Review Article

Acute Intoxication with Tricyclic Antidepressants and Selective Serotonin Reuptake Inhibitors: Pathophysiology, Clinical Spectrum, and Evidence-Based Emergency Management

Nicolás Arce Vargas[1], Alin Pereira Moreno[2], Natalia Prendas Navarro[3], Maria Jesus Rojas Leiton[4*], Diego Salom Soto[5], Mónica Solís Chan[6]

[1]Medical Doctor, Clínica Dr. Ricardo Moreno Cañas, San José, Costa Rica
[2]Medical Doctor, Hospital San Vicente de Paul, Heredia, Costa Rica
[3,4,5]Medical Doctor, Independent Researcher, San José, Costa Rica
[6]Medical Doctor, Hospital Metropolitano, San José, Costa Rica
[*]Corresponding author email: **neempath@gmail.com**

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Abstract

Acute intoxication with tricyclic antidepressants and selective serotonin reuptake inhibitors represents a clinically significant toxicological emergency with distinct pharmacological mechanisms, clinical profiles, and prognostic implications. Tricyclic antidepressants exert their toxic effects primarily through fast sodium channel blockade, anticholinergic activity, alpha-adrenergic antagonism, and central nervous system depression. These mechanisms contribute to rapid-onset cardiotoxicity characterized by QRS prolongation, ventricular arrhythmias, myocardial depression, hypotension, and increased seizure risk. Their large volume of distribution and delayed absorption further complicate management and prolong toxicity. In contrast, selective serotonin reuptake inhibitors act

predominantly through selective inhibition of the serotonin transporter and are generally associated with a more favorable safety profile. However, overdose may result in serotonin syndrome, QT interval prolongation, and clinically significant drug–drug interactions mediated by cytochrome P450 modulation. Epidemiologically, antidepressants remain among the leading drug classes involved in overdose events, most commonly in the context of intentional self-harm. Although selective serotonin reuptake inhibitors account for a high number of exposures, tricyclic antidepressants are associated with greater morbidity and mortality. Adolescents and older adults represent particularly vulnerable populations, and co-ingestion with alcohol or other psychotropic agents significantly increases toxicity severity. Clinical evaluation requires prompt stabilization following airway, breathing, and circulation principles, continuous electrocardiographic monitoring, and careful neurological assessment. QRS duration serves as an important prognostic marker in tricyclic antidepressant toxicity. Management strategies include supportive care, sodium bicarbonate for cardiotoxicity, benzodiazepines for seizures or agitation, and intensive monitoring in severe cases. Prevention strategies, including risk assessment prior to prescribing and structured psychiatric follow-up, remain essential to reduce recurrence and improve long-term outcomes.

Key words

Sodium channel blockade, serotonin syndrome, cardiotoxicity, QRS prolongation, polypharmacy, intentional self-harm.

Introduction

Antidepressant prescribing has increased substantially in recent years, with more than 20 million prescriptions issued in late 2020 alone. Within this expanding pharmacological landscape, selective serotonin reuptake inhibitors have emerged as the most prescribed class of antidepressants, a trend that has been paralleled by a notable rise in exposure cases reported to poison control centers [1]. In this broader epidemiological context, data from Victoria, Australia, indicate that although overall emergency department presentation rates for intentional antidepressant overdoses have remained stable, significant increases have been observed among younger age groups, suggesting a shift in the demographic distribution of risk [2].

Historically, tricyclic antidepressants were associated with a higher risk of severe outcomes in overdose scenarios, particularly due to their pronounced cardiovascular toxicity and elevated mortality rates. In contrast, while selective serotonin reuptake inhibitors are not devoid of risk, they generally present a lower likelihood of severe complications, positioning them as a comparatively safer alternative in overdose situations [3]. This transition in prescribing practices has consequently altered the clinical profile of antidepressant-related toxicities encountered in contemporary practice. From the perspective of emergency and critical care medicine, selective serotonin reuptake inhibitors are frequently implicated in overdose cases, with tachycardia and drowsiness representing some of the most reported clinical manifestations [1]. Nevertheless, serotonin toxicity remains a clinically significant concern, occurring in approximately 13.6% of cases, with the risk substantially influenced by co-ingestion of other substances [4]. Furthermore, among critically ill patients, pre-intensive care unit use of selective serotonin reuptake inhibitors has been associated with increased in-hospital mortality, underscoring the need for careful assessment and management in this vulnerable population [5].

