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Toxicity Analysis: A Collection of Case Studies and Drug Management Strategies

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Abstract

Narcotics, Psychotropics, and Addictive Substances (NAPZA) refer to all compounds or drugs that can affect the central nervous system and behavior, with the potential to cause addiction. Narcotics and psychotropics can be classified into three groups of narcotics and four groups of psychotropics based on their therapeutic effects and potential for addiction. Since NAPZA can influence the central nervous system, the possibility of toxic effects must be carefully considered. This study aims to address gaps in the literature by providing an in-depth review of NAPZA management strategies, which have not been comprehensively discussed in previous research. The method used is a narrative review, examining and synthesizing information from various sources, including three websites, one book, seven national journals, and 26 international journals published between 2014 and 2024. Based on 11 documented cases, consisting of 4 cases of narcotics, 4 cases of psychotropics, and 3 cases of addictive substances, the majority involved NAPZA misuse among individuals in the productive age group. The primary treatment for narcotics toxicity includes maintaining. Airway patency, administering oxygen, and providing naloxone as an antidote. For psychotropic and addictive substance toxicity, management involves administering benzodiazepines, performing hemodialysis, or accelerating the elimination of drugs from plasma. These findings are expected to contribute to developing more effective management strategies in the future.

Keywords: NAPZA; Toxicology Analysis; Addiction

1. INTRODUCTION

The misuse of Narcotics, Psychotropics, and Addictive Substances (NAPZA) represents a significant health issue in Indonesia, particularly among adolescents who are vulnerable to negative influences. According to a survey by the Badan Narkotika Nasional (BNN) in 2019, approximately 2.40% of Indonesia's population has used narcotics at least once in their

lifetime, with the highest prevalence among individuals in the productive age group [1]. NAPZA misuse can lead to physical, mental, and social health problems, as well as damage to bodily systems, including the central nervous system, cardiovascular system, kidneys, liver, and reproductive system. The toxic effects include severe headaches, intense pain, respiratory disorders, and serious complications that may result in dependence, cognitive impairment, and death [2]. This article aims to provide a comprehensive review of the toxicological mechanisms of NAPZA and explore various approaches to managing toxicity.

Nasution et al. (2024) [3] discusses the phenomenon of NAPZA misuse, including substances such as alcohol, methamphetamine, cannabis, and tobacco. Nurmaya (2016) [4] examines the misuse of NAPZA, particularly tramadol and methamphetamine. However, these studies primarily focus on the factors and impacts of NAPZA misuse. Most existing research has not thoroughly explored the toxicity resulting from NAPZA misuse. This article aims to complement previous studies by presenting broader information encompassing various types of NAPZA and a more comprehensive approach to managing toxicity by compiling diverse case studies on NAPZA toxicity. As such, this article provides a more focused perspective on the toxicological consequences of NAPZA misuse, which is expected to contribute to developing more effective management strategies.

2. MATERIALS AND METHODS

This article uses the narrative review method, which gathers and reviews various literature relating to the toxicology of NAPZA. The narrative review method aims to collect and compile data from verified sources to provide a more complete image of the toxicological mechanism of NAPZA and its handling. The literature selection process is carried out in a structured manner through several steps. The first step includes searching through various literature with the keywords "toxicology of NAPZA," "toxicological mechanism of NAPZA," and "handling strategies of NAPZA" using an online database such as Google Scholar, PubMed, NCBI, and Elsevier. The literature used in this article consists of 3 websites (Medscape to acquire information on the handling of codeine, The United Nations Office on Drugs and Crime to obtain information on the international regulation of NAPZA, and Pusat Analisis Kebijakan Obat dan Makanan to acquire data on NAPZA misuse in Indonesia), one book to provide the general information of NAPZA and its regulation in Indonesia, seven national journals, and 26 international journals that were published in the span of 10 years from 2014 to 2024. The relevancy of each literature is determined by a few criteria, such as the relevancy of its content to the purpose of this article and the relevancy of its results to the focus of this article. Sources that fit the criteria will then be reviewed to confirm their information is supported by valid and current scientific evidence. The steps for analytical processing include identifying the literature, assessing the abstract and the whole content of each article, and compiling information. The selected literature will then be summarized to outline the main points, the toxicological mechanism, and the approaches to handling NAPZA toxicity.

3. RESULT AND DISCUSSION

The toxicology of NAPZA focuses on the harmful effects of these addictive substances on the body, particularly the central nervous system [2]. Each group of NAPZA exhibits unique pharmacological mechanisms, especially in influencing the mesolimbic dopamine system. The use of NAPZA, whether acute or chronic, significantly increases dopamine release in the nucleus accumbens (NAc), up to 5–10 times higher than normal conditions. This surge in dopamine triggers euphoria, reinforcing addictive behaviors and dependence. Additionally, environmental cues or specific conditions can amplify the brain's feedback system, further exacerbating the compulsive drive to consume NAPZA [5].

The toxicity caused by NAPZA not only affects the brain but also other organs in the body. Long-term use can lead to organ damage, respiratory disorders, and decreased cardiac and liver function, depending on the type of substance used [6]. According to Ningrum et al. (2016) [5], opioids, for example, can cause life-threatening respiratory depression, while stimulants like amphetamines increase the risk of cardiovascular damage. Finlayson et al. (2022) [7] report that prolonged

benzodiazepine use can trigger tolerance, requiring patients to take higher doses to achieve the same effects, as well as cognitive impairments such as memory decline and reduced concentration. Even after cessation, severe withdrawal symptoms such as anxiety, insomnia, and depression can persist for months or longer, further diminishing the quality of life of users.

In Indonesia, the misuse of NAPZA is becoming increasingly concerning, particularly among adolescents who are more vulnerable to social influences and unstable psychological conditions. The toxicity caused by drug use in adolescents can lead to mental health disorders, cognitive decline, and significant physical impairments. Additionally, the social impacts, such as social isolation, involvement in criminal activities, and declining academic performance, further deteriorate their quality of life. Therefore, addressing this issue requires a comprehensive approach grounded in understanding NAPZA toxicology [8].

International regulations also play a crucial role in controlling NAPZA misuse. The Single Convention on Narcotic Drugs of 1961 and the Convention on Psychotropic Substances of 1971 restrict the use of narcotics and psychotropics for medical and research purposes while establishing measures to prevent misuse and their circulation outside the medical sector. The 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances focuses on combating illicit drug trafficking and strengthening international cooperation in addressing this issue. International bodies such as the Commission on Narcotic Drugs (CND) and the International Narcotics Control Board (INCB) play significant roles in monitoring and overseeing the implementation of these regulations globally [9].

