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Clinical Toxicology of Sodium Channel Blockers: An Evidence-Based Review for Pharmacists

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Abstract

Background: Sodium channel blockers are widely used in cardiology, neurology, and pain management, but their toxicity poses significant risks, including life-threatening arrhythmias and seizures. Understanding their toxicology is essential for pharmacists and clinicians.
Aim: To provide an evidence-based review of the clinical toxicology, pathophysiology, and management strategies for sodium channel blocker toxicity.
Methods: A comprehensive literature review was conducted, synthesizing data from toxicology reports, pharmacologic studies, and clinical guidelines. Epidemiologic trends, mechanistic insights, and therapeutic interventions were analyzed to inform best practices.
Results: Toxicity commonly arises from intentional overdose, medication errors, or drug interactions. Clinical manifestations include QRS widening, ventricular dysrhythmias, seizures, and metabolic acidosis. Tricyclic antidepressants and Class I antiarrhythmics are prominent culprits, with mortality rates reaching 22.5% for antiarrhythmic overdoses. Sodium bicarbonate therapy remains the cornerstone of treatment, effectively reversing conduction abnormalities through alkalinization and sodium loading. Adjunctive measures include hypertonic saline, lipid emulsion for local anesthetic toxicity, and extracorporeal membrane oxygenation (ECMO) in refractory cases. Prevention strategies emphasize safe prescribing, procedural safeguards, and patient education.
Conclusion: Sodium channel blocker toxicity is a high-risk, multisystemic emergency requiring rapid recognition and aggressive intervention. Early ECG monitoring, timely bicarbonate therapy, and coordinated interprofessional care significantly improve outcomes.
Keywords: Sodium channel blockers, toxicity, tricyclic antidepressants, antiarrhythmics, sodium bicarbonate, lipid emulsion, ECMO, clinical toxicology

Introduction

Medications that exert their therapeutic effects, in whole or in part, through blockade of voltage-gated sodium channels occupy a prominent role across multiple clinical disciplines, reflecting the central importance of sodium conductance in excitable tissues. By modulating the initiation and propagation of action potentials, sodium channel–blocking agents can alter myocardial conduction, attenuate peripheral and central nociceptive signaling, and suppress aberrant neuronal firing. Accordingly, this pharmacologic mechanism underpins diverse therapeutic indications ranging from cardiac rhythm control and regional anesthesia to the management of neuropathic pain and selected neuropsychiatric conditions. In broad terms, clinically relevant sodium channel blockers include Vaughan Williams Class I antiarrhythmic agents, local anesthetics, and numerous drugs employed in neuropathic pain and seizure disorders, as well as certain substances of abuse such as cocaine. Within cardiology, Class I antiarrhythmics are subdivided into Classes IA, IB, and IC based on their kinetic effects on sodium channels and their impact on action potential duration. Representative Class IA agents include quinidine and procainamide, whereas Class IB agents include lidocaine, mexiletine, and phenytoin, and Class IC agents include flecainide and propafenone.

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Beyond antiarrhythmics, sodium channel blockade is a defining feature of many local anesthetics, contributing to their capacity to produce reversible loss of sensation by preventing nerve depolarization. In neurology and pain medicine, several anticonvulsants—such as carbamazepine and lamotrigine—derive meaningful clinical benefit from sodium channel inhibition, thereby reducing repetitive neuronal firing and stabilizing hyperexcitable membranes. Tricyclic antidepressants (TCAs), though primarily recognized for effects on monoamine reuptake, also exhibit clinically relevant sodium channel blockade, which contributes both to therapeutic properties and to the distinctive toxicity profile associated with overdose. Many TCAs remain in active clinical use in the United States.[1]

Importantly, sodium channel blockade is not confined to traditional categories of antiarrhythmics, anesthetics, and anticonvulsants. Certain beta-adrenergic receptor antagonists—most notably propranolol and acebutolol—also possess "membrane-stabilizing" activity attributable to sodium channel inhibition. Additionally, exposure to selected insecticides has been associated with sodium channel–blocking effects, underscoring that this toxicodynamic mechanism may arise from nonpharmaceutical sources as well. Regardless of intent, toxicity from sodium channel–blocking substances—whether resulting from therapeutic misadventure, drug interactions, or intentional self-harm—can precipitate rapid clinical deterioration, including life-threatening dysrhythmias, seizures, hemodynamic collapse, and death. Given the potential for catastrophic outcomes, a rigorous understanding of the pathophysiology, recognition, and evidence-informed management of toxicity and adverse effects related to sodium channel blockade is essential for optimizing patient safety and improving clinical outcomes.[1]

