Chapter 10

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Psychotropic drug intoxication is an increasing problem in emergency medicine (Sorge *et al*., 2015). Although psychoactive drugs are beneficial in many cases of psychiatric illnesses, they also pose a risk of intoxication to patients (Pfeifer *et al*., 2020). Reactions to intoxication vary according to

the type and dose of the substance, combined with the patient›s level of tolerance (Sorge *et al.*, 2015). Causes of intoxication are related to suicide attempts, recreational drug overdoses, and overdoses for pain relief without suicidal intent (Sorge *et al.*, 2015).

Studies report that among the psychotropics used in suicide attempts, benzodiazepines and antidepressants are the leading causes of intoxication after ICU admissions. It is also known that tricyclic antidepressants have a higher mortality rate and higher risks of severe outcomes after overdose compared to other antidepressants (Pfeifer *et al.*, 2020). Other medications, such as pregabalin, prescribed for the treatment of anxiety, seizures, and other disorders, are increasingly associated with recreational use intoxication (Isoardi *et al.*, 2020). While studies report that recreational use of pregabalin does not cause severe outcomes, it can cause sedation, hallucinations, and other symptoms (Isoardi *et al.*, 2020). Therefore, analyzing the toxicity of these drugs, the possible outcomes of their combination with other medications, and considering the patient›s history of mental disorders is very important before prescribing any medication (Pfeifer *et al.*, 2020).

Intoxication from New Psychoactive Substances (NPS) is associated with serious health problems, with symptom development ranging from central nervous system toxicity, resulting in seizures and acute psychosis, to cardiac and hepatic toxicity, causing arrhythmias and systemic failures. Severe intoxications can be fatal, especially without access to intensive care, and the lack of data on the toxicity and lethality of many NPS increases these risks (Kronstrand *et al.*, 2018). Inconsistency in the purity and composition of products containing NPS places users at high risk, as evidenced by the increase in hospital admissions and related deaths (Kronstrand *et al.*, 2018).

Synthetic opioids are the leading cause of fatal intoxications from NPS, with an increase in the abuse of fentanyl analogs since 2013. The most common lethal symptoms of opioid toxidrome include respiratory depression, pulmonary and cerebral edema. The combination of opioids with P-glycoprotein inhibitors elevates the risk of fatal complications. Synthetic cannabinoid receptor agonists also present serious risks, such as cardiovascular events and acute renal failure, although no established toxidrome exists. Synthetic cathinones and phenethylamines can cause sympathomimetic and hallucinogenic toxidromes, increasing the risk of serotonin syndrome and severe cardiovascular effects. Compared to classic drugs, NPS exhibit more severe adverse effects, with a significant increase in deaths attributed to them in recent years (Kronstrand *et al.*, 2018).

Substance abuse induces changes in neurobehavioral symptoms, which can simultaneously exacerbate liver injury. Many biochemical alterations of the liver are observed in individuals who abuse illicit or recreational drugs. The clinical characteristic of drug-induced hepatotoxicity is usually acute hepatic necrosis and markedly elevated serum aminotransferase and LDH levels with increased alkaline phosphatase (Roy; Goswami, 2016). The mechanisms involved in liver injury can be induced by some drugs of abuse and dependence, such as cocaine, amphetamine, oxycodone, heroin, nicotine, methadone,

cannabis/marijuana, fentanyl, meperidine, hydromorphone, and chemotherapeutic drugs (Roy; Goswami, 2016). Major risk factors for substance abuse include smoking, alcohol consumption, unemployment, poor education, and psychiatric disorders. Psychostimulants induce liver toxicity in a dose-dependent process, with acute or chronic use of these substances causing liver damage, hepatic steatosis, cholestatic jaundice, hepatic granulomas, hepatitis, and liver cirrhosis (Roy; Goswami, 2016). The mechanisms of drug-induced hepatotoxicity depend on reactive reactions, formation of metabolites, modification of the connections between component cells with drugs and their metabolites, activation of signaling pathways that alter apoptosis or survival mechanisms, mitochondrial damage that alters ATP formation, and cytokines modulated by these substances (Roy; Goswami, 2016).