At the national level, Law No. 22 of 1997 on Narcotics provides a strong legal foundation for addressing NAPZA misuse. This regulation not only includes strict criminal penalties for individuals involved in drug misuse and trafficking but also promotes rehabilitation for users. With clear policies, such as severe punishment for offenders involved with Class I narcotics and protections for children from exploitation, it is hoped that the adverse effects of drug misuse can be mitigated [2].

With strong regulatory support and consistent law enforcement measures, the issue of NAPZA misuse can be effectively addressed. Collaboration between government agencies, society, and the healthcare sector is key to mitigating the toxicological impacts of NAPZA, reducing the prevalence of misuse, and accelerating recovery for victims.

Table 1. Case Table

Case	Symptoms in the Case	Toxicity Mechanism	Management
Case 1: Cocaine	Mental status changes, agitation, left-sided body weakness	Cocaine inhibits the reuptake of dopamine, serotonin, and norepinephrine, causing excessive stimulation of postsynaptic receptors	Administering benzodiazepines to manage agitation, cardiopulmonary resuscitation if necessary, and using vasopressin in cases of cardiac arrest
Case 2: THC	Heart attack, coma, ventricular fibrillation	THC triggers vasospasm and increases the heart's oxygen demand, which can lead to myocardial ischemia and heart attack at high doses	Management with benzodiazepines for seizures, intravenous fluids, and close monitoring. In some cases, antipsychotics are given for psychosis symptoms.
Case 3: Morphine	Paralysis, decreased consciousness, respiratory depression	Morphine acts on mu-opioid receptors in the central nervous system, suppressing the respiratory center, causing respiratory depression and hypotension	Stabilization of breathing, administration of Naloxone as an antidote, and close monitoring of vital functions
Case 4: Codeine	Tachycardia, abdominal distension, excessive stomach acid production	Codeine is metabolized into morphine, which can cause respiratory depression and excessive sedation in	Discontinuation of codeine, administration of Naloxone if respiratory depression occurs, and close monitoring of vital functions

		individuals with ultrarapid metabolism	
Case 5: LSD and Marijuana	Status epilepticus, hallucinations, seizures	LSD and marijuana affect serotonin and dopamine receptors, causing neurological hyperactivity and seizures	Administration of midazolam for seizures, intubation if necessary, and sedation with propofol
Case 6: Methamphetamine	Seizures, aphasia, brain hemorrhage	Methamphetamine increases blood pressure and causes vasospasm, which can lead to rupture of blood vessels in the brain and bleeding.	Administration of benzodiazepines to manage agitation and psychotic symptoms, blood pressure monitoring, and cardiopulmonary support if needed
Case 7: Phenobarbital	Coma, central nervous system depression	Phenobarbital enhances GABA activity, leading to central nervous system depression, coma, and potentially respiratory failure at high doses.	Hemodialysis to reduce phenobarbital levels in the body, close monitoring of vital functions, and respiratory support
Case 8: Diazepam	Loss of consciousness, hypoventilation	Diazepam affects the central nervous system, causing depression in the CNS, loss of consciousness, and respiratory depression.	Molecular Adsorbent Recirculating System (MARS) therapy to accelerate benzodiazepine elimination, and mechanical ventilation support and monitoring
Case 9: Caffeine	Hyperventilation, tetany, tachycardia	Caffeine blocks adenosine receptors, causing excessive stimulation of the central nervous and cardiovascular systems, leading to symptoms such as tachycardia and tetany.	Supportive management, administration of benzodiazepines for neurological symptoms, intravenous fluids for hypotension, and close monitoring of vital functions
Case 10: Nicotine	Dizziness, nausea, headache, vomiting	Nicotine affects the central nervous and cardiovascular systems, increasing heart rate, blood pressure, and sensory disturbances.	Immediate decontamination, fluid resuscitation to address dehydration, and benzodiazepine administration if seizures occur
Case 11: Belladonna	Altered consciousness, agitation, mydriasis	Tropane alkaloids like atropine and scopolamine are anticholinergic, disrupting the autonomic system and consciousness.	Administration of benzodiazepines for agitation and seizures, monitoring of vital functions, and supportive care in an intensive care unit

3.1 Case 1

According to a case report in the article by Alouazen et al. (2024) [10], an 18-year-old female patient with no medical history presented to the emergency department with altered mental status and agitation. Upon examination, no signs of infection were found, but the urine toxicology test revealed the presence of cocaine. The patient experienced weakness on the left side of her body but remained hemodynamically stable. Based on the symptoms and test results, this case is indicative of leukoencephalopathy caused by cocaine use.

In the review by Bravo et al. (2022) [11], which discusses cocaine, it is mentioned that cocaine inhibits presynaptic transporters responsible for the reuptake of dopamine, serotonin, and norepinephrine. This leads to the accumulation these neurotransmitters in the synaptic cleft, ultimately resulting in excessive stimulation of postsynaptic receptors. Increased dopaminergic activity, particularly in the mesocorticolimbic pathway in the brain, plays a role in inducing pleasurable effects. On the other hand, it also triggers agitation and hyperactivity. By inhibiting the reuptake of norepinephrine, cocaine

stimulates α- and β-adrenergic receptors, causing an increase in adrenergic responses. This excessive sympathetic activity can trigger increased heart rate, blood pressure, and intense physical agitation.

According to Bravo et al. (2022) [11], patients experiencing cocaine intoxication may suffer from cardiac arrest and respiratory distress. If life-threatening conditions occur, cardiopulmonary resuscitation (CPR) must be performed immediately. If initial resuscitation is unsuccessful, the administration of vasopressin is recommended, as it is considered more effective than epinephrine in some cases to maintain blood circulation. Benzodiazepine medications help manage agitation anxiety, as well as symptoms of tachycardia and hypertension experienced by some patients. Benzodiazepines not only alleviate anxiety but also lower blood pressure and cardiac output, making them the initial treatment in cases of acute cocaine intoxication. In some patients, chest pain may persist even after receiving oxygen therapy, aspirin, benzodiazepines, and nitroglycerin. The administration of phentolamine, a non-selective α-adrenoceptor antagonist, can help induce vasodilation. Beta-blockers are not recommended as they are ineffective for chest pain caused by cocaine. Additionally, calcium channel antagonists such as verapamil can be used to reverse vasoconstriction induced by cocaine after benzodiazepine administration to protect the central nervous system from complications.