Etiology

Sodium channel blocker toxicity most commonly arises in the context of intentional overdose, reflecting the wide availability of agents with sodium channel–inhibiting properties and the potentially severe consequences of ingesting supratherapeutic amounts. In many toxicology presentations, deliberate self-poisoning remains the predominant mechanism, particularly with medications that are routinely prescribed for chronic conditions such as depression, neuropathic pain, seizures, or cardiac arrhythmias. Nevertheless, clinicians should recognize that clinically significant toxicity may also develop outside of overt intentional ingestion, and a careful medication history is essential to identify less apparent pathways to excessive exposure. Unintentional toxicity may occur when patients inadvertently increase their dose, misunderstand prescribing instructions, or self-adjust therapy in response to persistent symptoms. Family members or caregivers may also contribute to dosing errors, particularly in pediatric, geriatric, or cognitively impaired patients, where medication administration is shared and complex regimens increase the risk of duplication. In addition, the introduction of a new medication can precipitate toxicity even when the prescribed dose of the sodium channel–blocking agent itself has not changed. Such scenarios may involve pharmacokinetic interactions that alter absorption, hepatic metabolism, or renal clearance, resulting in impaired elimination and accumulation to toxic concentrations. Because many sodium channel–blocking drugs have narrow therapeutic indices, nonlinear kinetics, or active metabolites, even modest changes in elimination kinetics may convert a previously tolerated regimen into an unsuspected toxic exposure [1][2].

Iatrogenic overdose represents another clinically important etiology and is most often linked to medication errors or inadvertent administration of supratherapeutic doses within healthcare settings. This mechanism is particularly relevant to local anesthetics used to facilitate procedures, where dosing is weight-based, and rapid administration, incorrect concentration selection, or failure to account for cumulative dosing can lead to systemic toxicity.[2] In such cases, toxicity may develop abruptly, with neurologic and cardiovascular manifestations emerging shortly after administration. Additional iatrogenic contributors include prescribing errors, compounding inaccuracies, infusion pump programming mistakes, or failure to adjust doses in the setting of hepatic dysfunction, renal impairment, or drug–drug interactions. Accordingly, etiologic assessment should extend beyond intent to include dosing history, recent medication changes, comorbid organ dysfunction, and procedural exposures, as these factors collectively determine risk and guide appropriate prevention strategies.[2]

Epidemiology

Epidemiologic patterns of sodium channel blocker toxicity are shaped by the breadth of agents that possess membrane-stabilizing properties and by the clinical contexts in which these agents are encountered. In contemporary toxicology practice, intentional self-poisoning constitutes a major driver of severe presentations, and it is important to recognize that most deliberate ingestions involve more than one substance. This frequent co-ingestion complicates attribution of clinical findings to a single agent, influences toxidromic expression, and may amplify cardiotoxic and neurotoxic effects when multiple drugs converge on sodium channel blockade or related electrophysiologic pathways. Consequently, case counts and outcomes vary substantially across drug classes, reflecting differences in prescribing prevalence, access, toxicity thresholds, and the likelihood of combination use. Surveillance data illustrate the scale and heterogeneity of reported exposures. According to the 2021 American Association of Poison Centers

National Poison Data System, exposures span a wide range of medication categories and include substantial case volumes for several agents that may exert sodium channel–blocking effects directly or indirectly. Reported exposures included 14,595 cases involving antihistamines with 101 fatalities, 27,541 cases involving beta-adrenergic receptor antagonists with 18 fatalities, and 5,471 cases involving local or topical anesthetics.[3] Tricyclic antidepressants (TCAs), which are clinically notable for their prominent sodium channel blockade and high-risk overdose profile, accounted for 7,781 reported exposures, representing 5.6% of total exposures to all antidepressants; within this group, 42 fatalities were documented.[3] Anticonvulsants that may produce clinically meaningful sodium channel blockade or related conduction disturbances were also prominent, with 6,755 cases involving carbamazepine or oxcarbazepine, 1,374 cases involving phenytoin or fosphenytoin, and 10,863 cases involving lamotrigine.[3] Although these figures primarily represent reported exposures rather than confirmed poisoning events, they provide a useful estimate of the public health burden and highlight which medication classes commonly feature in toxicologic consultations [1][2][3].

