# Toxicology of psychoactive substances

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**Key points:**

- In recent years, monitoring agencies have reported a significant increase in the introduction and production of new psychoactive substances (NPS) paralleled by increasing use of long-time available psychoactive drugs (PAD)
- The nonmedical use of prescription drugs obtained from licit channels or illegally manufactured has increased.

**Synopsis**

An increasing trend in the use of prescription psychoactive drugs (PADs) including antidepressants, antipsychotics and mood stabilizers has been reported in the US and globally (National Center for Health Statistics, National Health and Nutrition Examination Survey, 2015–2018)[1] [2-4]. In addition, there has been a global increase in the production and usage of illicit PADs and emergence of new psychoactive substances (NPS)[5]. Whether used for prescription or illicit indications, PADs pose unique challenges for critical care providers who may encounter toxicology issues due to drug interactions, side effects, or drug overdoses. This chapter provides a summary of the toxicological features of commonly used and abused PADs: antidepressants, antipsychotics, mood stabilizers, hallucinogens, NPS, caffeine, nicotine and cannabis.

# 1. Introduction

## 1.1. Epidemiology of Psychoactive substances

Approximately 6% of the world population uses cannabis with reported incidence of 15.3% use in United States (United Nations Office on Drugs and Crime report 2018)[6]. 13.8 million young people aged 15–16 years used cannabis in the United States in 2018 [7]. Young people in high-income countries use the so-called "club drugs" such as "ecstasy", methamphetamine, cocaine, ketamine, lysergic acid diethylamide (LSD), and gamma-hydroxybutyrate (GHB) for recreational experiences. On the other hand, young people living in poverty use PADs for coping and choose drugs for their low price, legal and widespread availability, and ability to rapidly induce a sense of euphoria (such as inhalants, like paint thinner, petrol, paint, correction fluid and glue)[8] . The proportion of older adults using PADs as well as seeking treatment of admission for PAD related condition is increasing [9-11]. There are gender-based differences in the use of PADs as well with emerging data supporting an increasing prevalence of use in women of all ages and women seem to be the fastest-growing population of substance abusers in the United States [12-15].Women are more likely to seek treatment for misuse of central nervous system depressants[16,17].

# 2. Antidepressants

Antidepressants were the most frequently prescribed drugs to young patients (18–44 years) between 2005 and 2008 in the US and were the third most prescribed drugs among patients of all ages[18]. The American Association of Poison Control Centers' (AAPCC) National Poison Data System reported that antidepressants were among the top 5 substances involved in human exposure in 2019 with a 3.9% increase per year in cases with serious outcomes over the last 10 years[19].

## 2.1. Tricyclic antidepressants (TCAs)

### *2.1.1. Pharmacology and Use*

Tricyclic antidepressants have been prescribed for the treatment of depression since the late 1950s. Newer antidepressants have replaced TCAs limiting their use to treatment of depression refractory to newer agents. Despite this, there is an increase in the TCA-overdose associated

hospitalization and lethality, predominantly in patients with chronic pain and neuropsychiatric disorders receiving TCAs[20,21]. Although antidepressant overdose is more frequent with selective serotonin reuptake inhibitors (SSRIs), admissions to hospital are more frequent after TCA overdose compared to SSRIs, because of the narrower therapeutic index of TCAs.

The chemical classification, mechanism of action, and pharmacology of TCAs is shown in Table 2 [22,23] .

### *2.1.2. Toxicity*

TCA intoxication can be rapidly fatal with life threatening arrhythmias and death occurring within 24 hours of ingestion in settings of altered mental status, dysrhythmias, hypotension and seizures. The rapid absorption in the gastrointestinal (GI) tract is promoted by alkaline conditions of the small intestine. The ingestion of 10 to 20 mg/kg is potentially life-threatening with onset of initial symptoms in 30 to 40 minutes and signs of toxicity becoming clinically apparent within 2 hours [24]. However, symptom onset may be delayed if a mixed overdose has caused delayed gastric emptying. Many of the initial signs and symptoms are attributable to the anticholinergic effects of TCAs: dry mouth, blurred vision, urinary retention, constipation, decreased or absent bowel sounds, dizziness, and vomiting. Plasma concentrations of TCAs greater than 450 ng/ml can lead to agitation, confusion, memory impairment, and anxiety. Toxicity and death are reported at plasma levels of 2000–3000 ng/ml with most TCAs; dothiepin levels as low as 1000 ng/ml can be fatal[25]. The most severe cases may present with central nervous system (CNS) depression with reduced level of consciousness, hypoventilation, coma, and seizures[26-28]. Cardiac effects include conduction abnormalities with prolonged QRS, QT and PR intervals that can lead to ventricular tachycardia, torsade de pointes, and ventricular fibrillation. Hypotension results from a combination of reduced myocardial contractility and reduced systemic vascular resistance due to alpha-adrenergic blockade occur [26,29]. TCA toxicity is worsened by acidemia, hypotension, hypoxia, and hyperthermia. History of co-ingestion with other medications like acetaminophen, aspirin, and alcohol is frequent and may confound the clinical presentation.

### *2.1.3. Management*

Treatment of TCA overdose depends on the severity of symptoms. It is important to record the patient's vital signs and repeat the physical examination to assess for evidence of *anticholinergic syndrome* (Table 3), cardiac toxicity, and neurologic toxicity to guide proper management[30,31]. Most patients should receive supplemental oxygen. Normovolemia should

be maintained . Gastric decontamination with activated charcoal can be considered with due airway precautions and protection due to risk of emesis. Activated charcoal adsorbs the drug in the GI tract and is therefore most effective if given within 1 to 2 hours of TCA ingestion. Other decontamination methods (stomach pumps, gastric lavage, whole bowel irrigation, or ipecac induced emesis) are not recommended.

TCAs are protein bound and become free in more acidic conditions. Increasing arterial or venous pH to ≥7.45 significantly reduces the available free drug and may avoid toxicity. An intravenous 8.4% sodium bicarbonate (SB) bolus of 1-2 mEq/kg followed by infusion using 150 mEq/L in D5W titrated to blood pH and QRS is recommended in cases with metabolic acidosis along with mild hyperventilation until the QRS falls below 100 milliseconds. The sodium load in SB solutions also helps to reverse the sodium channel blocking effects of TCAs and is the treatment of choice to prevent seizures and dysrhythmias. SB should be given in all cases of metabolic acidosis, QRS prolongation (even in the absence of metabolic acidosis), malignant dysrhythmias, hypotension, and cardiac arrest due to TCAs[32]. Hypertonic saline or lipid emulsion can be used in patients not responding to standard therapies[33].

Continuous cardiac monitoring is essential in TCA overdose, and lidocaine may be used for dysrhythmias after SB if sodium load fails with caution to avoid precipitating seizures[34,35]. Magnesium has been recommended as well given its anti-arrhythmic and anti-epileptic properties[31,36,37]. Class 1a and 1c agents should not be administered due to sodium channel effects.