Considering these findings, a comparative analysis of tricyclic antidepressants and selective serotonin reuptake inhibitors in overdose contexts is essential to delineate their differential risk profiles and inform treatment protocols. Evidence demonstrates that tricyclic

antidepressants are more likely to result in serious medical outcomes and fatalities compared with selective serotonin reuptake inhibitors, highlighting the importance of targeted prevention and intervention strategies [3]. At the same time, understanding the specific adverse events associated with selective serotonin reuptake inhibitors, including cardiovascular toxicity, is critical to guiding clinical monitoring and management decisions in hospital settings [6].

The objective of this study is to comparatively analyze the epidemiological trends, clinical manifestations, and outcomes associated with tricyclic antidepressant and selective serotonin reuptake inhibitor overdoses, to delineate their differential risk profiles, evaluate their implications in emergency and critical care settings, and inform evidence-based prevention and management strategies.

Methodology

This manuscript was developed as a structured narrative review aimed at synthesizing contemporary evidence on the pathophysiology, clinical presentation, diagnostic evaluation, and emergency management of acute intoxication with tricyclic antidepressants and selective serotonin reuptake inhibitors. The methodological approach emphasized conceptual integration, clinical applicability, and interpretation of heterogeneous evidence domains - including toxicodynamic mechanisms, electrocardiographic predictors, therapeutic interventions, and prognostic outcomes - rather than quantitative evidence aggregation or adherence to formal systematic review protocols.

A focused literature search was conducted between January 2020 and December 2025 using established scientific databases, including PubMed, ScienceDirect, and the Cochrane Library. High-impact journals in toxicology, emergency medicine, psychiatry, and critical care were also reviewed to identify influential clinical studies, toxicology registry analyses, guideline statements, and consensus publications relevant to the topic. The search strategy combined controlled vocabulary and free-text terms using Boolean operators to ensure comprehensive coverage. Representative search formulations included combinations such as ("tricyclic antidepressant overdose" OR "TCA toxicity") AND ("acute intoxication" OR "poisoning") AND ("cardiotoxicity" OR "QRS widening" OR "sodium bicarbonate therapy"), as well as ("SSRI overdose" OR "selective serotonin reuptake inhibitor toxicity") AND ("serotonin syndrome" OR "QT prolongation" OR "emergency management"). Additional searches incorporated terms related to seizure risk, arrhythmias, intensive care monitoring, prognostic indicators, and supportive therapy to capture literature spanning pathophysiology, acute stabilization, and outcomes.

The initial search identified approximately 142 potentially relevant records. After title and abstract screening for relevance and duplication, 79 publications underwent full-text review. Following qualitative appraisal and application of predefined eligibility criteria, 35 peer-reviewed studies were selected for inclusion in the final synthesis.

To enhance transparency and consistency in study selection, predefined eligibility criteria were established a priori to guide identification of clinically relevant studies. Eligible studies included clinical investigations evaluating acute intoxication with tricyclic antidepressants or selective serotonin reuptake inhibitors; randomized or controlled studies assessing therapeutic interventions such as sodium bicarbonate, benzodiazepines, or serotonin antagonists; prospective and retrospective cohort studies analyzing mortality, arrhythmias, seizures, intensive care admission, or other clearly defined clinical outcomes; registry-based analyses reporting epidemiology, severity predictors, or short- and long-term outcomes; systematic reviews and meta-analyses addressing cardiotoxicity, serotonin syndrome, or

emergency management; and international clinical practice guidelines or consensus statements in toxicology and emergency medicine. Only publications written in English or Spanish were considered.