Outcomes reported in the broader literature further contextualize the clinical impact of specific agents. For TCA overdoses, published data suggest a high hospitalization rate, reported at 78.7%, underscoring the propensity for clinically significant toxicity and the need for prolonged monitoring in many cases.[4] Despite the severity of potential cardiotoxicity, overall mortality in these reports is comparatively low, with a cited rate of 0.73%, which may reflect improvements in early recognition, resuscitation protocols, and targeted therapy.[4] In contrast, the incidence of systemic toxicity from local anesthetics is generally described as low, with reported estimates ranging from 0.02% to 0.18%.[2][5] This comparatively infrequent occurrence likely relates to procedural safeguards and weight-based dosing practices, although it remains clinically important because onset can be abrupt and consequences potentially catastrophic. Collectively, these epidemiologic observations emphasize that sodium channel blocker toxicity is not a single-entity problem but rather a spectrum of exposures whose frequency and severity depend strongly on the specific agent, context of use, and the common reality of multi-drug ingestion.[2][3][4][5]

Pathophysiology

The toxicodynamic signature of sodium channel blocker exposure is best understood through its effects on excitable membranes, particularly within the myocardium and central nervous system. In the heart, fast voltage-gated sodium channels are the principal determinants of rapid depolarization in atrial and ventricular myocytes as well as in the His–Purkinje network. By contrast, the atrioventricular (AV) node relies predominantly on slower, calcium-dependent depolarization, and therefore sodium channel blockade does not typically exert a primary, direct depressant effect on AV nodal conduction in the same way it does on tissues that depend on fast sodium current. The most clinically consequential electrophysiologic effects instead arise from altered myocyte action potential kinetics. With variable potency and kinetics, Class I antiarrhythmics and other sodium channel–blocking agents reduce both the slope and the amplitude of phase 0 depolarization. This translates into a decreased depolarization rate and a reduction in conduction velocity through sodium-dependent tissue, resulting in delayed impulse propagation across the myocardium. At therapeutic exposures, these properties can be beneficial by interrupting re-entrant circuits and suppressing tachydysrhythmias; however, in overdose they become maladaptive, producing conduction slowing that predisposes to malignant arrhythmias and circulatory failure. Many sodium channel–blocking substances also possess additional receptor-mediated properties that modulate, amplify, or obscure the primary electrophysiologic toxidrome. Anticholinergic effects are particularly relevant because they may increase heart rate, impair thermoregulation, reduce gastrointestinal motility, and produce neuropsychiatric manifestations, thereby complicating clinical interpretation of the observed hemodynamic state.[6] Several non-antiarrhythmic agents with sodium channel blockade—most notably tricyclic antidepressants (TCAs) and some antihistamines, with diphenhydramine as a prominent example—exhibit effects resembling Class IA activity, including conduction slowing that can manifest with widening of depolarization-related intervals and heightened arrhythmogenic potential.[6] Importantly, sodium channel blockade is not an isolated cardiac phenomenon; it often occurs in parallel with systemic metabolic derangements. Severe intoxication can produce a triad of metabolic, cardiac, and neurologic toxicity, with progression to hemodynamic compromise. Reduced cardiac output and impaired perfusion promote tissue hypoxia and lactate generation, while seizures and sustained adrenergic activation further increase metabolic demand. The resultant metabolic acidosis is clinically significant because it can potentiate toxicity: acidemia increases the fraction of protonated drug and may enhance binding to sodium channels in a manner that deepens conduction slowing and further destabilizes the myocardium.[1] This creates a deleterious feedback loop in which shock and acidosis amplify sodium channel blockade, and intensified blockade further worsens shock [1][4][5][6].

Agent-specific pharmacology can meaningfully influence the severity and phenotype of poisoning. Propafenone provides a salient example because, in addition to its sodium channel–blocking effects, it also exhibits β-adrenergic and calcium channel–blocking activity. These additional mechanisms can intensify myocardial depression, producing bradycardia, hypotension, and reduced contractility. In overdose, diminished inotropy may be profound, thereby increasing the risk of acute heart failure and refractory cardiovascular collapse.[6] Such mixed-mechanism agents are clinically important because their presentation may extend beyond pure conduction slowing and include features of combined negative chronotropy and negative inotropy, complicating resuscitation strategies and potentially limiting the physiologic reserve required for recovery. Central nervous system toxicity reflects the ability of many sodium channel blockers to cross the blood–brain barrier and disrupt neuronal excitability through multiple pathways. In addition to direct effects on neuronal sodium channels, several mechanistic interactions have been described that collectively push the nervous system toward instability. These agents may inhibit components of the gamma-aminobutyric acid (GABA) system—an effect notably described with lidocaine—thereby diminishing inhibitory tone and lowering seizure threshold.[6] Additional reported actions include activation of the sodium ouabain-sensitive current, stimulation of serotonin (5-HT)2C receptors, antagonism of histamine H1 receptors, and broad interference with noradrenergic signaling. Through these combined effects, adrenergic stimulation may become prominent, contributing to agitation, tremor, tachycardia, and, at higher exposures, seizures.[6] The pro-convulsant tendency of sodium channel blockers at toxic doses is clinically pivotal because seizures not only represent direct neurologic harm, but also exacerbate metabolic acidosis and catecholamine surges, thereby increasing myocardial oxygen demand and worsening systemic instability. In advanced intoxication, this interplay between neurologic excitation and cardiovascular compromise can precipitate rapid clinical deterioration, making early recognition and supportive intervention essential [6].

