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Review

Intravenous Lipid Emulsions in Anticonvulsants' Toxicity

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Abstract: In recent years, an innovative approach has emerged in the field of toxicology for managing acute intoxications caused by lipophilic substances: intravenous lipid emulsions (ILEs). Through numerous experiments and case reports, the efficacy of lipid emulsions in counteracting toxicities induced by lipophilic agents, including a significant number of antiepileptic (AE) drugs, have become increasingly evident. Data spanning a 10-year period (2010–2020) were analyzed by searching through multiple scientific publication platforms like PubMed, Science Direct, Research Gate, and Springer Link. This study focused on reviewing relevant case reports detailing successful intravenous lipid emulsion (ILE) administration in patients with acute intoxications with antiepileptics, specifically examining the impact of fat emulsions on neurological status, Glasgow Coma Scale (GCS) scores, and corrected QT interval concerning hemodynamic instability. The typical symptoms of antiepileptic toxicity include central nervous system depression, ataxia, and nystagmus. Intravenous lipid emulsion application resulted in an increase in Glasgow Coma Scale scores and enhanced recovery from drug intoxication. This study provides a comprehensive overview of the potential utility of ILE as a component to antidote therapy in cases of acute AE poisoning involving neurotropic drugs. The process involves the engagement of various mechanisms of antitoxic activity.

Keywords: intravenous lipid emulsion; acute intoxication; antiepileptics; antidote; Glasgow Coma Scale scores; QT interval

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1. Introduction

Acute medication poisoning is a significant social and health issue on a global scale [1,2]. Medicinal substances are the primary cause of hospitalization among all intoxications [3]. In children, acute drug intoxications rank second in frequency after carbon monoxide poisoning [4]. Acute drug intoxications, particularly linked to the consumption of benzodiazepines, neuroleptics, and cardiovascular medications, are prevalent worldwide [5]. The prevalence of acute drug intoxication varies significantly among different countries. It ranges from 2.3% (147 from total 6211 patients were treated for acute intoxication in the Intensive Care Unit of Frankfurt, Germany) to 5.4% (284 poisoning cases among 11,834 patients admitted to the Emergency Unit in Istanbul, Türkiye) to as high as 13.8% (from 218 poisoning deaths from a Department of Forensic Medicine in a University of China). In certain predominantly Asian countries, this rate can reach as high as 88.2% (from 153 (8.9%) acute intoxication from 1375 patients in the Intensive Care Unit in Rize, Türkiye) [6]. Poisonings involving antiepileptic (anticonvulsant) drugs, including benzodiazepines, hold significant social importance. These medications are traditionally used to decrease the frequency, severity, and duration of seizures in epilepsy.

Most xenobiotics (from "xenos" meaning foreign and "bios" meaning "life") do not have specific antidotes. In cases of acute poisoning with drugs that have a neurotoxic effect, a range of mental and somatic–vegetative symptoms may be observed, along with potentially fatal neurological and cardiovascular complications. These symptoms result from the direct impact of toxic agents on various structures of the central and peripheral nervous system (exogenous toxicosis) or from primary damage and dysfunction of

parenchymal organs and systems responsible for detoxification (endogenous toxicosis). The most severe clinical symptoms of toxic damage to the nervous system include toxic coma and acute intoxication psychoses. Toxic coma typically occurs in poisonings involving CNS depressants. It is crucial for healthcare professionals to assess the level of consciousness suppression and depth of unconsciousness in order to provide appropriate care. These critical conditions demand prompt intensive care, calling for the adoption of more effective strategies in everyday practice.

In recent years, a relatively new method for treating acute intoxications with lipophilic substances has been introduced in toxicological practice—the intravenous infusion of fat emulsions. This method was discovered 16 years ago during the management of systemic toxicity caused by local anesthetics, specifically bupivacaine [7]. It relies on certain fat emulsions, when introduced in large quantities into the bloodstream, to create an extended lipid phase known as the "lipid sink" phenomenon, which absorbs and "captures" lipid-soluble drugs, extracting them from high-concentration areas such as the heart and brain. By keeping these drugs away from the site of toxic action and preventing them from binding to biological targets, this method effectively mitigates their harmful effects. Polyunsaturated fatty acids in the formulation help to decrease the inhibition of sodium channel transport function caused by bupivacaine in heterologous tissue culture. This modulation of cardiac sodium channels may help in reducing the effects of local anesthetic toxicity. The suppression of sodium channels indicates a potential impact on these transporters in acute toxicity induced by other channel blockers, including certain antiepileptic medications.

Thus far, lipid emulsions have found application in clinical settings primarily along two main avenues: as parenteral nutrition since the mid-20th century [8], and, more recently, as an antidote [9]. Intravenous fat emulsion plays a crucial role as an energy source for patients receiving parenteral nutrition, fulfilling 30% to 50% of their non-nitrogen caloric needs, equivalent to approximately 20% to 30% of total calories or 9 kcal/g of energy. The caloric content of intravenous lipid emulsions varies depending on their concentration [10,11].

Despite the increasing amount of research providing information on the positive therapeutic effects of lipid emulsion and its use as an additional treatment method for acute intoxications, there are few and insufficient reports on its alleged neuroprotective role. This innovative approach is relatively underutilized. Since 2012, intravenous lipid emulsions (ILEs) have been sporadically used in treating acute poisoning with certain neuroleptics, antidepressants, and benzodiazepines, as well as more recently with cardiovascular and antiepileptic medications. Worldwide, there is no standard protocol for the application of ILE as an antidote. A dosing regimen has been developed in the Toxicology Clinic of the Military Medical Academy-Varna, according to which the dosage is tailored to the severity of the symptoms of intoxication [12].

A review of the contemporary literature examines the available scientific studies and research on the potential role of ILE as a supplement to in-hospital therapy for acute antiepileptic drug poisonings, with a particular focus on its impact on GCS results in these cases.

Given that many of these drugs are lipophilic compounds, the goal of this study is to summarize the antidote properties and effectiveness of ILE in cases of acute poisonings involving various antiepileptic medications.

2. References and Data Collected

The study included clinical reports on the treatment of acute toxicity caused by antiepileptic drugs over a 10-year period (2010–2020). We searched PubMed, ScienceDirect, ResearchGate, and SpringerLink using the keywords "intravenous lipid emulsion", "acute", and "antiepileptics" in combination with the keywords "poisoning", "intoxication", "toxicity", and "overdose". All individual generic names of antiepileptic drugs were also searched separately with "neurological status" or "neurological toxicity" in case of acute

poisoning. We included all those cases in which the authors stated that the diagnosis was "acute poisoning" in patients receiving intravenous lipid emulsion during the development of symptoms. Cases published in the English language literature between 1 January 2010 and 1 January 2020 were included. We chose 2010 as the cut-off point because this was the first time that the American Society of Regional Anesthesia (ASRA) published a practice advisory on the toxicity of local anesthesia, emphasizing the role of lipids in LAST treatment. In 2010, the first case of resuscitation was also published, suggesting the efficacy of lipid emulsion infusion for the treatment of antiepileptic drug overdose.

References of all reports were also hand-searched for additional cases. Additionally, we searched the articles citing these references through Google Scholar. We excluded articles that were duplicates of non-English language articles, letters to editors, those that did not specifically address clinical features related to neurologic toxicity, chronic toxicity studies, and studies that did not address the antidote use of ILE for management of toxicity. Consent of at least two subgroup members was required before an article was excluded.

The following data were collected and systematically entered into Microsoft Excel: first author's name, year of publication, age, gender, intake of antiepileptic drugs, concomitant use of other drugs, indications for administered drugs, prominent clinical features (coma scale scores of Glasgow; QT interval), and specific treatment. As a result, the final analysis included 112 articles: 92 on humans and 30 on animals, among which were two randomized control trials (RCTs) in humans and three in animals.

3. Acute Intoxications with Antiepileptics

Classical antiepileptic medications work by reducing excessive excitability in the central nervous system. They achieve this by either inhibiting sodium channels or affecting GABAergic neurotransmission. Examples of these medications include carboxamides (such as carbamazepine and oxcarbazepine), valproate (VPA), benzodiazepines, and barbiturates. However, the frequent and severe side effects associated with hydantoins (like phenytoin) limit their use. Some medications, like valproate, have multiple mechanisms of action in treating epilepsy. In addition to inhibiting the enzyme responsible for breaking down the inhibitory neurotransmitter GABA, they also block calcium channels in the hippocampus. Additional cellular mechanisms involve blocking the excitatory communication between glutamate and N-methyl-D-aspartate (NMDA) receptors, as well as inhibiting neuronal exocytosis by interacting with synaptic vesicle protein 2A (SV2A). Acute poisonings from these substances usually present with a set of three symptoms: central nervous system depression, ataxia, and nystagmus, which are indicative of their toxic effects [13].