3.2 Case 2

According to the case report in the article by Laverteu et al. (2023) [12], a 27-year-old Caucasian male with no prior medical history experienced a sudden heart attack after consuming 600 mg of delta-9-tetrahydrocannabinol (THC) in the form of homemade edibles, along with inhaled marijuana. The patient was found unresponsive two hours after consumption and experienced recurrent ventricular fibrillation, requiring six defibrillations and the administration of 450 mg of amiodarone during resuscitation. The patient arrived at the emergency department with cardiopulmonary resuscitation support and amiodarone infusion in a coma with a Glasgow Coma Scale of 3. The ECG results showed ST elevation in the anterolateral leads, and troponin levels were >270,000 pg/mL, indicating acute myocardial injury. Echocardiography revealed a very low ejection fraction (15%) with extensive myocardial hypokinesis. Toxicology testing of the urine detected only THC without evidence of synthetic drugs or other opioids, although further evaluation was limited. Despite receiving intensive support in the ICU, the patient's neurological condition did not improve, and cerebral perfusion imaging on day 10 confirmed brain death. The patient passed away after the ventilator was removed upon the family's decision. This case demonstrates the potentially toxic effects of high-dose THC on the cardiovascular and neurological systems.

THC (the main active compound in marijuana) can cause a decrease in coronary blood flow and trigger vasospasm. This vasospasm occurs through the activation of CB1 receptors, which triggers vasoconstrictive effects. On the other hand, THC also increases blood pressure and heart rate, thus increasing the oxygen demand in the heart muscle. The imbalance between the limited oxygen supply due to vasospasm and the increased oxygen demand can lead to myocardial ischemia or even a heart attack in vulnerable individuals. Additionally, THC affects platelet activity, which plays a role in blood clot formation. The activation of CB1 and CB2 receptors on platelets by THC stimulates the production of thromboxane and prostaglandins, which promote blood clotting. This process increases the risk of blood clots forming in the coronary arteries, which can block blood flow and result in a heart attack. THC also increases pro-inflammatory compounds like 2-arachidonoylglycerol (2-AG), further stimulating platelet aggregation. In this way, THC increases the risk of acute cardiovascular events such as heart attacks, especially in individuals who consume THC in high doses [13].

Management of marijuana/THC poisoning focuses on maintaining the patient's stability by ensuring they are in a safe and comfortable environment while monitoring symptoms to support bodily functions. Agitation or seizures can be managed with benzodiazepines as the first-line treatment, while hypotension is addressed with intravenous fluid administration and blood pressure monitoring. If the patient experiences chest pain, further examination is required to detect possible serious complications such as pneumothorax or myocardial infarction. In children who are more sensitive to the toxic effects of THC, benzodiazepines may also be administered to manage seizures while closely monitoring neurological and cardiopulmonary functions. Additionally, in cannabinoid hyperemesis syndrome, which often does not respond to typical antiemetic treatments, intravenous haloperidol or droperidol may be used, and the application of capsaicin cream to the abdomen

has been shown to help alleviate mild symptoms. Monitoring body temperature is crucial to detect hyperthermia or hypothermia, and blood glucose levels should also be monitored to prevent metabolic complications [14].

In a case report written by Richard et al. (2017) [15], naloxone was used as an adjunctive therapy in the management of acute marijuana poisoning with symptoms of hypoventilation, somnolence, and hypothermia. The report described a case in which a patient with severe marijuana toxicity was successfully managed using continuous naloxone infusion. However, the response was not as rapid as in opioid overdose cases. The effectiveness of naloxone, in this case, was believed to be related to the interaction between the endocannabinoid system and the opioid system, which could influence the symptoms of central nervous system depression. These findings suggest that naloxone may be an experimental therapeutic option in certain situations, especially when symptoms resemble opioid poisoning. This is in line with a case report in an article by Jones et al. (2016) [16], where naloxone showed improvement in symptoms in several patients with synthetic cannabinoid toxicity, including increased responsiveness and normalization of vital signs.

3.3 Case 3

In the case report by Kim & Kang (2021) [17], a 58-year-old woman was brought to the emergency department with left-sided paralysis and an inability to speak. Four years prior, the patient had undergone implantation of an Intrathecal Drug Administration System (ITDAS) due to back pain. MRI findings showed no abnormalities. After the MRI examination, the patient's symptoms temporarily improved. Still, three hours later, the patient experienced a decline in consciousness and breathing, accompanied by a decrease in peripheral oxygen saturation to 80%. Arterial blood gas analysis revealed respiratory acidosis with hypoxia and hypercapnia. The patient was diagnosed with opioid overdose, as evidenced by the loss of consciousness, constricted pupils with slow movement, and slow respiration.

Morphine acts as an agonist at the mu (μ) opioid receptors in the central nervous system, primarily causing respiratory depression as the main toxic effect. Activation of the mu receptor in the brainstem suppresses the response to increased levels of carbon dioxide (CO_2) in the blood, disrupting respiratory regulation. Additionally, morphine can induce hypotension through vasodilation and decreased consciousness associated with central nervous system depression. Other toxic mechanisms include the contraction of smooth muscle in the gastrointestinal tract, leading to severe constipation, and an increased risk of dependency through stimulation of the dopaminergic system, which triggers euphoria. The combination of these toxic effects can be exacerbated by high doses, long-term use, or interactions with other central nervous system depressant medications [18].

The management of morphine toxicity in patients begins with initial stabilization using a manual resuscitation bag to address respiratory depression. Following this, Naloxone 0.4 mg is administered intravenously as an antidote, closely monitoring the patient's response. If the symptoms are not fully resolved, Naloxone is given in repeated doses every 2 minutes until respiration improves. Once the condition is stabilized, further evaluations are performed, including checking the function of the ITDAS pump and MRI imaging to rule out other potential issues, such as structural lesions. The final diagnosis concluded that the patient's symptoms were caused by morphine intoxication due to ITDAS dysfunction, likely triggered by MRI exposure [17]. In the article by Lynn & Galinkin (2017) [19], studies show that naloxone is effective in reversing respiratory depression caused by opioid toxicity. However, there are risks of complications, such as pulmonary edema, which have been observed in some cases following naloxone administration.

