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REVIEW ARTICLE

Antidepressant Overdose: An Updated Review on Dignosis and Outcome

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ABSTRACT

Background: Antidepressant medications are frequently implicated in cases of self-poisoning. These drugs can be classified into tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), atypical antidepressants, and *N*-methyl-D-aspartate receptor (NMDA) antagonists. One of the primary concerns with antidepressants is cardiac toxicity. TCAs tend to exhibit higher toxicity levels in overdose, while MAOIs and SSRIs are relatively non-cardiotoxic when taken alone. Overdoses of combinations of MAOIs and either SSRIs or TCAs that block serotonin reuptake can lead to serotonin syndrome. This work aimed to give an overview of the clinical management of antidepressant drug overdose with respect to the role of cardiac biomarkers in improving the outcome of toxicity, and new trials of treatment.

Conclusion: Cardiotoxicity is the main cause of morbidity and mortality of antidepressant drugs poisoning. Cardiac biomarkers, such as protein B-type natriuretic peptide, B-type natriuretic peptide, creatine kinase, and creatine kinase-MB, may have a role in predicting early cardiac complications in antidepressants. In the absence of a specific antidote, Sodium bicarbonate remains the preferred treatment for severe toxicity, but various supportive measures, including 0.9% sodium chloride, vasopressors, and lidocaine may also be implemented. Searching for new lines of therapy is recommended to improve the outcome of antidepressant drugs overdose.

Keywords: Antidepressants, tricyclic antidepressants, Cardiotoxicity, B-type natriuretic peptide, Cardiac biomarkers.

INTRODUCTION

After 1950, which is known as the golden decade of psychopharmacology, new medications were discovered as imipramine, iproniazid, and lithium but they showed several side effects. A new class of antidepressant drugs was introduced called selective serotonin reuptake inhibitors. This medication transformed the field once again [1]. Antidepressant drugs are used for depression treatment, also recommended by doctors for anxiety disorders, insomnia, panic disorders, pain, nocturnal enuresis, social phobia, migraine, obsessive-compulsive disorders, attention-deficit/hyperactivity disorder, digestive system diseases, and vasomotor symptoms of menopause [2].Intentional self-poisoning with antidepressant medications has become a growing issue in recent times. Antidepressant drugs accounted for 20% of all intoxicated cases by psychotropic drugs presented in Cairo University hospitals according to a descriptive prospective study done from April 2018 to September 2018 [3]. Additionally, in a study done at Zagazig University Poisoning Treatment Unit (ZU-PTU) from January to December 2023, Khayal et al. [4] reported that psychotropic drugs including antidepressants were among the most prevalent toxicities within the therapeutic poisoning category which was the most common type of poisoning overall (41.33%), and according to the mortality rate psychotropic drugs were the third cause of death.This review article aimed to give an overview of the clinical management of antidepressant drug overdose with respect to the role of cardiac

biomarkers in improving the outcome of toxicity, and new trials of treatment.

CLASSIFICATION OF ANTIDEPRESSANT DRUGS:

Antidepressant drugs can be classified according to their pharmacological mechanism of action into six categories: TCAs, MAOIs, SSRIs, SNRIs, atypical antidepressants, and NMDA antagonists **(Figure 1)** [5].

PHARMACOKINETIC AND TOXICOKINETIC OF ANTIDEPRESSANT DRUGS:

Tricyclic antidepressant drugs are rapidly absorbed in the gastrointestinal tract but could have delayed absorption and toxicity due to their anticholinergic effects, especially in overdoses. Co-ingestion of other anticholinergic drugs can lead to erratic absorption. TCAs have a long elimination half-life, are highly lipid-soluble, and are significantly bound to plasma proteins, with notable enterohepatic circulation. They undergo substantial first-pass hepatic metabolism, primarily via cytochrome CYP2D6. Both the primary compound and its metabolites can cause toxicity. Metabolic or respiratory acidosis can increase the free fraction of TCAs, enhancing their deleterious effects [6]. Selective serotonin reuptake inhibitors are well absorbed from gastrointestinal tract, have a wide volume of distribution, and are highly bound to protein. They are metabolized in the liver by cytochrome enzymes, showing various elimination patterns and having multiple active metabolites, which extend their duration of action. SSRIs interact with various psychotropics, including MAOIs, TCAs, clozapine, lithium, and methadone, as well as other drugs like carbamazepine, phenytoin, and oral anticoagulants, increasing the risk of overdose. The risk of hyponatremia is heightened when SSRIs are taken with diuretics [7].Monoamine oxidase inhibitors are rapidly absorbed when taken orally, reaching peak plasma levels within 2-3 hours. They are lipophilic, crossing the blood-brain barrier easily, and are metabolized in the liver, with metabolites excreted through renal system. MAOIs can interact with tyramine-rich foods, causing dangerously high blood pressure, and must not be combined with other antidepressants because of the hazard of serotonin syndrome. They can also interact problematically with attention-deficit hyperactivity disorder medications and drugs of abuse like cocaine [6]. Serotonin and noradrenaline reuptake inhibitors are well absorbed orally, but undergo significant first-pass metabolism, leading to a bioavailability of 50%. Peak plasma concentrations occur between 6-8 hours. They handle a significant volume of distribution. The liver converts them into water-soluble, less active metabolites. Their metabolites are eliminated in urine, with an elimination half-life of approximately 15 hours [6]. Atypical antidepressants are quickly absorbed in the gastrointestinal tract. For immediate-release formulations, the peak serum concentration is reached within 2 hours, 3 hours for sustained release, and 5 hours for extended-release formulation. They are broken down by cytochrome enzymes in the liver. Bupropion may inhibit hepatic cytochrome p450 enzymes that metabolize other drugs, resulting in drug-drug interactions [8]. *N*-methyl-D-aspartate antagonists may be absorbed orally, nasally, or sublingually. Their bioavailability is limited (20-45%) due to a strong first-pass effect, with peak plasma levels 20-40 minutes after dosage. Cytochrome p450 enzymes in the liver convert them into inactive metabolites, which are then eliminated by the kidney [9].