Benzodiazepines and propofol are treatments of choice for sedation and treatment of seizures due to TCA induced central GABA-A receptor inhibition. Phenytoin should be avoided due to its sodium channel effect. Levetiracetam or barbiturates could be used as a second line. Lacosamide is avoided due to cardiac side effects.

## *2.2.* Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitor (SNRIs), and Monoamine oxidase inhibitors (MAOIs)

### *2.2.1. Pharmacology and use*

Use of SSRIs, SNRIs and MAOIs are the major agents used in outpatient treatment of depression [38]. During the decade between 2009–2010 and 2017–2018, antidepressant use increased from 10.6% to 13.8%[39]. During 2015–2018, 13.2% of adults used antidepressants in the past 30 days with higher us in women and older age groups. The American Association of Poison Control Centers reported over 50,000 overdose cases in 2016 where SSRIs were

mentioned with 102 fatalities [40]. Clinical indications, mechanism of action, and pharmacology of SSRIs, SNRIs and MAOIs are described in Table 2.

### *2.2.2. Toxicity*

SSRIs are the most frequently prescribed first line antidepressants due to decreased toxicity compared to MAOIs and TCAs. The most common toxicity of SSRIs manifests in autonomic instability leading in severe cases to *serotonin syndrome* (Table 3) [22][41]. Toxicity is enhanced when SSRIs are co-ingested with other drugs with serotonergic effects. The prognosis is generally favorable, and long-term sequelae are rarely observed in single agent overdose.

Among the SSRIs, citalopram is associated with the greatest risk of cardiotoxicity (QTc prolongation) and neurotoxicity (seizures). In a case series, 26 adults ingested between 200 and 4960 mg of citalopram (plasma concentration 0.21 to 7.5 mg/L after 20 minutes to 8 hours between suggested time of ingestion and blood sampling); the most frequent symptoms were drowsiness, tachycardia, QTc prolongation, decreased level of consciousness, coma and seizures. The median hospital stay was 3 days (range 1-8 days) and two patients died (one cardiac arrest and one respiratory arrest)[42]. Citalopram (>600 mg) and escitalopram (>300 mg) cause dose-dependent QT prolongation with high risk of torsade de pointes [43].

Most SNRIs are well tolerated in overdose and symptoms are rarely severe. Patients do not need intensive care unit (ICU) admission unless they have decreased level of consciousness and need airway protection. Venlafaxine in particular is associated with increased reports of deaths, dysrhythmias, and seizures compared to other SNRIs[44].

MAOI toxicity presents as a syndrome of catecholamine excess followed by hypotension, seizures, coma, and death[45]. People taking MAOIs are instructed to avoid excessive ingestion of foods and beverages containing tyramine (cheese, soy sauce, and salami). Large amounts of ingested tyramine can trigger a fatal hypertensive crisis. Furthermore, certain drug combinations with MAOIs can cause lethal reactions; these include SSRIs, TCAs, ecstasy, meperidine, tramadol and dextromethorphan.

### *2.2.3. Management*

The treatment of SSRI and SNRI intoxications is symptomatic with a focus on supportive care and discontinuation of all serotonergic agents. Supplemental oxygen, if indicated, and normovolemia are recommended with continuous ECG monitoring. Consensus based guidelines have been developed to guide the out-of-hospital management of SSRI overdose

[46,47]. Patients with ingestions less than 5 times the therapeutic dose can be monitored at home but patients with mixed overdoses or ones involving >5 times the therapeutic dose should be referred to the hospital. Asymptomatic patients with a normal 12-lead ECG can be discharged after 6-12 hours of observation, whereas symptomatic patients with or without abnormal ECG may need an additional 12-24 hours of monitoring and supportive care. Several side effects are transient with supportive care, but others may take a few weeks to disappear.

Benzodiazepines are the drugs of choice for management of seizures, agitation, and muscle rigidity (diazepam or lorazepam 0.1-0.2 mg/kg) associated with serotonin syndrome. Butyrophenones (e.g., haloperidol) and droperidol inhibit sweating so are contraindicated for agitation. Severe toxicity may require aggressive support including cooling, intubation, ventilation and neuromuscular paralysis[48,49]. Muscle rigidity propagates hyperthermia and uncontrolled fevers can trigger seizures and dehydration hence should be controlled. Administration of serotonin antagonists like cyproheptadine or chlorpromazine for mild to moderate serotonin toxicity refractory to benzodiazepines has been reported but definitive evidence of effectiveness and impact on outcomes is lacking. Cyproheptadine is a first generation antihistaminic with anti-serotonergic effects and can be considered for severe *serotonin syndrome* but is limited by enteral formulation only requiring nasogastric access[46]. Depolarizing muscle relaxants should be avoided in patients with suspected rhabdomyolysis who need intubation and paralysis.

Short acting beta-blockers can be used to treat hypertension and tachycardia but should be avoided in the case of predominant MAOI overdose where unopposed alpha-adrenoreceptor stimulation may exacerbate the hypertension. Nitroglycerin and sodium nitroprusside are acceptable options for management of MAOI-related hypertension. Patients who develop severe serotonin toxicity often require ICU admission[50]. Patients with single agent intoxication have a good prognosis and recover without complications unless renal failure and refractory hypotension are present. Serotonin syndromes involving MAOIs tend to produce the most severe and prolonged cases. The differential diagnoses of serotonin syndrome in cases without a clear-cut exposure to serotonergic agents include neuroleptic malignant syndrome (NMS), malignant hyperthermia, anticholinergic toxicity, sympathomimetic toxicity, or infectious causes such as meningitis or encephalitis (Table 3).

## 3. Antipsychotics

### *3.1 Pharmacology and Use*

Antipsychotics or neuroleptic drugs are indicated in several neurological and psychiatric

conditions (Table 4). Developed in the 1950's, this category accounts for approximately thirty currently available drugs with increasing use over the years in younger age group while decreasing use in elderly with dementia [51-53]. The toxicity of these drugs is generally high and can vary considerably although death from a pure neuroleptic ingestion is uncommon[54]. Antipsychotics are often classified in two groups: typical antipsychotics (TA, known as first generation drugs) and atypical antipsychotics (AA) (Table 4).

### *3.3. Toxicity*

The most common side effects of antipsychotics include acute extrapyramidal symptoms including dystonia, oculogyric crisis, torticollis, acute parkinsonism, akathisia, and other movement disorders[55]. AAs are generally preferred over TAs because the extra- pyramidal side effects, dyskinesia and withdrawal symptoms are less frequent. Chronic use of both AAs and TAs is associated with tardive dyskinesia (mainly buccolingual movements), parkinsonism, and akathisia. Additional adverse effects include anticholinergic symptoms (tachycardia, hyperthermia, urinary retention, ileus, mydriasis, toxic psychosis, dry mouth, and hot, dry, flushed skin), seizures, QT interval and QRS prolongation, orthostatic hypotension, hypothermia, sedation, and respiratory depression. Antipsychotics (TAs more frequently than AAs) could also lead to the development of NMS, a life-threatening condition that affects multiple organ systems and results in significant mortality (Table 3)[56]. Patients may develop signs of serious toxicity days after exposure with rigidity, fevers, possible dysrhythmias, status epilepticus, autonomic instability, or coma and may present for intensive care management despite no apparent antecedent exposure.