3.1. Benzodiazepines

Based on their half-elimination period ($t_{1/2}$), which determines how quickly and for how long they act, benzodiazepines (BZDs) are categorized into the following groups: long-acting (1 to 3 days): clorazepate, chlordiazepoxide, diazepam, flurazepam; intermediate-acting (16 h): alprazolam, bromazepam, clonazepam, clotiazepam, lorazepam, loprazolam, nitrazepam, oxazepam, temazepam, triazolam; short-acting (3 to 8 h): midazolam, triazolam.

Benzodiazepines are lipid-soluble drugs that exert their effects by modulating GABA-A receptors. They bind to a specific region of this pentameric structure of the ligand-gated ion channel, which increases the frequency of channel opening and the influx of Cl^- ions. This leads to membrane hyperpolarization and reduces neuron excitability. As a result, the effects of the natural neurotransmitter gamma-aminobutyric acid (GABA) are enhanced. GABA is the primary inhibitory mediator in the central nervous system. The increased GABA neurotransmission results in anxiolytic, sedative, soporific, myorelaxant, and anticonvulsant effects, including raising the seizure threshold. Activation of GABA receptors in the peripheral nervous system decreases myocardial contractility and promotes vasodilation [14].

Benzodiazepines are classic sedative–hypnotic medications that were introduced into medical practice in the 1960s. They were developed through extensive research

using the chemical structure of barbiturates as a model, with the goal of mitigating their adverse effects, broadening their therapeutic range, and reducing the risk of addiction. BZDs are commonly used to treat various sleep disorders, anxiety, withdrawal symptoms, seizures, as muscle relaxants, for presurgery sedation, and other conditions. Currently, there are over 50 medications in this class available worldwide. The wide range of available benzodiazepine preparations and their frequent use increase the risk of acute poisoning [15].

Numerous studies have consistently demonstrated that poisonings caused by benzodiazepines (BZDs) are the most prevalent among cases of drug intoxication [16,17]. Marinov et al. (2016) reported that they constitute approximately 30% of such cases, primarily stemming from suicide attempts, and are more common among women under 30 years of age [18]. The widespread usage of BZDs is linked to an elevated risk of developing tolerance and dependence on the medication. Abuse typically occurs through the ingestion of high doses, either alone or in conjunction with other psychoactive substances, notably alcohol. While ingesting BZDs independently in toxic amounts seldom results in significant toxidrome, they do heighten the neurotoxic effects of other psychotropic agents, including alcohol. This leads to significant respiratory depression, compromised airways, and often life-threatening intoxications. Patients experiencing this type of poisoning typically exhibit hyperemia and edema of the soft membranes and brain structures. In addition to brain alterations, there is stagnation in the internal organs. Clinical symptoms of acute intoxication include central nervous system depression characterized by slurred speech, difficulty breathing, slow and shallow breaths, and suppression of the thermoregulatory center, cardiovascular instability, hypotension, ataxia, altered mental status, and consciousness disturbances ranging from somnolence to coma. Death primarily results from respiratory depression, a phenomenon uncommon in benzodiazepine poisoning alone.

3.2. Barbiturates

Barbiturates are functionally categorized into four groups based on their half-elimination period: those with ultrashort action (<0.5 h) including methohexital, thiamylal, and thiopental; those with short action (3 to 4 h) such as hexobarbital, nembutal, pentobarbital, and secobarbital; those with intermediate action (4 to 6 h) like amobarbital, aprobarbital, and cyclobarbital; and those with long action (6 to 12 h) including barbital and phenobarbital [7].

In clinical practice, barbiturates are primarily employed as antiepileptic agents, notably phenobarbital, and for the induction of general anesthesia, such as thiopental. They were extensively prescribed before the advent of benzodiazepines (BZDs), which are now more commonly used. This shift is attributed to the broader therapeutic range, reduced drug tolerance, lower potential for abuse, decreased risk of overdose, and the availability of an antidote for BZDs [19]. Barbiturates, generally, possess a narrow therapeutic range, meaning that even a slight overdose can be life-threatening, resulting in respiratory distress, severe hypotension, and hypothermia, potentially culminating in fatality. Their concurrent usage with other central nervous system depressants and alcohol exacerbates these risks. Tolerance to barbiturates develops rapidly within a few days, and prolonged use engenders both mental and physical dependence, underscoring the imperative to restrict their administration. Notably, in recent years, there has been a marked decline in the incidence of acute poisonings, attributable to diminished utilization of these substances.

Sedative–hypnotic drugs exert nonselective effects. In lower doses, they alleviate anxiety and emotional tension, while higher doses induce sedation, progressing to deep anesthesia and potentially fatal outcomes. Individual susceptibility to lethal doses of barbiturates varies. Respiratory depression, exotoxic shock, or pneumonia are the primary causes of death. Typically, clinical symptoms of poisoning manifest around 2 h post-ingestion, peaking at 12 h. A distinctive feature of barbiturate intoxication is hypothermia. Early mortality is linked to central nervous system depression and acute respiratory failure. Subsequently, complications may arise such as heart and kidney failure, and cerebral and pulmonary edema [20]. Complications such as pneumonia, gastrointestinal

bleeding, urinary tract infections, and thrombophlebitis are common during barbiturate intoxication [21].

In the context of intoxication, the predominant concern is the cerebral syndrome, which encompasses six distinct forms: cerebrotoxic, respiratory, cardio-circulatory, dysmetabolic, epidermal (occurring in severe cases alongside a comatose state), and delirium (arising during emergence from a comatose state). Based on the manifestation of these forms within the cerebral syndrome, acute poisoning is classified into four degrees: mild, moderate, severe, and extremely severe.

3.3. Carboxamides

Carbamazepine is frequently prescribed to manage epilepsy and various conditions such as neuropathic pain, postherpetic neuralgia, schizophrenia, and bipolar disorder in both pediatric and adult patients. Its primary modes of action involve inhibiting potential-dependent sodium channels and reducing membrane excitability. Additionally, carbamazepine impedes the reuptake of norepinephrine and acts as an antagonist for muscarinic, nicotinic, and NMDA receptors, along with central adenosine receptors. Overdosing on carbamazepine typically results in predictable, dose-dependent central nervous system depression and anticholinergic effects [22]. There is selective suppression of the motor zone of the cerebral cortex, inhibition of the transmission of excitatory impulses in the epileptogenic focus, and reduction in the potential of propagation to neighboring areas.

Selective suppression of the motor zone of the cerebral cortex, inhibition of excitatory impulse transmission in epileptogenic foci, and reduction in propagation potential to adjacent areas characterize the action of oxcarbazepine. It serves as a keto-analog of carbamazepine and functions as a prodrug swiftly converted to 10-hydroxycarbazepine. While oxcarbazepine was engineered to circumvent unwanted effects caused by metabolites of carbamazepine, notable distinctions exist between the two medications. Oxcarbazepine primarily acts by blocking sodium channels, and, unlike carbamazepine, also modulates various types of calcium channels. Moreover, the involvement of hepatic CYP450-dependent enzymes in oxcarbazepine metabolism is minimal, as the major metabolic pathway of its active metabolite licarbazepine is through conjugation with glucuronic acid. Due to the difference in chemical structure compared to carbamazepine, metabolic oxidation is avoided, reducing the risks to the liver [23].

The first reported case of carbamazepine overdose dates back to 1967 [24]. Acute toxicity is typically observed at concentrations surpassing 40 mg/L, whereas therapeutic levels range from 4 to 12 mg/L. The toxicity progression of the drug unfolds through distinct stages: disorientation and ataxia manifest at blood concentrations of 11 to 15 mg/L; aggression and hallucinations emerge at 15 to 25 mg/L; convulsions and coma occur at levels exceeding 25 mg/L. Following the initial dose, the elimination half-life ($t_{1/2}$) is approximately 30 h [25]. Symptoms of acute intoxication encompass dizziness, drowsiness, generalized convulsions, respiratory failure, cardiac arrhythmia, and fluctuating mental status, occasionally culminating in coma. Additionally, anticholinergic symptoms frequently manifest. Some patients may exhibit hyperchromic anemia, minor rhabdomyolysis, and consequent movement disorders. Notably, carbamazepine serum levels reliably predict the severity of intoxication in cases of massive poisoning in adults [26].