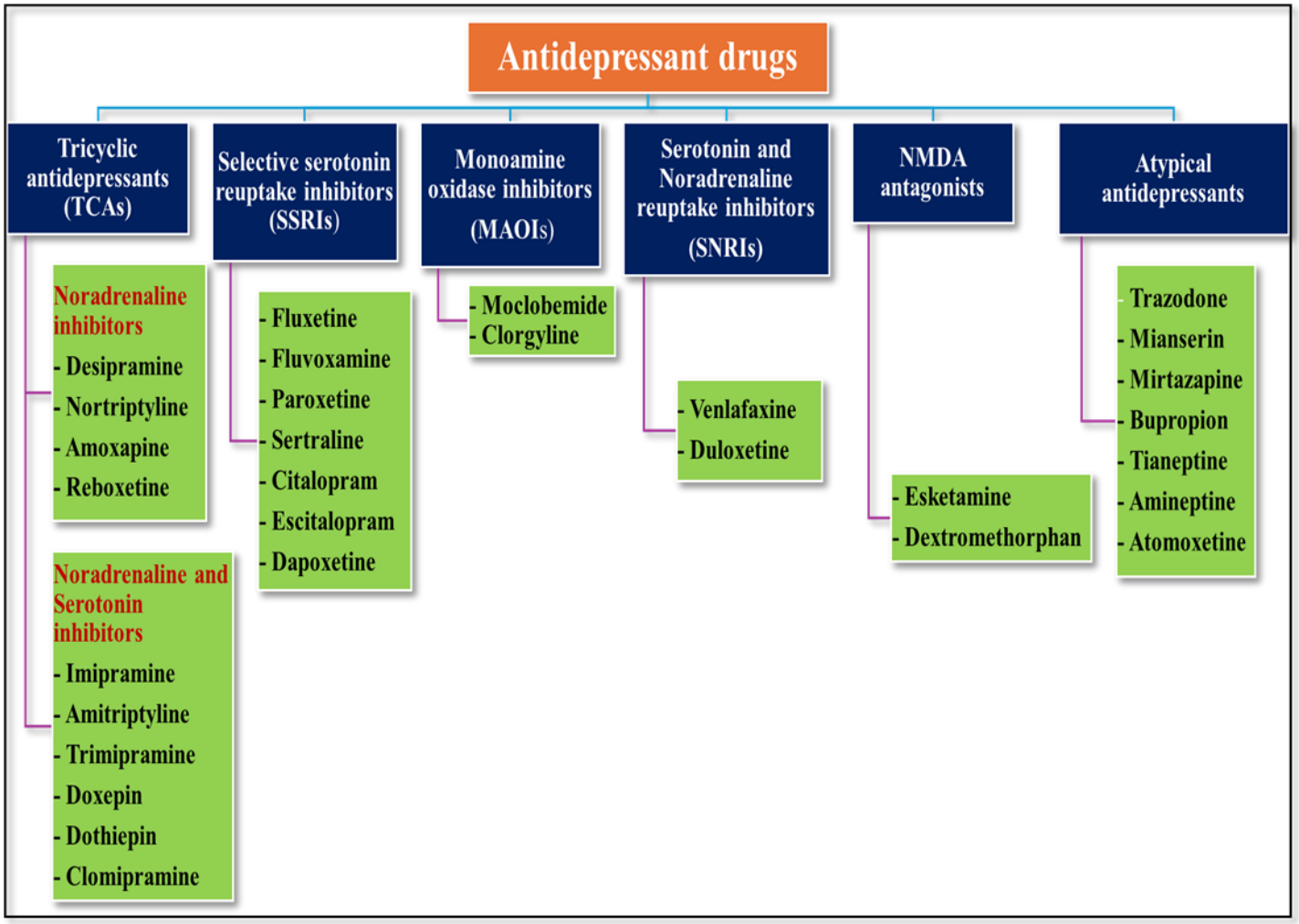

Figure 1: Types of antidepressants **[5].**

PATHOPHYSIOLOGY OF ANTIDEPRESSANT DRUGS:

The tricyclic antidepressant drugs work by inhibiting the reuptake of adrenaline, noradrenaline, and serotonin at the brain's post-synaptic nerve terminals. Additionally, these drugs exhibit anticholinergic and antihistaminic properties, alpha-adrenergic and dopaminergic (D2) blockade, and sodium channel blockade, which slows the action potential and provides a membrane-stabilizing effect [10].Selective serotonin reuptake inhibitors prevent serotonin from being reabsorbed presynaptically, increasing serotonin levels at the postsynaptic membrane of the serotonergic synapse. This increased serotoninergic activity regulates dopamine release. SSRIs have less direct interaction with sodium channels, cholinergic receptors, and adrenergic reuptake than cyclic and other atypical antidepressants [7] Monoamine oxidase inhibitors work by inhibiting monoamine oxidase enzymes, which prevent presynaptic breakdown of monoamines, increasing the concentration of monoamine neurotransmitters accessible for synaptic storage and release. Inhibition of monoamine oxidase causes some indirect release of norepinephrine into the synapse. Elevated synaptic concentrations of serotonin may be related to relatively delayed modulation of postsynaptic central nervous system serotonin receptors [11]. Because monoamine oxidase inhibitors impede dopamine-β-hydroxylase, they hinder the manufacture of norepinephrine, which eventually causes norepinephrine reserves to be depleted. Furthermore, increased dopamine concentrations at synapses cause indirect dopamine agonism. At large concentrations, dopamine agonism causes direct alpha-adrenergic

activation, peripheral vasodilation, and beta-adrenergic stimulation [12]. Serotonin and noradrenaline reuptake inhibitors suppress the reuptake of serotonin and noradrenaline. Venlafaxine produces rapid attenuation of central beta-adrenergic receptors [13]. Atypical antidepressants have diverse mechanisms of action, for instance, Bupropion inhibits norepinephrine and dopamine reuptake at the presynaptic cleft, Agomelatine increases the release of dopamine and norepinephrine by acting as an agonist at melatonin receptors and antagonizing serotonergic receptors, and Mirtazapine blocks alpha-2 adrenergic receptors, increasing norepinephrine release into the synapse, and also antagonizes serotonergic receptors, enhancing dopamine and norepinephrine levels in the cerebral cortex[5]. Esketamine is a non-selective, non-competitive *N*-methyl-D-aspartate antagonist (NMDA) that modulates the actions of glutamate and gamma-aminobutyric acid (GABA) and Dextromethorphan is an opioid σ receptor agonist and an uncompetitive NMDA receptor antagonist [14].