Initiation of high dose, high potency antipsychotics or a rapid increase in dose of previously well tolerated doses can lead to NMS. Although the incidence of NMS is less common with AA use, it can occur when multiple agents are used even if smaller doses. Young males and postpartum females have an unexplained predisposition to NMS. NMS is characterized by fever, confusion, muscle rigidity and autonomic instability similar to serotonin syndrome. It is important to recognize that NMS may have *forme fruste* presentations with delayed onset. Serotonergic agents, carbamazepine, and mixed ingestions of serotonergics and antipsychotics can also cause *forme fruste* presentations of NMS. Similar symptoms may occur with rapid withdrawal of dopaminergic agents (e.g. levodopa/carbidopa). Several clinical decision tools have been proposed for NMS but no single one has gained widespread use[57]. Signs and symptoms of rhabdomyolysis and metabolic acidosis may occur.

### *3.4. Management*

The management of NMS centers on supportive care and cessation of the underlying offending agent. There is no specific antidote for antipsychotics. Activated charcoal may be considered in recent acute ingestions, but ileus could hinder this method of decontamination. Aggressive hydration with intravenous fluids is recommended in case of hypotension, hyperthermia, or rhabdomyolysis. Norepinephrine is recommended in cases with shock. Epinephrine and dopamine could induce paradoxical hypotension due to simultaneous neuroleptic alpha-blockade and unopposed beta-agonist peripheral vasodilation. Benzodiazepines (e.g., lorazepam, midazolam) can be used for most seizure given they are self-limited[58].

Patients presenting with NMS and worsening hyperthermia must be treated immediately with physical and pharmacological cooling methods. In case of severe hyperthermia (core temperatures > 40.6º C) and significant muscle rigidity, dantrolene 1-2.5 mg/kg initial dose dose followed by followed by 1 mg/kg infusion 6-hourly (maximum 10 mg/kg/day) may be considered using a large cannula avoiding extravasation[59,60]. Bromocriptine and amantadine, central dopaminergic agonists only available in enteral formulations, can be used to reverse the neuroleptic-induced dopaminergic blockade, although their effect has slow onset (e.g., several days). Once NMS resolves, they should be tapered gradually to avoid rebound episodes of dopamine withdrawal mimicking NMS. Parkinson's patients or patients on long term metoclopramide or other dopamine agonists could develop NMS on sudden withdrawal of their dopaminergic therapy[59] (Table 3). In these cases, levodopa-/carbidopa, bromocriptine, and/or amantadine should be supplemented urgently[61]. Anecdotal reports of refractory NMS cases treated with pulse steroid therapy have shown to reduce the illness duration and improve symptoms[62].

## 4. Mood stabilizers

### *4.1. Pharmacology and Use*

Mood stabilizers include some antipsychotics, anticonvulsants (lamotrigine, valproic acid, and carbamazepine), and lithium (the "classic" mood stabilizer). The mechanisms of action and therapeutic action of this class of drugs on psychiatric disorders is not entirely clear (Table 4). Mood-stabilizers are often used in combination with an increased risk of toxicity with lithium notable for its narrow therapeutic index. The safest and most efficient combination appears to be valproic acid plus lithium[63].

### *4.3.Toxicity*

A recent UK study reported little difference in toxicity between different mood stabilizers, but when poisoning with multiple drugs was studied, carbamazepine co-intoxication was fatal more than two-fold compared to lithium [64]. Carbamazepine and lamotrigine have systemic and neurological side effects. Systemic effects include nausea, vomiting, diarrhea, and hyponatremia, pruritis and rash, whereas the neurological effects include headache, dizziness, blurry vision or diplopia, tremor, stupor, and drowsiness. Acute valproate toxicity manifests with lethargy while the chronic use of valproic acid causes weight gain, GI disturbances, alopecia, tremor, and easy bruising. Around 5-10% of patients develop self-resolving transaminitis. More severe forms of valproic acid toxicity include encephalopathy secondary to hyperammonemia, hepatotoxicity, and acute pancreatitis[65].

Acute intoxication with lithium presents with GI symptoms (nausea, diarrhea, vomiting, cramps), neuromuscular signs (tremor, dystonia, hyperreflexia, ataxia), and rarely cardiac side effects such as T wave flattening, sinus node dysfunction and QT prolongation which are often reversible[66]. The therapeutic range of lithium is 0.5–1.0 mmol/l and levels may increase in renal failure or elderly patients. Chronic intoxication is more challenging to treat and is precipitated by impaired kidney function and hypovolemia. Symptoms are primarily neurological (altered mental status, coma, seizures), and severely intoxicated patients present with the *"syndrome of irreversible lithium-effectuated neurotoxicity" (SILENT)*, characterized by cognitive dysfunction, cerebellar dysfunction, brainstem dysfunction, extrapyramidal motor symptoms, myopathy, nystagmus, and sometimes loss of vision[67]. This a rare but important to recognize sequela of lithium toxicity despite normalization of levels. Lithium is a potent renal toxin causing nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephritis, renal tubular acidosis, and nephrotic syndrome. Endocrine disorders such as hypothyroidism and myxedema can occur in cases of chronic toxicity[68]. It is important to recognize that acute over chronic toxicity of lithium can develop in patients taking daily lithium in settings of dehydration, drug interactions or changes in renal function [69]

### *4.4. Management*

Management of carbamazepine toxicity includes supportive care, addressing airway protection, and close cardiac monitoring[70]. Activated charcoal (repeated dose of 1 g/kg each, every 2-4 hours) can be used if the patient is able to protect their airway with aspiration precautions. It can be given even after 2 hours if extended-release preparations are ingested. Whole-bowel irrigation after ingestion of modified-release carbamazepine may be considered (adults and

adolescents: 1.5-2 L/h of polyethylene glycol electrolyte lavage solution; small children: 0.5 L/h) but evidence of improved outcomes is lacking.

SB should be administered when the QRS complex is longer than 100 msec. Given the high fatality rate up to 13%, an aggressive treatment plan may require charcoal hemoperfusion, hemodialysis, intravenous lipid emulsion, and/or multiple doses activated charcoal [71]. Seizures can be controlled with benzodiazepines or propofol depending on severity and patients intubation status.

Treatment of patients with valproic acid toxicity is also mainly supportive[72]/ Levocarnitine may be used for hyperammonemia by loading 100 mg/kg intravenously followed by 50 mg/kg every 8 hours. Naloxone has been reported in anecdotal reports to reverse the CNS depression from valproate although he effect is not universal[73,74]. Hemodialysis and hemoperfusion may be indicated for severe cases with hyperammonemia[75].