A noteworthy case involves acute oxcarbamazepine intoxication in a 20-year-old pregnant woman with epilepsy, who deliberately ingested approximately 36 g of oxcarbamazepine in an attempt to terminate her pregnancy. She was admitted to the Clinic for Intensive Treatment of Acute Poisonings and Toxic Allergies at Naval Hospital—Varna, presenting with slightly compromised general condition, but maintaining contact and displaying adequate responsiveness with pale skin, within 2 h of the intoxication. Despite the situation, she remained independently mobile. Mild drowsiness and lethargy were noted. Respiratory function appeared normal, with vesicular breathing and a rate of 16 breaths/min, devoid of wheezing. Cardiovascular examination revealed no anomalies, with a heart rate of 90 beats/min and mild hypotension (blood pressure 110/70 mm/Hg).

The uterine size corresponded to a pregnancy of the fifth month. Biochemical analysis indicated no elevation in liver enzyme activities (ALT, AST, GGT). Remarkably, the anticipated toxic syndrome did not manifest, and the fetus remained viable (unpublished data).

The side effects linked with oxcarbazepine resemble those caused by carbamazepine, including dizziness, drowsiness, headache, nausea, vomiting, and double vision, with these symptoms being notably less common and less intense compared to carbamazepine, according to studies [27].

3.4. Valproate

Valproate (VPA) is primarily prescribed for the management of epilepsy, bipolar disorder, and the prevention of migraine headaches [28].

Acute intoxications involving VPA often result in central nervous system depression, presenting symptoms such as drowsiness, tremors, stupor, respiratory depression, metabolic acidosis, and, in severe cases, coma or even death. Under controlled therapy, serum or plasma concentrations typically range from 50 to 100 mg/L, whereas acute poisoning may elevate levels to 150 to 1500 mg/L. Generalized tonic–clonic seizures are infrequent in VPA poisoning, typically occurring only with massive overdoses [29]. Moreover, cases of cerebral edema, metabolic acidosis, hypoglycemia, hypophosphatemia, hypocalcemia, and hypernatremia have been documented in such instances [30]. Furthermore, VPA inhibits the β-oxidation of mitochondrial fatty acids, thereby causing autoinhibition or saturation of its metabolism. The unsaturated metabolites of valproate, particularly 4-en-valproate, might play a role in the drug's liver toxicity, including fulminant hepatitis [31]. Consequently, alternative metabolic pathways are activated, potentially leading to the production of various hepatotoxic compounds. Valproate metabolism could be shifted towards omega-oxidation, leading to heightened production of the harmful compound 4-en-valproate. However, it might also result in increased formation of a toxic metabolite originating from isoleucine, as the beta-oxidation of isoleucine derivatives could also be compromised.

3.5. Lamotrigine

Lamotrigine is an antiepileptic medication utilized in the treatment of partial and tonic–clonic seizures, and it serves as a mood stabilizer for bipolar disorder. Its mechanism of action is multifaceted: it inhibits potential-dependent T-type calcium channels and blocks voltage-dependent sodium channels, thereby suppressing glutamate exocytosis. Additionally, it inhibits serotonin reuptake, which may underlie its antidepressant properties [32].

Patients with epilepsy or psychiatric conditions are at an elevated risk of intentional overdose. Lamotrigine toxicity primarily affects the central nervous and cardiovascular systems. The serotonin syndrome characterizes central nervous system toxicity, particularly pronounced when lamotrigine is combined with other substances that potentiate this effect. Symptoms of CNS serotonin syndrome encompass severe depression accompanied by altered mental status, ranging from agitation to coma. Additionally, neuromuscular hyperactivity may present with hyperreflexia, ataxia, nystagmus, and generalized tonic-clonic seizures. Cardiovascular manifestations commonly include bradycardia, atrioventricular (AV) block, and tachycardia, reflecting its impact on cardiac conduction [33].

3.6. Hydantoins (Phenytoin)

Since its discovery in 1908, phenytoin has been extensively studied as an anticonvulsant and is also utilized as a class IB antiarrhythmic drug. However, its narrow therapeutic index and widespread usage often result in acute intoxications [34]. Phenytoin functions by blocking membrane potential-dependent sodium channels responsible for activating neuronal action potential. Consequently, it inhibits the positive feedback, thus averting excitatory neurotoxicity [35].

Toxicity from phenytoin primarily manifests in the nervous and cardiovascular systems. Oral overdose predominantly induces neurotoxicity, with cardiovascular toxicity

being relatively rare. Neurotoxic effects vary with drug concentration, ranging from mild nystagmus (20 to 30 mg/L) to ataxia (30 to 40 mg/L), slurred speech, vomiting, and lethargy (40 to 50 mg/L), progressing to coma and potentially death (>50 mg/L) [36]. Paradoxically, very high concentrations of the drug may trigger seizures. Cardiovascular toxicity is characterized by arrhythmias and conduction system blockade (SA and AV), albeit less frequently observed after oral ingestion [37].

4. Toxic Damage to the Nervous System

In clinical settings, a classification system is utilized to evaluate quantitative alterations in consciousness, outlining four levels of consciousness suppression:

Obnubilation: This represents the mildest degree of clouding of consciousness, where the patient appears lethargic and struggles to maintain focused attention.

Somnolence: Characterized by pathological sleepiness, interaction with the patient becomes challenging and incomplete. They may only comprehend basic questions and respond with brief utterances.

Sopor: At this stage, contact with the patient is nearly impossible. They may react to pain with defensive movements and produce unclear sounds or words. However, their pupils react to light, and reflexes in tendons, periosteum, skin, and mucosa remain intact. Swallowing is feasible, but there may be incontinence of pelvic contents.

Coma: Here, the patient experiences complete loss of consciousness.

Introduced in 1974 by two professors of neurosurgery at the Institute of Neurological Sciences at the University of Glasgow, the Glasgow Coma Scale (GCS) is widely employed for the objective assessment of consciousness [38]. Initially developed to evaluate consciousness levels following craniocerebral injuries, it is now utilized in both emergency and intensive care medicine settings, spanning from patients with acute injuries and illnesses to those in terminal conditions. The Glasgow Coma Scale is used to assess the neurological status of patients following traumatic brain injury or other cerebral conditions. It evaluates three aspects of neurological function: eye responses, verbal responses, and motor responses. Each category is scored, with the total score ranging from 3 to 15. Lower scores typically indicate more severe injuries or impairment of brain function.

Remarkably, the GCS has proven applicable even in cases of acute poisonings. As per the Glasgow Coma Scale, brain damage can be categorized as severe (values below 9), moderate (values 9–12), and mild (values equal to or greater than 13).

In the neurological manifestations of acute poisonings, somatic–vegetative disturbances hold significant prominence [7]. These are characterized by symmetric alterations in pupil size, disruptions in sweating, and impaired secretion from salivary and bronchial glands. Common accompanying symptoms include a muscarinic-like syndrome, featuring pinpoint pupils, excessive sweating, heightened salivation, increased bronchial secretions, bronchospasm, bradycardia, and accelerated intestinal peristalsis. Toxic mono- and polyneuritis are also frequently observed, particularly affecting the lower limbs, with symptoms including altered sensitivity, reflexes, and mobility. Morphological changes are evident in nerve cells, myelin, or the Schwann sheath.

One of the most perilous complications of exotoxic coma is cerebral edema, where factors such as hypoxia, metabolic imbalances, impaired cellular membrane transport, disruption of the blood–brain barrier, and cerebral circulation disorders play pivotal roles in its pathogenesis. The onset of cerebral edema manifests a range of neurological symptoms, including transient paralysis, epileptiform seizures, hyperthermia, bulbar disturbances, and congestive papillae.

Unconsciousness is a prevalent occurrence in emergency departments, with various conditions besides acute poisoning potentially leading to impaired consciousness. Exogenous intoxications, metabolic imbalances, and cerebral injuries are among the primary culprits behind the comatose state.

Coma entails a complete loss of consciousness endured for an extended period. It is essential to differentiate coma from syncope, characterized by brief, transient loss of

consciousness lasting from seconds to minutes, and from stupor, wherein reactivity remains intact despite a subdued state of wakefulness, typically observed in mental illnesses such as schizophrenia. Coma can manifest suddenly, even in individuals previously considered healthy. Extensive clinical investigations have underscored the pivotal role of identifying and quantifying toxic substances through chemical–toxicological analysis of blood and urine for precise diagnosis [39].