CLINICAL PRESENTATION OF ANTIDEPRESSANT DRUGS OVERDOSE:

Tricyclic antidepressant overdose: Cardiovascular toxicity is the main reason for morbidity and fatality related to TCAs. The most frequent cause of death in TCAs overdose is refractory hypotension due to myocardial depression. Sinus tachycardia is the most frequent dysrhythmia seen in TCAs poisoning, with rates of 120-160 beats per minute in adults, seen in most patients with significant TCAs poisoning. Intraventricular conduction delay is commonly seen on the electrocardiogram (ECG) as a longer QRS duration and a rightward shift of the T40-ms QRS axis [15]. Wide-complex tachycardia is the typical possibly fatal dysrhythmia seen in people with severe poisoning. The most common causes of ventricular tachycardia include hypotension and/or prolonged QRS complex duration. Torsade de pointes and fatal dysrhythmia are infrequent in cases of acute TCAs overdose. Additionally, TCAs can cause neurological symptoms like coma, convulsions, and extrapyramidal manifestations in addition to anticholinergic side effects including sinus tachycardia, impaired vision , and dry mouth [16]. Selective serotonin reuptake inhibitors overdose: Selective serotonin reuptake inhibitors are safer than TCAs. Citalopram and its isomers are the most hazardous among SSRIs. Overdose with SSRIs can include tachycardia, agitation, nausea, vomiting, and convulsions. QT prolongation, Torsade de pointes, hypertension, and cardiomyopathy are some of the most harmful effects connected to SSRIs overdose [17]. Serotonin syndrome can occur following a substantial overdose or in combination with other medicines that have serotonergic effects, such as MAOIs. Serotonin syndrome is a severe medication reaction. It is induced by medication, which raises serotonin levels in the body. The pathophysiologic processes of serotonin syndrome are not known, however, they include excessive selective activation of serotonin receptors [18]. Serotonin syndrome is diagnosed clinically, which necessitates complete drug review and physical assessment. Symptoms typically appear quickly after ingestion of the triggering drug: 30% within one hour, 60% within six hours, and almost all individuals with poisoning develop symptoms within 24 hours post ingestion [19]. The spectrum might range from barely detectable tremors to potentially fatal heat and shock. Serotonin syndrome signs and symptoms are agitation, restlessness, anxiety, disorientation, hyperthermia , diaphoresis, tachycardia, nausea, vomiting, increased bowel sounds, tremor, myoclonus , hyperreflexia, muscle rigidity, dilated pupils, ocular clonus, flushed skin, dry mucous membranes, and bilateral Babinski sign [20]. Several diagnostic criteria exist, including the Radomski [40], Sternbach[41], and Hunter criteria. Though the criteria were created particularly for individuals with SSRI overdose rather than serotonin syndrome from other medicines, the Hunter test is thought to be the most accurate. Hunter's criteria are: 1) History of exposure to a serotonergic drug, 2) One or more of the following [21]:

- Involuntary clonus
- Triggerable clonus with diaphoresis and agitation
- Tremors and exaggerated reflexes
- Increased muscle tone
- Temperature over 38^{o} C with inducible or ocular clonus

Monoamine oxidase inhibitors overdose can produce clinical effects after at least 12 hours.

Although many of the symptoms of MAOIs poisoning are nonspecific, the patient's history will raise a lot of red flags. The signs of MAOIs poisoning are also vague[22]. Agitation, diaphoresis, tachycardia, and a little increase in temperature are all modest symptoms. Symptoms of intermediate disease include tachypnea, vomiting, hyperthermia, dysrhythmias, altered mental status, and hypertension. Extreme indications include extreme heat, convulsions, cardiorespiratory depression, central nervous system depression, coma myoclonus, , and muscle stiffness [23]. Monoamine oxidase inhibitors can occasionally produce dangerously high amounts of serotonin, a disorder called serotonin syndrome. It usually happens when MAOIs are taken with other drugs that increase serotonin. These include, for example, antidepressants and sympathomimetic medications. Furthermore, serotonin syndrome can arise when MAOIs are combined with significant dietary tyramine intake [24]. Selective serotonin and noradrenaline reuptake inhibitors overdose: Clinical presentation varies between TCAs and SSRIs, including cardiac convulsion and arrhythmia but without anticholinergic effects. Patients with acute venlafaxine overdose may have dizziness, nausea, vomiting, hypotension, tachycardia, central nervous system depression, seizures, liver toxicity (zone 3 rhabdomyolysis, necrosis), and hyperthermia. Sodium and potassium channel-blocking effects are hardly clinically manifest; yet, QRS prolongation, QT prolongation, and ventricular tachycardia have led to mortality [25]. Atypical antidepressant overdose: Tachycardia, hypertension, and seizures can all be signs of a bupropion overdose. Mirtazapine poisoning is characterized by disorientation, drowsiness, poor memory, and bradyarrhythmias. Trazodone overdose symptoms include arrhythmias, respiratory arrest, coma, and priapism. Vilazodone overdose symptoms include sleepiness, tachycardia, vomiting, and serotonin syndrome (autonomic instability, altered mental status, and neuromuscular irregularities) [5]. *N*-methyl-D-aspartate receptor antagonist overdose: Dextromethorphan poisoning may be manifested by seizures, serotonin toxicity, and psychosis [10, 26]. Esketamine overdose may be presented by nausea, vomiting, dry mouth, dizziness, drowsiness, confusion, headache, high blood pressure, tremor, and sweating [27].