3.4 Case 4

Based on the case reported in the article by Singhal et al. (2020) [20], a 75-year-old older woman with a history of chronic illness was hospitalized due to worsening back pain. The patient was given a combination of tramadol, codeine, and duloxetine to manage the pain. However, she developed tachycardia, crackling sounds in the chest, abdominal pain, abdominal distension, excessive gastric acid production, slowed bowel activity, increased abdominal diameter, and dilated stomach. As a result, the administration of codeine and duloxetine was discontinued. In this case, no preventive or management measures for opioid toxicity were taken, such as the administration of naloxone. The high dose of codeine given to an elderly patient with impaired kidney and liver function increased the risk of toxicity, which was further

exacerbated by the interaction with tramadol and duloxetine. Complications such as tachycardia and respiratory depression occurred. Despite being treated intensively with a ventilator and tracheostomy, the patient's condition continued to deteriorate, ultimately leading to death on January 3, 2014.

Codeine is a weak opioid prodrug that is metabolized in the liver by the CYP450 enzyme system. In individuals with the ultrarapid metabolizer (UM) genotype for the CYP2D6 enzyme, there is an increased conversion of codeine into morphine, which has a higher opioid potency. This leads to the accumulation of morphine in the body, increasing the risk of opioid toxicity, such as respiratory depression, excessive sedation, and other serious complications [21].

Opioid toxicity can be identified based on its toxic effects on the central nervous system. Clinical manifestations include depression, respiratory disturbances, and miosis (pupil constriction). The most characteristic symptom of opioid toxicity is respiratory depression. Emergency management provides for efforts to maintain an open airway and administration of oxygen. Naloxone is administered as an antidote if there is a decline in central nervous system function or severe respiratory depression [20]. Similarly, in the study by Lynn & Galinkin (2017) [19], it was shown that naloxone is effective in reversing respiratory depression caused by opioid toxicity. However, there are risks of complications, such as pulmonary edema, which can occur in some cases after naloxone administration.

3.5 Case 5

Based on a case report in the article by Burish et al. (2014) [23], an 18-year-old male with a history of migraines and febrile seizures during childhood presented to the emergency department in a status epilepticus condition after using LSD and marijuana. Initial symptoms included restlessness, hallucinations, and seizures with neurological signs such as leftward gaze and abnormal limb movements. The seizures were temporarily stopped with intranasal midazolam but recurred. Vital signs showed tachycardia and tachypnea, with an ECG showing sinus tachycardia and prolonged QTc interval (492 ms). 2,5-dimethoxy-4-chloramphetamine (DOC) is an amphetamine derivative that can be synthesized from 2,5-dimethoxy-amphetamine hydrochloride and is known to have a duration of action between 12 to 24 hours. This substance acts as an agonist at serotonin receptors (5-HT2), specifically the 5-HT2A subtype, which is believed to be responsible for its hallucinogenic effects, similar to other hallucinogens. DOC is metabolized through O-demethylation at the 2 and 5 positions mediated by the CYP2D6 enzyme, producing metabolites that can contribute to its pharmacological effects and toxicity [23].

The general management of DOC toxicity starts with the administration of intranasal midazolam or intravenous lorazepam as first-line therapy to control seizures. If seizures persist, the patient needs to be intubated and sedated using propofol and a midazolam drip. Fosphenytoin is given to prevent recurrent seizures, while intravenous fluids are administered to manage complications such as rhabdomyolysis and metabolic acidosis. Further examinations such as EEG and MRI are performed to monitor brain condition, although no significant abnormalities are usually found. LC-HRMS is used to diagnose DOC as the cause of toxicity through toxicological analysis. The management aims to support the patient's recovery and reduce the risk of further complications [23].

3.6 Case 6

Based on a case report in a review by Hemphill et al. (2024) [24], a 47-year-old male with untreated hypertension presented with seizures and aphasia accompanied by systolic blood pressure above 250 mmHg. A CT scan of the head revealed intraparenchymal hemorrhage in the left basal ganglia (7.4 x 4.5 x 5.1 cm) with vasogenic edema, subfalcine herniation, and a 1 cm midline shift. Urine toxicology showed positive results for methamphetamine and benzodiazepines, with methamphetamine use suspected to trigger the hemorrhage.

The review explains the mechanism of hemorrhagic stroke caused by methamphetamine. Methamphetamine triggers a significant spike in blood pressure, which can cause direct damage and rupture of small arteries in the brain, especially in individuals with hypertension or even those without a history of hypertension. Methamphetamine also causes vasospasm, which is the narrowing of blood vessels in the brain, hindering blood flow and increasing the risk of vessel rupture, leading to hemorrhagic stroke. Additionally, methamphetamine can damage the blood-brain barrier (BBB), making the brain's

blood vessels more susceptible to rupture due to high blood pressure or other factors. Methamphetamine can also contribute to the development of vasculitis, or inflammation of blood vessels, which, though rare, can cause brain bleeding in some cases. All these mechanisms increase the risk of hemorrhagic stroke [24].

In the guidelines for managing acute complications related to methamphetamine toxicity, initial management is symptomatic to address sympathetic symptoms such as hypertension, tachycardia, hyperthermia, seizures, or psychotic symptoms, with close monitoring of vital signs such as blood pressure, heart rate, body temperature, and oxygen saturation. Benzodiazepines such as diazepam, midazolam, or lorazepam are the primary choice for managing severe agitation, aggressive behavior, or psychotic symptoms. If benzodiazepines are not effective enough, second-generation antipsychotics such as olanzapine can be administered. At the same time, haloperidol can be used as an alternative, although it carries a higher risk of acute motor side effects. Patients are advised to be treated in a low-stimulation environment to help calm them down and prevent escalation of agitation. In cases of severe poisoning, resuscitation equipment and close monitoring of cardiovascular parameters must be available. After acute symptoms are managed, the patient should undergo psychiatric evaluation and be referred to addiction services for psychoeducation and further treatment [25].

A meta-analysis (2019) also emphasizes the same approach, focusing on the management of acute toxicity symptoms such as behavioral disturbances, medical complications, and psychiatric symptoms. The primary approach involves symptomatic care to manage agitation, psychosis, and cardiovascular complications such as hypertension, tachycardia, or arrhythmias. Patients often require pharmacotherapy, such as the use of benzodiazepines for agitation and aggression and antipsychotics in cases of acute psychosis. Management also includes close monitoring of vital signs and, if necessary, cardiopulmonary support. Patients experiencing hyperthermia or severe toxicity symptoms require intensive resuscitation [26].