5. Lipid Emulsions

5.1. Historical Data

The experimental use of intravenous lipid emulsion dates back to the 18th century. In 1712, William Courten made the initial attempt by administering parenteral fats, infusing intravenous olive oil into a dog. Unfortunately, the dog succumbed within hours to respiratory distress attributed to fat embolism [40]. Subsequently, in 1869, Wentzel and Perco, following possible animal experiments, subcutaneously injected fat into a severely asthenic patient suffering from Potts disease [41]. In 1873, Hodder in Toronto employed intravenous milk infusion to treat cholera in three patients, with two of them recovering [42].

The first systematic endeavors to apply artificial fat emulsion to humans occurred in Japan between 1920 and 1930. In the United States, despite ongoing discussions, no documented results were recorded until 1950. The first clinical and experimental data on the utilization of lipid emulsion derived from cottonseed oil were not published until 1957 [43]. However, post-infusion, this elicited acute side effects of clinical significance, including fever, liver damage, jaundice, and bleeding, leading to the cessation of its application.

In 1963, Swedish physician and nutrition researcher Arvid Wretlind pioneered the development of the first intravenous lipid emulsion for human intravenous administration named Intralipid [44]. It consists of soybean oil, emulsified by egg phospholipids for stabilization. Over nearly six decades, it has remained the most widely used ILE, benefiting millions of patients worldwide. Initially, these emulsions were primarily utilized as an effective glucose-free energy source to mitigate the adverse effects associated with high dextrose intake. They serve two primary functions: providing a source of energy and supplying essential fatty acids in parenteral nutrition regimens for patients [45].

5.2. Composition of ILE

A fat emulsion designed for intravenous administration typically comprises vegetable oil dispersed in water, along with one or two emulsifiers to ensure emulsion stability. Recent years have seen extensive studies on various fats and triglycerides. Initially, five ILEs were introduced, incorporating cotton or soybean oil. Different phospholipids serve as emulsifiers. To achieve the necessary isotonicity with blood, the aqueous phase commonly includes glucose, sorbitol, or glycerol. Lipids within these emulsions exist as dispersed particles abundant in triglycerides, stabilized by phospholipids, with particle sizes akin to chylomicrons (200 ÷ 400 nm). Triglycerides are predominantly derived from vegetable oils or fish oil, found in newer emulsions with concentrations ranging from 10% to 30% [46].

The fatty acid composition varies among different emulsion types.

5.3. Neuroprotective Role of ILEs

There are scarce studies in the literature regarding the use of ILEs in acute drug intoxications. Information on their protective effects against ethanol-induced neurotoxicity remains limited. Studies have shown that as little as a few days of ethanol intoxication can lead to neuronal loss in several brain areas of adult rats [47,48].

The likely rationale behind this protective effect of emulsions predominantly stems from their high content of triglycerides containing both saturated and unsaturated fatty acids. Unsaturated fatty acids are known to serve as scavengers in reactive oxidative stress scenarios. Neurotoxicity of ethanol consumption is well known. One of the main mechanisms in the damaging effect of alcohol is related to the induction of oxidative stress in brain tissue. A study revealed the beneficial properties in acute ethanol intoxication in

rats, wherein brain tissue was shielded from the deleterious effects of induced oxidative stress after ILE and caffeic acid phenyl ester (CAPE) administration [49]. Experimental rodents were administered ethanol (3 mg/kg orally), with ILE (18.6 mL/kg, orally) and CAPE (10 µmol/kg, intraperitoneally) immediately after ethanol application. Brain tissue of the rats was taken for biochemical analysis and for histologic examination. ILE treatment enhanced antioxidant defense against the background of general oxidative stress associated with ethanol-induced neurotoxicity. In addition, the histopathological tests confirmed these biochemical results, showing decreased neurodegeneration parameters (such as pyknotic nucleus, vacuolation, oedema, congestion, and necrosis).

Another observation made in human endothelial cell culture was that ILEs directly interact with cell membranes and induce structural alterations, thereby reducing the release of free radicals, also showing scavenger potential towards reactive oxygen species into the extracellular environment [50].

5.4. Application of ILE in Acute Drug Intoxications

There is a notable absence of rigorous and comprehensive clinical trials involving ILE, including both single and double blind studies. The scientific literature primarily consists of case reports or case series detailing purported positive effects of intravenous ILEs in acute poisonings involving numerous substances, albeit lacking reliable evidence. However, synthesizing information from these reports offers valuable clinical insights into specific toxic syndromes, shedding light on the typical course of overdose and its response to lipid therapy.

ILEs are believed to possess the capacity to ameliorate the condition of patients experiencing acute intoxication with lipophilic medicinal substances. Animal studies and select human reports delineate their utility in treating poisonings involving substances such as clomipramine, verapamil, propranolol, bupropion/lamotrigine, and quetiapine/sertraline. Additionally, according to Moshiri et al. (2012), ILEs have demonstrated successful outcomes in acute poisonings involving various drugs with potential impacts on the nervous and cardiovascular systems, including antiepileptics [51] (refer to Table 1).

Table 1. Use of ILEs in acute drug intoxications.

Drug Group		Drug	Application in Humans	Application in Animals
Local anesthetics		Bupivacaine	18	10
		Ropivacaine	13	
		Mepivacaine	2	
		Lidocaine	4	
		Lupivacaine	1	
		Propofol	1	
Antidepressants	TCA	Amitriptiline	5	1
		Clomipramine	1	4
		Imipramine	1	
		Doxepin	1	
	TeCA	Mirtazapine	1	
		Amoxapine	1	
	SSRIs	Fluoxetine	1	
		Sertraline	1	
	SNRIs	Venlafaxine	1	
	Others	Bupropion	1	
Calcium channel blockers		Verapamil	5	6
		Diltiazem	1	
		Amlodipine	3	
		Nifedipine	1	

Table 1. *Cont.*

Drug Group		Drug	Application in Humans	Application in Animals
Beta-blockers		Propranolol	1	3
		Atenolol	2	1
		Carvedilol	2	
Sedative-hypnotics	Non-BDZ	Zopiclone	1	
	BDZ	Midazolam	1	
Antipsychotics		Quetiapine	3	
		Haloperidol	2	1
		Chlorpromazine		1
Antiepileptics		Carbamazepine	1	
		Lamotrigine	1	
		Thiopental	1	
Organophosphorus compounds		Paraoxon		1
		Diazinon		1
Other		Digoxin	1	
		Cyclobenzaprine	1	
		Ketorolac	1	
		Ivermectin		1
		Ethanol	2	
		Amphetamine	1	
		Hydroxychloroquine	1	
		Flecainide	1	
		Lithium	1	

TCA—tricyclic antidepressants; TeCA—tetracyclic antidepressants; SSRIs—selective serotonin reuptake inhibitors; SNRIs—selective norepinephrine reuptake inhibitors; BDZ—benzodiazepines.

6. Mechanisms of Antidotal Action of ILE in Acute Systemic Toxicity

6.1. "Lipid Sink" Phenomenon

A widely accepted mechanism of action for intravenous lipid emulsions is the "lipid sink" phenomenon, first identified by G. Weinberg in 1998 [52]. This concept revolves around certain ILEs, when introduced in significant quantities into the bloodstream, creating a lipid phase capable of absorbing ("capturing") lipophilic xenobiotics. By extracting these substances from areas of high concentration, particularly the heart and brain, the lipid phase prevents their binding to targets, thus thwarting their toxic effects.

The distribution of drugs from regions of high concentration to those of lower concentration adheres to pharmacokinetic principles. Lipid infusion establishes an expanded lipid phase, facilitated by the concentration gradient, which drives the migration of substances from the aqueous plasma phase of blood and tissues to the lipid phase of the emulsion. This setup ensures the swift removal of toxic agents from sites of high accumulation, such as the brain and heart, facilitating their incorporation into the lipid fraction via blood plasma. Consequently, the concentration of lipophilic toxic agents decreases in tissues, elucidating the organ-protective effect of ILEs. This process of redistribution is commonly referred to as the "lipid sink" or "lipid shuttle". Emulsified fat droplets form the lipid phase in which lipophilic substances, such as local anesthetics, are theoretically incorporated, effectively moving the toxicant away from critical organs like the heart and brain [53]. In an experimental in vitro rat model, G. Weinberg et al. (1998) demonstrated through high-performance liquid chromatography that radiolabeled bupivacaine, when added to lipid-treated rat plasma, exhibited preferential incorporation into the lipid phase with a partition coefficient of 11.9 [52]. Subsequent experiments conducted in 2006 using an isolated heart model to simulate bupivacaine toxicity illustrated that infusion of ILE not only expedited the removal of radiolabeled bupivacaine from myocardial tissue and enhanced its elimination rate but also reinstated drug-induced asystole [54]. According to the authors, these findings

support the hypothesis that bupivacaine partitions into the emulsion and substantiate the concept of a "lipid sink", although they do not preclude the existence of other potential mechanisms of action.