MANAGEMENT OF ANTIDEPRESSANT DRUG OVERDOSE:

Diagnosis of antidepressant drug overdose:

Antidepressant medication overdose is mostly diagnosed based on a proper history and physical presentation. There are no unique characteristics of overdose, although the combination of CNS depression and CVS presentation can predict antidepressant overdose. To rule out hypoglycemia in an altered mental state, take random blood sugar tests. Paracetamol and salicylate levels must be measured to rule out co-ingestion. Chest X-ray to rule out aspiration in comatose individuals [28]. The ECG is one of the most commonly used assays for detecting heart injury due to its simplicity and specificity in many cases. An ECG must be performed for possible QT prolongation, which is a well-accepted alternate measure for the pro-arrhythmic potential of a medication [29].

Diagnostic biomarkers:

In clinical practice, various blood indicators are utilized or proposed for use in the detection of myocardial damage. The protein B-type natriuretic peptide (proBNP), an established marker for cardiac failure. It was found raised in a case of acute poisoning of amitriptyline (tricyclic antidepressant), implying that proBNP could be employed as a biomarker for cardiac toxicity [30]. B-type natriuretic peptide (BNP) showed high sensitivity and high diagnostic accuracy in the detection of cardiotoxicity induced by tricyclic antidepressants. According to these findings, using BNP may improve the precision of clinical assessments of cardiotoxicity [31]. Wu et al, [32] discovered that patients who have taken SSRIs antidepressants, particularly females, may be more likely to have raised creatine kinase and creatine kinase-MB Levels, which are markers of cardiac muscle injury.

Treatment of antidepressant drug overdose:

1- Patient stabilization

The cornerstone of antidepressant overdose treatment is patient-centered assistance. Intubation and breathing may be required for patients with severe overdoses or co-ingestion. However, they are rarely required in single-drug

intake. Patients with impaired mental status should take thiamine and glucose [28].

2- Decontamination

Digestive tract detoxification with activated charcoal must be administered if the patient is alert and attends within an hour of consumption, but it is not recommended if the patient is in danger of aspiration. In cases of tricyclic antidepressant overdose, several doses of charcoal are more beneficial than a single dose. The increased effect of several doses could be attributed to a stoppage of enterohepatic circulation. Orogastric lavage and entire bowel irrigation will not help the situation. Ipecac syrup and the induction of emesis are contraindicated [28]. Antidepressant medications have significant protein binding and a high volume of distribution, thus hemodialysis, hemoperfusion, and forced diuresis are unlikely to be beneficial and are not indicated [6].

3- Symptomatic and supportive treatment:

In the absence of a specific antidote, treatment of acute antidepressants depends mainly on supportive treatment determined by the clinical condition of the patient [33].

a. Treatment of cardiovascular complications:

A parenteral infusion of 0.9% sodium chloride is used to treat hypotension. If there is no response to the 0.9% sodium chloride infusion, vasopressors will be administered. Norepinephrine or phenylephrine are chosen as vasopressors over dopamine [34]. In case of ventricular arrhythmia, wide QRS complex, and QT prolongation, sodium bicarbonate (1-2 mEq/kg) is the first choice of therapy. Repeated bicarbonate boluses are indicated to reach a blood pH of around 7.5. The second-line antiarrhythmic medication is lidocaine, which can operate as a sodium channel antagonist [35]. Hypokalemia should be avoided during treatment since it can worsen heart block, lengthen the QT interval, and cause Torsade de pointes. Magnesium sulfate is used for treatment of Torsade de pointes. If magnesium sulfate does not work, overdrive pacing with isoproterenol, as well as transvenous or transcutaneous pacing, can be used, however, this can exacerbate rate-dependent sodium channel blockage. Anticholinergic-related tachycardia does not require therapy unless it is linked with ischemia [36]. The suggested treatment for severe hypertension caused by MAOIs is to employ an alpha-adrenergic receptor-blocking medication such as phentolamine or phenoxybenzamine [24].