Drug–drug interactions can further shape pathophysiology by increasing exposure to one or more cardiotoxic agents or by prolonging their effects through impaired metabolism and clearance. In real-world poisoning events, co-ingestion is common, and even therapeutic co-prescribing may become hazardous when one agent alters the elimination kinetics of another. A clinically instructive example is described in a recent case report in which propafenone delayed metoprolol metabolism through inhibition of cytochrome P450 2D6. The resulting interaction produced more pronounced combined toxicity and, in that case, culminated in cardiovascular collapse.[7] This illustrates a broader principle: sodium channel blockade may coexist with and be amplified by concurrent β-blockade, calcium channel blockade, or other depressant mechanisms, resulting in a toxicity profile that is both more severe and less predictable than would be expected from either medication alone. Finally, certain drug classes that are frequently implicated in sodium channel blocker toxicity display additional receptor and ion-channel effects that complicate the clinical picture. TCAs exemplify this complexity. Although their anticholinergic properties are well recognized and contribute to characteristic peripheral and central manifestations, TCAs may also induce potassium channel blockade, peripheral alpha-adrenergic antagonism, and inhibition of norepinephrine reuptake.[8] Potassium channel effects can influence repolarization and contribute to arrhythmogenic risk, while alpha blockade can worsen hypotension through vasodilation. Inhibition of norepinephrine reuptake may initially augment adrenergic tone yet paradoxically destabilize hemodynamics and CNS function, particularly when combined with anticholinergic delirium and seizure propensity. Collectively, these layered mechanisms help explain why sodium channel blocker toxicity is often multisystemic, why clinical severity may escalate rapidly, and why the phenotype varies markedly across agents and exposures. Understanding this mechanistic interplay provides the conceptual framework for targeted resuscitation strategies and for anticipating complications such as refractory hypotension, malignant dysrhythmias, seizures, and acidosis-mediated worsening of sodium channel blockade.[1][6][7][8]

Toxicokinetics

The toxicokinetic behavior of sodium channel–blocking agents is highly dependent on the specific drug, formulation, and route of exposure, and it often diverges substantially from expected pharmacokinetics at therapeutic dosing. As with many xenobiotics, supratherapeutic ingestion or administration can overwhelm normal absorption, distribution, metabolism, and elimination pathways, creating nonlinear kinetics, prolonged drug persistence, and unpredictable peak effects. These deviations are clinically important because they influence the onset and duration of toxicity, determine monitoring requirements, and shape the selection and timing of decontamination or enhanced elimination strategies. For orally ingested agents, absorption may be delayed or extended by drug-induced effects on gastrointestinal physiology. Medications such as tricyclic antidepressants (TCAs) and many antihistamines exhibit anticholinergic activity, which can reduce gastrointestinal motility and slow gastric emptying. This anticholinergic-mediated ileus may result in delayed absorption, prolonged time to peak concentration, and extended toxicity, particularly when large numbers of tablets are ingested or when sustained-release preparations are involved.[9][10] Clinically, this means that significant deterioration can occur well after presentation, and recurrent or delayed cardiotoxicity and neurotoxicity may emerge despite initially reassuring findings. Furthermore, anticholinergic effects may promote pill bezoar formation or erratic absorption, complicating attempts to predict clinical course from reported ingestion time or initial drug levels [9][10].

TCAs also demonstrate toxicokinetic features that amplify systemic exposure in overdose. Their hepatic first-pass metabolism is saturable; when metabolic capacity is exceeded, a greater fraction of the ingested dose escapes first-pass extraction, leading to a disproportionate increase in bioavailability compared with therapeutic dosing. Consequently, relatively "moderate" increases in dose can produce unexpectedly high circulating concentrations and severe toxicity. In addition, distribution dynamics and protein binding become clinically relevant. Free (unbound) TCA concentration rises when serum pH decreases, in part because acidemia reduces protein binding and increases the pharmacologically active fraction of the drug. This effect has practical implications: metabolic acidosis—whether due to seizures, hypoperfusion, or co-ingestants—can intensify toxicity by increasing the free drug burden and facilitating deeper tissue effects, including enhanced sodium channel blockade. For anticonvulsants with sodium channel–blocking properties, toxicokinetic variability is also prominent and may involve capacity-limited metabolism. Carbamazepine is metabolized predominantly by cytochrome P450 3A4 (CYP3A4) to the active metabolite carbamazepine-10,11-epoxide, and in large overdoses it may exhibit zero-order kinetics, reflecting saturation of metabolic pathways.[11] Under such conditions, elimination proceeds at a relatively fixed rate independent of concentration, thereby prolonging toxicity and increasing the risk of delayed complications. Lamotrigine, by contrast, is primarily cleared through hepatic glucuronidation to lamotrigine-2-N-glucuronide.[12] Although glucuronidation is generally efficient, it may be influenced by patient-specific factors such as hepatic function, age, and co-administered drugs that induce or inhibit glucuronidation, which can alter clearance and prolong exposure during overdose. Local anesthetic toxicity illustrates the critical role of route and local pharmacodynamics in systemic uptake. Agents such as lidocaine and bupivacaine can cause local vasodilation, which increases regional blood flow and thereby enhances systemic absorption from the site of injection. This is particularly relevant when large doses are administered, when injection is inadvertent intravascular, or when highly vascular sites are involved. The concomitant use of epinephrine can counteract vasodilation through vasoconstriction, reducing systemic uptake and lowering peak plasma concentrations, thereby improving procedural safety when used appropriately. Collectively, these principles underscore that toxicokinetics in sodium channel blocker exposure are dynamic and context-dependent, requiring clinicians to anticipate delayed absorption, nonlinear metabolism, and physiologic modifiers such as pH and co-medications when assessing risk and planning monitoring and treatment.[9][10][11][12]