3.7 Case 7

In a case report by Patel (2023) [27], an 18-year-old man was reported to have overdosed on phenobarbital and arrived at the emergency department in a coma. Physical examination showed central nervous system depression, as evidenced by the patient's inability to respond to painful stimuli, absent bilateral plantar reflexes, and small bilateral pupils. Vital signs showed a pulse rate of 70 beats per minute, blood pressure of 110/70 mmHg, a respiratory rate of 16 per minute, and oxygen saturation of 94% in room air. Laboratory results indicated a serum phenobarbital level of 107 mg/L, which falls within the toxic range (the standard therapeutic dose is 10-30 mcg/mL). This case highlights the harmful effects of phenobarbital overdose, especially on the central nervous system, which can lead to coma and require emergency medical intervention. Phenobarbital enhances GABA activity, the primary inhibitory neurotransmitter in the central nervous system, by prolonging the opening of chloride ion channels at GABA-A receptors. This increases chloride ion influx into neurons, leading to cell membrane hyperpolarization, and reduces neuronal excitability, which is beneficial in controlling seizures. However, when overdosed, its toxic effects can occur due to overstimulation of the GABA-A receptors, leading to central nervous system depression, altered consciousness, coma, or respiratory failure. Furthermore, phenobarbital also increases liver enzyme activity, posing a risk of liver damage or hepatotoxicity [28].

Hemodialysis is an effective method for managing phenobarbital toxicity, especially in cases of severe overdose. This procedure involves the patient's blood passing through a dialysis machine that filters phenobarbital and other harmful substances from the body. Due to phenobarbital's physicochemical properties, such as low molecular weight, high water solubility, and small volume of distribution (0.54–0.9 L/kg), its elimination through hemodialysis is very efficient. Studies show hemodialysis has a plasma phenobarbital clearance rate 30 times higher than liver clearance and is 10 times more efficient than activated charcoal. Additionally, hemodialysis is more affordable and accessible compared to other methods, such as hemoperfusion, making it the primary option for patients with phenobarbital overdose. In this case, a male patient with a phenobarbital overdose resulting in a coma was successfully treated with two sessions of hemodialysis. This procedure reduced the serum phenobarbital level from 107 mg/L to 24 mg/L, significantly reducing toxic effects and improving the patient's condition. Hemodialysis not only helps eliminate the drug from the body but also provides support in managing the systemic effects of the overdose [27].

3.8 Case 8

Based on a case report by Dobisova et al. (2021) [29], a 44-year-old man was admitted to the ICU for impaired consciousness after ingesting 20 g of diazepam. Blood and urine tests revealed extremely high benzodiazepine levels. Repeated administration of flumazenil failed to restore consciousness. The patient's condition worsened, marked by loss of consciousness, hypoventilation, and a drop in SpO2 to 88%, requiring intubation and mechanical ventilation. On the fourth day of treatment, the patient remained unresponsive and showed no spontaneous breathing efforts. Plasma benzodiazepine levels were recorded at 1.772 μg/L. To aid in the elimination of benzodiazepines, Molecular Adsorbent Recirculating System (MARS) therapy was conducted for five days, with one session per day. After the first session, plasma benzodiazepine levels decreased from 1.772 to 780 μg/L. After the final session on the eighth day, the patient was extubated and weaned from mechanical ventilation. Two days later, the patient was transferred to the internal medicine unit and later referred to psychiatry.

Diazepam is a benzodiazepine that affects the central nervous system. One of its effects is memory impairment, where benzodiazepines can cause long-term disruptions to episodic memory, while implicit memory is only temporarily affected. The use of benzodiazepines can also reduce inhibition, decreasing a user's ability to assess risk accurately and triggering dangerous behavior. In elderly patients, especially those in intensive care units, benzodiazepines may increase the risk of delirium. Research in rats shows that diazepam can extend deep sleep duration but also suppresses mRNA expression critical for synaptic plasticity, such as CaMKIIa, BDNF, GIF, c-fos, and NGFIa. The decrease in CaMKIIa expression has long-term effects by reducing neuronal responses to intracellular calcium changes and lowering GABA-A receptor sensitivity [29].

General management of diazepam toxicity involves primary approaches using activated charcoal (AC) to clear the digestive system, especially when administered within 30 minutes to 1 hour after poisoning. AC is effective at absorbing diazepam and other harmful substances that may have been consumed simultaneously, even if antidotes like flumazenil are present. However, flumazenil is not the primary choice, especially in overdoses involving multiple drugs, as its use can cause severe complications like seizures (mainly if the overdose involves benzodiazepines, tricyclic antidepressants, or cocaine), arrhythmias, and withdrawal symptoms. Flumazenil should not be used in patients with high intracranial pressure. In general, if diazepam overdose is detected early, immediate AC administration is highly recommended. Flumazenil should be used only when necessary, considering the risks of complications. Close monitoring of vital signs, respiration, and potential drug interactions is essential in managing this toxicity [30].

Treatment for severe diazepam poisoning, in this case, involved the use of Molecular Adsorbent Recirculating System (MARS) to speed up the elimination of the drug from plasma, given that diazepam has a high protein binding affinity (98%) with albumin. This therapy was proven to effectively reduce plasma benzodiazepine levels significantly, with an average reduction of 43% per session. Although there was a rebound in benzodiazepine levels due to redistribution from peripheral tissues like muscles and fat, the condition gradually improved as the drug was released from the tissues. By accelerating recovery time from 16 days to 7 days, MARS expedited toxin elimination and reduced the risk of ICU complications, such as infections and lung injuries due to mechanical ventilation [29].

3.9 Case 9

Based on a case report in the article by Ito et al. (2023) [31], a 39-year-old man with no relevant medical history presented to the emergency department with symptoms of numbness, weakness in the extremities, and hyperventilation after consuming more than 3 mg/kg of caffeine from packaged coffee. The patient experienced tetany from hyperventilation, with vital signs showing a blood pressure of 143/104 mmHg, pulse rate of 119 beats per minute, a body temperature of 38°C, and oxygen saturation of 98%. Physical examination revealed normal consciousness, tetany-like fingers, and sensory disturbances at the fingertips without paralysis. Laboratory results showed hypophosphatemia (phosphorus 1.2 mg/dL).