Concrete evidence supporting the lipid sink model is found by the studies conducted by Mazoit et al. (2009), revealing that ILEs bind substantial quantities of lipid-soluble local anesthetic [55]. Complementing this in vitro experiment, Niiya et al. (2010) observed that pretreatment of pigs with an ILE shielded them against amiodarone-induced hypotension [56]. Moreover, through ultracentrifugation of plasma to segregate the lipid-bound drug fraction, it was discerned that amiodarone exhibited a preference for partitioning into the newly formed lipid phase. This observation constitutes direct substantiation of the "lipid sink" effect, as the resultant lipid-free aqueous phase exhibited lower amiodarone concentrations compared to control animals administered saline instead of lipid. Samuels et al. (2012) assessed the efficacy of fractionation by examining the impact of drugs with varying lipid solubility on blood methemoglobin production [57]. They found that the addition of fat emulsion notably decreased the process induced by most lipid-soluble drugs, although it failed to suppress the process induced by less-lipid-soluble drugs. This underscores the significance of the lipid sink in mitigating the adverse physiological effects associated with drug toxicity.

Collectively, these studies lend support to the hypothesis that "lipid uptake" plays a pivotal role not only in the treatment of bupivacaine toxicity but also in the management of other lipophilic substances. However, the findings of other experiments challenge the notion of "lipid uptake" as the primary mechanism of action of ILEs. For instance, Litonius et al. (2012) conducted a study measuring bupivacaine concentrations in the blood of volunteers who received small doses of the local anesthetic followed by either ILE or a control infusion of Hartmann's solution [58]. Their results indicated no discernible difference in the concentration of free (nonlipid or protein-bound) bupivacaine compared to controls, suggesting the absence of a "lipid sink" effect. Conversely, the infusion of ILE significantly shortened the plasma half-life of the anesthetic by more than 40%, implying a decrease in the drug's distribution in peripheral tissues.

Following successful laboratory reports on resuscitation from bupivacaine toxicity, the efficacy of lipid infusion has been investigated in animal models of overdose with various other drugs. Naturally, attention has been directed towards substances that frequently cause acute poisonings, such as TCAs, beta-blockers, and calcium channel blockers. The publication by Sirianni et al. (2008) details the administration of an intravenous lipid emulsion in patients with severe cardiotoxicity resulting from bupropion and lamotrigine intoxication. Numerous studies conducted on animal models provide impetus to expand the use of ILE for treating acute poisoning involving other lipophilic drugs such as verapamil, diltiazem, amlodipine, quetiapine, sertraline, haloperidol, lamotrigine, olanzapine, propranolol, atenolol, nebivolol, doxepin, dosulepin, imipramine, amitriptyline, and others [9]. It is important to acknowledge that not all reports subscribe to the hypothesis that the direct mechanism of action of intravenous lipid emulsion is responsible for toxicological reversal. Nonetheless, researchers concur that the administration of oil emulsions demonstrates efficacy in cases involving lipophilic agents, albeit varying in amounts and concentrations. Harvey and Cave (2012) supported the effectiveness of this therapeutic approach in managing multidrug overdose [59]. They documented a case involving profound neurological and cardiovascular manifestations in acute tricyclic antidepressant (TCA) intoxication. A 51-year-old male, weighing 75 kg, presenting with a medical background of ischemic heart disease, chronic back pain, and depression, consumed undisclosed amounts of various pharmaceutical agents (such as quetiapine, citalopram, metoprolol, quinapril, acetylsalicylic acid, and amitriptyline), with intake surpassing 43 mg/kg (>65 $\times$ 50 mg tablets) intentionally as a self-poisoning event. The clinical presentation of symptoms was characteristic of TCA-cardiotoxicity. Following unsuccessful active therapy to mitigate the developing shock, a 100 mL bolus of 20% ILE was administered, followed by an additional 400 mL over 30 min. This intervention restored hemodynamic stability, eliminating the

need for further vasopressor medication. Blood levels tested were consistent with the "lipid sink" playing a significant role in the observed improvement. Based on the patient's recovery history and laboratory parameter dynamics, the authors concluded that ILE likely contributed significantly to the favorable outcome of the case.

Fettiplace and Weinberg (2018) meticulously delineated the concentration-dependent restoration of cardiovascular function [60]. They asserted that the mechanism of action of intravenous lipid emulsion relies on the tissue concentration of the drug. Improvement in cardiovascular function is not anticipated until bupivacaine concentrations drop below threshold levels for channel blockage, with recovery contingent upon the redistribution of the drug from the heart to the muscles and liver. The incorporation of lipids facilitates the expedited removal of the drug from cardiac tissue. The primary advantage of ILE lies in its cleansing effect. According to this study, in the bloodstream, bupivacaine exists as a combination of neutral and cationic (positively charged) forms, with the positively charged ions binding to plasma proteins, such as albumin, through electrostatic interactions. The introduction of lipids provides a third phase (lipid + plasma) for bupivacaine binding. Lipid droplets consist of a monolayer shell of phospholipid (and some phytosterols) surrounding hydrophobic triglyceride cores. Through lipophilic partitioning, the amphiphilic bupivacaine molecule integrated into the membrane or transported into the hydrophobic core. Additionally, the positively charged molecules will adhere to the negatively charged phospholipids on the droplet surface due to electrostatic forces. Weinberg (2012) discovered that integrating ILE application into the treatment protocol for mixed acute intoxication involving lipophilic drugs led to a reduced requirement for intubation and shorter stays in the intensive care unit compared to patients in the control groups who were treated without fat emulsion [61].

It is widely accepted that two potential mechanisms of action, namely, partitioning and enhanced metabolism, are believed to explain the beneficial effects of lipid infusion in bupivacaine toxicity. However, in recent times, additional evidence has emerged suggesting several other significant potential mechanisms of action, such as impact on ATP synthesis in cardiomyocytes, activation of calcium channels, affecting the enzyme translocase, inotropic effect, etc.

6.2. Impact on ATP Synthesis in Cardiomyocytes

According to this theory, the rapid infusion of a substantial amount of fatty acids (bolus administration) offers an energy substrate for myocardial dysfunction. Lipids serve as a primary energy source for cardiac cells under normal aerobic conditions, suggesting that the administration of ILE may directly influence cardiac function. Thus, it was proposed that the high lipid load could potentially compensate for the potent inhibition of fatty acid metabolism caused by bupivacaine. Stehr et al. (2007) presented the initial evidence supporting this theory [62]. They demonstrated in isolated rat hearts that, despite the lipid content being insufficient to significantly lower the local anesthetic concentration in the perfusate, ILE could mitigate bupivacaine-induced depression of cardiac function. Preventing the oxidation of fatty acids inhibits the lipid reversal of bupivacaine-induced cardiac toxicity. Enhanced metabolism was linked with supplementary cytoprotective effects, which mitigate mitochondrial permeability, a pivotal stage in programmed cell death.

Local anesthetics and other potentially cardiotoxic drugs can hinder fatty acid transport in cardiomyocyte mitochondria by inhibiting carnitine-acylcarnitine translocase, functioning as both enzyme and transporter [63]. It is believed that high plasma triglyceride levels can counteract this inhibition.

In a contrasting approach, Rahman et al. (2011) discovered that in rodents, lipid infusion decreased reperfusion injury during cardiac ischemia [64]. Incorporating metabolic inhibitors into experimental protocols decreases the probability of mitochondrial permeability activation and apoptosis induction.

Theoretically, intravenous lipid emulsion could augment intracellular fatty acid content, thereby counteracting the diminished adenosine triphosphate (ATP) production re-

sulting from local anesthetic blockade. It is conceivable that the therapeutic effect of ILE stems from an elevation in intracellular fatty acid levels, which also contributes to enhanced ATP synthesis in cardiomyocytes. Given that fatty acids serve as a primary substrate for oxidative phosphorylation under aerobic conditions, generating roughly 80–90% of cardiac ATP, their impaired transport leads to diminished ATP production, adversely impacting cardiomyocyte viability and potentially inducing cardiac toxicity [65]. ILE infusion enhances contractility by fostering improved fatty acid oxidation. Consequently, ILE may sufficiently elevate intracellular fatty acid content to counteract or alleviate the reduction in cardiac ATP synthesis.