It is important to admit patients with suspected acute lithium intoxication with significant symptoms regardless of the plasma levels of lithium. Li is an intracellular ion similar to K+, so serum levels do not reflect the total body load. Since most lithium formulations are sustained release, serial levels are necessary to assess for ongoing absorption. The treatment of acute lithium toxicity may include gut decontamination with gastric lavage or bowel irrigation using polyethylene glycol if ingestion occurred within one hour. Activated charcoal does not adsorb lithium and is not recommended unless there is suspicion of a mixed ingestion [76]. Volume resuscitation is necessary in the management of lithium intoxication with a goal to restore glomerular filtration rate (GFR), normalize urine output, and enhance lithium clearance[77]. Extracorporeal treatment is recommended in severe lithium poisoning and is recommended in the situations with lithium levels > 4.0 mEq/L with impaired renal function or presence of neurological or cardiac side effects irrespective of levels. Patients who receive chronic lithium therapy should be admitted if the plasma levels are higher than 2.0 mEq/L, and those who present with severe neurotoxicity require extracorporeal renal support and ICU admission [78]. The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup (https://www.extrip-workgroup.org) has specific recommendation on the use of extracorporeal treatment in lithium poisoning. Extracorporeal treatment is continued for minimum of 6 hours until there is a clinical improvement or the lithium levels fall below 1.0 mEq/L with q12 hours monitoring of serum levels for possibility of lithium rebound from redistribution or ongoing absorption. Hemodialysis is the most efficient extracorporeal treatment, but continuous renal replacement is an acceptable alternative.

## 5. Hallucinogens

### *5.1. Diffusion and Pharmacology*

Hallucinogens comprise a unique group of substances that are used to induce hallucinations or alterations of consciousness such as alteration of visual, auditory, or tactile perceptions but also drugs that induce alteration of thought and emotion. Natural hallucinogens can be found in plants and mushrooms and continue to be used worldwide for religious and recreational purposes.

Hallucinogens can be classified according to chemical family (indole alkaloids such as tryptamines and ergolines, piperidines/piperazines, 3-trifluoromethylphenylpiperazine, and phenylethylamine derivatives) or to CNS effect (psychedelics, dissociatives, and deliriants) (Table 5)[79,80]. Use of ketamine as a dissociative hallucinogen is also increasing with illicit access being sourced from veterinary offices.

### *5.3. Toxicity*

Most patients presenting with hallucinogen intoxication have a history of recent exposure, but mixed use of hallucinogens with drugs such as acetaminophen, caffeine, barbiturates, antipsychotics, or other pharmaceuticals is very common[81]. While mushrooms containing psilocybin are recognizable, other hallucinogenic mushrooms (*Amanita muscaria)* look similar to poisonous ones (*Amanita phalloides)* , and may be ingested by mistake causing severe hepatotoxicity.

Patients present with a wide range of behaviors that tend to fluctuate from a calm euphoric state to one of extreme agitation and aggressiveness. An accurate history may be difficult and often depends on circumstantial evidence[82]. Delayed GI effects (nausea and vomiting) can present after 6 hours from ingestion of hallucinogenic mushrooms. Most agents once ingested or inhaled have a predictable duration of effect. DMT has onset of action in a few seconds and duration of less than 60 minutes. The effects of MDMA last for 4-8 hours, and LSD can be active for more than 12 hours. General features of hallucinogen intoxication include altered sensorium, tachypnea, tachycardia, and mild to moderate hypertension. Hyperthermia is not a characteristic feature of mild toxicity with single-substance hallucinogens; if present, fever should trigger suspicion of polysubstance intoxication, serotonin syndrome, or anticholinergic syndrome[83,84]. Marked mydriasis is seen in tryptamine or LSD use. Phencyclidine and ketamine can produce horizontal, vertical, or rotatory nystagmus. Muscle tremors and fasciculation are characteristic of phenylethylamine use, whereas muscular rigidity, hyperreflexia of the lower extremities, and clonus should be features

of serotonin syndrome (LSD, psilocybin, and mescaline) [80]. GI alterations are common with mescaline and DMT.

### *5.4. Management*

Due to altered behavior, patients with acute hallucinogen intoxication should be placed in a calm and relaxed environment. If this is not sufficient, physical restraints and sedatives may be required. Most patients who present without medical complications do well with sedatives and reassurance[82]. The first line of sedatives includes benzodiazepines. Haloperidol or droperidol could be considered in addition to benzodiazepines, but can cause QT prolongation and torsade de pointes, seizures, or temperature dysregulation[85]. Atypical antipsychotics are contraindicated, as they can precipitate serotonin syndrome.

A thorough physical examination should pay attention to traumatic injuries, cardiac dysrhythmias, and hyperthermia. Hyperthermia and agitation following ingestion of hallucinogens are life-threatening emergencies and should be managed aggressively. Phencyclidine and new hallucinogens also act as stimulants causing severe hyperthermia and diffuse muscle fasciculations. Rapid cooling is recommended, and patients may require neuromuscular paralysis. Patients should be given intravenous fluids and observed for the development of rhabdomyolysis.

## 6. Other commonly used licit psychoactive substances

### 6.1. Caffeine

Popular beverages, such as coffee, tea, soda, and energy drinks, contain caffeine. According to the Mayo Clinic, the maximum recommended amount of caffeine is 400 milligrams per day for healthy adults (100 mg/day for adolescents and < 200 mg/day for pregnant women). The exact amount of caffeine that can lead to overdose is difficult to establish due to its unpredictable half-life (Table 6) [86]. A caffeine overdose can be life-threatening, but most people notice only some unpleasant symptoms that are self-resolving when the substance is metabolized. The diagnosis can be difficult. Symptoms of acute severe intoxication include anxiety, hallucinations, irritability, uncontrollable muscle movements, vomiting and diarrhoea, seizures and in extreme cases status epilepticus, chest pain, and dysrhythmias[86]. Chronic use of high doses of caffeine could lead to hormonal imbalances.

### 6.2. Nicotine

Nicotine poisoning is rare with traditional tobacco-containing cigarettes and cigars but has become more frequent in recent years due to increasing availability of alternative nicotine products such as e-cigarettes and pure liquid nicotine that are more likely to cause poisoning [87]. There is also a worrisome increase in intoxications involving children[88]. Consuming a few e-cigarettes at once could be fatal given that 30 to 60 mg of nicotine is considered lethal in adults[87]. Adults who are not used to nicotine and try vaping for the first time are at higher risk of poisoning compared to others who have smoked cigarettes before. Rarely, exposure can occur from skin contact and ingestion. Another population at risk includes workers of nicotine-based products (tobacco plants and harvesting fields).