The case report also describes how caffeine from the coffee the man consumed caused toxicity. Caffeine blocks adenosine receptors, which typically induce sleepiness and relaxation. This inhibition prevents adenosine's sedative effects, leading to increased alertness and central nervous system activity. As a result, symptoms like anxiety, insomnia, headaches, and

heightened alertness occur in caffeine toxicity. Additionally, caffeine stimulates the release of catecholamines like adrenaline from the adrenal medulla, triggering beta-receptor activation in the heart and blood vessels. This stimulation increases heart rate, cardiac contraction, and vasodilation, contributing to tachycardia. Catecholamine release can also cause hypokalemia, characterized by low potassium levels in the blood, which may trigger muscle weakness and arrhythmias. Caffeine also inhibits phosphodiesterase, raising cAMP levels thus enhancing cardiac and nervous system stimulation. The inhibition of GABA receptors, which have an inhibitory function in the brain, also leads to neurological symptoms such as anxiety and seizures [31].

In an article by Wilson (2018) [32], caffeine toxicity involves several molecular mechanisms, particularly as an antagonist of adenosine A1 and A2A receptors, disrupting physiological function regulation such as muscle relaxation, heart rate, and neurotransmitter activity while increasing nerve stimulation and catecholamine levels. Caffeine also affects calcium channels (ryanodine receptors) at high doses, disrupting calcium release, which may increase muscle contraction and heart activity but can lead to muscle seizures and arrhythmias at high doses. Caffeine at borderline consumption levels can also inhibit phosphodiesterase, enhancing stimulation effects on the heart, nervous system, and metabolism. Caffeine also affects potassium channels, increasing muscle and nerve cell excitability leading to arrhythmias and electrolyte imbalances. These effects may cause rapid heart rate, hypertension, anxiety, and dehydration risk. Effects on GABA(A) receptors may lower seizure thresholds linked to seizures in severe toxicity.

Management of caffeine toxicity generally involves supportive care tailored to the patient's symptoms and condition. For mild overdoses, monitoring and benzodiazepines may suffice. Severe overdoses may require hemodialysis to reduce caffeine levels. Cardiovascular side effects such as hypotension are treated with intravenous fluids and vasopressors; supraventricular tachycardia with benzodiazepines or calcium channel blockers; and ventricular dysrhythmias with anti-dysrhythmic medications [32]. This is reinforced by a retrospective study conducted by Beauchamp et al. (2016) [33], where benzodiazepines were effectively used to manage central nervous system hyperactivity symptoms like agitation and seizures in caffeine toxicity cases. Several cases recorded that their use rapidly stabilized the patient's condition. Gastrointestinal side effects like nausea and vomiting are treated with antiemetics. Psychological effects and seizures are managed with benzodiazepines or barbiturates/propofol if necessary. Metabolic effects and rhabdomyolysis are treated with sodium bicarbonate, potassium chloride, and intravenous fluid resuscitation. Decontamination is performed with activated charcoal within 1-2 hours post-consumption and hemodialysis or intralipids for faster caffeine elimination. Treatment should be adjusted to the patient's condition, as no standard method exists for caffeine overdose [32].

3.10 Case 10

Based on the case report in the journal by Becam et al. (2023) [34], a 22-year-old man working at an e-liquid factory experienced a workplace accident in which 300 mL of pure nicotine solution (>99%) spilled on his right foot. At the time of the incident, he was not wearing personal protective equipment. Less than a minute after the exposure, the patient began experiencing initial symptoms such as dizziness, nausea, headache, a burning sensation, and pain in the area of the skin affected by the nicotine. As an initial measure, he removed his pants and rinsed his foot with water. Two hours after the incident, the patient arrived at the emergency department with additional symptoms, including a respiratory rate of 25 breaths per minute, a heart rate of 70 beats per minute, headache, abdominal pain, pallor, and continuous vomiting. Examination showed a good neurological response (Glasgow Coma Scale of 15), normal oxygen saturation, and no abnormalities in the heart and lungs. Laboratory results five hours after exposure showed nicotine plasma levels of 447 ng/mL, cotinine levels of 1254 ng/mL, and hydroxy tobacco levels of 197 ng/mL, which were significantly higher than the nicotine levels found in regular smokers (5-55 ng/mL), indicating a considerable exposure to nicotine. However, the patient did not require any specific additional treatment and was discharged in stable condition within 24 hours. This case highlights the serious risks of exposure to pure nicotine without adequate protection in the workplace.

The mechanism of nicotine toxicity involves several pathways related to inflammation, protein synthesis, cell-to-cell adhesion, apoptosis, and mitochondrial function. Nicotine exposure can cause mitochondrial phenotype changes in

keratinocytes, as well as a significant reduction in mitofusin two after exposure to nicotine at specific concentrations. In addition, nicotine can be internalized through inhalation, ingestion, or skin contact, leading to harmful effects such as nausea, dizziness, and increased heart rate and blood pressure. The toxicological mechanism of nicotine on the skin involves several pathways. Nicotine can cause skin damage, infections, and disease progression. Furthermore, nicotine inhibits the NF-kB pathway and toll-like receptor 2 (TLR2) signaling, leading to a reduced receptor response to bacteria and other pathogens and interfering with wound healing [35].

According to Becam et al. (2023) [34], the management of nicotine poisoning due to transdermal exposure involves several essential steps. First, supportive care is provided to maintain the patient's condition, followed by fluid resuscitation to address dehydration or electrolyte imbalances. Symptoms arising from poisoning should also be treated. Atropine is used to address possible cholinergic syndrome, while benzodiazepines are given if the patient experiences seizures. Immediate decontamination removes nicotine from the skin and prevents further exposure. Additionally, continuous removal of nicotine is crucial. In severe cases, extracorporeal membrane oxygenation (ECMO) may be considered, although this intervention is rarely needed.

3.11 Case 11

Based on a case report by Saputera and Saputera (2022) [36], a 16-year-old male was brought to the emergency department with complaints of altered consciousness for the past four hours. The symptoms began at school, where the patient initially exhibited strange behavior, which then worsened to restlessness, irritability, unresponsiveness to conversation, vacant stare, and difficulty standing. The patient also had not urinated for more than 6 hours. A friend of the patient, who also exhibited similar but milder symptoms, reported that they had lunch together with instant noodles and vegetables suspected to be kecubung leaves. The patient showed signs of autonomic system disruption on physical examination, including tachycardia (120 beats per minute), mydriasis (pupil diameter 7 mm), and dry mucous membranes. No abnormalities were found in other vital signs, neurological systems, or laboratory results. There was no indication of head trauma, metabolic disturbances, or electrolyte imbalance to explain the patient's condition. The patient was diagnosed with kecubung intoxication, admitted to an internal medicine ward, and closely monitored. This case highlights the toxic effects of tropane alkaloids from kecubung, such as scopolamine and atropine, which can cause altered consciousness and autonomic symptoms.