6.3. Activation of Calcium Channels

Another potential mechanism of action of intravenous lipid emulsion in acute poisonings involves the direct activation of voltage-dependent calcium channels, leading to an elevation in intracellular calcium levels and subsequent stimulation of cardiac activity. Supporting this hypothesis is a study by Huang et al., demonstrated that long-chain fatty acids enhance calcium currents in cardiac myocytes [66]. Interestingly, ILEs exhibit a rapid onset of action in vivo, suggesting that their direct cardiotonic effects may also contribute to their mechanism of action.

Elevated levels of calcium in cardiomyocytes produce a direct positive inotropic effect, as demonstrated in a study by Gueret et al. [67]. The authors investigated the impact of intralipid treatment on verapamil toxicity in rats and found that standard therapy with ILE enhances hemodynamic stability and survival in an animal model of severe verapamil toxicity.

6.4. Affecting the Enzyme Translocase

One vital cardiac protein with enzymatic properties is carnitine-acylcarnitine translocase, which facilitates the transport of acyl-CoA-bound fatty acids across mitochondrial membranes for their oxidation. This transfer of fatty acids, possessing long hydrocarbon chains, across the inner mitochondrial membrane occurs via the shuttle mechanism, aided by the low-molecular-weight transported carnitine.

Carnitine exists in two forms, L- and D-, with the L-form being physiologically active. L-carnitine, closely associated with fat metabolism, plays a crucial role in preventing the accumulation of lactic acid in muscle cells. A study conducted by Ok et al. explored the effects of lipid emulsions on various enzymes including carnitine palmitoyltransferase I (CPT-I), carnitine acylcarnitine translocase (CACT), and carnitine palmitoyltransferase II (CPT-II), as well as mitochondrial dysfunctions induced by toxic doses of local anesthetics [68]. The findings suggest that lipid emulsion mitigates levobupivacaine-induced inhibition of CACT, potentially through the sequestration of levobupivacaine mediated by lipid emulsion.

6.5. Inotropic Effect

Intravenous administration of lipid emulsion (LE) has been proposed to exert a positive inotropic effect. Stehr et al. (2007) demonstrated that lipid infusion produced a positive inotropic effect in the isolated rat heart and reversed bupivacaine-induced cardiac depression at lipid levels below those required to reduce the concentration of bupivacaine in the aqueous phase [62]. The infusion of lipid emulsion can induce a direct cardiotonic effect both in vivo and in isolated rat hearts. Although the exact mechanism behind this phenomenon remains unknown, its action is notably rapid, making lipid emulsion a preferred choice for acute poisoning situations.

The administration of ILE "reversed" bupivacaine-induced cardiodepression at concentrations too low to facilitate the "lipid sink" phenomenon, suggesting a metabolic explanation for the positive effect, as proposed by Fettiplace and Weinberg (2018) [65]. According to their theory, lipid emulsion significantly contributes to cardiovascular recovery through an additional cardiotonic effect. The triglycerides and phospholipids present in

the lipid emulsion exert a favorable influence on the cardiovascular system (CVS) either directly on the heart or the vascular system. This effect becomes evident only after the concentration of the respective drug falls below the threshold required for blocking the ion channels. In cases of acute toxicity leading to asystole and cardiovascular collapse, circulating lipid "droplets" of the lipid emulsion can extract the drug from the tissue, thereby restoring cardiac function. These lipid droplets facilitate the rapid redistribution of the drug to skeletal muscle and the liver, where it undergoes conjugation and subsequent excretion. This hypothesis was supported by a prospective, randomized experiment that involved rats anesthetized with isoflurane and treated with a bolus infusion of ILE [69]. The study revealed that the lipid emulsion induced a swift and positive inotropic effect, leading to a faster and more pronounced increase in aortic flow and arterial pressure compared to the control group.

6.6. Other Mechanisms

According to Mottram et al. (2011), free fatty acids mitigated bupivacaine-induced inhibition of transport function of sodium channels in heterologous tissue culture [7]. Their findings suggest that the modulation of cardiac sodium channels may play a role in alleviating the effects of local anesthetic toxicity. The suppression of sodium channels by these fatty acids implies an impact on these transporters, potentially increasing the toxicity induced by other blockers of these channels, including certain antiepileptics and local anesthetics.

Lipid-based resuscitation presents a far more intricate clinical landscape than initially perceived. At present, the impacts of intravenous lipid emulsion administration can be categorized into intracellular (metabolic, signaling), intravascular (sequestration, sink), and membrane (channel) effects. It is plausible that forthcoming research endeavors will unveil all the primary beneficial effects of ILE and delineate their respective contributions to the treatment of acute intoxications involving various xenobiotics. An overview of these mechanisms is provided in Table 2.

Table 2. Mechanisms of antidote activity of ILE in acute intoxications.

Mechanism	Species	Method	Medicine	Refs.
"Lipid sink"	Rat (plasma)	In vitro	Bupivacaine	[52]
	Rat (isolated heart)	In vitro	Bupivacaine	[54]
	Pig	In vivo	Amiodarone	[56]
	Human	In vivo	Bupivacaine	[58]
	Human	In vivo	Bupropion + Lamotrigine	[9]
	Human	In vivo	TCA	[59]
Impact on bioenergy	Rat (isolated heart)	In vitro	Bupivacaine	[62]
	Rat (heart tissue)	In vitro	Bupivacaine	[63]
	Rat	In vivo	Ischemia	[64]
	Mice (isolated heart)	In vitro	Ischemia	[65]
Activation of calcium channels	Pig	In vitro	Nifedipin	[66]
	Rat	In vivo	Verapamil	[67]
Affecting the enzyme translocase	Rat	In vitro	Levobupivacaine, Bupivacaine, Rropivacaine, Mepivacaine	[68]
Inotropic effect	Rat (isolated heart)	In vitro	Bupivacaine	[61]
	Rat (isolated heart)	In vitro	Isofluran	[69]
Inhibition of sodium channels	Cell line	In vitro	Bupivacaine	[7]

7. Effects of ILEs in Acute Intoxications with Antiepileptics

There is scientific evidence regarding the efficacy of fat emulsions in acute poisoning involving antiepileptic drugs. The primary mechanisms of action of antiepileptics are

associated with enhancing inhibitory GABAergic neurotransmission, decreasing excitatory glutamatergic system activity, and blocking voltage-dependent sodium channels, thereby mitigating excessive excitability in the brain. These drugs may operate through one or a combination of the aforementioned mechanisms.

It has been observed that the administration of ILE in patients with severe intoxications can reverse the progression of clinical symptoms of poisoning and potentially save lives. The effectiveness of ILE was demonstrated in a retrospective study involving 75 patients with acute exogenous intoxications at a clinic for intensive treatment of acute poisoning and toxic allergies at the Military Medical Academy-Varna, spanning the period from 2010 to 2020 [11]. Among these patients, six received intravenous lipid emulsion as an adjunct therapy alongside the standard treatment regimen, while the remaining patients underwent only standard resuscitation and detoxification protocols.

Based on data from the screening of acute poisoning patient records (n = 75, of which 69 were female and 6 were male), ILE was administered to both sexes. The distribution by age shows a peak of poisonings in the group up to 24 years and in both groups divided by the factor "gender".

Almost all intoxications with antiepileptics were the result of suicide attempts. The distribution by toxic nox was of interest. Acute intoxications with valproic acid are leading, followed by those with carbamazepine. ILE was administered in five patients with valproic acid poisoning and in one with carbamazepine intoxication.

Quantitative assessment of consciousness was reported, since antiepileptic drugs in acute intoxications mainly have pronounced CNS effects. Data analysis showed that ILE was administered at the discretion of specialists in more severe cases of depressed CNS function—most commonly in sopor (33.3% of all cases) and coma (16.67% of all cases). These data showed that ILE was applied in case of severe impairment of consciousness due to acute exogenous intoxications with AE, where the cerebrotoxic syndrome was leading.

In the six clinical cases with additional administration of ILE, intoxication and toxic sopor were controlled during the course of treatment. Positive dynamics and the gradual reduction in cerebrotoxicity (GCS) and cardiovascular syndromes (arterial hypotension and tachycardia) were observed, without the development of seizures, significant CNS depression, and other complications. The average hospital stay was significantly reduced in patients with applied ILE from 3.5 to 2 days. Categorical performance data are also the mortality indicator. In severe acute intoxications without ILE, the fatal outcome was 1.45%, compared to 0% after administration of ILE.