EPIDEMIOLOGY

Psychotropic drug intoxication is a frequent public health issue in hospital emergency and urgent care departments worldwide, with alarming incidence rates. During the study period of the STRIDA Project in Sweden, which lasted approximately six years, over 2,600 patients were treated in emergency departments and ICUs with suspected psychotropic drug intoxication. There has also been an increase in mortality in the United States, involving psychotropic drugs across different age and racial groups (Helander; Bäckberg, 2018; Goldstein, 2019). Associated risk factors include male gender, age, ethnicity, psychiatric diagnosis, cardiovascular problems, obesity, smoking, alcoholism, and drug abuse (Roversi *et al*., 2023). This highlights the need for better public health strategies and structures to address these cases.

In recent years, studies have shown an increase in the use of psychotropic drugs worldwide. In Denmark, usage among children aged 0 to 17 increased ninefold between 1996 and 2010. In Canada, there was a fourfold increase between 1998 and 2008 in individuals under 18, and similar increases in antipsychotic use were observed in the United States and the United Kingdom (Cairns et al., 2019). Mortality rates from poisoning with psychotropic drugs have increased more than prescription rates, especially for people between 45 and 64 years old. People with psychiatric diagnoses had more different compounds at the time of death compared to those without psychiatric diagnoses, with intoxication being the most frequent cause of death (40.6%), with methadone as the main intoxicant in Denmark (Reuss et al., 2021). In the UK and the European Union, mortality rates from drug and medication poisoning are notably lower than in the US (Goldstein, 2019).

In the US, there has been an increase in mortality from poisoning, suicide, and other comorbidities among white Americans over 50 years old, compared to Hispanics and blacks. These deaths occurred in urban and rural areas, mainly from poisoning. Data extracted from the CDC›s Wonder database show that age groups 25 to 74 and racial groups, especially non-Hispanic blacks, have higher chances of deaths from poisoning. People aged 55 to 74, particularly in recent years, showed a significant increase in mortality rates (Goldstein, 2019).

The incidence and prevalence of psychotropic drug intoxication have varied significantly over the years, influenced by different social, economic, and technological factors. The increase in the use of psychotropic drugs, such as antidepressants, antipsychotics, and ADHD medications, observed between 2009 and 2012 in Australia, is associated with the growth of suicidal tendencies in young people under 25 years old (Cairns *et al.*, 2019). Studies indicate that young people aged 10 to 19 often intoxicate themselves with non-opioid analgesics, antipyretics, and antirheumatics due to easy access to these medications (Pawer *et al.*, 2021).

There has been a significant increase in mortality rates due to intoxications with non-narcotic and psychodysleptic medications between 2000 and 2017, especially among non-Hispanic Native Americans and whites in the United States, suggesting possible misuse of medications (Goldstein, 2019). Data show that intentional drug intoxication is the leading cause of poisoning among adolescents, with an incidence rate varying from 0.4% to 10.3% internationally (Roversi *et al.*, 2023). Factors such as rapid psychological, biological, and social changes increase adolescents› vulnerability to environmental stress and psychopathology.

Patients with psychiatric diagnoses present a greater variety of compounds at the time of death, indicating greater clinical complexity (Reuss *et al.*, 2021). Recent technological advances, such as the increased use of the internet, social networks, and smartphones among young people, may be influencing mental health and responses to distress (Cairns *et al.*, 2019). The growth of smartphone use among adolescents is correlated with increased rates of self-harm, possibly due to an increase in mental illnesses in this population or changes in behavioral responses.

Although controversial, the internet can benefit young people by promoting positive mental health and well-being strategies through new means of communication (Cairns *et al.*, 2019). In British Columbia, resources such as Kids Help Phone and YouthinBC Online Chat encourage the sharing of ideas with trusted adults (Pawer *et al.*, 2021). However, individuals who do not seek help have an elevated risk of self-poisoning, especially in regions with limited access to mental health services.

The implementation of programs such as the Self-Injury Signs Program (SOSI) in secondary schools can be an effective strategy to reduce self-harm events (Pawer *et al.*, 2021). This cost-effective workshop, aligned with the BC Coroner›s recommendation to incorporate emotional learning and well-being strategies into the school environment, can reach a vast audience of children and young people, regardless of socioeconomic status. In summary, changes in the incidence and prevalence of psychotropic drug intoxication are influenced by a combination of social, economic, technological, and public health factors. Multifaceted approaches, including prevention, education, and social support, are essential to mitigate these public health issues (Pawer *et al.*, 2021).

