating injection drug use, patches on the body, and history of treatment for opioid use disorder. The physical examination is typical for depressed sensorium, decreased breath rate (<12/minute), decreased tidal volume, decreased bowel sounds, miosis, and cold extremities. Amongst these signs, reduced breath rate and miosis are the best markers and help in starting treatment.[12] However, miosis may be absent in tramadol, meperidine poisoning, co-ingestion of stimulants, or in advanced cases due to cerebral anoxia.

### Investigations, Diagnosis, and Treatment (Flowchart 4)

Opioid poisoning is a clinical diagnosis and should not be withheld awaiting toxicology examination. Investigations to rule out other conditions can also wait until adequate respiratory functions are restored. As shown in Flowchart 4, the focus is on restoring adequate respiratory functions. A careful examination of breath rate, chest wall excursion, and end-tidal capnography should be done for triaging and monitoring. It bears repeating that only capnography or pulse oximetry will miss increasing hypercapnia and impending respiratory failure.[13] An escalating dose regimen of naloxone[14] is used to reverse the respiratory depression as shown in Flowchart 4.

Although there is a theoretical reason to use a higher initial dose of naloxone in poisoning due to fentanyl analogs and buprenorphine, in our review, we could not find adequate evidence to recommend so. Thus, the treatment can be started with the standard dose, and rapid escalation in case of nonresponse is advised.

## Stimulant and Cocaine Poisoning

Globally, cocaine and ATS-related overdose deaths are increasing in the last 3–4 years.[15,16] The reported rates of ATS and cocaine use are low in India. However, recent seizures of mephedrone in metropolis and increasing number of patients at our center indicate an increase in stimulant abuse. We believe that management of poisoning due to these classes of drugs will be novel and challenging for our country.

### Pathophysiology

Cocaine, amphetamines, mephedrone, methylenedioxymethamphetamine (MDMA), and methylphenidate share the ability to increase catecholamine and serotonin transmission, albeit by different mechanisms of action. Also, MDMA has profound serotonergic effects responsible for serotonin syndrome and syndrome of inappropriate diuretic hormone (SIADH). Similarly, cocaine has sodium channel blocking properties accounting for cardiac and neuronal toxicity. Consumption of cocaine and ethanol has a synergistic effect due to cocaethylene which is more potent, long-lasting, and cardiotoxic than cocaine itself.