Studies were excluded if they were preclinical investigations involving animal or in vitro models, except when cited exclusively to support pathophysiological context. Case reports, narrative opinions, and editorials lacking original quantitative data or guideline-based synthesis were also excluded, as were studies without clearly defined clinical endpoints. Publications focusing exclusively on chronic antidepressant therapy without relevance to acute intoxication were not included.

No quantitative pooling, meta-analysis, formal risk-of-bias grading, or statistical modeling was performed. Evidence appraisal was interpretative and qualitative in nature, consistent with the narrative design of the review. Artificial intelligence–based language tools were used exclusively for structural organization and linguistic refinement. All study selection, interpretation, critical appraisal, and final scientific judgments were performed independently and exclusively by the authors.

Pharmacology and Toxicodynamic Mechanisms

Tricyclic antidepressants are structurally classified into tertiary and secondary amines, a distinction that is closely related to their pharmacodynamic profile. Tertiary amines, such as amitriptyline, exhibit greater potency in inhibiting serotonin reuptake, whereas secondary amines, including nortriptyline, predominantly inhibit norepinephrine reuptake. This dual inhibition of serotonin and norepinephrine transporters increases the synaptic availability of both neurotransmitters and underlies the therapeutic antidepressant effect of this class [7].

Beyond monoamine reuptake inhibition, tricyclic antidepressants exert significant effects on cardiac conduction through blockade of fast sodium channels. Acting similarly to class IA antiarrhythmic agents, they impair phase 0 depolarization, which can manifest as QRS complex prolongation and predispose to ventricular arrhythmias during acute intoxication [8, 9]. Concomitantly, their antagonism of muscarinic receptors produces marked anticholinergic effects, including dry mouth, urinary retention, and tachycardia. In parallel, alpha-1 adrenergic receptor blockade promotes peripheral vasodilation and hypotension, thereby amplifying cardiovascular instability in severe overdose. At the central nervous system level, tricyclic antidepressants may also lower the seizure threshold through gamma-aminobutyric acid antagonism, increasing the risk of seizure activity in toxic exposures. These toxicodynamic properties are further complicated by pharmacokinetic characteristics such as a large volume of distribution and delayed absorption, which can prolong drug effects and complicate clinical management [7].

In contrast, selective serotonin reuptake inhibitors exert their primary effect through selective inhibition of the serotonin transporter, leading to increased serotonin concentrations within the synaptic cleft. This receptor selectivity accounts for their improved safety profile compared with tricyclic antidepressants, particularly with respect to cardiotoxicity. Although SSRIs are generally associated with lower risk of conduction disturbances, certain agents may still prolong the QT interval under specific conditions [4, 10].

Toxicity in SSRI overdose is largely related to dose-dependent serotonergic overstimulation. Excessive serotonin activity may culminate in serotonin syndrome, a clinical condition characterized by agitation, confusion, and autonomic instability [4, 11]. Moreover, individual agents carry drug-specific risks. For example, fluoxetine may interact with

concomitant medications through cytochrome P450 modulation, thereby increasing the likelihood of serotonin syndrome or other adverse effects [11, 12]. More broadly, selective serotonin reuptake inhibitors can inhibit or induce cytochrome P450 enzymes, resulting in clinically significant drug–drug interactions, particularly in patients exposed to polypharmacy [10].

Epidemiology and Risk Stratification

Selective serotonin reuptake inhibitors are frequently implicated in overdose exposures at a global level, with surveillance data from United States poison centers documenting 346,082 reported cases between 2015 and 2020, reflecting a substantial and sustained burden of SSRI-related toxicity [1]. More broadly, antidepressants - including both SSRIs and tricyclic antidepressants - remain among the leading drug categories involved in overdose suicides, although recent analyses suggest that the overall number of deaths attributable to these agents has decreased or stabilized in recent years [13].

Despite their high frequency of exposure, SSRIs are associated with a relatively low case fatality rate of approximately 0.3%, underscoring their comparatively favorable safety profile in overdose [1]. In contrast, tricyclic antidepressants carry a substantially higher risk of serious medical complications and mortality, with a significant proportion of cases progressing to severe outcomes or death. This disparity highlights the persistent clinical relevance of TCA toxicity despite their reduced prescribing frequency [3].