Nicotine primarily effects the heart and CNS, regardless of the amount ingested or inhaled. Nicotine poisoning usually presents in two stages. Early symptoms that may last 15 minutes to 2 hours in case of mild overdose, and up to 24 hours in severe overdose include dizziness, abdominal pain, sialorrhea, tachypnea, tachycardia, hypertension, headache, and confusion [89]. More severe symptoms may appear in 30 minutes to 4 hours and include diarrhoea, hypoventilation, bradycardia, hypotension, stupor, weakness, uncontrollable muscle movements, and seizures.

### 6.3. Cannabis and synthetic cannabinoids

The easy availability of cannabis and the associated perception of a low risk of harm, make cannabis and synthetic cannabinoids among the most common substances used by adolescents. However, cannabis is often used together with other substances or it precedes the use of other more potent PADs. Cannabis and synthetic cannabinoids are usually smoked (inhaled) but inclusion of cannabis in health supplements and edible forms is increasing.

Worldwide, cannabis was used by 192 million people in 2018 and was the most common psychoactive drug in 2016[90]. Noteworthy, there has been a decline in the amount of cannabis herb seized globally (by 27% in 2016) particularly in North America, where many jurisdictions have legalized cannabis for recreational use[14,91].

All synthetic cannabinoids can cause severe agitation, hallucinations, delusions, paranoia, and schizophrenic behaviors. In severe intoxication, the patient can show severe agitation, panic attacks, tremor, seizures, and tachycardia. Cannabinoids adulterated with brodifacoum may present with signs and symptoms of coagulopathy[92]. The diagnosis of intoxication is usually made using urine drug screens for cannabis but synthetic cannabinoids are not detected[93].

### 6.4. Management

The treatment of caffeine intoxication focuses on increasing elimination from the blood while managing symptoms. If patients present within an hour of ingestion, activated charcoal can be used. Continuous cardiac monitoring and ongoing neurological assessment are required. The treatment of nicotine intoxication is similarly focused on increased elimination if ingested and supportive care aimed at protecting the airway and preventing or treating dysrhythmias. The treatment of cannabis or synthetic cannabinoid intoxication may include the use of benzodiazepines for sedation as well as ventilator support in case of respiratory depression or decreased level of consciousness.

## 7. New Psychoactive Substances

New Psychoactive Substances also known as "legal highs", "bath salts" or "research chemicals" have been synthesized for decades but are increasingly popular in the illicit drug market with more than 500 new NPS formulations identified on the market each year[14] . The United Nations Office on Drugs and Crime (UNODC) groups under the term NPS those *"substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat"*[14]. The majority of NPS identified by UNODC monitors are stimulants, cannabinoid receptor agonists, and classic hallucinogens (Figure 1) [14]. NPS in general have not replaced traditional drugs on a larger scale. NPS with opioid-like effects have been associated with fatalities, and injectable NPS have been associated with high-risk administration practices[94].

Globally, the large number of emerging NPS poses a significant risk to public health and a challenge to drug policy processes. NPS users are frequently hospitalized with severe intoxications. Safety data on many NPS are very limited, and details on long-term adverse effects and risks are still unknown. Little is known about NPS adverse effects and both prevention and treatment can be challenging. Known side effects of NPS include seizures, agitation, aggressiveness, and acute psychosis. Additionally, impurities or compounds added to stabilize formulations may have high risk of complex and unpredictable severe side effects. Deaths associated with NPS are often caused by polysubstance use[94]. Table 7 summarizes the neurological toxicity and targeted management for PADs and NPS.

## 8. Discussion

In recent years, there have been important changes in the PAD markets: first, there is increased production and use of NPS; second, there is ongoing use of long-time available PADs; third, there is a rise in the nonmedical use of prescription drugs that are either obtained from licit channels or illegally manufactured; fourth, more substances sold as alleged medicines but are destined for nonmedical use are supplied through illicit channels.

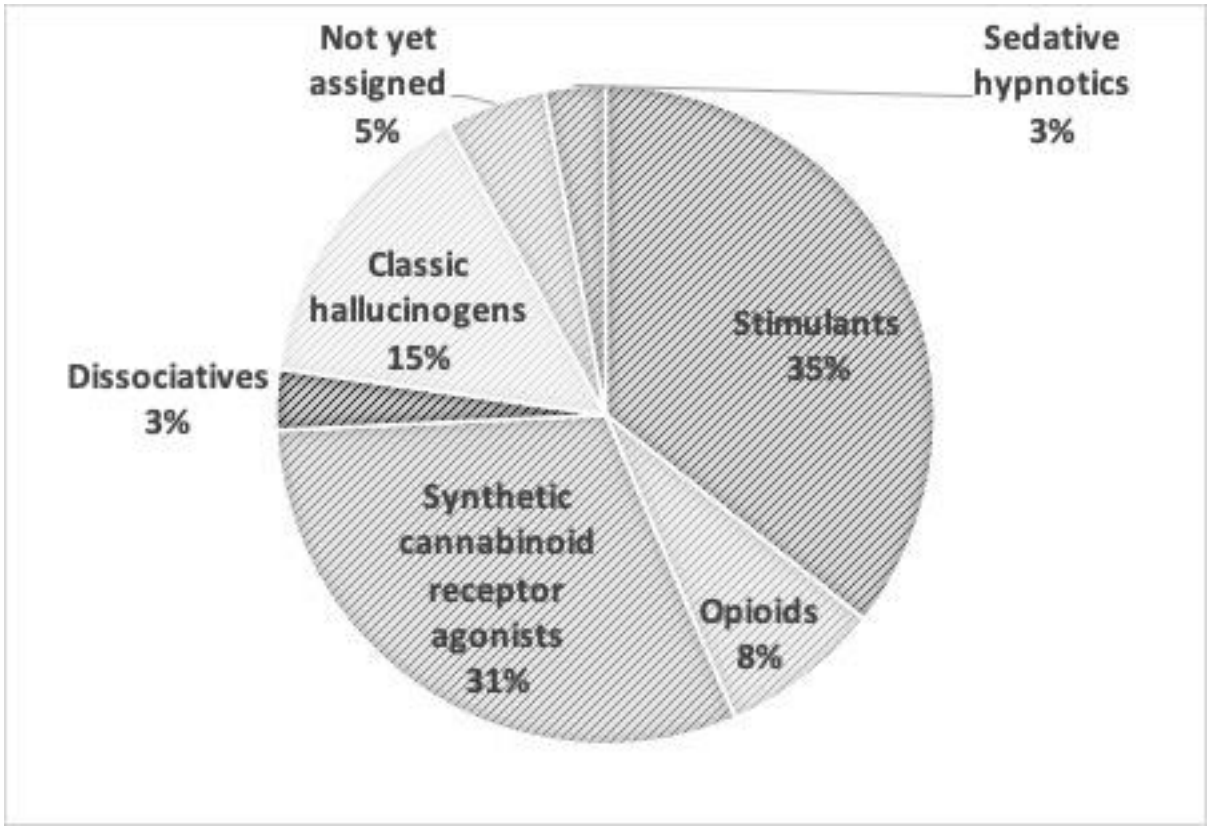
Similar to the 2008 economic crisis, reports suggest that the COVID-19 pandemic is shifting trends in PAD trafficking, consumption patterns, and shift in preferred substance of abuse based on accessibility and availability[14,95]. Cannabis use may have increased since the first lockdown measures[14]. Monitoring, reporting, information sharing, early warning, and risk awareness are essential to prepare the response to the emerging health threat associated with PAD use.

