Trends
in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF
(as accepted)

Trends

Brazilian Psychiatric Association Consensus for the Management of Acute Intoxication. General management and specific interventions for drugs of abuse

Leonardo Baldaçara, Amanda de Gouvêa Pettersen, Verônica da Silveira Leite, Flávia Ismael, Carolina Pereira Motta, Railson Alves Freitas, Nicoli Abrão Fasanella, Lucas Alves Pereira, Maria Elisa Lima Barros, Leonardo Barbosa, Ana Luiza Silva Teles, Ruy Palhano, Helio Penna Guimaraes, Maria Aparecida Braga, João Mauricio Castaldelli-Maia, Carla Bicca, Analice Gligliotti, Ana Cecilia Petta Roseli Marques, Antônio Geraldo da Silva

http://doi.org/10.47626/2237-6089-2022-0571

Original submitted Date: 18-Sep-2022

Accepted Date: 19-Nov-2022

Brazilian Psychiatric Association Consensus for the Management of Acute Intoxication. General management and specific interventions for drugs of abuse.

Leonardo Baldaçara, Amanda de Gouvêa Pettersen, Verônica da Silveira Leite, Flávia Ismael, Carolina Pereira Motta, Railson Alves Freitas, Nicoli Abrão Fasanella, Lucas Alves Pereira, Maria Elisa Lima Barros, Leonardo Barbosa, Ana Luiza Silva Teles, Ruy Palhano, Helio Penna Guimaraes, Maria Aparecida Braga, João Mauricio Castaldelli-Maia, Carla Bicca, Analice Gligliotti, Ana Cecilia Petta Roseli Marques, Antônio Geraldo da Silva

Filiação

Leonardo Baldaçara
Universidade Federal do Tocantins, Associação Brasileira de Psiquiatria, Rio de Janeiro (RJ), Brazil.

Amanda de Gouvêa Pettersen
Associação Brasileira de Psiquiatria, Rio de Janeiro (RJ), Brazil.

Verônica da Silveira Leite
Universidade Federal do Tocantins, Associação Brasileira de Psiquiatria, Rio de Janeiro (RJ), Brazil.

Flávia Ismael
Universidade de São Caetano do Sul, São Caetano do Sul (SP), Brazil.

Carolina Pereira Motta
Centro de Atenção Psicossocial de Porto Nacional (TO), Brazil. Hospital Regional de Porto Nacional (TO), ITPAC, Palmas (TO), Brazil.

Railson Alves Freitas
Centro de Atenção Psicossocial Álcool e outras drogas III de Palmas (TO), Brazil.

Nicoli Abrão Fasanella
Pontifícia Universidade Católica de São Paulo, São Paulo (SP), Brazil.

Lucas Alves Pereira
Escola Bahiana de Medicina e Saúde Pública e Universidade Salvador, Salvador, (BA), Brazil.

Maria Elisa Lima Barros
Centro Universitário UniFG, Guanambi (BA), Brazil. CAPS II Beija-Flor, Guanambi, (BA), Brazil.

Leonardo Barbosa
Associação Brasileira de Psiquiatria, Rio de Janeiro, (RJ), Brazil.

Ana Luiza Silva Teles
Centro Universitário de Brasília (UniCEUB), Brasília, (DF), Brazil.

Ruy Palhano
Associação Brasileira de Psiquiatria, Rio de Janeiro, (RJ), Brazil.

Helio Penna Guimaraes
Associação Brasileira de Medicina de Emergência, Porto Alegre, (RS), Brazil.

Maria Aparecida Braga
Associação Brasileira de Medicina de Emergência, Porto Alegre, (RS), Brazil.

João Mauricio Castaldelli-Maia
Department of Neuroscience, Medical School, FMABC University Center, Santo André, (SP), Brazil. Department of Psychiatry, Medical School, University of São Paulo, São Paulo, (SP), Brazil.

Carla Bicca
Associação Brasileira de Psiquiatria, Brazil.

Analice Gligliotti
Associação Brasileira de Psiquiatria, Rio de Janeiro, (RJ), Brazil.

Ana Cecilia Petta Roseli Marques,
Associação Brasileira de Psiquiatria, Rio de Janeiro, (RJ), Brazil.

Antônio Geraldo da Silva
Associação Brasileira de Psiquiatria, Rio de Janeiro, (RJ), Brazil.

Corresponding author:
Leonardo Baldaçara
ACSU SO 40, Avenida Joaquim Teotônio Segurado, 1, Espaço Médico, sala 1005 e 1006
Plano Diretor Sul – Palmas – TO – CEP 77015-550
Phone: +55-63-3217-7288
e-mail: Leonardobaldassara@gmail.com

Conflicts of interest? No

Abstract

Objective: To present the Brazilian Psychiatric Association's Consensus for the Management of Acute Intoxication.

Methods: A group of experts selected by the Brazilian Psychiatric Association searched for articles in the MEDLINE (by PubMed) and Cochrane Database, limited to human studies and acute intoxication. Groups reviewed these materials for appropriateness to the topic and the quality of the work. To perform a table of agreed recommendations at the end of the systematic review, a survey using the Delphi method was conducted. Three survey rounds were conducted to develop a consensus.

Results: Support for intoxication may start with Initial Management: Resuscitation/Life Support/Differential Diagnosis. For that, the group proposed these orders of assessment: A (airway), B (breathing), C (circulation), D.1. (disability), D.2. (differential diagnosis), D.3. (decontamination), D.4. (drug antidotes), E (enhanced elimination). Then, the group of experts presented specific interventions for the main drugs of abuse.

Conclusions: The approach to intoxication with drugs of abuse is complex and requires systematic protocols. The group of experts suggested the adoption of the classic use in welcoming the patient of the A-B-C-D-E technique with constant investigation of this patient until reaching a specific conduct and with the support to remit the picture. The group of experts believes that this document, at this time, can help psychiatric, general, and emergency doctors deal with psychiatric emergency episodes due to acute intoxication.

Keywords: poisoning, emergencies, drug abuse, detoxification, acute intoxication

Introduction

Acute intoxication is a clinically significant transient condition that develops during, or shortly after, the consumption of a drug that is characterized by disturbances in consciousness, cognition, perception, affect, behavior or coordination[1,2]. These alterations are caused by known pharmacological effects of substances in the brain, and their intensity is closely related to the amount consumed. They are time-limited and abate as the drug is cleared from the body[1,2]. Presenting features may vary for each substance and can evolve into several complications, from physical damage (toxic hepatitis, seizures, cardiac arrhythmias) to cardiorespiratory arrest, agitation with aggression, car accidents, and suicidal behavior.[1,2]

Poisoning is probably one of the leading causes of admission to emergency departments and intensive care units. The death frequency ranges from 0.05% (USA) to 4% (South Africa).[3] Data from WHO report mortality by unintentional poisoning ranges from 0.001 to 5.45 per 100,000 habitants in the world.[4] About suicide, suicide attempt, and self-harm, poisoning is the preferred method.[5] In England it represents 5%–10% of an ED's workload.[6]

In Brazil, between 2010 and 2014, there were registered 376,506 suspected cases of poisoning in the Information System for Notifiable Diseases (SINAN), although the dimension is not yet fully known. Notification of Exogenous Intoxications became mandatory as of 2011, which included exogenous intoxication (IE) in the list of compulsory notification diseases[7]. Another study analyzed compulsory notifications for exogenous intoxication in Brazil between 2007 and 2017 conducted at SINAN. Of