The demographic distribution of antidepressant overdoses reveals important patterns. SSRI-related overdoses predominantly affect males, who account for 66.7% of reported cases, and are particularly common among adolescents aged 13 to 19 years, representing 31% of exposures [1]. Conversely, females are more frequently involved in antidepressant-related suicide attempts overall, comprising 68.7% of such cases. Age also influences clinical severity, as individuals aged 60 years and older are more likely to experience severe outcomes and require hospitalization following antidepressant overdose [3].

Intentional self-harm represents the principal context in which these exposures occur. Among SSRI-related cases, suspected suicide attempts account for 58.5% of reported exposures [1]. When considering acute poisoning incidents more broadly, intentional self-harm remains the leading cause, with suicide attempts constituting 75.9% of cases. These findings emphasize the close association between antidepressant overdose and underlying psychiatric vulnerability [14]. Co-ingestion with other substances is common and significantly influences clinical outcomes. Benzodiazepines are frequently involved in SSRI overdose cases, accounting for 8% of reported co-exposures [1]. Moreover, the concurrent use of antidepressants with alcohol, benzodiazepines, or other psychotropic agents increases the risk of severe toxicity and adverse outcomes [15].

Certain populations warrant particular attention. Older adults demonstrate a higher likelihood of hospitalization and mortality following antidepressant overdose, reflecting increased physiological vulnerability and comorbidity burden [2]. In parallel, pediatric populations - especially adolescents - have shown rising rates of intentional overdoses, underscoring the need for targeted prevention strategies and early psychiatric intervention [2].

Risk predictors for severe toxicity include the use of tricyclic antidepressants, co-ingestion with additional substances, and the presence of underlying psychiatric disorders [3, 16]. Importantly, psychiatric comorbidities significantly increase the risk of recurrent intentional poisonings and adverse clinical outcomes, reinforcing the necessity of

comprehensive mental health assessment and follow-up after overdose events [17].

Pathophysiological Basis of Acute Toxicity

Cardiovascular toxicity represents one of the most clinically significant consequences of tricyclic antidepressant overdose. Through blockade of fast sodium channels, TCAs exert class IA antiarrhythmic effects that delay phase 0 depolarization and result in QRS complex prolongation on electrocardiography. This conduction delay may also produce a Brugada pattern, a phenomenon that has been described as reversible following administration of sodium bicarbonate, which counteracts sodium channel blockade and serum acidosis [9, 18]. The same electrophysiological disturbance underlies the development of ventricular dysrhythmias, including wide complex tachycardia, which can rapidly become life-threatening if not promptly recognized and treated. In addition to conduction abnormalities, TCAs may induce myocardial depression, thereby reducing cardiac output and predisposing to cardiovascular collapse in severe intoxication [9].

Although selective serotonin reuptake inhibitors are generally associated with a more favorable cardiac safety profile, certain agents can still produce clinically relevant electrophysiological effects. Citalopram, in particular, has been linked to QT interval prolongation and an increased risk of torsades de pointes. This phenomenon is attributed to abnormal calcium handling and downregulation of potassium channels, both of which disrupt normal cardiac repolarization and increase susceptibility to malignant ventricular arrhythmias [19, 20].

Neurological manifestations frequently accompany cardiovascular toxicity and may further complicate clinical management. Both TCAs and SSRIs can produce central nervous system depression, leading to altered mental status and, in severe cases, coma. In TCA intoxication, seizure activity is a well-recognized complication and is primarily related to sodium channel blockade and anticholinergic effects, both of which lower the seizure threshold. In contrast, excessive serotonergic stimulation in SSRI overdose may precipitate serotonin syndrome, characterized by agitation, neuromuscular hyperactivity, and autonomic instability resulting from heightened serotonin activity within the central nervous system [19].