7.1. Effects of ILE in Barbiturate Intoxications

Although a specific antidote for barbiturate toxicity remains elusive, several publications have explored the potential clinical utility of intravenous lipid emulsion as a countermeasure [70]. Initially, ILE administration reduced the duration of anesthesia induced by thiopental in rats. According to Moshiri et al. (2018), in rats experiencing acute toxicity induced by phenobarbital (100 mg/kg), the administration of 18.6 mL/kg ILE resulted in increased muscle strength and prolonged survival time among the rodents, although it did not affect overall mortality rates [71]. However, the average survival time of animals in the ILE group was notably higher compared to those treated with saline.

Due to the limited use of the drug as an antiepileptic in recent years, clinical data on isolated acute poisonings treated with intravenous lipid emulsion as an antidote are lacking. However, a groundbreaking report by Hameed et al. (2020) shed light on the use of ILE in pediatric patients experiencing severe life-threatening poisoning with benzodiazepines, barbiturates, and tricyclic antidepressants [72]. In this report, an 11-year-old girl was admitted unconscious with a GCS of 4/15 (E1V1M2), displaying moderately dilated and slowly reactive pupils along with metabolic acidosis. After flumazenil was used as an antidote for benzodiazepine poisoning, ILE therapy was initiated with two bolus applications of 1.5 mL/kg over 5 min. Remarkably, the patient's GCS improved to 12/15 (E4M5V3) after the second bolus, and lipid infusion was continued for the next 6 h. Ultimately, the patient

regained a full GCS status of 15/15 without any neurological deficit. This sequence of events provides substantial evidence supporting the role of ILE therapy in the successful management of acute combined barbiturate intoxications.

7.2. Effects of ILE in Lamotrigine Intoxications

Lamotrigine intoxication is characterized by the inhibition of voltage-gated sodium channels, the release of aspartate and glutamate, and the reuptake of serotonin. This blockade of sodium channels typically presents with ECG abnormalities, while serotonin toxicity manifests as intermittent myoclonus, confusion, tachycardia, hypertension, hyperreflexia, clonus, and widened QRS complex [32]. Following a systematic review of published cases of lamotrigine overdose in both adults and children, Alyahya et al. (2018) concluded that in patients aged $\leq$3.5 years, ingestion of the antiepileptic drug at doses exceeding 525 mg may result in severe CNS depression and seizures [73]. In 2008, Sirianni et al., at Riddle Memorial Hospital in Media, Pennsylvania, documented the utilization of ILE in a 17-year-old girl who experienced seizures and cardiovascular collapse due to an intentional overdose involving bupropion, lamotrigine, and amphetamine [9]. After 70 min of unsuccessful standard cardiopulmonary resuscitation, a 100 mL bolus of 20% ILE was administered. Remarkably, within a minute after the infusion, a pulse was detected, leading to an improvement in cardiovascular status and subsequent recovery of neurological function. Below are individual cases illustrating successful intravenous ILE treatment following acute lamotrigine intoxication. In 2012, Moore et al. documented the inaugural case of ILE administration alleviating severe neurological symptoms in acute lamotrigine toxicity in humans [74]. The patient, a 23-year-old man who ingested approximately 13 g of lamotrigine and 18 g of fludrocortisone in a suicide attempt, exhibited continued severe toxicity during his three-day hospitalization, marked by agitation, restlessness, and persistent ECG abnormalities due to the elevated lamotrigine level. Following the administration of ILE, initially as a bolus followed by a 40 min infusion, there was a notable improvement in the patient's mental state, with decreased agitation and restlessness. By the fifth day, he regained consciousness but remained disoriented to time and place, with alterations in gait. Similarly, in 2012, Castañares-Zapatero et al. employed ILE as an adjunctive therapy in intentional lamotrigine overdose cases where toxic ECG changes were unresponsive to bicarbonate therapy [75]. The 50-year-old patient lost consciousness and developed ECG abnormalities, including QRS-interval prolongation with left AV-block. After the infusion of 20% ILE, a prompt recovery of cardiac conduction was observed, demonstrating the efficacy of ILE as an adjunctive treatment in lamotrigine overdose scenarios. Following combined intoxication from quetiapine and lamotrigine ingestion, a 17-year-old girl experienced a spectrum of symptoms including depression of mental status, hypotension, tachycardia, and an exceedingly prolonged QT-interval with decreased heart rate, as documented by Klučka et al. in 2019 [76]. In response, intravenous ILE administration resulted in the normalization of the QT interval within 30 min, indicating the prompt efficacy of ILE in mitigating the cardiac effects of the intoxication.

7.3. Effects of ILE in Benzodiazepine Intoxications

Several studies have highlighted the prevalence of benzodiazepine poisonings as the most common form of drug intoxication [16,77–79]. As noted by Marinov et al. (2016), they account for approximately 26.37% of cases, predominantly stemming from suicide attempts and notably affecting women under 30 years of age [18]. The standard treatment protocol for acute benzodiazepine intoxication involves the administration of the specific antidote flumazenil intravenously, with repeat doses if necessary. Patients typically regain consciousness within 1–2 min following flumazenil administration in cases of pure benzodiazepine intoxication [80]. Flumazenil stands out as a highly effective antidote and can serve as a valuable diagnostic tool for suspected benzodiazepine poisoning [79]. Hemodialysis has been proven ineffective in treating benzodiazepine intoxications, and prognosis tends to be less favorable in cases involving elderly individuals. Several studies have documented

the successful use of ILE in the treatment of acute intoxications involving benzodiazepines in combination with other medications and with some non-benzodiazepine hypnotics (Z-drugs) between 2010 and 2020. In a case outlined by Hillyard et al. (2010) [81], a 55-year-old man was admitted to the hospital with depressed consciousness attributed to zopiclone and an extended-release formulation of venlafaxine (with an ingestion of 1.8 g of venlafaxine and an unspecified quantity of zopiclone prior to admission). Initially, the patient's consciousness, as measured by the Glasgow Coma Scale, was recorded at 10 (moderately severe), but it decreased to 3 (severe) after four hours. Following a 30 min infusion of ILE, the patient's GCS improved to 11, obviating the need for assisted breathing. Subsequently, the patient was discharged from the hospital two days later. Dagtekin et al. (2011) documented a case of combined intoxication in a 44-year-old woman who deliberately overdosed on lamotrigine, diazepam, and venlafaxine (an antidepressant) [82]. The patient experienced coma, convulsions, marked stiffness, and hyperreflexia. Despite undergoing hemodialysis, her condition remained unchanged. However, after receiving an intravenous bolus of ILE, the rigidity and hyperreflexia rapidly resolved. Subsequently, the patient experienced failure to fully recover. Orr and Bailie (2010) detailed a similar case involving combined intoxication with benzodiazepines (BZDs), influenced by the administration of ILE [83]. In this scenario, a 34-year-old man consumed high doses of liposoluble drugs along with other toxic substances, including diazepam, temazepam, citalopram, an unspecified amount of perindopril, doxazosin, amlodipine, a combination drug containing codeine and paracetamol, and 500 mL of ethylene glycol. Upon admission, he presented with hypotension, tachycardia, and GCS score of 5. Standard antidote therapy yielded no response, resulting in metabolic acidosis and reduced renal function. However, within thirty minutes of receiving the ILE bolus injection, the patient's GCS score improved. He was discharged on day 12 with restored neurological status and renal function. Additionally, a case of BZD self-poisoning during labor, successfully treated with ILE, has been documented [84]. The patient experienced altered mental status during labor, which subsequently improved following the administration of ILE.

7.4. Effects of ILE in Carbamazepine Intoxications

Carbamazepine poisoning typically results from overdose and is commonly associated with cardiac, neurological, and respiratory complications. Symptoms often include diplopia (observed in most patients with carbamazepine blood levels higher than 7 μg/mL), ataxia, and dysarthria [85]. In severe cases, coma, hypotension, respiratory depression, cardiac arrhythmias, and seizures may manifest. Unfortunately, there is currently no specific antidote available for carbamazepine poisoning. Multiple-dose activated charcoal (MDAC) application increased elimination and improved clinical outcome in patients with carbamazepine overdose, and was recommended for patients with life-threatening symptoms [86]. Extracorporeal treatments (ECTRs) are suggested if prolonged coma or respiratory depression requiring mechanical ventilation is present or expected [87].