History and Physical

Patients with sodium channel blocker toxicity most often present following an intentional overdose or after an iatrogenic exposure related to medication error or procedural administration. The history obtained at presentation has immediate implications for risk stratification and management, particularly because severe manifestations may occur abruptly and because co-ingestion is common in intentional poisonings. When an overdose is reported, clinicians should obtain the most comprehensive inventory possible of all substances potentially ingested, including prescription drugs, over-the-counter products, and any available "as-needed" medications in the home. This step is critical because multiple agents can produce overlapping cardiotoxic and neurotoxic effects, and because the identification of specific drug classes guides monitoring duration, laboratory evaluation, and targeted therapies. A deliberate high index of suspicion for co-ingestion of common over-the-counter agents—especially acetaminophen and aspirin—is warranted because these may be underreported, may not cause early symptoms, and can significantly alter morbidity if missed. Similarly, the potential use of intoxicants and drugs of abuse should be explored directly, including ethanol, cocaine, and opioids, as these substances can modify mental status, exacerbate respiratory compromise, worsen hemodynamics, or contribute independent toxicologic emergencies. Because history may be unreliable due to altered mentation, stigma, or incomplete information from family or bystanders, collateral sources are often indispensable. Medication lists, pill bottles, and prescription refill histories can clarify likely exposures and estimate dose. Medication reconciliation using the electronic medical record may identify active prescriptions and recent changes, while direct communication with the patient's community pharmacy can confirm dispensing details, quantities obtained, and timing of refills. In procedural settings, a focused review of the administered local anesthetic, concentration, total dose, route, and use of epinephrine can help determine the likelihood of systemic toxicity and the expected time course. Such structured history-taking is not merely descriptive; it directly informs whether delayed toxicity is plausible, whether drug–drug interactions may have impaired elimination, and whether additional toxic syndromes should be anticipated [10][11][12].

A comprehensive physical examination is equally essential, as bedside findings may reveal a toxidrome that narrows the differential and clarifies severity. Particular attention should be directed to mental status and behavior, as these may range from lethargy and confusion to agitation and delirium depending on the agent and co-ingestants. Pupillary size and reactivity can provide important clues, especially when anticholinergic features predominate. Clinicians should evaluate for diaphoresis versus dry skin, as impaired perspiration may suggest anticholinergic poisoning, while profuse sweating is more consistent with sympathetic excess. The absence of axillary sweat—sometimes colloquially referred to as the "toxicologist handshake"—may support anticholinergic toxicity in the appropriate context. Gastrointestinal findings, including decreased or absent bowel sounds, can further corroborate anticholinergic effects and may signal delayed absorption due to slowed gut motility. Neuromuscular tone and movement should be assessed for tremor, muscle rigidity, or hyperreflexia, as these may indicate stimulant toxicity or evolving seizure activity. Cutaneous flushing and elevated core temperature may reflect impaired heat dissipation and central dysregulation, both of which can be prominent in anticholinergic poisoning and may require urgent supportive measures. The expected phenotype varies by exposure. Patients with tricyclic antidepressant or antihistamine toxicity commonly appear lethargic or confused and may alternate between somnolence and agitation, particularly as delirium evolves. They are often tachycardic and demonstrate other anticholinergic features, including mydriasis, reduced perspiration, and hyperthermia. In contrast, cocaine toxicity is more typically characterized by psychomotor agitation and sympathetic upregulation manifested by tachycardia, diaphoresis, hypertension, and frequent complaints of chest discomfort, reflecting both increased adrenergic tone and potential myocardial ischemia. These distinctions are clinically useful because they help differentiate anticholinergic-dominant presentations from stimulant toxidromes, even though both may involve tachycardia and altered mental status [10][11][12].