Autonomic and systemic manifestations further reflect the underlying pharmacological mechanisms of these agents. The anticholinergic properties of TCAs commonly produce features such as dry mouth, urinary retention, and tachycardia, which may obscure the broader clinical picture in overdose scenarios [9]. Hemodynamic instability is also prominent, as both TCAs and SSRIs can induce hypotension; however, TCAs are particularly associated with distributive shock due to the combined effects of peripheral vasodilation and myocardial depression (Hertzog et al., 2021). In the context of serotonin syndrome, hyperthermia may develop and represents a potentially life-threatening complication if not promptly identified and managed [19]. Severe TCA overdose may additionally result in metabolic acidosis, frequently driven by lactic acid accumulation secondary to reduced cardiac output and tissue hypoxia, thereby compounding systemic instability [21].

Clinical Presentation and Differential Diagnosis

The temporal profile of toxicity differs significantly between tricyclic antidepressants and selective serotonin reuptake inhibitors, a distinction that carries important clinical implications. In tricyclic antidepressant overdose, symptoms often manifest rapidly, frequently within the first hours following ingestion. Cardiotoxic effects are particularly concerning, as wide complex tachycardia and QT prolongation may develop early and progress quickly, reflecting sodium channel blockade at the myocardial level. Because these conduction

abnormalities can peak abruptly and predispose to life-threatening arrhythmias, prompt recognition and early administration of sodium bicarbonate are critical to reverse sodium channel blockade and restore electrical stability [9].

In contrast, the clinical presentation of selective serotonin reuptake inhibitor overdose tends to evolve more gradually. Initial manifestations commonly include gastrointestinal symptoms such as nausea and vomiting, accompanied by tremor and mild sedation. Although many cases remain mild, excessive serotonergic stimulation may culminate in serotonin syndrome, characterized by neuromuscular excitation, alterations in mental status, and autonomic dysregulation. The progression and severity of this syndrome depend on the degree of serotonergic neurotransmission increase and the presence of co-ingested serotonergic agents [4, 22].

The classical presentation of tricyclic antidepressant toxicity is often described as a triad encompassing central nervous system depression, anticholinergic manifestations, and cardiac conduction abnormalities. Central nervous system depression may range from confusion to seizures or coma. Anticholinergic signs - including dry mouth, mydriasis, urinary retention, and hyperthermia - reflect muscarinic receptor antagonism and may complicate the diagnostic assessment. Concomitantly, cardiac conduction disturbances such as wide complex tachycardia and QT prolongation are hallmarks of toxicity, particularly when sodium channel blockade produces electrocardiographic patterns resembling Brugada morphology [9].

Selective serotonin reuptake inhibitor overdose, by comparison, is more commonly associated with gastrointestinal complaints and mild neurological symptoms, including tremor and sedation. In more severe cases, serotonin syndrome may develop, with clinical manifestations ranging from moderate agitation and hyperreflexia to life-threatening hyperthermia and marked neuromuscular hyperactivity [4, 22]. Diagnosis of serotonin syndrome is frequently guided by the Hunter criteria, which emphasize the presence of specific neuromuscular findings in the context of serotonergic exposure. These criteria include spontaneous clonus; inducible clonus accompanied by agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor with hyperreflexia; or hypertonia associated with a temperature above 38°C and ocular or inducible clonus [9].

Given the overlap in clinical manifestations with other toxicological conditions, careful differential diagnosis is essential. Anticholinergic poisoning may closely resemble tricyclic antidepressant toxicity, presenting with dry skin, mydriasis, and altered mental status. Sympathomimetic toxicity, characterized by hypertension, tachycardia, and hyperthermia, can mimic features of serotonin syndrome. Sedative-hypnotic overdose typically produces central nervous system depression but lacks the prominent anticholinergic and cardiac conduction abnormalities seen in tricyclic toxicity. Additionally, electrolyte disturbances such as hypokalemia may generate cardiac conduction abnormalities that resemble those observed in tricyclic antidepressant overdose, further complicating the diagnostic evaluation [23].