833,282 cases of exogenous intoxication, 54.25% were women, and 54.47% were between 15 and 39 years old. The injuries were recorded mainly in the urban area (86.3%) of the Southeast region (47.65%).[8]

In 2018, an estimated 269 million (range: 166–373 million) people had used a drug at least once in the previous year, equivalent to 5.4 percent (range: 3.3–7.5 percent) of the global population aged 15–64.2 Assuming no change in the global prevalence of drug use, considering solely the projected increase in the global population would result in the global number of people who use drugs rising by an estimated 11 percent, to 299 million people by 2030. The health consequences of drug use can include a range of negative outcomes such as drug use disorders, mental health disorders, HIV infection, hepatitis-related liver cancer and cirrhosis, overdose, and premature death.[9]

Despite being a frequent situation in emergencies, it is still a reason for great difficulty on the part of doctors[10,11]. The literature is extensive, but with little evidence. Lack of training and stigma related to mental illness are factors that further hinder the care of these patients[12]. Therefore, documents that standardize the care of such cases can help health professionals act more effectively and help in the planning of public prevention policies.

This work aims to standardize and supply information for doctors, especially psychiatrists, to manage patients in acute intoxication from drugs of abuse.

Methods

The first goal of this group was to develop a guideline and score the files according to the Oxford 2011 evidence levels. However, after a detailed search, not enough articles with sufficient evidence were found for this task. As an alternative, a Consensus was created. From then on, procedures focused on the discussion and integration of findings from peer-reviewed published research on the topic. Then, groups reviewed these materials for appropriateness to the topic and the quality of the work. To create a table of agreed recommendations at the end of the systematic review, a survey using the Delphi method was conducted.

The Panel of experts: A group of experts selected by the Brazilian Psychiatric Association, based on publications or clinical experience in psychiatric emergencies, medical emergencies, or substance abuse disorders.

Eligibility criteria: Inclusion criteria for the literature research included: papers published (or in press) on adults (18 years old), from 2010 to 2020. Editorials, narrative reviews, small naturalistic studies, case reports, animal or in vitro studies, and letters to the editor were excluded. However, other manuscripts outside the inclusion criteria were assessed, when needed, such as association guidelines, government documents and articles outside the search period.

Search strategy: Searched for articles in the MEDLINE (by PubMed), Scielo, and Cochrane Database, limited to human studies and acute intoxication. Keywords used were poisoning OR emergencies OR drug abuse OR detoxification OR acute intoxication AND management.

Selection process: At first, two members, LB and AGP, searched for abstracts and selected the most relevant. Secondly, LB, AGP, CPM, and RAF analyzed full manuscripts aiming to select the most important and with the best quality.

Data collection: This process was done by LB, AGP, CPM, and RAF.

Data items: LB, AGP, CPM, and RAF wrote an outline of the manuscript. Included items for discussions were selected by another panel of experts in the first phase of the Delphi process.

Delphi method

To form a table of agreed recommendations at the end of the systematic review, we conducted a survey using the Delphi method.[13] Three survey rounds were conducted to develop consensus. The first survey included open-ended questions at the end of each section, inviting participants to add comments and suggestions by email. Later, rounds were conducted online. The survey was sent to the members of the agitation task force for anonymous responses. Panel members rated survey items, ranging from ‘‘essential’’ to ‘‘should not be included.’’ We calculated the proportions of respondents rating each item. Survey items were classified as endorsed, re-rated, or rejected. The method used to conduct this survey is the same one used to develop clinical recommendations by the Assessment and management of agitation in psychiatry: Expert consensus.[14]

Endorsed items: Items rated by the panel of experts as "essential" or "important" were included in the recommendations.

Re-rated items: Items rated as "essential" or "important" by 65–79% of panel experts, were included in the next survey for re-rating after considering feedback from first-round results. Panel members could decide whether they wanted to support or change their earlier rating on these relatively controversial items. Items were re-rated only once; if they did not achieve the criterion for endorsement, they were rejected.

Rejected items: Items that were not included by at least 65% of panelists on the first round were rejected and excluded. The first survey included 102 items. The second survey included 57 items. The briefer third survey consisted of eight items that needed re-rating. Fifty-two were endorsed and formed the final manuscript in the item results.

Initial Management: Resuscitation/Life Support/Differential Diagnosis

All situations of acute intoxication must be taken extremely seriously. Screening and hospitalization will be necessary when intentional self-poisonings or recreation ingestion occur. If symptoms are initially unexplained, urinary drug screening may be showed, although they are rarely helpful in short-term decisions. [11,15] [16,17].

The patient's physical examination verifies the main signs and symptoms related to each intoxication condition, which, when grouped, can characterize a certain toxic syndrome[11,15].

Initial assessment of the patient must go through the following steps[16,17]:

Figure 1. PRISMA 2020 flow diagram.