In iatrogenic toxicity, particularly associated with local anesthetics, the time course is often decisive. Symptoms typically develop rapidly after administration, sometimes within minutes, especially if inadvertent intravascular injection occurs. Patients may initially describe perioral paresthesias, metallic taste, or circumoral numbness, followed by dizziness and progressive alterations in mentation. As exposure worsens, seizures, coma, respiratory depression, and ultimately cardiac arrest may occur secondary to dysrhythmia and myocardial depression. Notably, highly potent local anesthetics such as bupivacaine may produce profound cardiotoxicity with minimal or absent preceding central nervous system symptoms, reducing early warning signs and increasing the need for vigilant monitoring during and immediately after administration. Taken together, meticulous history-taking combined with targeted physical examination provides the clinical scaffold for early recognition, syndromic classification, and timely escalation of care in sodium channel blocker toxicity [10][11][12].

Evaluation

The evaluation of suspected sodium channel blocker toxicity must be prompt, structured, and centered on early identification of life-threatening cardiotoxicity, while simultaneously accounting for the heterogeneity of clinical presentations across different agents. No single pathognomonic physical finding or toxidrome reliably defines sodium channel blockade in all cases, and bedside examination alone cannot exclude clinically significant poisoning. Instead, physical findings are highly substance-dependent and may reflect the combined pharmacology of the ingested drug(s), including anticholinergic, sympathomimetic, β-blocking, or calcium channel–blocking effects. This variability has practical implications: for example, patients with tricyclic antidepressant ingestion often present with tachycardia, frequently driven by anticholinergic activity and catecholaminergic responses, whereas overdoses involving comparatively "pure" sodium channel–blocking agents may manifest with marked bradycardia due to direct depression of myocardial excitability and conduction.[13] Accordingly, clinical assessment should emphasize physiologic stability and objective cardiopulmonary evaluation rather than reliance on a single toxidromic label. An immediate electrocardiogram (ECG) is essential for all patients in whom sodium channel blocker toxicity is suspected, as electrophysiologic abnormalities are among the earliest and most prognostically significant indicators of severe poisoning.[13] Sodium channel blockade slows phase 0 depolarization in fast-conducting cardiac tissues, resulting in delayed intraventricular conduction and, classically, widening of the QRS complex. Progressive toxicity may be associated with additional repolarization abnormalities, including QT interval prolongation, which increases susceptibility to malignant ventricular dysrhythmias. ECG changes that may be observed include QRS widening, QT lengthening, a new right axis deviation, and the emergence of bradydysrhythmias. The spectrum of life-threatening rhythm disturbances includes ventricular tachycardia, ventricular fibrillation, and torsades de pointes.[13] These findings are not merely diagnostic; they inform urgency, dictate continuous cardiac monitoring, and guide therapeutic decisions aimed at reversing conduction delay and preventing sudden cardiovascular collapse [13].

Beyond conventional conduction and repolarization changes, acute sodium channel blocker toxicity may also produce Brugada phenocopy—an

ECG pattern resembling congenital Brugada syndrome but triggered by reversible conditions, including drug-induced sodium channel blockade.[14] Recognition of this phenomenon is clinically relevant because it signals significant sodium channel dysfunction and may be associated with heightened arrhythmic risk. Importantly, Brugada phenocopy should prompt clinicians to prioritize stabilization and reassessment after resolution of the inciting exposure rather than prematurely labeling the patient with an inherited channelopathy. Serial ECGs can be valuable, as the electrophysiologic profile may evolve with changing drug concentrations, acid–base status, and therapeutic interventions. Laboratory evaluation should be tailored to clinical severity but generally includes studies that identify metabolic derangements, evaluate end-organ function, and screen for common and dangerous co-ingestions. Measurement of electrolytes is important because disturbances in potassium, magnesium, and calcium can potentiate dysrhythmias, particularly in the setting of QT prolongation. Renal and hepatic profiles help anticipate altered clearance and guide supportive care. Given the frequency of polypharmacy overdoses, acetaminophen and salicylate levels should be obtained routinely when intentional ingestion is plausible, even in the absence of early symptoms. Assessment of acid–base status via arterial or venous blood gas is valuable, as acidosis can both reflect severity (e.g., shock or seizures) and worsen cardiotoxicity by potentiating sodium channel blockade. A toxicology drug screen may assist in identifying co-ingested substances that alter mental status or hemodynamics, though results should be interpreted cautiously and in clinical context. A complete blood count may be helpful for detecting infection, anemia, or other contributors to physiologic instability and for establishing baseline status during resuscitation. Collectively, these diagnostic elements—urgent ECG assessment, targeted laboratory testing, and serial reassessment—form the cornerstone of safe evaluation in suspected sodium channel blocker toxicity.[13][14]