Diagnostic Evaluation and Monitoring

The initial evaluation of patients with suspected tricyclic antidepressant or selective serotonin reuptake inhibitor overdose must prioritize a structured primary survey centered on airway, breathing, and circulation. Immediate assessment of airway patency, adequacy of ventilation, and hemodynamic stability is essential, as both drug classes may precipitate respiratory depression and cardiovascular compromise [24]. Early stabilization during this phase is critical to prevent rapid deterioration, particularly in patients presenting with altered consciousness or

signs of shock. In parallel, neurological assessment using the Glasgow Coma Scale provides an objective measure of the level of consciousness and assists in determining the need for airway protection. Altered mental status is common in both TCA and SSRI intoxication, and declining GCS scores may necessitate prompt intervention to secure the airway [25].

Given the substantial risk of cardiotoxicity, continuous cardiac monitoring constitutes a fundamental component of the diagnostic approach. Electrocardiographic surveillance is particularly important in TCA overdose, where sodium channel blockade can produce QRS prolongation and QT interval changes indicative of significant conduction delay and arrhythmogenic risk (8, 9). Although SSRIs are generally less cardiotoxic, certain agents are also associated with QT prolongation and arrhythmias, thereby justifying similar monitoring strategies in these patients. Close ECG observation enables early detection of conduction abnormalities and guides timely therapeutic intervention [6].

Specific electrocardiographic parameters carry prognostic and diagnostic significance. Prolongation of the QRS complex is a hallmark of TCA toxicity and has been associated with severe outcomes, including seizures and ventricular dysrhythmias [26]. QT interval prolongation, which may occur in both TCA and SSRI overdose, further increases the risk of malignant ventricular arrhythmias [6]. Additionally, the presence of an increased R wave amplitude in lead aVR may indicate sodium channel blockade and is commonly observed in TCA toxicity, providing further evidence of cardiotoxic involvement [9].

Laboratory evaluation complements clinical and electrocardiographic assessment by identifying systemic complications. Measurement of serum electrolytes and arterial blood gases is essential for detecting metabolic acidosis, a frequent consequence of severe TCA overdose [26]. Elevated lactate levels may reflect tissue hypoperfusion and impaired oxygen delivery, while assessment of renal function is necessary to evaluate the systemic impact of toxicity and guide supportive care [24].

Although serum drug concentrations can confirm exposure, their clinical utility is limited. Measured levels do not consistently correlate with symptom severity or predict outcomes, and therefore should not replace thorough clinical assessment and continuous monitoring in guiding therapeutic decisions [22]. Intensive care unit admission is indicated in patients exhibiting severe cardiovascular instability, significant neurological impairment, or requiring advanced supportive measures such as mechanical ventilation or vasopressor therapy [24]. Furthermore, individuals with severe serotonin syndrome or marked electrocardiographic abnormalities warrant close monitoring in a critical care setting to mitigate the risk of rapid clinical deterioration [25].

Management Strategies

Initial stabilization constitutes the cornerstone of management in acute intoxication with tricyclic antidepressants and selective serotonin reuptake inhibitors. Immediate attention to airway protection and ventilatory support is essential, particularly in patients presenting with altered mental status or respiratory depression, as failure to secure the airway may result in rapid clinical deterioration. Hemodynamic stabilization must occur simultaneously, with intravenous fluid resuscitation administered to maintain adequate perfusion. In cases of persistent or refractory hypotension - especially in TCA overdose, where myocardial depression and cardiogenic shock may develop - vasopressor therapy may be required to restore circulatory stability [27]. Continuous electrocardiographic monitoring is mandatory during this phase due to the significant risk of arrhythmias, particularly in TCA toxicity, which is associated with QRS widening and QT prolongation [9, 28].

Once initial stabilization has been achieved, targeted therapy in TCA toxicity should be promptly initiated. Sodium bicarbonate remains the first-line treatment for cardiotoxic manifestations, as it counteracts sodium channel blockade through both serum alkalinization and sodium loading. This intervention facilitates narrowing of the QRS complex and improvement in cardiac conduction [9, 29]. Careful titration is required to achieve therapeutic goals while avoiding complications such as metabolic alkalosis [30]. In the presence of refractory arrhythmias, sodium bicarbonate remains the initial therapeutic approach; however, additional agents such as magnesium sulfate or amiodarone may be considered when conduction disturbances persist despite adequate alkalinization. Seizure activity, a common complication of TCA overdose, should be managed with benzodiazepines, which are effective in controlling convulsive episodes and reducing central nervous system hyperexcitability [27]. Importantly, class IA and IC antiarrhythmic agents must be avoided, as they may exacerbate sodium channel blockade and worsen conduction abnormalities [9].