Kecubung is known to be a plant containing belladonna alkaloids, primarily atropine and scopolamine. The parts of kecubung that contain the highest amounts of belladonna compounds are the flowers, stems, and seeds. These compounds are often misused as addictive or psychotropic substances, with the seeds being the most commonly consumed for recreational drug use. The compounds in kecubung, such as atropine and scopolamine, are anticholinergic, which competes with acetylcholine for binding to muscarinic receptors. This results in antimuscarinic effects or anticholinergic crises. In a review by Saputera and Saputera (2022) [36], it was discussed that kecubung has hallucinogenic effects due to its alkaloid content, especially atropine, scopolamine, and hyoscyamine, which act as antagonists at muscarinic acetylcholine receptors (M1, M2, M3, M4, M5) and prevent acetylcholine binding. This mechanism produces classic signs of anticholinergic poisoning in various organs, including the gastrointestinal tract, salivary glands, eyes, and central nervous system.

According to Saputera & Saputera (2022) [36], the management of patients with tropane alkaloid intoxication with agitation and seizures involves benzodiazepines as the first-line treatment. Commonly used drugs include lorazepam, midazolam, and diazepam. Lorazepam works by enhancing GABA activity and inhibiting neurotransmitters in the brain. Midazolam can also be used as an alternative for refractory status epilepticus. Diazepam works by depressing the entire central nervous system and increasing GABA activity. In this case, the patient was given diazepam as an antidote alternative due to clinical considerations and the unavailability of physostigmine salicylate in Indonesia, as well as the controversy regarding its safety. According to an article by Kienitz et al. (2022) [37], lorazepam has a longer duration of action compared to diazepam and midazolam, and it has a 72% success rate in stopping seizures, which is better than diazepam in many clinical trials.

4. CONCLUSION

Substance abuse (NAPZA) is a complex issue that affects an individual's physical, mental, and social health. The toxicological mechanisms of NAPZA involve disturbances in various body systems, especially the central nervous system, cardiovascular, respiratory, and liver systems, which vary depending on the type of substance used. Managing NAPZA toxicity requires an evidence-based approach, including supportive care, administration of specific antidotes such as naloxone to address opioid overdose, and the use of benzodiazepines to manage agitation, seizures, or cardiovascular disturbances caused by substances like cocaine, THC, or methamphetamine. Both therapies play an essential role in mitigating the acute and chronic complications resulting from NAPZA toxicity. At the policy level, strict regulations and cross-sector collaboration are needed to reduce the incidence of substance abuse while also supporting the rehabilitation of users. This research paves the way for further studies to explore the mechanisms of NAPZA toxicity more deeply and develop more effective management strategies. By understanding the interactions between different types of NAPZA and the central nervous system, future research can provide better practical guidance in handling toxicity cases and contribute to developing more precise health policies.

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REFERENCES

1. Pusat Analisis Kebijakan Obat dan Makanan. Kajian Analisis Data Kasus Keracunan Obat dan Makanan Tahun 2023, **2023**. Available online: https://pusakom.pom.go.id/riset-kajian/detail/analisis-data-kasus-keracunan-obat-dan-makanan-tahun-2023 [Accessed 23 November 2024].
2. Alifia, U. *Apa Itu Narkotika dan Napza?*. PT. Bengawan Ilmu: Semarang, Indonesia, **2019**.
3. Nasution, A.S., Azzahra, T.M., Sari, R.I., Abdurrahman. Fenomena penyalahgunaan narkoba di kalangan remaja berdasakan teori interksionisme simbolik di Kota Medan. *Community Development Journal* **2024**, 5(1), 197-210.
4. Nurmaya, A. Penyalahgunaan NAPZA di kalangan remaja (Studi kasus pada 2 siswa di MAN 2 Kota Bima). *Jurnal Psikologi Pendidikan & Konseling* **2016**, 2(1), 26-32.
5. Ningrum, S.W., Sutarni, S., Gofir, A. Penyalahgunaan narkotika, psikotropika, dan zat adiktif sebagai faktor resiko gangguan kognitif pada remaja jalanan. *Berkala Neurosains* **2016**, 15(2), 85-95.
6. Puji, L.K.R., Kasumawati, F., Indah, F.P.S., Ratnaningtuas, T.O., Ilmi, A.F, Hasanah, N., Ismaya, N.W.A., Adha, M.Z., Bahri, S., Putri, W. G. The effect of drugs on mental health and reproductive health in adolescents. *Jurnal Abdi Masyarakat* **2022**, 3(2),155-163
7. Finlayson, A.J.R., Macoubrie, J., Huff, C., Foster, D.E., Martin, P.R. Experiences with benzodiazepine use, tapering, and discontinuation: An internet survey. *Ther Adv Psikofarmakol* **2022**, 12, 1-10.
8. Saragih, R., Saragi, P., Sianipar, A.W.H. Penegakan hukum dan perlindungan hukum terhadap peredaran dan penyalahgunaan narkoba di kalangan remaja: Studi kasus di Indonesia. *Honeste Vivere* **2024**, 34(2), 244-254.
9. United Nations Office on Drugs and Crime. Legal Framework for Drug Trafficking, **2024**. Available online: https://www.unodc.org/unodc/es/drug-trafficking/legal-framework.html [Accessed 23 November 2024].
10. Alouazen, O., Bekraoui, A., Fadel, H., Belfkih, R., Rachidi, S.A. Cocaine-induced multifocal leukoencephalopathy: A case report and literature review. *Radiology Case Reports* **2024**, 19, 6470-6473.