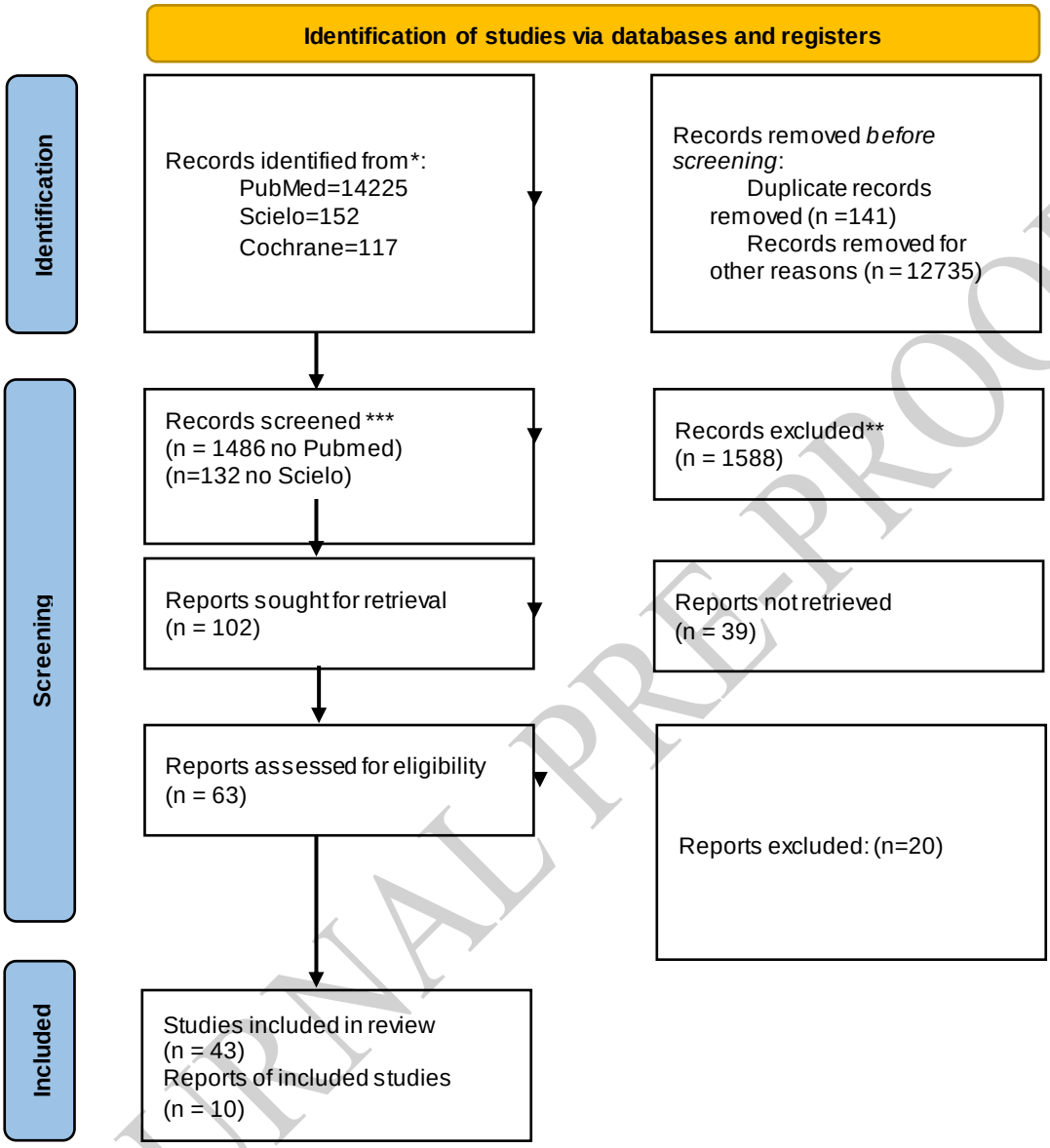
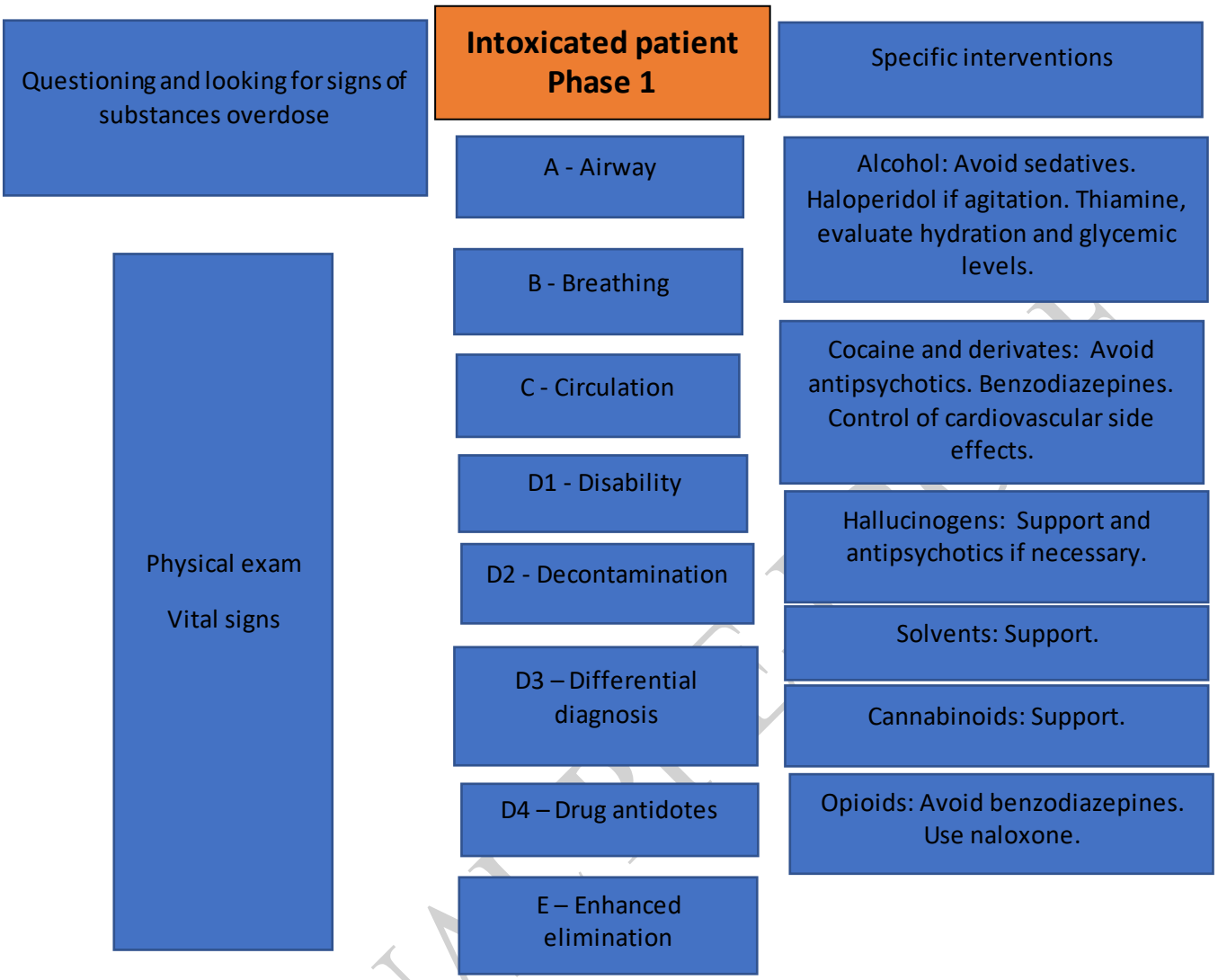


Figure 1. Flow diagram for the management of acute intoxication.



A. Airway

The airway must be kept patent through the positioning, suction, or insertion of an artificial nasal or oropharyngeal airway. If there are signs of coma or depressed airway reflexes, perform endotracheal intubation or insert an extra-glottic device (supraglottic or retroglottic)[17].

B. Breathing

- Clinically assess the quality and depth of respiration and assist, if necessary, with a bag valve-mask device or mechanical ventilator[17]. The arterial blood PO2 determination may reveal hypoxemia, which may be caused by respiratory depression, bronchospasm, pulmonary aspiration, or noncardiogenic pulmonary edema as soon as CO2 tension is useful in deciding the adequacy of ventilation. When using the pulse oximeter to assess oxygenation, one should be cautious as some may make misinterpretations, affected by ambient brightness, shock, and peripheral tissue perfusion.[17]

C. Circulation

- Measure the pulse and blood pressure and estimate tissue perfusion (e.g., by measurement of urinary output, lactate, skin signs, arterial blood pH). Use ECG for continuous monitoring. Collect blood, intravenously, to analyze levels of glucose, electrolytes, serum creatinine, liver enzymes, and possible quantitative toxicological test[17].
- Arrhythmia may occur and depends on different substances and reasons, such as hypoxia, metabolic acidosis, electrolyte imbalance (e.g., hyperkalemia, hypokalemia, hypomagnesemia, or hypocalcemia), following exposure to chlorinated solvents or by chloral hydrate overdose. Atypical ventricular tachycardia (torsade's points) is often associated with drugs that prolong QT interval or conditions associated with hypomagnesemia[17].