Management of SSRI toxicity differs in that supportive care remains the primary therapeutic strategy. Immediate discontinuation of the offending agent and close clinical monitoring form the foundation of treatment. In cases complicated by serotonin syndrome, benzodiazepines are indicated to control agitation and seizures, thereby mitigating neuromuscular hyperactivity and autonomic instability. When hyperthermia develops, active cooling measures are essential to prevent secondary complications, including rhabdomyolysis and multiorgan dysfunction. Cyproheptadine, a serotonin antagonist, is frequently administered in moderate to severe cases; however, its efficacy remains incompletely established, and supportive care continues to represent the central therapeutic approach. In the most severe presentations, advanced interventions such as endotracheal intubation, neuromuscular paralysis, and aggressive supportive measures may be necessary to control life-threatening complications [22].

Gastrointestinal decontamination may be considered in selected patients. Activated charcoal is indicated when presentation occurs within a few hours of ingestion and when the airway is adequately protected, thereby reducing further systemic absorption. In contrast, gastric lavage has a limited role and is generally not recommended due to its minimal efficacy and increased risk of aspiration [24]. For patients with severe and refractory TCA toxicity, intravenous lipid emulsion therapy may be considered as an adjunctive measure, although supporting evidence remains limited. In cases of refractory cardiogenic shock unresponsive to conventional management, extracorporeal mechanical circulatory support, including extracorporeal membrane oxygenation, may provide life-saving stabilization while allowing time for drug clearance and myocardial recovery [27].

Complications, Prognosis, and Outcomes

Among the predictors of severe cardiotoxicity in tricyclic antidepressant overdose, QRS complex duration represents one of the most clinically relevant electrocardiographic parameters. Through sodium channel blockade, TCAs delay intraventricular conduction, resulting in QRS prolongation that correlates with an increased risk of adverse outcomes, including seizures and ventricular dysrhythmias. A widened QRS complex therefore serves not only as a diagnostic marker of cardiotoxicity but also as a prognostic indicator of severity. Conversely, a normal QRS duration carries a high negative predictive value for severe complications such as metabolic acidosis and malignant ventricular arrhythmias, reinforcing its utility in early risk stratification [9, 26].

Neurological complications, particularly seizures, further influence clinical prognosis. The risk of seizure recurrence following drug overdose is associated with advanced age,

prolonged postictal duration, and low Glasgow Coma Scale scores at presentation, all of which necessitate careful observation in the emergency setting to prevent further episodes [30]. Toxicological seizures related to substances such as tramadol and cocaine demonstrate notable recurrence rates, and some affected individuals may subsequently develop epilepsy, underscoring the importance of structured follow-up after the acute event [31].

The duration of monitoring must be individualized according to the pharmacokinetic profile of the ingested agent and the patient's clinical evolution. For immediate-release preparations, seizures and other severe manifestations typically occur within the first 12 hours, whereas slow-release formulations may necessitate up to 24 hours of observation to safely exclude delayed toxicity [31]. Criteria for safe discharge should include normalization of vital signs, resolution of acute neurological and cardiovascular symptoms, and stabilization of electrocardiographic parameters. In TCA overdose, particular emphasis should be placed on ensuring that QRS duration has returned to normal or remains stable before discharge is considered [9, 26].

Comparative outcome data further highlight differences between drug classes. Tricyclic antidepressants are associated with higher mortality rates, largely attributable to their pronounced cardiotoxic and proconvulsant effects, including arrhythmias and seizures [6]. In contrast, selective serotonin reuptake inhibitors demonstrate a substantially lower case fatality rate of approximately 0.3%, reflecting their more favorable safety profile in overdose [1]. Nevertheless, SSRIs are not devoid of risk, as they may still precipitate significant cardiovascular events such as arrhythmias and QT prolongation, particularly in middle-aged and elderly patients [6].