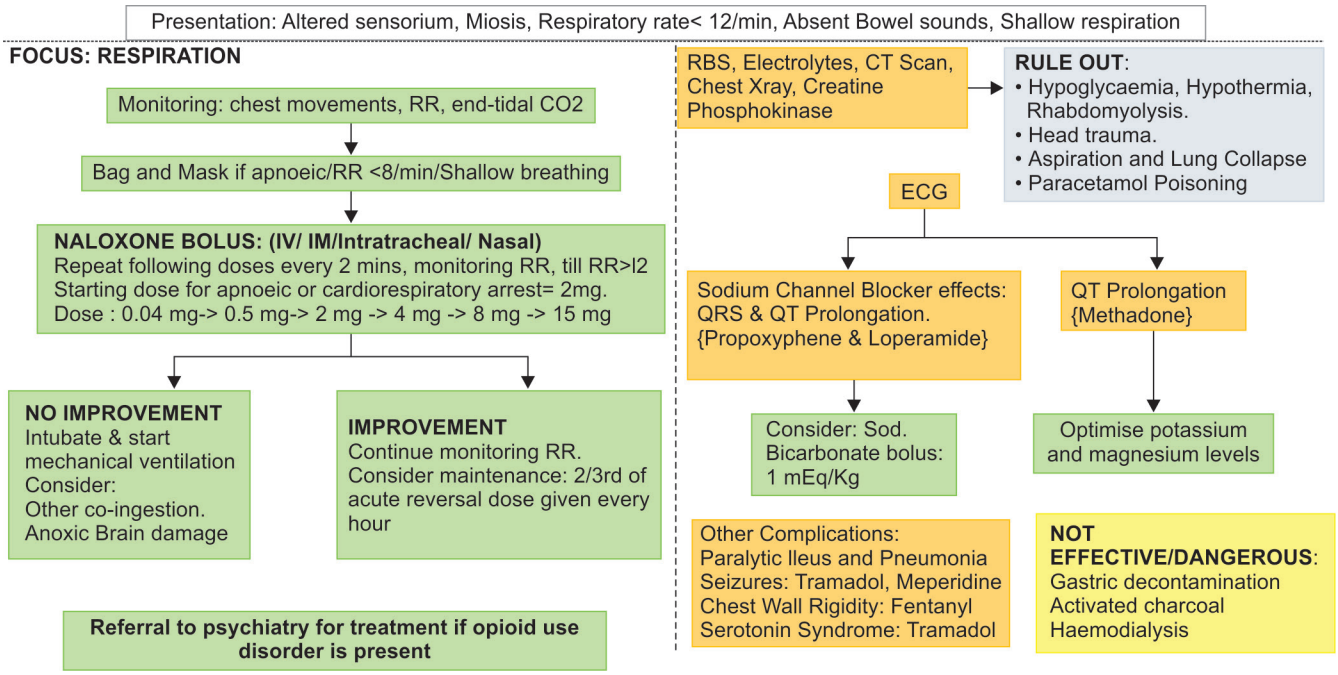
### Typical Scenarios and Presentation

Sympathomimetic toxidrome, i.e., raised pulse, blood pressure, peripheral vasoconstriction along with an agitated delirium is the hallmark of poisoning with this group of substances. Over this, the symptoms of end-organ damage if any are superimposed. The patient can frequently report the substance they use, and it may be recovered from their person, especially nose and hands.

### Investigations, Diagnosis, and Management (Flowchart 5)

Similar to opioid poisoning, the diagnosis of stimulant poisoning is made clinically. However, identification of the offending agent may be useful in case of MDMA poisoning to anticipate hyponatremia

**Flowchart 4:** Management of opioid overdose[a]. [a]RR, respiratory rate; $CO_2$, carbon dioxide; ECG, electrocardiogram



and serotonin syndrome. The focus of management is to control agitation, autonomic arousal, and rapid identification of secondary complications which require directed management. There is a role of decontamination measures like nasal irrigation for cocaine (if taken nasally) and gastric decontamination if a large amount has been consumed in the last 1–2 hours. Whole bowel irrigation can be considered if large amount of sustained-release preparations are involved like methylphenidate. Finally, it is most important to avoid medications that may worsen the course of toxicity like β-blockers.

## Summary of Poisoning due to other Substances

Table 3 summarizes the salient features of poisoning due to other groups of substances which are either not severe enough to require intensive care or are not very prevalent in India.

## Summary

With the growing use of substances of abuse, poisoning or overdose presenting to emergencies is likely to increase. Physicians must be trained in the recognition of symptoms of such poisoning, be aware of tests available (if any) to identify the noxious agent, know how to stabilize such patients, specific treatment strategies for each poisoning, and have referral arrangements with more specialized centers for patients who need specialized or prolonged support. Following recovery, every physician should provide brief interventions that aim to educate the patient of substance-related harm, advise them of the importance of quitting, offer support to quit, or refer them to a psychiatrist or addiction specialist. As the pattern of substance use is constantly changing, the physician

**Flowchart 5:** Management of stimulant poisoning[a]. [a]RFT; renal function test; RBS, random blood sugar; $SpO_2$, oxygen saturation; CPK, creatine phosphokinase; IV, intravenous; IM, intramascular; SBP, systolic blood pressure; NS, normal saline; SR, sustained release