- Various medications can cause hypotension, such as antihypertensives, beta-blockers, calcium channel blockers, disulfiram (ethanol interaction during treatment), iron, trazodone, quetiapine, and other antipsychotic and antidepressant agents. Poisons that cause hypotension include cyanide, carbon monoxide, hydrogen sulfide, aluminum or zinc phosphide, arsenic, and certain mushrooms. When this symptom occurs, most patients respond to empirical treatment with repeated intravenous boluses of 200 ml or 4 ml/kg of 0.9% saline or other isotonic crystalloids up to a total of 1-2 L in 1 hour[17].
- Some intoxications can cause hypertension. The most common substances in this case are amphetamines and synthetic stimulants, anticholinergics, cocaine, performance-enhancing products (e.g., having caffeine, phenylephrine, ephedrine, or yohimbine), monoamine oxidase (MAO) inhibitors, and other drugs. It is important to consider which antihypertensive to use, if necessary, considering the mechanism of action and which adrenergic receptors will be blocked[17].

D.1. Disability

- Seizures are always generalized and usually respond to benzodiazepines with barbiturates second line. Phenytoin is ineffective[16].
- Drug-induced syndromes such as malignant hyperthermia, serotonin syndrome, and neuroleptic malignant syndrome should be investigated[12]
- Glucose levels should be checked and treated if the value is <4mmol / L (hypoglycemia link)[16]. Once hypoglycemia is confirmed, in all obtunded, comatose or convulsive patients, give 50% dextrose, 50-100 mL by intravenous bolus[17].
- Consider thiamine reposition, or in the intravenous fluids if chronic alcohol consumption or signs of malnutrition [11,17-21].
- If hyperthermia, consider poisoning by stimulants, atropine salicylates, strychnine, 2,4-dinitrophenol, antidepressants, antipsychotics, and various other medications[11,17-21].
- If hypothermia and coma, consider poisoning by opioids, ethanol, hypoglycemic agents, phenothiazines, barbiturates, benzodiazepines, and other SNC agents[11,17-21].

D.2. Differential diagnosis

In the initial assessment of an intoxicated patient, the “5 Ws” strategy is used in the clinical interview of the patient and/or companions, The "5 Ws" refer to the data related to the patient (Who?) - to obtain the history of diseases, medications in use, previous suicide attempts, occupation, access to substances, drug use, and pregnancy; the substance used (What?) - find out which substance was used and the quantity; (When?) - check the time of exposure and for how long the substance was used, in cases of repeated exposures; place of occurrence (Where?) - where the exposure occurred and if bottles, packages, syringes, or pill packs were found close to the patient, check which medicines the patient has access to, and reason for the exposure (Why?) - to identify the circumstance of the exposure, since it is extremely important to know if it was a suicide attempt, homicide, accident, recurrent episodes of drug abuse and others[11,15]. Basic support should be provided for all patients as described below. However, its continuity will depend on the type of substance used, and its identification is essential. Three measures can be used to find the substance: 1- Questioning the patient and his companions; 2- Finding substances or documents in their clothes; 3- Indirectly, by the signs or symptoms of identification; 4- Through toxicological examination[11,15].

D.3. Decontamination

In case of contact with eyes, irrigate with saline solution[17]. In case of skin contamination, remove clothes and wash with plenty of water and soap [22].

Regarding the gastrointestinal tract, a variety of methods may be considered, such as e*mesis* (no role in the hospital setting) and administration of ipecac at the site of ingestion or in the emergency department and should be avoided[22]. G*astric lavage* should not be performed routinely, and in situations where gastric lavage might seem proper, consider treatment with activated charcoal and always observe for supportive care [23]. A*ctivated charcoal*, used for prompt adsorption of drugs or toxins in the stomach and intestine, is contraindicated in patients with an altered conscious state, ethanol/glycols, alkalis /corrosives, metals including lithium, iron compounds, potassium, fluoride, cyanide, hydrocarbons, and mineral acids as Boric acid [16,17,24]. A w*hole bowel irrigation*, is not routinely indicated, but can be considered for cases of potentially toxic ingestion of sustained-release or enteric

substances such as coated drugs, drugs not adsorbed by activated charcoal (e.g. lithium, potassium, and iron) and for the removal of illicit drugs in "packers" or "stuffers" from the body[25].

D.4. Drug antidotes see specific guidelines.

Aiming to help in diagnosis and treatment, the possibility of dosing serum drugs can also be useful in choosing antidotes, if there are any[11,17].

E Enhanced elimination

- **Forced diuresis:** Forced diuresis is hazardous; the risk of complications (fluid overload, electrolyte imbalance) usually outweighs its benefits[17].

- **Urinary alkalinization:** Useful for salicylate toxicity if performed meticulously. This practice enhances poison elimination by administering intravenous sodium bicarbonate to produce urine with a pH ≥ 7.5. It may be considered the first choice for patients with moderate to severe salicylate poisoning (with no criteria for hemodialysis). It may also be effective in eliminating chlorpropamide, 2,4-dichlorophenoxyacetic acid, diflunisal, fluorine, mecoprop, methotrexate, and phenobarbital (second choice, more effective activated charcoal in this substance). The most common complication is hypokalemia, but it can be corrected with the administration of potassium[26].

- **Urinary acidification[17]:** Sometimes used for intoxication with amphetamines, and phencyclidine, but is not remarkably effective and is contraindicated in the presence of rhabdomyolysis or myoglobinuria.

- **Multi-dose activated charcoal:** should only be considered in cases with ingestion of potentially fatal amounts of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Despite well-known pharmacokinetics, there is no evidence of improvement in clinical outcomes[27].

- **Dialysis:** For known or suspected potentially lethal amounts of a dialyzable drug, poisoning, deep coma, apnea, severe kidney, cardiac, pulmonary, or hepatic disease who will not be able to eliminate toxin by the usual mechanisms[16,17]. Although the drugs discussed in this article do not present indications for dialysis, the individual under intoxication may use medications for different causes, which increases the number of complications and damages. Examples of dialyzable substances: barbiturates, lithium, methylxanthines (theophylline and caffeine), metformin, valproic acid, and carbamazepine.

Attention: Whenever there are doubts, contact the Information Centers. If there is no sufficient structure and team for support, consider transferring to a tertiary center.

Specific interventions

Alcohol

Alcohol is a substance commonly used all over the world, mainly in Western countries. It also stands for the oldest and the most diffuse substance of abuse[28]. Ethanol is a biphasic psychoactive substance, a depressant of the central nervous system whose effects of intoxication can vary according to the dose, type of drink ingested, speed of ingestion, genetic factors, and consumption pattern (degree of tolerance of the user)[10,11]. The manifestations of intoxication are heterogeneous, affecting neurological, cardiac, gastrointestinal, pulmonary, and metabolic functions. Among the many alcohol-related problems referred to emergency units, acute intoxication is the most common, mainly in adults and adolescents[10,11].

***Signs and symptoms*:** Ethyl breath, conjunctival hyperemia, altered speech, altered motor coordination, impaired attention, altered ability to discern, altered affect (euphoria, joy, sadness, irritation), behavior change, ability to cooperate, and presence of nystagmus[1,28-30] can be seen.

An alcoholic drink is considered to have 14 grams of alcohol. Consumption is abusive when it exceeds 4 drinks per day or 8 drinks per week for women and 5 drinks per day or 15 drinks per week for men[1,28-30]. The use is considered compulsive or binge drinking when, in a period of two hours, there is the consumption of 4 or more drinks in

the case of women and 5 or more drinks in the case of men. People over 60 years old should avoid drinking more than 1 dose per day or 7 doses per week, with no difference between genders[1,28-30].