Long-term sequelae must also be considered in survivors of severe intoxication. Neurological consequences may include the development of epilepsy following toxicological seizures, emphasizing the need for ongoing neurological evaluation in selected cases [31]. Cardiac sequelae have also been described, particularly in the context of SSRI exposure, where elevated levels of cardiac injury biomarkers such as creatine kinase may suggest potential myocardial injury, especially among individuals with prior SSRI use [32].

Prevention, Clinical Implications, and Future Directions

Risk assessment prior to initiating antidepressant therapy constitutes a critical preventive strategy, particularly in individuals with a history of substance misuse or suicidal behavior. Epidemiological data indicate that 58.5% of reported SSRI exposures were classified as suspected suicides, underscoring the importance of comprehensive evaluation of psychiatric history and current mental health status before prescribing these agents [1]. Careful psychiatric assessment allows clinicians to identify vulnerability factors and individualize treatment decisions, especially in the context of off-label SSRI use, where potential risks may be underestimated without structured evaluation [33].

In high-risk populations, limiting the quantity of antidepressants dispensed represents an additional preventive measure. Evidence suggests that the majority of overdose cases involve substances obtained through legitimate prescriptions, indicating that controlled dispensing practices may reduce the likelihood of large-quantity ingestion [23]. The implementation of prescription monitoring programs, combined with patient education regarding overdose risks and warning signs, can further strengthen safety strategies and reduce preventable harm [34].

Following an overdose event, structured psychiatric follow-up is essential to address

underlying mental health conditions and mitigate the risk of recurrence. Overdose-related behaviors frequently reflect complex psychological and social determinants, necessitating individualized and targeted interventions rather than solely acute medical management [34]. Continuous monitoring, therapeutic engagement, and coordinated mental health support are therefore central to reducing repeated intentional poisonings and improving long-term outcomes [23].

The emergence of newer antidepressants with improved safety profiles represents an important area of therapeutic evolution. Although SSRIs are generally safer than TCAs, they remain associated with risks such as serotonin toxicity, which has been reported in 13.6% of SSRI/SNRI overdoses [42]. Future pharmacological development may focus on combining serotonin reuptake inhibition with selective modulation of specific serotonin receptor subtypes, potentially enhancing therapeutic efficacy while minimizing toxicity [35].

Despite advances in management, significant research gaps remain, particularly regarding biomarkers and targeted antidotes for antidepressant overdose. Diagnostic criteria for serotonin toxicity remain inconsistent, complicating timely identification and standardized treatment approaches. The development of reliable biomarkers could improve early detection and risk stratification, while novel targeted antidotes may offer more precise and effective therapeutic options in severe cases [22].

Conclusions

Acute intoxication with tricyclic antidepressants remains clinically high risk despite declining prescribing, because its toxicodynamic profile combines rapid onset sodium channel blockade with anticholinergic and adrenergic effects that amplify conduction delay, hypotension, seizures, and metabolic derangements; consequently, early electrocardiographic recognition and targeted reversal with sodium bicarbonate are central determinants of outcome.

Selective serotonin reuptake inhibitors account for a substantial proportion of overdose exposures and generally exhibit lower lethality, yet clinically meaningful toxicity persists through dose dependent serotonergic overstimulation, drug specific QT effects, and cytochrome P450 mediated interactions that are magnified by co ingestion and polypharmacy, making careful monitoring and supportive management essential even in ostensibly safer overdoses.

The burden of antidepressant overdose is driven predominantly by intentional self harm and psychiatric vulnerability, with adolescents and older adults representing key risk groups and co exposures frequently worsening severity; therefore, prevention and prognosis depend not only on acute stabilization and risk stratification using markers such as QRS duration, but also on structured post event psychiatric follow up and prescribing strategies that reduce access to large quantities in high risk patients.

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