Adolescence is a developmental stage marked by rapid psychological, biological, and social changes. These changes can significantly contribute to the vulnerability of young people to a variety of risk factors that can lead to self-harming behaviors, including suicide, self-intoxication, and non-suicidal self-injury (NSSI). In this chapter, we explore the known risk factors for these conditions, categorizing them into genetic, environmental, socioeconomic, and lifestyle factors.

Among genetic factors, a family history of NSSI stands out as an important predictor. Adolescents with a family history of self-harm have a significantly higher prevalence of NSSI, reaching 15% compared to 8% among those without such a history, suggesting a possible genetic predisposition or, alternatively, the impact of a family environment where self-harming behaviors are more common (Pawer *et al.*, 2021).

Environmental factors play a crucial role in the development of self-harming behaviors among adolescents. Exposure to violence, whether domestic or school-related, is one of the strongest predictors of NSSI, with a prevalence of 16% among young people exposed to such forms of violence, compared to 7% among those not exposed (Pawer *et al.*, 2021). Additionally, the phenomenon of self-harm contagion, where exposure to self-harming behaviors leads to imitation, is well-documented and amplified by the increasing use of social media (Cairns *et al.*, 2019).

The COVID-19 pandemic has also brought new challenges. Repeated exposure to information about the pandemic has been identified as a risk factor for anxiety, exacerbating mental health problems among adolescents (Roversi, 2023).

The socioeconomic status (SES) of a family is a significant determinant of NSSI prevalence among adolescents. Young people from families with low annual income (<30,000 SEK) have a prevalence of 12% of NSSI, compared to 9% among those from middle-income families (30,000-60,000 SEK) and 7% among those from high-income families (>60,000 SEK) (Pawer et al., 2021). Parental education level is also a determining factor: adolescents whose parents have only primary education have a prevalence of NSSI of 13%, while those with parents who have higher education have a prevalence of 6% (Pawer *et al.*, 2021).

Furthermore, material deprivation, defined as the lack of basic resources and comfort, is strongly associated with NSSI. Adolescents living in areas of high material deprivation have a prevalence of NSSI of 14%, compared to 6% in areas of low deprivation (Pawer *et al.*, 2021). This data emphasizes the need for public policies aimed at reducing socioeconomic inequality as a form of preventive intervention.

The lifestyle of adolescents also significantly influences the risk of self-harming behaviors. Substance abuse, including over-the-counter medications like acetaminophen and ibuprofen, is common in cases of self-intoxication. Acetaminophen, due to its wide availability, is frequently the most used substance in self-intoxications (Reuss, 2020; Cairns *et al.*, 2019).

Parental mental health is another critical factor. Adolescents whose parents have a history of mental health problems have a prevalence of NSSI of 14% (Pawer *et al.*, 2021).

Additionally, the increased use of psychotropic medications, such as antidepressants and antipsychotics, especially among young people, has been notable. Among children aged 10 to 14, the use of antidepressants like fluoxetine is particularly high (Cairns *et al.*, 2019).

DIAGNOSIS

To obtain a diagnosis of psychotropic drug intoxication, it is necessary to relate clinical events considering the toxicokinetics of the substances, which can present with distinct signs and symptoms. This is a fundamental factor in determining the medication and antidote to be used (Sacre *et al.*, 2017). Early diagnosis is crucial in emergency services to reverse acute intoxication, as these services often have the first contact with patients in mental distress using psychotropic substances, often in suicide attempts through intentional poisoning, with adolescents being the most affected group (Perera *et al.*, 2018).

Among the most frequently marketed medications in most countries are benzodiazepines, which, when metabolized, release two active compounds: nordazepam and oxazepam. Intoxication by nordazepam primarily manifests as drowsiness and mental confusion, with other possible symptoms including gait disturbances, dizziness, hypotonia, nausea, and vomiting, even when ingested in doses up to 45 times the maximum daily dose (Sacre *et al.*, 2017).

In intoxication caused by oxazepam, the most severe signs and symptoms include coma and decreased consciousness, as well as hypotonia, hypotension, and tachycardia. These symptoms can appear in doses 26 times higher than the maximum recommended dose, requiring greater attention from emergency services due to their severity at lower doses compared to nordazepam (Sacre *et al.*, 2017). For early diagnosis, it is essential to identify the time of ingestion, understand the half-life of each medication, and relate the doses to the magnitude of effects. This underscores the importance of early diagnosis for reversing intoxication (Sacre *et al.*, 2017; Perera *et al.*, 2018).