Clinical Care Points

- Sodium bicarbonate is the mainstay of therapy for severe TCA toxicity by alkalinisation effect as well sodium load to reverse the sodium channel blocking effect of TCAs
- Benzodiazepines are the mainstay of seizure management in most overdose related seizures related to psychoactive substances.
- Early recognition, discontinuation of drugs and supportive care are central to managing serotonin syndrome and Neuroleptic Malignant Syndrome. Dantrolene should be considered in hyperthermia related to NMS.
- Extracorporeal treatments should be considered in lithium toxicity severe valproate toxicity
- Symptomatic management of agitation in most hallucinogen ingestions can be managed by careful use if sedatives.

**Figures**

**Figure 1. New Psychoactive Substances (NPS) by effect group, up to December 2019. Source: World Drug Report 2020 (United Nations publication, Sales No. E.20.XI.6)[14].**



## Tables

**Table 1. Neurotransmitter pathways, major systemic effects and interfering substances (mimics and blockers).**

| Neurotransmitter | Effects | Substances |
|---|---|---|
| **Norepinephrine** | ↑ Heart rate<br>↑ Euphoria<br>↑ Alertness and responsiveness<br>↑ Pain threshold | ***Mimics***<br>Amphetamines, cocaine, TCAs, SNRIs, MAOIs, LSD, pseudoephedrine, pyridostigmine<br><br>***Blockers***<br>Propranolol, clonidine, phentolamine, lithium |
| **Dopamine** | ↑ Euphoria<br>↑ Alertness and responsiveness<br>↓ Hunger | ***Mimics***<br>Amphetamines, cocaine, MAOIs, ergolines<br><br>***Blockers***<br>Antipsychotics, tetrabenazine, lithium |
| **Serotonin (5-HT)** | ↑ Euphoria<br>↑ Happiness<br>↑ Pain threshold | ***Mimics***<br>Amphetamines, cocaine, LSD, psychedelics, SSRIs, SNRIs, TCAs, MAOIs, lithium<br><br>***Blockers***<br>Atypical antipsychotics, ondansetron |
| **Acetylcholine** | ↓ Heart rate<br>↑ Sweat, salivation<br>↑ Enhanced memory<br>↑ Muscle tone/contraction | ***Mimics***<br>Nicotine, muscarine, physostigmine, pilocarpine<br><br>***Blockers***<br>Benzodiazepines, scopolamine, benztropine, TCAs, atypical antipsychotics |
| **Glutamate** | ↑ Enhanced learning and memory<br>↑ Diffuse neuronal depolarization (seizures) | ***Mimics***<br>None<br>***Blockers***<br>Phencyclidine, ketamine, dextromethorphan, |

| | | |
|---|---|---|
| **Gamma-Aminobutyric Acid** | ↑ Drowsiness<br>↓ Anxiety<br>↓ Alertness and responsiveness<br>↓ Memory<br>↓ Muscle tone/contraction | ***Mimics***<br>Alcohol, barbiturates, benzodiazepines, GHB, muscimol, lithium<br><br>***Blockers***<br>Flumazenil |
| | | |
| **Cannabinoids** | ↑ Hunger<br>↓ Nausea and vomiting<br>↓ Cognition and memory<br>↓ Neuroinflammation<br>↑ Pain threshold | ***Mimics***<br>THC (marijuana, hashish), nabilone<br><br>***Blockers***<br>Rimonabant |
| **Histamine** | ↑ Alertness and responsiveness<br>↑ Gastric acid production<br>↑ Pruritis<br>↓ Hunger | ***Mimics***<br>Opiates, betahistine<br><br>***Blockers***<br>TCAs, atypical antipsychotics, ranitidine |

TCA-Tricycle Antidepressant, SNRI- Serotonin-Norepinephrine Reuptake Inhibitor, MAOI- Monoamine Oxidase Inhibitors, LSD-Lysergic acid diethylamide**,** GHB- Gamma Hydroxybutyrate, THC- Tetrahydrocannabinol

1 **Table 2. Antidepressant drugs**

| Class | Drugs | Mechanism of action | Medical use | Pharmacology |
|---|---|---|---|---|
| Tricyclic antidepressants | Dibenzazepines *(imipramine, desipramine, clomipramine, trimipramine, lofepramine),* dibenzocycloheptadienes *(amitriptyline, nortriptyline, protriptyline, butriptyline),* dibenzoxepins *(doxepin),* dibenzothiepines *(dosulepin),* dibenzoxazepines *(amoxapine)* | • Norepinephrine reuptake inhibitors<br>• Serotonin reuptake inhibitors<br>• Acetylcholine receptor antagonist (muscarinic)<br>• H1 histamine receptor antagonists | Depressive disorder (refractory to SSRI, SNRI, MAOI), migraine prophylaxis, neuralgic pain, obsessive-compulsive disorder, nocturnal enuresis (children only) | ***Time to onset of signs of toxicity***<br>30-40 minutes for initial symptoms; signs of toxicity clinically apparent within 2 hours<br>***Half-life***<br>Average elimination $t_{1/2}$ ~1 day (up to 3 days for protriptyline)<br>***Metabolism***<br>Substantial pre-systemic first-pass metabolism, large volume of distribution, extensive protein binding, metabolized by hepatic cytochrome P450 oxidative enzymes |
| Monoamine oxidase inhibitor (MAOI) | Isocarboxazid, phenelzine, tranylcypromine, selegiline | • Monoamine oxidase inhibitors | Panic disorder with agoraphobia, depression or anxiety disorders, bulimia, post-traumatic stress disorder, borderline personality disorder, obsessive compulsive disorder, bipolar depression, Parkinson's disease (selegiline), migraine prophylaxis, dysthymia complicated by panic disorder or hysteric dysphoria | ***Time to onset of signs of toxicity*** Symptoms slowly apparent within the first 24 to 48 hours<br>***Half-life***<br>Irreversible MAOIs are rapidly absorbed & quickly eliminated, with plasma elimination $t_{1/2}$ 1.5–4 hours<br>***Metabolism***<br>Because of irreversible inhibition of MAO, the physiological effects of phenelzine, isocarboxazid, and tranylcypromine persist for up to 2–3 weeks |
| Selective serotonin reuptake inhibitors (SSRI) | Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline | • Serotonin reuptake inhibitors | Depression, panic attacks and panic disorders, anxiety, agoraphobia | ***Time to onset of signs of toxicity*** 1-2 weeks<br>***Half-life***<br>Elimination half-life is approximately 24 hours<br>***Metabolism***<br>Good oral absorption, highly protein bound, large volume of distribution (12 – 97 L/kg), hepatic metabolism to water soluble and less active metabolites |
| Serotonin-norepinephrine reuptake inhibitors (SNRI) | Atomoxetine, duloxetine, venlafaxine, desvenlafaxine | • Norepinephrine reuptake inhibitors<br>• Serotonin reuptake inhibitors | Generalised anxiety disorders, social anxiety disorder, panic disorder, agoraphobia | ***Time to onset of signs of toxicity*** 3-6 weeks<br>***Half-life***<br>5-11 hours (depending on metabolites half-life)<br>***Metabolism***<br>Good oral absorption, large volume of distribution, metabolites might need long time to eliminate |