Treatment / Management

Management of sodium channel blocker toxicity is time-sensitive and prioritizes prevention of sudden cardiovascular collapse, progressive neurologic deterioration, and secondary metabolic derangements. Initial care follows standard resuscitation principles with immediate assessment and stabilization of airway, breathing, and circulation. Patients may present with hypotension, bradycardia or tachycardia, seizures, and altered mental status, and the early clinical trajectory can be dynamic. Airway protection is essential in individuals who cannot maintain protective reflexes, demonstrate respiratory failure, or progress toward cardiac arrest. Endotracheal intubation should be performed without delay in patients with declining mental status, recurrent seizures, severe agitation compromising ventilation, or refractory shock requiring escalating vasopressor support. In addition to securing oxygenation and ventilation, advanced airway placement can facilitate controlled hyperventilation when clinically appropriate and allows safe administration of therapies in patients at risk for aspiration. When ingestion is recent and severe toxicity is plausible, gastrointestinal decontamination may be considered. Activated charcoal may be administered early in large overdoses where the expected clinical course includes substantial morbidity or death. However, its use requires careful risk–benefit assessment, particularly in patients with depressed consciousness, active vomiting, or ongoing seizures, all of whom have elevated aspiration risk. In these settings, charcoal is generally deferred unless the airway is protected. Because many implicated agents slow gastrointestinal motility, absorption may be delayed, and the window for benefit may extend beyond that seen with other toxins; nonetheless, decisions should remain individualized and aligned with patient safety [14].

The cornerstone of therapy for sodium channel blocker cardiotoxicity is sodium bicarbonate, indicated in patients with electrocardiographic evidence of conduction delay or electrical instability. In practice, sodium bicarbonate is recommended when the ECG demonstrates a QRS duration greater than 100 milliseconds or when there is concern QT prolongation or dysrhythmia in the context of suspected sodium channel blockade.[13] The therapeutic rationale is twofold: bicarbonate increases serum pH and increases extracellular sodium concentration. Alkalinization helps reduce drug binding at sodium channels and may improve channel availability; it may also increase protein binding of certain offending agents, thereby lowering the free, pharmacologically active fraction. The increased sodium load augments the electrochemical gradient across cell membranes and is thought to competitively mitigate channel blockade, improving myocardial conduction and narrowing the QRS complex. A commonly used initial dosing strategy is a bolus of 1 to 2 mEq/kg of sodium bicarbonate.[1] Boluses may be repeated while monitoring clinical status and serial ECGs, with many protocols aiming to reduce the QRS duration to less than 100 milliseconds. Once stabilization is achieved or if recurrent widening occurs, clinicians often transition to a continuous bicarbonate infusion, typically at 1.5 to 2 times maintenance fluid rate, with a target serum pH not exceeding 7.55.[13] A standard preparation is created by adding 2 to 3 ampules (50 mEq each) of sodium bicarbonate to 1 liter of 5% dextrose in water (D5W).[13] Close monitoring is required during alkalinization, including serial blood gases and electrolytes, because overcorrection can precipitate complications such as hypokalemia, ionized hypocalcemia, and volume overload, each of which may worsen arrhythmia risk or hemodynamic instability [13].

In cases where instability persists despite optimized bicarbonate therapy and hemodynamic support, escalation strategies may be required. Hypertonic saline is considered in refractory scenarios, particularly when further alkalinization is not advisable because the patient's pH has already reached approximately 7.55.[15] The goal is to further increase serum sodium concentration and enhance the transmembrane gradient without pushing alkalemia to dangerous levels. Although supporting evidence is limited, its use has been described in dire circumstances, including a reported case of flecainide overdose.[16] Similarly, lidocaine—a Class IB antiarrhythmic—may be used for refractory dysrhythmias related to sodium channel blockade. Its favorable "fast on, fast off" kinetics allow it to compete for sodium channel binding sites while producing less persistent blockade than many toxic agents; conceptually, this competition increases the proportion of time channels are unbound, facilitating partial restoration of conduction. (B3) Lidocaine is therefore considered a potential adjunct when malignant ventricular dysrhythmias persist despite bicarbonate and supportive care. Hemodynamic management is frequently complex and often requires simultaneous volume resuscitation, vasopressor therapy, and, in some cases, inotropic support. Initial treatment typically includes isotonic fluid administration, guided by perfusion parameters and the risk of pulmonary edema. When hypotension is refractory to fluids, norepinephrine is generally regarded as the preferred first-line vasopressor because it provides potent α-adrenergic vasoconstriction with supportive β-adrenergic effects that can improve perfusion without excessive tachyarrhythmia in many patients.[17] If shock persists, additional agents such as epinephrine or vasopressin may be added to achieve adequate mean arterial pressure and end-organ perfusion. In mixed-mechanism overdoses—such as agents that also produce β-blockade or calcium channel blockade—clinicians should anticipate more profound myocardial depression and may require higher vasopressor doses and careful titration based on bedside echocardiography or invasive hemodynamic monitoring when available [15][16][17].