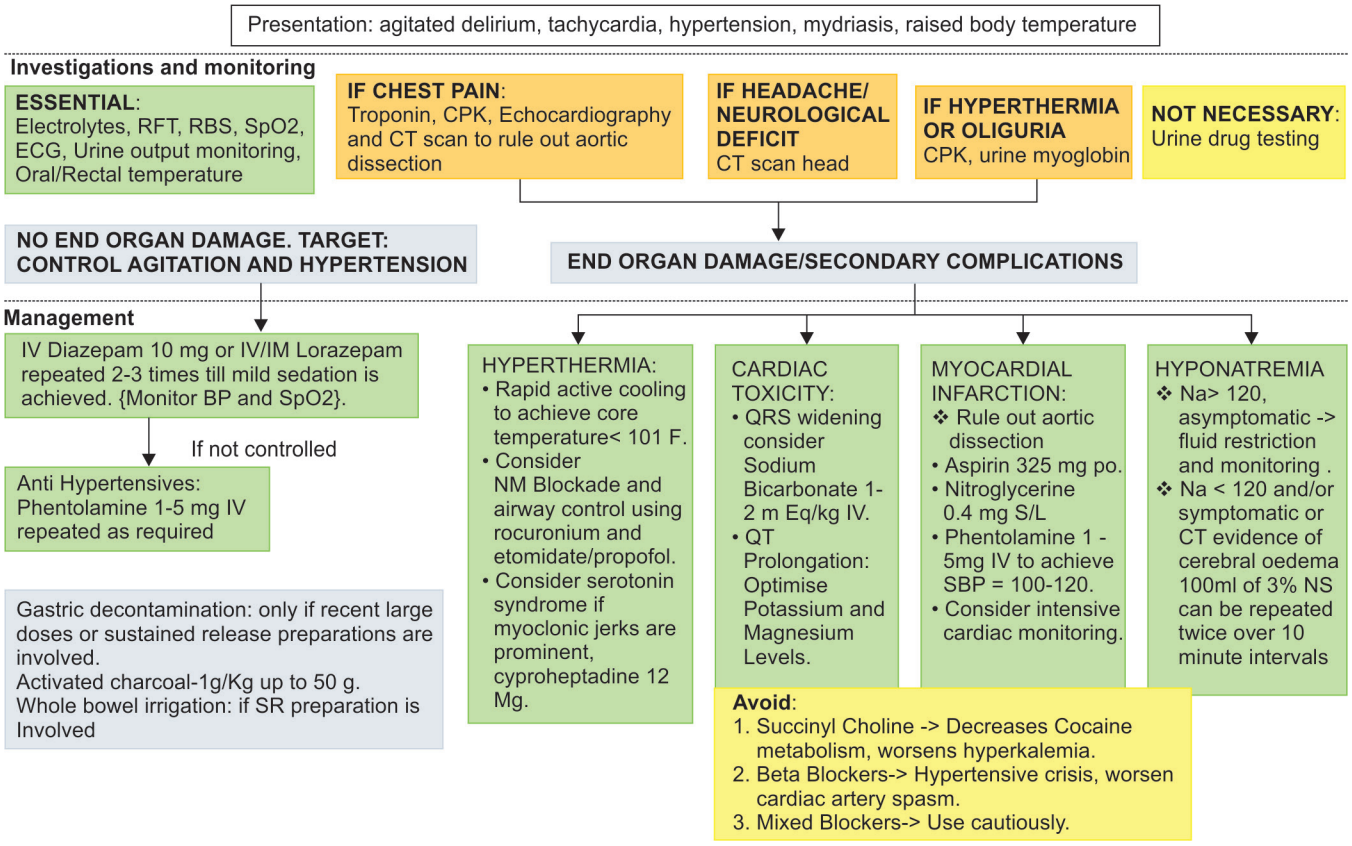



**Table 3:** Poisoning due to selected drugs of abuse

| *S. no.* | *Drug* | *Characteristics of poisoning* | *Management* |
|---|---|---|---|
| 1 | Ethanol | Rarely stupor and coma in adults | Airway breathing and circulatory support (ABC) |
| | | Can cause respiratory depression, hypotension, and death at blood alcohol levels above 0.30% in nontolerant individuals | Thiamine 100 mg IV followed by dextrose for hypoglycemia. |
| | | | Rule out head trauma |
| 2 | Cannabis (marijuana) | Respiratory depression, hypotonia, and seizures reported in children exposed to high concentration oral products[17] | ABC |
| | | | Diazepam can be used to control seizures |

*Contd…*

*Contd…*

| *S. no.* | *Drug* | *Characteristics of poisoning* | *Management* |
|---|---|---|---|
| 3 | Synthetic cannabinoids: K2 and spice, etc.[18] | Typically seen in adolescents who report using 'incense sticks' | ABC |
| | | | Prompt control of agitation with parenteral diazepam |
| | | Highly variable toxidrome, consistent elements—agitated psychosis and conjunctival injection | |
| | | Death due to hyperthermia and rhabdomyolysis | |
| | | Bradycardia and seizures also reported | |
| 4 | Lysergic acid diethylamide (LSD)[19] | Toxic reactions recorded in adults at doses above 400 mcg | ABC |
| | | | Diazepam to control sympathetic arousal |
| | | Sympathomimetic toxidrome—mydriasis, tachycardia, hyperthermia, and serotonin syndrome | |
| | | | Cyproheptadine for serotonin syndrome |
| 5 | NBOMe hallucinogens[20] | Agitated delirium, hyperthermia and a high likelihood of rhabdomyolysis | ABC |
| | | | Rapid control of agitation with diazepam |
| | | | Aggressive rehydration and cooling to prevent rhabdomyolysis |
| 6 | Psilocybin and tryptamines like dimethyltryptamine (DMT) | Prominent gastrointestinal symptoms | Cyproheptadine for serotonin syndrome |
| | | Myoclonic jerks, hyperreflexia, and hyperthermia | Cooling and rehydration |
| 7 | Carisoprodol or meprobamate | Stupor/coma with disproportionate hypotension due to cardio depression, loss of deep tendon reflexes, and hypotonia | Consider early intubation and invasive mechanical ventilation. hypotension should be treated with dobutamine and fluids. Pulmonary edema is likely with fluid overload. Early hemodialysis should be considered |
| 8 | Rohypnol (flunitrazepam) | Sedative toxidrome | Same as benzodiazepines |

must constantly be updated on the current substances of use and manifestation of poisoning.

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