11. Bravo, R.R., Faria, A.C., Brito-da-Costa, A.M., Carmo, H., Mladěnka, P., Silva, D.D., Remião, F. Cocaine: An updated overview on chemistry, detection, biokinetics, and pharmacotoxicological aspects including abuse pattern. *Toxins* **2022**, 14(4), 1-25.
12. Laverteu, S. M., Signorella, S., Baig, R., Emerson, A., Joyce, J., Zhang, R. Death after marijuana use in a 27-year-old male: A case report. *Advances in Clinical Medical Research and Healthcare Delivery* **2023**, 3(2), 1-4.
13. Lee, J., Sharma, N., Kazi, F., Youssef, I., Myers, A., Marmur, J.D., Salifu, M.O., McFarlane S.I. Cannabis and myocardial infarction: Risk factors and pathogenetic insights. *Scifed J Cardiol* **2018**, 1(1), 1-9.
14. Schep, L.J., Slaughter, R.J., Glue, P., Gee, P. The clinical toxicology of cannabis. *The New Zealand Medical Journal* **2020**, 133(1523), 96-103.
15. Richard, J.R., Schandera, V., Elder, J.W. Treatment of acute cannabinoid overdose with naloxone infusion. *Toxicology Communications* **2017**, 1(1), 29-33.
16. Jones, J.D., Nolan, M.L., Daver, R., Comer, S.D., Paone, D. Can naloxone be used to treat synthetic cannabinoid overdose?. *Biol Psychiatry* **2017**, 81(7), 51-52.
17. Kim, S., Kang, K. Morphine over infusion of intrathecal drug administration system under magnetic resonance evaluation for the diagnosis of stroke: A case report. BMC Neurology **2021**, 21(147), 1-3.
18. Ofoegbu, A., Ettiene, E.B. Pharmacogenomics and morphine. *The Journal of Clinical Pharmacology* **2021**, 61(9), 1149-1155.
19. Lynn, R.R., Galinkin,J.L. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Therapeutic Advances in Drug Safety* **2018**, 9(1), 63-88.
20. Singhal, K.C., Garg, K.C., Rahman, S.Z. Who is pushing patients to death trap by improper use of codeine? Time now to reorient physicians or ban the use of codeine!. *Journal of Pharmacovigilance and Drug Safety* **2020**, 17(1), 15-18.
21. Lubis, N.M.D., Ramadhania, Z.L. Artikel tinjauan: Efek samping penggunaan kodein pada pediatrik. *Farmaka* **2018**, 16(2), 64-79.
22. Stephens, E. MedScape. [Online]. Opioid Toxicity **2024**. Available online: https://emedicine.medscape.com/article/815784-overview [Accessed 28 November 2024].
23. Burish, M.J., Thoren, K.L., Madou, M., Toossi, S., Shah, M. (2014). Hallucinogens causing seizures? A case report of the synthetic amphetamine 2,5-dimethoxy-4-chloroamphetamine. *The Neurohospitalist* **2014**, 5(1), 1-3.
24. Hemphill, K., Tierney, S., Tirschwell, D., Davis, A.P. A review of methamphetamine use and stroke in the young. *Frontiers in Neurology* **2024**, 15, 1-12.
25. Wodarz, N., Scheidler, A.K., Christ, M., Fleischmann, H., Looser, W., Schoett, K., Vilsmeier, F., Bothe, L., Schaefer, C., Mayfrank, E.G. Evidence-based guidelines for the pharmacological management of acute methamphetamine-related disorders and toxicity. *Pharmacopsychiatry* **2016**, 50(3), 87-95.
26. Sibanda, N.J., Kornhaber, R., Hunt, G.E., Morley, K., Cleary, M. Prevalence and risk factors of emergency department presetations with methamphetamine intoxication or dependence: A systematic review and meta-analysis. *Issues in Mental Health Nursing* **2019**, 40(7), 567–578.
27. Patel, A., Parate, T., Bhure, N., Charde, S. Effect of haemodialysis in phenobarbital toxicity: A case report. *International Journal of Science and Research* **2023**, 12(12), 791-792.
28. Kaur, N., Kaur, M., Sohal, H.S., Han, H., Bhowmik, P.K. A review on barbituric acid and its derivatives: Synthesis, reactions, and bio-applications. *Organics* **2024**, 5(3), 298-345.
29. Dobisova, A., Vavrinec, P., Yaghi, D.V., Gebhardtove, A., Henning, R.H., Yaghi, A. Case report: Enhanced diazepam elimination with the molecular adsorbents recirculating system (MARS) in severe autointoxication: A survival case report. *Frontiers in Medicine* **2021**, 8, 1-4.
30. Sah, S.K., Joshi, D., Pathak, S., Regmi, S., Regmi, B.M., Manandhar, P.N., Pandeya, S., Marasini, N. Effect of ethanol and pH on the *in vitro* adsorption of diazepam onto activated charcoal from simulated gastric fluid and simulated intestinal fluid. *Indian Journal of Pharmaceutical Sciences* **2016**, 78(5), 624-630.
31. Ito, M., Ando, T., Yamamoto, K., Ishido, A. Caffeine intoxication as a result of excessive consumption of bottled coffee products: A case report. *Journal of Rural Medicine* **2023**, 18(3), 200–204.
32. Wilson, C. The clinical toxicology of caffeine: A review and case study. *Toxicology Reports* **2018**, 5, 1140-1152.
33. Beauchamp, G.A., Johnson, A.R., Crouch, B.I., Valento, M., Horowitz, B.Z., Hendrickson, R.G. A retrospective study of clinical effects of powdered caffeine exposures reported to three US poison control centers. *J. Med. Toxicol.* **2016**, 12, 295–300.

34. Becam, J., Martin, E., Pouradier, G., Doudka, N., Solas, C., Guilhaumou, R., Fabresse, N. Transdermal nicotine poisoning: A rare case report of occupational exposure. *Toxicans* **2023**, 11(5), 1-6.
35. Pozuelos, G.L., Vargas, M.R.S., Ramirez, E., Bandaru, D., Sha, J., Wohlschlegel, J., Talbot, P. Nicotine affects multiple biological processes in EpiDerm™ organotypic tissues and keratinocyte monolayers. *Atmosphere* **2022**, 13(5), 1-19.
36. Saputera, M.D., Saputera, J.D. Kecubung intoxication: A case report on a 16-year-old male at Kuningan District. *Jurnal Penyakit Dalam Indonesia* **2022**, 9(4), 226-230.
37. Kienitz, R, Kay, L., Beuchat, I., Gelhard, S., Brauchitsch, S.V., Mann, C., Lucaciu, A., Schäfer, J.H., Siebenbrodt, K., Zöllner, J.P., Bast, S.S., Rosenow, F., Strzelczyk, A., Willems, L.M. 2022. Benzodiazepines in the management of seizures and status epilepticus: A review of routes of delivery, pharmacokinetics, efficacy, and tolerability. *CNS Drugs* **2022**, 36, 951–975.