b. Treatment of seizures:

Therapy is usually not necessary for antidepressant-associated seizures. However, diazepam, phenobarbitone (phenobarbital), phenytoin, and paraldehyde have all been shown to help manage convulsions when delivered alone or in combination. Convulsions may become resistant to anticonvulsant medicines, necessitating neuromuscular paralysis and mechanical ventilation [34].

c. Treatment of anticholinergic effects:

Neostigmine can be utilized to treat peripheral anticholinergic symptoms. There are minimal indications for treating peripheral anticholinergic symptoms, such as uncomfortable urine retention. In more severe situations, catheterization is favored over physostigmine because it allows for continuous monitoring of urine output. Physostigmine is contraindicated as it is associated with complete heart block, asystole, and hypotension [37].

d. Treatment of serotonin syndrome:

Hyperthermia can be treated by actively cooling the patient. Benzodiazepines, such as diazepam or lorazepam, can be used to relieve agitation, seizure-like movements, and muscle rigidity. Cyproheptadine, a serotonin inhibitor, can be used. The patient must receive intravenous fluids and discontinue the medications that produced the condition [19].

4- Trends in the treatment of antidepressant drug overdose:

When an amitriptyline overdose causes cardiac arrest, intravenous lipid emulsion treatment has been shown to increase survival rates. Lipid administration separates the lipophilic medication from its target receptors by transporting it into the lipid phase. Lipophilic medicines with high lipid solubility enhance extraction of lipid from serum, which is called the lipid sink theory. In addition, infusion of triglycerides and phospholipids provides a prolonged fatty acid energy source to cardiac myocytes under situations of drug toxicity [33]. Animal investigations have demonstrated that TCAs-specific Fab (antibody binding) fragments can reduce the number of unbound TCAs in the

blood and increase the urine excretion of TCAs. This shows that anti-TCAs Fab fragments may be effective in cases of TCAs overdose, but this strategy has not yet been tested in humans. TCAs bind with limited affinity to albumin and strong affinity to acid glycoprotein. The expense and potential for renal toxic effects restrict the usage of Fab fragments [38]. One or more liver cytochrome oxidase enzymes (CYPs) are primarily responsible for the processing of antidepressant drugs. Their activity varies greatly from patient to patient because, like all CYPs, it is genetically controlled. The half-lives or clearances of antidepressants and their metabolites vary significantly amongst patients as a result. Genetic variations in cytochromes, especially those influencing cytochrome P2D6 and cytochrome P2C19, aid in the elimination of medications. Determining whether these cytochromes metabolize slowly or quickly might be important in situations where their substrates are overdosed. With the growing availability of tests for polymorphisms of important CYP enzymes, the effect of pharmacogenetics on medication clearance in overdose is an intriguing research topic [25]. A case report details the effective use of Continuous Veno-venous Hemodiafiltration (CVVHDF) in conjunction with normal protocols to treat a severe amitriptyline intoxication. Hemodialysis and hemofiltration are utilized in CVVHDF, a kind of renal replacement therapy, to address electrolyte abnormalities. A high level of ultrafiltration is applied to the blood during this procedure, which improves the transfer of water and other solutes from the blood into the dialysate. Regular infusions are often necessary to restore lost volume when water is lost [39].

CONCLUSION

Acute intoxication with antidepressants, particularly TCAs can lead to severe cardiovascular toxicity, including arrhythmias, refractory hypotension, and myocardial depression. Symptoms often manifest as sinus tachycardia, intraventricular conduction delays, and prolonged QRS duration. In clinical practice, various serum biomarkers are suggested for the diagnosis of antidepressant-induced cardiotoxicity. Management includes early intervention with intravenous sodium bicarbonate, benzodiazepines for seizures, and activated charcoal. Intravenous lipid emulsion therapy can mitigate toxicity. Identifying genetic polymorphisms in cytochrome enzymes can help tailor treatments for overdoses.

Conflicts of interest:

No conflicts of interest exist.

Financial Disclosure

There are no financial conflicts of interest to disclose

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