A high dose of alcohol detrimentally affects several functions associated with the prefrontal and temporal lobes, including planning, verbal fluency, memory, and complex motor control, induced changes in inhibitory mediated motion repulsion[31,32]

Table 1. Conditions that can mimic acute alcohol intoxication and should be considered as a differential diagnosis.

Intoxication by other substances	Intoxication by alcohol other than ethanol
	Cocaine, opioids, cannabis
	Barbiturates
	Benzodiazepines
	Tricyclic antidepressants
	Disulfiram
	Carbon monoxide
Metabolic causes	Hepatic encephalopathy
	Hypoglycemia
	Changes in electrolytes (hypo / hypernatremia, hypo / hypercalcemia)
	Alcoholic ketoacidosis
	Diabetic ketoacidosis
	Non-ketotic hyperosmolar coma
	Uremia
	Hypertensive encephalopathy
Infectious diseases	Sepsis
	Meningitis
	Encephalitis
Neurological causes	Alcohol withdrawal syndrome
	Wernicke-Korsakoff syndrome
	Cerebrovascular disease
	Epilepsy
Trauma	Intracranial bleeding (subdural hematoma)
	Concussion
Respiratory causes	Hypoxia

	Respiratory depression
Others	Hypotension
	Hyper / hypothermia
	Hyper / hypothyroidism
	Dehydration

Factors that can influence the severity of alcohol intoxication: the amount of alcohol ingested, body weight, gender, and tolerance to alcohol, alcoholic percentage of the drink, length of time the drink was ingested, the association of alcohol with opioids and/or benzodiazepines, and presence of food in the stomach. In view of the unavailability of serum alcohol dosage, the level of intoxication can be assessed according to clinical criteria. Commonly, there are comorbid clinical conditions to alcohol poisoning, when more tests are suspected, including laboratory and central nervous system imaging[1,28-30] [10,11,28].

Complications: Fall and consequent trauma (mainly head trauma), vomiting with broncho aspiration, cardiac arrhythmias, decompensated cardiac output, hypertensive crises, car accidents, respiratory depression, hypothermia agitation, aggression, triggering mood and psychotic episodes, death[10,11,28].

Table 2. Serum alcohol levels and clinical repercussion[20]

< 50 mg/dl	Deficiency in some tasks that require skills
	Increased speech
	Relaxation
> 100 mg/dl	Change in feeling of the environment
	Ataxia
	Hyperreflexia
	Impaired judgment
	Lack of coordination
	Change in mood and behavior

	Nystagmus
	Extended reaction time
	Slurred speech
> 200 mg/dl	Amnesia
	Diplopia
	Dysarthria
	Hypothermia
	Nausea and vomiting
> 400 mg/dl	Respiratory depression
	Coma
	Death

* Lethal dose is variable; it can occur in individuals "without tolerance" with serum levels of 300 mg / dl [20]

Management of alcohol intoxication: The treatment of acute ethanol intoxication begins with immediate interruption of alcohol consumption and protection of the airways in all cases, considering that the main clinical complication is respiratory depression. Aspiration prevention is mandatory and positioning the patient laterally can be useful[28]. Hydration and intravenous glucose should only be administered if the patient has dehydration or hypoglycemia[10,11]. The administration of thiamine is recommended for all patients with alcohol-related disorders, considering that the detection of hidden thiamine deficiency and Wernicke's encephalopathy is difficult and stands for an increased risk [28,33].

In cases of mild to moderate intoxication, checking of vital signs is showed and if there is evidence of dehydration, intravenous fluid administration. The patient must be kept under observation, hospital, or outpatient, to find signs of alcohol withdrawal. The presence of psychomotor agitation and aggressiveness is common in patients with severe intoxication and, in these situations, the use of intramuscular injectable haloperidol in monotherapy is showed, but after verbal de-escalation[28,34,35]. It is important to avoid benzodiazepines and antihistamines[23], with the risk of cross effects with alcohol. In extreme cases of agitation, when the patient is a risk to himself or others, helped

mechanical restraint may be necessary. Antiemetic medications can be useful in case of nausea and/or vomiting[28]. Effects of acute intoxication are associated with a greater possibility of situations of violence, in addition to the considerable risk of infection by sexually transmitted diseases[21,28,29,36-38].

In case of severe intoxication, with a semi-comatose or comatose state, mechanical ventilatory support is necessary; treatment of hypoglycemia (with 5% glucose solution) and correction of hydro electrolytic disorders, if present; administration of vitamins, including thiamine[21,28,29,36-38].

Cocaine and other stimulants

Cocaine, benzoylmethylecgonine is an alkaloid, extracted from the leaves of Erythroxylon coca[39,40]. Cocaine increases the activity of monoamine neurotransmitters in the central and peripheral nervous system by blocking reuptake pumps (transporters) of dopamine, norepinephrine, and serotonin[39,40].

In addition to the dangers of cocaine overdose and the effects of acute intoxication, the use of cocaine is associated with a greater possibility of situations of violence, and to an elevated risk of infection by sexually transmitted diseases.

Signs and symptoms: The usual symptoms of cocaine intoxication include a general excitatory state, feeling of euphoria, increased energy, agitation, aggression, anxiety, restlessness, hallucinations, and delusions. On physical examination, it's possible to observe mydriasis, diaphoresis, tachycardia, hyperthermia, hypertension, tremors, or convulsions. Paranoid delusions, associated with anxiety and psychomotor agitation, are also common. Special attention should be paid to clinical symptoms, especially chest pain, dyspnea, decreased level of consciousness, seizures and hyperthermia, due to the risk of life to the patient[11,17,41].

Complications: The main cardiovascular complications of acute cocaine poisoning are Acute Myocardial Infarction, Cardiac arrhythmias, coronary aortic dissection, aortic rupture, and myocarditis. Neurological complications are seizures, hemorrhage, intracranial infarction, altered mental status, and spinal cord infarction[10,11,40,41]. Other

common complications we should keep our attention on are severe hypertension, acute renal failure, hyperthermia, pneumothorax, and deep vein thrombosis[10,11,40,41].

Management of cocaine and other stimulants intoxication:

The treatment for cocaine intoxication must be of vital and symptomatic support according to the patient's symptoms. Antidotes are not yet known. Screening tests for psychoactive substances are also poorly available in emergency units in Brazil. In addition to careful physical examination, if possible, a detailed anamnesis is recommended, and it's also important to obtain more information about the condition from family members, friends, the removal team who brought the patient to the hospital, or the police authority who accompanied the patient. The first action is to diagnose and treat any eventual organic changes that could put the patient's life at risk. Special attention should be given to the cardiovascular and neurological systems due to the specific fatal harms.