2 Legend: SSRI- Serotonin-norepinephrine reuptake inhibitors, SNR- Serotonin-norepinephrine reuptake inhibitors, MAO-Monoamine oxidase inhibitor

**Table 3. Comparison of the clinical features of *serotonin syndrome*, *anticholinergic syndrome*, *neuroleptic malignant syndrome*, and *malignant hyperthermia*.**

| Condition | Serotonin Syndrome | Anticholinergic Syndrome | Neuroleptic Malignant Syndrome | Malignant Hyperthermia |
|---|---|---|---|---|
| ***Exposure*** | Serotonergics (antidepressants, fentanyl, tramadol, linezolid, sumatriptan, ondansetron) | Anticholinergics | Antipsychotics (dopamine antagonists) and dopamine withdrawal | Inhalational anesthetics, depolarizing muscle blockers (succinylcholine) |
| ***Onset after exposure*** | <12 hours (25% of cases can develop symptoms after 24 hours) | <12 hours | 24-72 hours | 0.5-24 hours |
| ***Resolution after treatment initiation*** | Within 24 hours | Hours to days | Up to 10 days | 24-48 hours |
| ***Temperature*** | Hyperthermia (>41.1 C) | Hyperthermia (<38.8 C) | Hyperthermia (>41.1 C) | Hyperthermia (up to 46 C) |
| ***Cardiorespiratory signs*** | Hypertension, Tachycardia, Tachypnoea | Hypertension (mild), Tachycardia, Tachypnoea | Hypertension, Tachycardia, Tachypnoea | Hypertension, Tachycardia, Tachypnoea |
| ***Pupils*** | Dilated | Dilated | Normal | Normal |
| ***Neuromuscular signs*** | Neuromuscular hyperactivity, increased tone (lower limbs > upper limbs), tremor, myoclonus | Normal muscle tone | Neuromuscular hypoactivity, diffuse rigidity ("lead pipe" like), bradykinesia | Rigor-mortis like rigidity |
| ***Reflexes*** | Hyperreflexia, clonus | Normal | Bradyreflexia | Hyporeflexia |
| ***Mental status*** | Agitation, delirium, coma | Hypervigilance, agitation, delirium, hallucinations, mumbling speech, coma | Stupor, mutism, coma | Agitation |
| ***Mouth*** | Sialorrhea | Dry | Sialorrhea | Normal |
| ***Skin*** | Sweaty | Red, hot, dry | Pale, sweaty | Mottled, sweaty |

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| ***Gastrointestinal signs*** 1 | Increased bowel sounds | Decreased bowel sounds | Normal or decreased bowel sounds | Decreased bowel sounds |

1 ***Table 4. Antipsychotics and Mood stabilizers***

| | Class | Drugs | Mechanism of action | Medical use | Pharmacology |
|---|---|---|---|---|---|
| **Antipsychotics** | Typical antipsychotics | Phenothiazines *(chloropromazine, fluphenazine, perphenazine, thioridazine)* thioxanthenes *(chlorprothixene)* butyrophenones *(haloperidol)* diphenypbutylpiperidines *(pimozide)* dihydroindolones *(molindone)* | • Dopamine receptor antagonists | Prophylaxis of postoperative nausea and vomiting, Schizophrenia, psychosis, Paranoid psychosis | ***Time to onset*** >1 week (up to 6 weeks) ***Half-life*** >100 hours ***Metabolism*** High protein binding, hepatic metabolism and renal excretion |
| | Atypical antipsychotics | Aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone | • Acetylcholine receptor antagonist (muscarinic)<br>• Dopamine receptor antagonists<br>• Norepinephrine reuptake inhibitor (quetiapine)<br>• Serotonin receptor antagonists<br>• H1 histamine receptor antagonists | Schizophrenia, treatment of mania in bipolar disorder | ***Time to onset*** < 1 week ***Half-life*** 7-12 hours ***Metabolism*** Hepatic metabolism |
| **Mood stabilizers** | Anticonvulsants | Carbamazepine, valproic acid, lamotrigine | Mechanisms of action are not completely elucidated<br>• Sodium channel blocker (lamotrigine) with suppression of glutamate and aspartate release | Epilepsy, neuropathic pain (trigeminal neuralgia, peripheral neuropathy), resistant obsessive disorders, migraine, cluster headaches, affective disorders, bipolar disorders, schizophrenia, borderline personality disorders | ***Time to onset*** 4 hours ***Half-life*** 12 to 30 hours ***Metabolism*** Hepatic metabolism: some drugs are strong inducers of hepatic enzymes |
| | Mineral | Lithium | • Decreases norepinephrine release<br>• Increases serotonin release<br>• Interference with dopamine signaling<br>• Modulation of glutamate levels<br>• Increases levels of GABA<br>• Inhibition of enzyme inositol monophosphate<br>• Interference with the sodium–potassium pump | Bipolar disorders, depressive disorder refractory to antidepressants, schizophrenic disorders. | ***Time to onset*** 7-14 days ***Half-life*** 18-36 hours ***Metabolism*** Absorbed in the small intestine and renally excreted |