Recent advances in the diagnosis of psychotropic intoxication include the development of a rapid and sensitive method: Liquid Chromatography Coupled to Mass Spectrometry (LC-MS/MS). This method allows the quantification and identification of 12 different types of psychotropic drugs and their metabolites in hair. The hair test has proven promising due to its ability to identify low doses, continuous exposures, short- and long-term exposures, and it is a non-invasive examination (Ji *et al.*, 2019).

LC-MS/MS has high sensitivity, allowing the detection of extremely low doses (pg/mg levels) and the identification of various medications, including quetiapine, clozapine, paroxetine, clonazepam, midazolam, and ketamine (Ji *et al.*, 2019). Due to the lipophilic nature of these medications, there is greater accumulation in hair, facilitating rapid identification by passive diffusion and binding to hair keratin. This method can quantify and qualify medications in hair samples taken between 5 minutes and 6 hours after drug

administration, proving to be an innovation for the diagnosis of acute intoxication by quetiapine and other drugs, especially when other biological matrices are not available (Ji *et al*., 2019).

In cases of psychotropic intoxication, early diagnosis and identification of the drug of abuse are essential for the outcome of the acute condition, as they guide therapeutic conduct and symptom management, control the progression of damage caused by toxicity, and improve prognosis. In cases of poly-consumption of psychotropic drugs, the identification of administered drugs is more challenging due to the limited ability to associate clinical signs and intoxication severity (Muñiz *et al*., 2023).

The use of psychoactive substances can result in severe central and peripheral adverse effects and even death. Therefore, a detailed understanding of the mechanism of action of each substance helps assess potential neurological consequences and the risk of neurotoxicity (Rudin; Liechti; Luethi, 2021). The signs and symptoms of intoxications vary depending on the substance involved, the amount ingested, and the time elapsed since ingestion.

Table 1. Common signs and symptoms in each class of psychotropics:

Class	Common Symptoms
Antidepressants	Seizures, delusions, disorientation, confusion, hallucinations, incoherent speech, agitated and erratic behavior, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypotension, dizziness, syncope, cold skin, sweating, circulatory shock, nausea, vomiting, paralytic ileus.
Antipsychotics	Delusions, disorientation, confusion, hallucinations, incoherent speech, agitated and erratic behavior, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypotension, dizziness, syncope, cold skin, sweating, circulatory shock, neuroleptic malignant syndrome, severe muscle pain, weakness, reddish-brown urine.
Anxiolytics	Sedation, coma, seizures, respiratory depression, hypothermia.
Hypnotics	Sedation, coma, seizures, respiratory depression, slowed breathing, cyanosis, respiratory failure, hypothermia.
Stimulants	Agitation, psychosis, hyperactivity, perceptual distortions, extreme anxiety, paranoia, seizures, cardiac arrhythmia, tachycardia, bradycardia, QT interval prolongation on ECG, hypertension, severe headache, epistaxis, stroke, muscle rigidity, rhabdomyolysis, severe muscle pain, weakness, reddish-brown urine, hyperthermia.
Hallucinogens	Agitation, psychosis, hyperactivity, perceptual distortions, extreme anxiety, paranoia.
Opioids	Sedation, coma, respiratory depression, slowed breathing, cyanosis, respiratory failure, nausea, vomiting, paralytic ileus.

Despite the development of various prognostic scoring systems, such as the Simplified Acute Physiology Score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE), these systems may not be suitable for acutely intoxicated patients. Loss of consciousness upon arrival is significant in determining the final score but has little

impact on the outcome of intoxication, making them less sensitive in predicting mortality (Hamdi et al., 2016). Blood gas analysis is frequently performed in cases of acute poisoning as part of the clinical assessment to check the condition of patients (Hamdi *et al*., 2016). In the present study, significantly increased mortality rates were demonstrated in patients with primary respiratory alkalosis or severe metabolic acidosis, suggesting that blood gas analysis can be useful in the early assessment of survival in cases of acute poisoning (Hamdi *et al*., 2016).