A successful treatment of carbamazepine toxicity with multiple doses of activated charcoal and hemodialysis in a 19-year-old woman with a carbamazepine suicide attempt (186 mg/kg) was described [88]. Patient's pupillary reflexes were isochoric and mydriatic, and deep tendon reflexes were bilaterally identical. Glasgow Coma Scale score was seven. Hypotension (70/40 mm Hg) with rhythmic heart rate (112 b/min) and respiratory rate of 22/min were observed. Carbamazepine serum levels before hemodialysis were 57.7 μg/mL (normal value, 4–10 μg/mL; toxic dose, >15 μg/mL) and after the procedure rated 28.9 μg/mL. The patient was conscious on day three with a GCS of 15 and a serum carbamazepine level of 6.8 μg/mL.

The combined use of ILE therapy and ECTR methods shows ILE treatment as a safe, easy and fast method, but does not provide additional benefit in clinical practice. This result is presented with a case of carbamazepine poisoning in a 35-year-old man [89]. On admission, the patient was unconscious, with blood pressure 90/60 mmHg, heart rate of 96 bpm, respiratory rate of 19/pm, and Glasgow Coma Scale score of seven. Gastric

lavage was performed, and activated charcoal was given. Initially, carbamazepine level was 70.8 mg/L. Treatment by hemoperfusion (HP), hemodialysis (HD), ILE, and MDAC were envisaged. The intravenous lipid emulsion was administered as a 135 mL bolus and 375 mL for the first hour, followed by a 25 mL/h infusion. After HP and HD, the carbamazepine blood level decreased to 58.7 mg/L. After 18 h of hospitalization, GKS scored 11 and the patient became conscious.

According to Ghannoum et al. (2014), conventional treatment approaches may prove ineffective in reducing absorption and enhancing the elimination of overdose, particularly with delayed-release formulations [87]. Consequently, extracorporeal clearance is recommended for managing carbamazepine toxicity, despite its lipophilic nature (Log *P* of 2.5), which traditionally makes it less amenable to hemodialysis. Toxic doses of carbamazepine can induce cardiac depression, possibly attributed to the blockade of cardiac sodium channels. Agulnik et al. (2017) proposed that neurotoxicity might arise from the hyperpolarization of mitochondrial membranes [90]. This suggests that carbamazepine toxicity at elevated doses can lead to mitochondrial dysfunction. There are isolated reports detailing the successful use of ILE in acute intoxications involving the classical antiepileptic drug carbamazepine. Agulnik et al. reported an analogous case of carbamazepine intoxication in another 15-year-old girl who displayed impaired mental status (GCS 5) and severe acidosis. The patient experienced seizures and severe EEG changes indicative of significant cortical dysfunction. Treatment involved a therapeutic regimen comprising ILE, hemodialysis, plasmapheresis, continuous veno-venous filtration, and endoscopic intestinal decontamination. Remarkably, the patient achieved full recovery without any organ or neurological complications. In a case described by Hirose et al. (2014), a 15-year-old girl presented with acute carbamazepine and mirtazapine intoxication, exhibiting respiratory depression and seizures [91]. ILE was administered, and the patient was discharged without complications after 8 days. Avcil et al. (2015) documented a case of poisoning in a young man who ingested 2.8 g of extended-release carbamazepine [92]. The patient presented with confusion and depression (GCS 12), along with mild hypotension, tachycardia, and a prolonged QT interval. In response, a bolus administration of ILE was followed by a four-hour infusion, in conjunction with multiple doses of activated charcoal and intravenous saline hydration. Remarkably, within 60 min of the ILE bolus administration, the patient regained consciousness and orientation. He was discharged from the intensive care unit on the third day without any neurological or cardiac complications. Lee et al. (2023) proposed that the reduction in carbamazepine toxicity mediated by lipid emulsion might be attributed to the restoration of inhibited sodium channels in the excitatory conduction system of the heart, as well as the correction of mitochondrial dysfunction [93].

7.5. Effects of ILE in Valproate Intoxications

The central nervous system symptoms associated with acute valproic acid (VPA) intoxication, characterized by dysfunction, can manifest as mild drowsiness progressing to coma and potentially fatal cerebral edema. Caution is recommended when administering VPA salts to critically ill patients with hypoalbuminemia, uremia, or those receiving medications that can displace valproate from its albumin binding sites [94]. Such medications include acetylsalicylic acid, ibuprofen, propofol, and others, including intravenous lipid emulsions. These substances interact with valproate at the level of plasma protein binding, leading to an increase in the free fraction of the antiepileptic drug. This interaction mechanism, resulting in elevated non-albumin-bound drug fractions, underscores the incorporation of ILE into the treatment regimen for acute poisoning, with the objective of expediting the elimination of the toxic agent from the body. Intentional ingestion, often for suicidal purposes, or insufficient therapy monitoring and control, can result in poisoning with sodium valproate, a commonly prescribed drug for treatment of epilepsy and bipolar disorder. Some reports suggest that an overdose of sodium valproate tablets may lead to delayed toxicity characterized by clinical symptoms arising when hyperammonemia develops [95]. While there are rare instances of intravenous lipid emulsion use in clinical

practice within intensive care units for acute valproate intoxications, limitations exist due to risks of incompatibility and drug interactions identified in certain studies [96]. Consequently, combined administration of sodium valproate and ILE via the same infusion line is not recommended.

7.6. Effects of ILE in Phenytoin Intoxications

The metabolism of phenytoin is known to follow first-order kinetics at lower doses and zero-order kinetics at higher doses. The latter poses challenges in managing its toxic manifestations due to its prolonged elimination from the body. This can lead to a change in toxic symptoms and, thus, to prolonged hospitalization with accompanying complications [97]. Although treatment methods such as activated charcoal, activated charcoal hemoperfusion, and molecular adsorbent recirculation system have been attempted to address phenytoin toxicity, there is currently no specific antidote [98,99].

Only one report has documented the use of intravenous lipid emulsions in a case of phenytoin toxicity in the resuscitation of a 15-month-old child [100]. The patient was in status epilepticus. Bradycardia and hyposaturation occurred shortly thereafter. Cardiopulmonary resuscitation (CPR) was started immediately. On the sixth resuscitation cycle, an ILE bolus was introduced. After the 12th cycle of resuscitation, spontaneous sinus rhythm was restored. The child was extubated the next day and left the hospital with no visible deficits.

A summary of the effect on GCS values and CVS of ILE in acute intoxications is given in Table 3.

Table 3. Effect of ILE on GCS and CVS in acute intoxications; GCS—Glasgow Comma Scale; CVS—cardiovascular system; "+" stands for combination.

Medicine	Species	Results on GCS	Results on CVS	Refs.
Lamotrigine + Bupropion + Amphetamine	Human	Positive	Positive	[9]
Phenobarbital	Rat	Positive	Negative	[71]
Phenobarbital + BDZ+TCA	Human	Positive	-	[72]
Lamotrigine + Fludrocortisone	Human	Positive	Positive	[74]
Lamotrigine	Human	Positive	Positive	[75]
Lamotrigine + Quetiapine	Human	Positive	Positive	[76]
Zopiclone + Venlafaxine	Human	Positive	-	[81]
Diazepam + Lamotrigine + Venlafaxine	Human	Positive	Positive	[82]
Diazepam + Temazepam + Citalopram + Perindopril + Doxazosin + Amlodipine + Codeine + Paracetamol + Ethylene glycol	Human	Positive	Positive	[83]
Carbamazepine	Human	Positive	Positive	[90]
Carbamazepine + Mirtazapine	Human	Positive	Positive	[91]
Carbamazepine	Human	Positive	Positive	[92]
Phenytoin + Valproate Sodium	Human	Positive	Positive	[98]

8. Conclusions

The widespread use of drugs from these categories in modern practice, together with their serious consequences and risk of death, highlights the urgent requirement for researchers to explore and adopt more effective strategies.

Intravenous lipid emulsions (ILEs) are cost-effective, readily available, safe, and effective. Their use to treat poisonings caused by other lipid-soluble toxicants has been suggested to show potential for therapeutic intervention. However, to date, ILEs have not been widely used in toxicological clinical settings. For this reason, there is a lack of scientific literature, especially case reports describing the effects of intravenous lipid emulsions in cases of acute external intoxication involving neuroactive substances such as drugs. In addition, there is a lack of experimental data elucidating the exact mechanism of action of ILEs in acute intoxications.

Treatment with ILEs as adjunctive therapy in neurotropic drug poisoning is associated with improvements in Glasgow Coma Scale (GCS) scores and improved recovery from drug intoxication. Multiple mechanisms of antitoxic action are believed to be involved in this process.

Conducting a multicenter, prospective, randomized study would help to prove the effect of lipid emulsions in lipophilic drug intoxications, as well as contribute to improving treatment.

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