2

1 ***Table 5. Hallucinogens***

| Class | Drugs | Mechanism of action | Medical use | Pharmacology |
|---|---|---|---|---|
| Psychedelics | Tryptamines<br><br>*Psylocybin and psilocin (mushrooms), bufotenin (toads), N,N-Dimethyltryptamine (DMT, plants)* | • Serotonin receptor partial agonist (5-HT2) | None | ***Time to onset***<br>20-30 minutes<br>***Half-life***<br>1 hour<br>***Metabolism***<br>Metabolised by a number of pathways including monoamine oxidase, limiting the oral bioavailability of some compounds |
| | Ergolines<br><br>*Lysergic Acid Diethylamide (LSD), Lysergic Acid Amide (LSA, plants)* | • Serotonin receptor agonist<br>• Dopamine receptor partial agonist<br>• Norepinephrine receptor agonist | Psilocybin and LSD have been investigated in the treatment of cluster headache | ***Time to onset***<br>3-4 hours (depending on the route of administration)<br>***Half-life***<br>6-24 hours<br>***Metabolism***<br>Extensively metabolised by the liver, predominantly via hydrolysis |
| | Phenethylamines<br><br>*Mescaline (peyote cactus), 2C-series drugs (2C-B, 2C-I, 2C-C, 2C-T-7), 3C-E, 4-MTA, PMA, DO-series drugs (DOC, DOB, DOI, DOM)* | • Serotonin receptor agonist | | ***Time to onset***<br>>1 hour (up to 24 hours)<br>***Half-life***<br>5-10 minutes<br>***Metabolism***<br>Urinary excretion of the main metabolite, phenylacetic acid |
| Dissociative drugs | Phencyclidine (PCP), dextromethorphan, ketamine | • NMDA receptor antagonist<br>• Sigma-1 receptor agonist | Anesthesia | ***Time to onset***<br>2-60 minutes<br>***Half-life***<br>6 hours – 3 days<br>***Metabolism***<br>Complex active metabolites |
| Deliriants | Scopolamine and atropine (plants), diphenhydramine, dimenhydrinate | • Acetylcholine receptor antagonist (muscarinic) | Multiple legitimate uses (anesthesia, resuscitation, cardiology, ophthalmology, etc.) | ***Time to onset***<br>1-5 minutes<br>***Half-life***<br>2-9.5 hours<br>***Metabolism***<br>Destroyed by enzymatic hydrolysis, particularly in the liver, with 13% to 50% excreted unchanged in the urine |

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|---|---|---|---|---|
| | Salvinorin A (Salvia Divinorum) | • Selective agonist of the kappa opioid receptor | Similar to some pain relief medications (pentazocine) | ***Time to onset***<br>Rapid when smoked (40 seconds)<br>***Half-life***<br>8 minutes<br>***Metabolism***<br>Quick metabolism in the gastrointestinal tract |
| | Muscimol (amanita muscaria) | • GABA-A agonist | Research only | ***Time to onset***<br>30-120 minutes<br>***Half-life***<br>5-10 hours<br>***Metabolism***<br>Urinary excretion |

***Table 6. Other psychoactive drugs***

| Drug | Mechanism of action | Medical use | Pharmacology |
|---|---|---|---|
| Caffeine (coffee, tea, other plants) | • Adenosine receptor antagonist<br>• Monoamine oxidase inhibitor | Headache | ***Time to onset***<br>10 minutes<br>***Half-life***<br>From 1.5 to 9.5 hours.<br>***Metabolism***<br>Metabolized by the cytochrome P450 enzyme |
| Nicotine (tobacco) | • Nicotinic acetylcholine receptor agonist | Nicotine addiction | ***Time to onset***<br>20 seconds<br>***Half-life***<br>1-2 hours<br>***Metabolism***<br>Metabolised to N-oxide, product of the hepatic oxidation by P-450 cytochrome |
| Cannabis (THC) | • Cannabinoid receptor partial agonist | Chemotherapy induced nausea and vomiting, neuropathic pain, sleep disorders, epilepsy | ***Time to onset***<br>Smoking onset in minutes, orally slow onset<br>***Half-life***<br>12-36 hours (longer for frequent users)<br>***Metabolism***<br>Cytochrome P450 enzyme |

***Table 7. Toxicology and management strategies for neurological symptoms.*** *(NMS, Neuroleptic malignant syndrome; AC, Activated Charcoal; SB, Sodium Bicarbonate; CNS, central nervous system)*

| **Drug class** | **Neurological symptoms of toxicity** | **Management strategies focused on neurological symptoms** |
|---|---|---|
| Tricyclic antidepressants | • Agitation, confusion, memory impairment, and anxiety<br>• CNS depression with reduced level of consciousness, hypoventilation, coma and seizures | • Increasing arterial pH to ≥7.45 with SB<br>• Lipid emulsion in refractory cases<br>• Benzodiazepines and propofol for seizures, avoid phenytoin and lacosamide |
| Selective serotonin reuptake inhibitors, Serotonin-norepinephrine reuptake inhibitor, and Monoamine oxidase inhibitors | • Neuromuscular excitation, autonomic instability-Hunter's criteria<br>• Altered level of consciousness and coma<br>• Serotonin syndrome in case of serotonergic agents<br>• Fatal hypertensive crisis in adrenergic agents | • Muscle relaxants to target rigidity and hyperthermia<br>• Benzodiazepines for management of seizures, agitation and muscle rigidity (diazepam or lorazepam 0.1-0.2 mg/kg)<br>• Butyrophenones (e.g., haloperidol) and droperidol worsen hyperthermia and are contraindicated<br>• Cyproheptadine or chlorpromazine may be considered for symptoms refractory to benzodiazepines<br>• Avoid depolarizing muscle relaxant drugs |
| Antipsychotics | • Acute extrapyramidal symptoms<br>• Seizures and status epilepticus<br>• Tardive dyskinesia<br>• NMS | • Benzodiazepines (e.g., lorazepam, midazolam) for treatment for seizures<br>• NMS-<br>dantrolene sodium (1-10 mg/kg) for muscle rigidity and fever in severe cases. Bromocriptine and amantadine for less severe cases<br>• Pulse steroid therapy for refractory cases |
| Carbamazepine and lamotrigine | • Headache, dizziness, blurry vision or diplopia, tremor, stupor, drowsiness, seizures | • Charcoal hemoperfusion, hemodialysis, intravenous lipid emulsion and multiple doses activated charcoal<br>• Benzodiazepine for seizure control |
| Valproate | • Tremors, agitation, miosis | • L-carnitine for hyperammonemia |

| | | |
|---|---|---|
| | • Hyperammonemia causing stupor, coma, or death | • Hemodialysis and hemoperfusion for refractory cases |
| Lithium | • Tremor, dystonia, hyperreflexia, ataxia, confusion, lethargy, seizure<br>• SILENT- syndrome of irreversible lithium-effectuated neurotoxicity | • Intravenous fluids to restore renal perfusion<br>• Hemodialysis for removing lithium |
| Hallucinogens | • Altered sensorium<br>• Marked mydriasis in tryptamine or lysergic acid use<br>• Phencyclidine horizontal, vertical, or rotatory nystagmus<br>• Life-threatening hyperthermia and agitation | • Benzodiazepines for agitation and seizures<br>• Avoid atypical antipsychotics<br>• Aggressive cooling |
| Caffeine | • Anxiety, hallucinations, irritability, uncontrollable muscle movements<br>• Seizures and status epilepticus | Supportive care<br>Benzodiazepines for agitation and seizures |
| Nicotine | • Headache, confusion, stupor<br>• Weakness, uncontrollable muscle movements<br>• Seizures | Supportive care<br>Benzodiazepines for agitation and seizures |
| Cannabis | • Severe agitation, hallucinations, delusions, paranoia, schizophrenic behaviors | Benzodiazepines for agitation and seizures |
| New Psychoactive Substances | • Seizures, agitation, aggressiveness, and acute psychosis | Supportive care<br>Benzodiazepines for agitation and seizures |

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