A lower survival rate was observed in patients with primary respiratory alkalosis or severe metabolic acidosis. The findings indicated an independent statistical association between these acid-base disorders and mortality rate. Therefore, interpreting blood gases not only facilitates diagnosis but also provides indications for determining prognosis and helps identify patients requiring special intensive care. Although the direct role of acidosis in clinical outcomes remains uncertain, it has been identified as a predictor of negative outcomes in critically ill patients. Similar to other studies, it was observed that many patients with unfavorable outcomes had some component of metabolic acidosis (Hamdi *et al*., 2016).

TREATMENT

The importance of effective treatment for psychotropic drug intoxication is crucial, given the significant increase in the use of these substances and the high risk of severe and fatal adverse effects. Social development and increased mental stress have led to the excessive use of psychotropic medications, resulting in poisonings and various health impairments that affect patients› quality of life (Ghannoum *et al.,* 2015).

Therapeutic approaches to psychotropic intoxication vary depending on the substance involved. However, initial patient stabilization is a priority, ensuring patent airways, respiratory and cardiovascular support, and gastrointestinal decontamination with activated charcoal and gastric lavage, if appropriate (Ghannoum*et al.,* 2015; Lavonas; Buchanan, 2015; Yang *et al.,* 2018).

Among the main medications frequently associated with intoxication are carbamazepine, quetiapine, valproic acid, and lithium. Overdose with carbamazepine can cause choreiform movements, ataxia, and pulmonary edema, as well as central nervous system depression, seizures, and respiratory depression (Yang *et al.,* 2018). Lithium intoxication can result in symptoms such as extrapyramidal syndrome, cerebellar alterations, and cardiac conduction irregularities (Lavonas; Buchanan, 2015). Overdose of valproic acid can cause cerebral edema, hemodynamic shock, and laboratory abnormalities, including hypernatremia, thrombocytopenia, and hypokalemia (Ghannoum *et al.,* 2015).

Supportive measures and patient monitoring are crucial in cases of overdose with carbamazepine, quetiapine, and lithium, as these medications do not have specific antidotes. However, valproic acid intoxication can be treated with the specific antidote

L-carnitine (Reuchsel; Gonnert, 2022; Lavonas; Buchanan, 2015; Ghannoum *et al.,* 2015). For all cases, it is essential to ensure a patent airway and consider the use of activated charcoal and gastric lavage as indicated.

New therapeutic approaches are being explored to improve the management of psychotropic intoxication. Hemodialysis has been studied as a potential intervention for severe cases of lithium intoxication, improving the elimination of the drug from the body. Studies indicate that hemodialysis can be effective, although there is no absolute consensus on its indication in all cases (Lavonas; Buchanan, 2015; Gosselin *et al.,*2016).

The use of hemodialysis and other extracorporeal elimination techniques has shown promise in reducing serum lithium levels and improving clinical outcomes in severe intoxications. However, it is essential to evaluate each case individually to determine the best therapeutic approach (Lavonas; Buchanan, 2015; Gosselin *et al.,* 2016). Personalizing treatment is crucial to optimizing therapeutic outcomes. Continuous evaluation of the patient›s clinical status and adjustment of interventions based on individual response are fundamental to effective management of psychotropic intoxication (Ghannoum *et al.,* 2015).

Multidisciplinary collaboration is essential for the successful treatment of psychotropic intoxication. Teams that include toxicologists, psychiatrists, pharmacists, and emergency professionals can offer a holistic approach, ensuring comprehensive patient care (Yang *et al.,* 2018). Proper management of toxicities is vital for patient recovery. Careful monitoring and rapid intervention in cases of complications such as cardiac arrhythmias and respiratory depression are crucial to minimizing adverse effects and improving prognosis (Ghannoum et al., 2015).

Challenges in treating psychotropic intoxication include the precise identification of the involved substance, management of polysubstance use symptoms, and rapid adaptation to patient needs. Ongoing development of diagnostic and treatment methods is necessary to overcome these difficulties and improve clinical outcomes (Reuchsel; Gonnert, 2022). Continuous research and development of new therapies, such as hemodialysis for lithium intoxication, promise to further improve the effectiveness and safety of psychotropic intoxication treatment. The implementation of new technologies and personalized approaches will continue to evolve, offering better prognoses for patients (Lavonas; Buchanan, 2015; Gosselin *et al.,* 2016).

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