In case of mild cocaine intoxication, in which the patient does not have any alarm signs such as chest pain, severe hypertension, great increase in heart rate, or signs of neurological impairment, one should only see the patient's evolution, keeping the same in a safe place, with regular evaluation, and without environmental stimuli. In patients with severe intoxication, the initial priority involves clinical support to the patient, mainly protecting the airways, maintaining oxygenation and ventilation, in addition to venous access[39,41]. For cases with moderate psychomotor agitation, collaborative, without an alarm signal indicating immediate risk, and without significant changes in vital signs, benzodiazepines such as Diazepam orally in a dose of 5-10mg are recommended, which can be repeated according to the patient's evolution. In patients with intense psychomotor agitation and/or aggressiveness, the recommendation is to use benzodiazepine intravenously (diazepam) or intramuscularly (midazolam). The most available in Brazil is Diazepam 0.2-0.3mg/kg/dose, by slow infusion, without dilution. In case of lack of intravenous access, the choice is Midazolam 0.2-0.7mg/kg administered intramuscularly. In some cases of severe agitation, to protect the patient, a shortest time mechanical restraint may be necessary[39,41].

Haloperidol can also be used in cases of intense psychomotor agitation and paranoid delusions; however, special attention should be paid to its cardiovascular effects, the decrease in the seizure threshold, in addition to a possible increase in heart

temperature. This medication should be avoided in people who have seizures, hyperthermia, severe hypertension, or cardiac arrhythmias, in these cases, the use of benzodiazepines should be prioritized[11,17,34]. Phenothiazine antipsychotics such as chlorpromazine should be avoided due to the significant reduction in the seizure threshold and the potential to trigger cardiac arrhythmias. The use of beta-blockers should be avoided in patients who have used cocaine in the past 24 hours, due to its potential to trigger a reduction in blood flow and increase severe coronary events[10,11,35].

The challenge for the physician in the ED is to find patients at risk who would receive help from a specific intervention. All patients with acute coronary syndrome, especially young men, without other risk factors than smoking, should be asked about cocaine usage[39]. First-line treatment of a patient with cocaine-related chest pain compatible with myocardial ischemia and ST-segment elevation consists of administration of oxygen, and sublingual nitroglycerin or verapamil. If there is no response, immediate coronary angiography should be performed. Both nitroglycerin and verapamil have been shown to reverse cocaine-induced hypertension, coronary arterial vasoconstriction, and tachycardia[39]. Beta-blockers (especially non-selective β-blockers) are relatively contraindicated in cocaine-associated acute coronary syndrome. Beta-receptor blockade causes unopposed α-receptor stimulation which may lead to aggravation of coronary arterial vasoconstriction and systemic hypertension. Some authors recommend labetalol, a joint α- and β-blocker. However, labetalol is a non-selective β-blocker with only modest α-blocking properties[39]. Thrombolysis should only be given when a thrombus has been shown on angiography or if pharmacological treatment has failed and angiography is not possible. Administration of naloxone and flumazenil should be avoided since they may lead to severe complications[39].

In severe and resistant cases, there may be a need for patient intubation for better clinical stabilization, and protection of the airway, in which case benzodiazepines or propofol should be prioritized. The use of succinylcholine in intubation is contraindicated in these cases.

Hallucinogens

This group includes serotonin 2A receptor (5-HT2AR) agonists (lysergic acid diethylamide, psilocybin, and N, N-dimethyltryptamine; mixed serotonin and dopamine

reuptake inhibitors and releasers (3,4-methylenedioxy-methamphetamine) N-methyl-D-aspartate antagonists (ketamine and dextromethorphan); kappa opioid receptor agonist salvinorin A; anticholinergics, and others[42,43].

Signs and symptoms: Drug-induced conditions associated with perceptual changes are generally accompanied by physiologic abnormalities. With hallucinogens, sympathomimetic effects are common, occur shortly after ingestion, and usually precede the hallucinogenic effects[43,44]. Delirium or psychosis, however, is also observed with other drugs that show similar effects, such as PCP, amphetamines, cocaine, and anticholinergics[43]. Patients with amphetamine intoxication typically present with elaborate and paranoid delusions, as well as visual disturbances. Agitation or extreme agitation along with marked hyperthermia should suggest possible exposure to drugs such as cocaine or PCP.

Complications: Induced psychosis, arrhythmias, hyperthermia, agitation and aggressiveness, delirium, coma[43].

Management of hallucinogen intoxication: Support as described previously. The patient should be placed in a quiet room with close observation. Most patients typically need only supportive care[43]. Support airway and administer oxygen, if comatose. Administer naloxone if concurrent opiate use is suspected. If agitated, combative, or hyperactive, administer benzodiazepines[35,43]. If benzodiazepines are ineffective, may give haloperidol[35,43]. Cool, if hyperthermic, and watch for rhabdomyolysis. Substance abuse/detoxification referral and counseling[43].

Solvents

The "Organic solvents" belong to a group of volatile compounds or mixtures that are relatively chemically stable and exist in a liquid state at 0° to 250°C (32° to 482°F). The most common are classified as aliphatic hydrocarbons, cyclic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, ketones, amines, esters, alcohols, aldehydes,

and ethers. There are also mixtures or combinations of chemical compounds. The underlying pathology, biological processes, or modes of action include the release of catecholamines (acute effects of solvents, effects on ion channels (including GABA receptors) in the brain (inhalation anesthetics), and effects on GABA receptors (sedatives)[45].

Signs and symptoms: The acute, transient toxic effects of organic solvent exposure in humans result from the pharmacologic action of the solvent within the CNS[35]. These effects include CNS depression, psychomotor impairment, narcosis, respiratory failure, drowsiness, headache, dizziness, dyspepsia, nausea, impaired psychomotor functions, impairment of choice reaction time, perceptual and sensory-motor speed, and impairment of body balance. A progression of signs and symptoms includes possible first agitation, progressing to confusion, slurred speech, ataxia, and loss of consciousness[45].

Complications: The main ones are coma, seizures, respiratory arrest, and cardiac dysrhythmias. Cardiac arrest may be the first sign of a high dose of solvent[45].

Management: General life support measures, removal from exposure, and use of antidotes are recommended. Flumazenil can also be used but is not recommended if other toxics may be involved[45].

Cannabinoids

Cannabis (Cannabis sativa) has over 500 found natural compounds, including cannabinoids, terpenoids, flavonoids, and alkaloids. Among these, Δ9-tetrahydrocannabinol (THC), the primary psychoactive ingredient, has promoted widespread recreational use and misuse of the plant. Over time, other major plant cannabinoids (termed phytocannabinoids), such as cannabidiol (CBD), cannabichromene, cannabigerol (CBG), cannabidivarin, D9-tetrahydrocannabivarin (THCV), and many others, have also been elucidated.[46] Today, over 100 phytocannabinoids have been discovered, with THC and CBD being the two most studied cannabinoids (9). These phytocannabinoids can interact with the brain's endogenous

cannabinoid system (ECS) to elicit a range of neurobehavioral outcomes, including perturbation to the normal structure and function of the brain. The ECS consists of two main cannabinoid receptors (CB1 and CB2 receptors), endogenous cannabinoids (termed endocannabinoids, with two of the most well-studied being anandamide [AEA] and 2-AG [2-arachidonoylglycerol]) that act as natural ligands at the cannabinoid receptors, and enzymes that participate in their synthesis, uptake, or metabolism (e.g., FAAH [fatty acid amide hydrolase] and MAGL [monoacylglycerollipase]).[46,47] CB1 receptors are, predominantly, widely distributed in the central nervous system but also are found across peripheral neurons in the cardiovascular, reproductive, and gastrointestinal systems.[46-48] Within the central nervous system, their relative densities vary across brain regions. Early autoradiography studies in rodents and humans showed a high concentration of CB1 receptors in the cerebellum, hippocampus, and basal ganglia.[48] [46] They are also densely expressed across the cortex, particularly in the frontal, cingulate, and temporal cortices).[46] Meanwhile, CB2 receptors are predominantly found in immune cells across the body.[46,47] While cannabinoids (both endogenous and exogenous) have distinct chemical structures, they all interact with different affinities with the ECS. The widespread distribution of cannabinoid receptors reflects their diverse function within the brain and body. The endocannabinoids themselves are important signaling molecules that take part in a variety of functions including motor behavior, appetite, emotion, cognition, memory, sensory, autonomic, and immune function.[46-48] Despite some contentious discussions about the addictiveness of cannabis, the evidence shows that long-term use can lead to addiction. Indeed, approximately 9% of those who experiment with marijuana will become addicted.[49]

Signs, symptoms, and complications:

Regular marijuana use is associated with an increased risk of anxiety and depression,23 but causality has not been set up. Marijuana is also linked with psychoses (including those associated with schizophrenia), especially among people with a pre-existing genetic vulnerability,24 and it also worsens the course of illness in patients with schizophrenia.[49] Cannabis use impairs critical cognitive functions, both during acute intoxication and for days after use.[49] Both immediate exposure and long-term exposure to cannabis impair driving ability; cannabis is one of the most frequent illicit drugs reported in connection with impaired driving and accidents, including fatal accidents.[49]

During acute intoxication, the main symptoms that may occur are euphoria, decreased attention, impaired judgment, perceptual changes, changes in sociability, increased appetite, anxiety, impaired short-term memory, and sluggishness. Physical signs include conjunctival hyperemia and tachycardia[1]. In more severe cases, panic attacks, paranoia, and psychosis can occur[50]. The psychotic symptoms may occur but are not necessary for the diagnosis of intoxication, however, the insight must be preserved, and psychosis must not be severe or persistent. If these psychotic symptoms persist, the possibility of diagnosing cannabis-induced psychotic disorder should be assessed[51].

Management of cannabis intoxication

The main aim of the pharmacological treatment is to improve acute symptoms of intoxication. Thus, when there are intense anxiety symptoms associated with somatic symptoms and panic episodes, benzodiazepines can be used for symptom relief, and, generally, the use of lorazepam 1mg 4/4h is sufficient[52]. In a review article, Gorelick, 2016, found a study that reports the subjective improvement of acute effects, tachycardia, and conjunctival hyperemia with the use of propranolol up to 120mg/day; and two clinical trials that show that haloperidol, olanzapine, and risperidone are equally effective in treating the psychosis induced by cannabis intoxication[50].

No drug currently has a specific action in the treatment of intoxication with action on cannabinoid receptors. Studies are still limited, but drugs approved for other uses, such as those mentioned above, can help improve symptoms[50].

Opioids

Opioids are substances that increase the activity of one or more G protein-coupled transmembrane molecules, known as mu, delta, and kappa opioid receptors[53]. These receptors are activated by endogenous peptides and exogenous ligands (morphine) and are distributed throughout the human body. Those that mediate nociception are in the anterior and ventrolateral thalamus, amygdala, and dorsal root ganglia[53]. Modulation of respiratory responses to hypercarbia and hypoxemia occurs in the brainstem with contributions from dopaminergic neurons, and control of pupillary constriction occurs by receptors in the Edinger-Westphal nucleus of the oculomotor nerve[53].

Signs and symptoms: Changes in mood (predominance of euphoria). The classic syndrome of opioid toxicity includes apnea, stupor, and miosis. However, not all these findings are always present[53]. The essential symptom of opioid intoxication is respiratory depression. In non-tolerant individuals, therapeutic doses of opioids cause a noticeable decline in all phases of respiratory activity, which is progressive depending on the dose[53]. In cases of overdose, the decline in respiratory rate is the most noticeable and can progress to apnea[53].

Complications: Coma, respiratory depression[53], pulmonary edema, lung injury, hypothermia, seizures, rhabdomyolysis, myoglobinuric renal failure, and compartment syndrome (caused by immobility)[53].

Management of opioid intoxication: First, follow support as mentioned previously (A – B – C – D – E), especially respiratory support[53]. The opioid overdose antidote, naloxone, is a competitive mu opioid–receptor antagonist that reverses all indicators of intoxication. Adults should receive a starting dose of 0.1 to 2 mg of naloxone; if no response occurs, the dose should be raised every 2 minutes according to the schedule, up to a maximum of 15 mg [44, 45]. Orotracheal intubation is an alternative to naloxone administration. Activated charcoal for gastrointestinal decontamination should be reserved for individuals who present within 1 hour after [44]. Examine the axillae, perineum, scrotum, and oropharynx; any patches should be removed, and the skin should be cleaned with soap and cool water.[53].

Multiple drug intoxication

The management of acute multidrug intoxication is a challenge. First, all conducts should focus on support (ABCD). As for the specific procedures, they can only be performed in case of serious effects (of any of the substances) that can put the patient's life at risk (e.g., severe tachyarrhythmia or severe hypertensive crisis due to severe cocaine intoxication associated with acute alcohol intoxication). In the case cited as an

example, the use of benzodiazepines, vasodilators and antiarrhythmics should be considered and monitoring should be redoubled.

Limitations

The Delphi method allowed the production of a document based on the opinion of a group of experts. It was not possible to quantify the quality of evidence by the Oxford method, GRADE, or the Amstar instrument. However, it allowed us to provide standards for decision-making on a topic with little evidence in the literature and allowed us to bring together diverse types of knowledge in a document. The Delphi technique was used to minimize the chance of error and bias.

Conclusion

The approach to acute poisoning is complex and requires systematic protocols. We suggest the adoption of the classic use in welcoming the patient of the A-B-C-D-E technique, with a constant investigation of this patient until reaching a specific conduct and with the support to remit the picture. The literature is still scarce in evidence on the subject. Therefore, this consensus was necessary. We believe that this document at this time can help psychiatric, general, and emergency doctors deal with psychiatric emergency episodes due to acute poisoning, and it also presents some main doubts that could be a picture of new research soon.

Disclosures

There is no disclosure to declare.

References

1. WHO. ICD-11 for Mortality and Morbidity Statistics. 2018; 11:https://icd.who.int/browse11/l-m/en, 2020.
2. WHO. Acute intoxication. 2020; https://www.who.int/substance_abuse/terminology/acute_intox/en/.
3. van Hoving DJ, Veale DJH, Müller GF. Clinical Review: Emergency management of acute poisoning. African Journal of Emergency Medicine. 2011;1(2):69-78.

4. WHO; World directory of poisons centers. 2021; https://www.who.int/data/gho/data/themes/topics/indicator-groups/poison-control-and-unintentional-poisoning, 2022.
5. Baldaçara L, Meleiro A, Quevedo J, Vallada H, da Silva AG. Epidemiology of suicides in Brazil: a systematic review. GLOBAL PSYCHIATRY ARCHIVES. 2022;5(1):10-25.
6. Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. Postgraduate medical journal. 2005; 81:204-216.
7. Brasil. PORTARIA Nº 104, DE 25 DE JANEIRO DE 2011. In: Saúde Md. Brasília-DF2011.
8. Alvim ALS, França RO, Assis BBd, Tavares MLdO. Epidemiologia da intoxicação exógena no Brasil entre 2007 e 2017 / Epidemiology of exogenous intoxication in Brazil between 2007 and 2017. Brazilian Journal of Development. 2020;6(8):63915–63925.
9. Nations; U. World Drug Report 2021. Vol 2: United Nations publication; 2021.
10. Baldaçara L, Tung TC. Condutas em psiquiatria: Manole; 2020.
11. Baldaçara L, Cordeiro DC, Calfat ELB, Cordeiro DC, Chung TC. Emergências Psiquiátricas. Rio de Janeiro: Elsevier; 2019.
12. da Silva AG, Baldaçara L, Cavalcante DA, Fasanella NA, Palha AP. The Impact of Mental Illness Stigma on Psychiatric Emergencies. Front Psychiatry. 2020; 11:573.
13. Jones J, Hunter D. Consensus methods for medical and health services research. Bmj. 1995;311(7001):376-380.
14. Garriga M, Pacchiarotti I, Kasper S, et al. Assessment and management of agitation in psychiatry: Expert consensus. World J Biol Psychiatry. 2016;17(2):86-128.
15. Baldacara L, Ismael F, Leite V, et al. Brazilian guidelines for the management of psychomotor agitation. Part 1. Non-pharmacological approach. Braz J Psychiatry. 2019;41(2):153-167.
16. The Royal Children's Hospital Melbourne. Poisoning - Acute Guidelines for Initial Management. 2020; https://www.rch.org.au/clinicalguide/guideline_index/Poisoning_-_Acute_Guidelines_For_Initial_Management/.
17. Somlling C, Olson KR. Posoning. In: Papadakis MA, McPhee SJ, Rabow MW. 2021 CURRENT Medical Diagnosis & Treatment. 6ed. New York Chicago San Francisco Athens London Madrid Mexico City Milan New Delhi Singapore Sydney Toronto: McGrawHill; 2021.
18. Baldaçara L, da Silva AG. Suporte em Emergências Psiquiátricas (SEP). 1 ed. Belo Horizonte-mG: AMPLA; 2021.
19. Baldaçara L. Emergências Psiquiátricas. In: da Silva AG, Nardi AE, Diaz AP. Programa de Educação Continuada em Psiquiatria (PEC-ABP). Temas fundamentais. 1 ed. Porto Alegre: Artmed; 2021.
20. Baldaçara L, Pereira LA, Cordeiro Q, Tung TC. Medicina Psiquiátrica de Emergência. In: Meleiro AMAS. Psiquiatria - Estudos Fundamentais. 1 ed. Rio de Janeiro: Guanabara Koogan; 2019.
21. Diehl A, Cordeiro DC, Laranjeira R. Dependência quíimica. Prevenção, tratamento e políticas públicas. 2 ed. Porto Alegre: Artmed; 2019.
22. Hojer J, Troutman WG, Hoppu K, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):134-139.
23. Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140-146.
24. American Academy of Clinical T, European Association of Poisons C, Clinical T. Position Paper: Single-Dose Activated Charcoal. Clinical Toxicology. 2005;43(2):61-87.
25. Thanacoody R, Caravati EM, Troutman B, et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila). 2015;53(1):5-12.

26. Proudfoot AT, Krenzelok EP, Vale JA. Position Paper on urine alkalinization. J Toxicol Clin Toxicol. 2004;42(1):1-26.

27. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol. 1999;37(6):731-751.

28. Vonghia L, Leggio L, Ferrulli A, et al. Acute alcohol intoxication. Eur J Intern Med. 2008;19(8):561-567.

29. NIAAA. Alcohol Facts and Statistics. 2020; https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics.

30. Vorstius C, Radach R, Lang AR. Effects of acute alcohol intoxication on automated processing: evidence from the double-step paradigm. J Psychopharmacol. 2012;26(2):262-272.

31. Peterson JB, Rothfleisch J, Zelazo PD, RO P. Acute alcohol intoxication and cognitive functioning. Journal of studies on alcohol. 1990;51(2):114-122.

32. Wang Z, Wang H, Tzvetanov T, Zhou Y. Moderate acute alcohol intoxication increases visual motion repulsion. Sci Rep. 2018;8(1):1607.

33. LaHood AJ, Kok SJ. Ethanol Toxicity. [Updated 2020 Apr 17]. 2020; https://www.ncbi.nlm.nih.gov/books/NBK557381/.

34. Baldaçara L, Ismael F, Leite V, et al. Brazilian guidelines for the management of psychomotor agitation. Part 1. Non-pharmacological approach. Braz J Psychiatry. 2019;41(2):153-167.

35. Baldaçara L, Diaz AP, Leite V, et al. Brazilian guidelines for the management of psychomotor agitation. Part 2. Pharmacological approach. Braz J Psychiatry. 2019;41(4):324-335.

36. Elbogen EB, Johnson SC. The intricate link between violence and mental disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2009;66(2):152-161.

37. WHO. Unidade de Álcool, Drogas e Comportamentos Aditivos. 2020; https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/about.

38. Merikangas KR, McClair VL. Epidemiology of substance use disorders. Hum Genet. 2012;131(6):779-789.

39. Vroegop MP, Franssen EJ, van der Voort PH, van den Berg TN, Langeweg RJ, Kramers C. The emergency care of cocaine intoxications. Neth J Med. 2009;67(4):122-126.

40. Baldacara L, Cogo-Moreira H, Parreira BL, et al. Efficacy of topiramate in the treatment of crack cocaine dependence: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2016;77(3):398-406.

41. Havakuk O, Rezkalla SH, Kloner RA. The Cardiovascular Effects of Cocaine. J Am Coll Cardiol. 2017;70(1):101-113.

42. Garcia-Romeu A, Kersgaard B, Addy PH. Clinical applications of hallucinogens: A review. Exp Clin Psychopharmacol. 2016;24(4):229-268.

43. Williams RH, Erickson T. Evaluating Hallucinogenic or Psychedelic Drug Intoxication in an Emergency Setting. Laboratory Medicine. 2000;31(7):394-401.

44. Dolder PC, Schmid Y, Steuer AE, et al. Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects. Clin Pharmacokinet. 2017;56(10):1219-1230.

45. U.S. Department of Health & Human Services, Office of the Assistant Secretary for Preparedness and Response, National Library of Medicine. Organic Solvents (Acute Exposure to Solvents, Anesthetics, or Sedatives (SAS) Toxidrome). 2020; https://chemm.nlm.nih.gov/sas.htm.

46. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012;2(6):241-254.
47. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 2016;79(7):516-525.
48. Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int J Mol Sci. 2018;19(3).
49. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-2227.
50. Gorelick DA. Pharmacological Treatment of Cannabis-Related Disorders: A Narrative Review. Curr Pharm Des. 2016;22(42):6409-6419.
51. Pearson NT, Berry JH. Cannabis and Psychosis Through the Lens of DSM-5. Int J Environ Res Public Health. 2019;16(21).
52. Schatzberg A, DeBattista C. Manual de Psicofarmacologia Clínica. 8 ed. Porto Alegre: Artmed; 2016.
53. Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012;367(2):146-155.