Local anesthetic systemic toxicity represents a particularly important subset because it may develop abruptly after procedural administration and can produce refractory arrhythmias and cardiovascular collapse. In severe cases, administration of 20% lipid emulsion has demonstrated benefit and is now widely incorporated into treatment algorithms for significant local anesthetic toxicity.[18] The precise mechanism is not fully defined, but a prevailing hypothesis is that lipid emulsion acts as a "lipid sink," sequestering lipophilic anesthetic molecules within an intravascular lipid phase and thereby reducing tissue bioavailability; an electrochemical gradient may facilitate redistribution away from target organs such as the heart and brain. (B3) Recommended dosing includes a 1.5 mL/kg bolus followed by a continuous infusion at 0.25 mL/kg.[19] Much of the evidence base derives from case reports and series, particularly involving bupivacaine, which is highly lipophilic and notably cardiotoxic.[20][21][22] Clinical practice has extended lipid emulsion therapy to other local anesthetics as well, although robust comparative trials are limited, and evidence for lipid use in non–local anesthetic sodium channel blocker poisonings remains comparatively sparse. Nonetheless, in selected life-threatening presentations involving highly lipophilic agents, lipid therapy may be considered as a rescue adjunct when conventional measures fail, recognizing that the supporting data are weaker outside local anesthetic toxicity. Because many sodium channel–blocking toxins are highly lipophilic, exhibit large volumes of distribution, and are extensively tissue-bound, conventional extracorporeal elimination methods such as hemodialysis generally provide limited benefit. Therefore, management relies heavily on antidotal/physiologic reversal (bicarbonate and sodium loading), aggressive supportive care, and advanced rescue modalities. Seizure control is a parallel priority because convulsions worsen acidosis and hypoxia, which can intensify cardiotoxicity and create a self-propagating spiral of physiologic deterioration. Benzodiazepines such as lorazepam and midazolam are first-line agents for toxin-induced seizures. Importantly, phenytoin and related agents are generally avoided in this context because they possess sodium channel–blocking properties themselves and may exacerbate conduction slowing and precipitate clinical decline. For seizures that are refractory to benzodiazepines, endotracheal intubation with deep sedation—often with agents such as propofol—should be considered to terminate ongoing convulsive activity, facilitate ventilation, and reduce metabolic demand [18][19][20][21][22].

When hemodynamic instability remains refractory despite optimized sodium bicarbonate therapy, appropriate vasopressor escalation, correction of acid–base and electrolyte abnormalities, and management of seizures, extracorporeal life support should be considered. Extracorporeal membrane oxygenation (ECMO) has been used as a salvage therapy in refractory cases with reported survival, including severe flecainide overdose.[16] More broadly, successful resuscitation using ECMO has been reported in overdoses involving local anesthetics,[23] tricyclic antidepressants,[24] and diphenhydramine.[25][26] The rationale for ECMO in these settings is to provide temporary circulatory and oxygenation support while the offending agent is redistributed, metabolized, and eliminated, thereby "buying time" when conventional pharmacologic and hemodynamic interventions are insufficient. Clinicians should therefore maintain early awareness of ECMO candidacy in severe poisonings—particularly when profound conduction abnormalities, recurrent ventricular dysrhythmias, or shock persist—because timely mobilization of an ECMO-capable team can be decisive. In summary, treatment of sodium channel blocker toxicity hinges on rapid stabilization, early ECG-driven recognition of cardiotoxicity, prompt sodium bicarbonate therapy with careful monitoring of pH and electrolytes, aggressive hemodynamic support, seizure control with benzodiazepines while avoiding sodium channel–blocking anticonvulsants, and selective use of rescue strategies such as hypertonic saline, lidocaine, lipid emulsion (especially for local anesthetic systemic toxicity), and ECMO in refractory cardiovascular collapse.[1][13][15][16][17][18][19][20][21][22][23][24][25][26]

Differential Diagnosis

Patients who present with ventricular dysrhythmias warrant an expansive differential diagnosis because malignant ventricular rhythms represent a final common pathway for numerous cardiac, metabolic, and toxicologic processes. From a primary cardiac perspective, acute coronary syndrome must be considered early, as myocardial ischemia can precipitate ventricular tachycardia or ventricular fibrillation even in the absence of classic chest pain, particularly among older adults, patients with diabetes, or those with altered mental status. Structural heart disease—including cardiomyopathies, prior myocardial infarction with scar-related reentry, and valvular pathology—also increases susceptibility to ventricular arrhythmias and may be unmasked during physiologic stress. In addition, congenital cardiac disorders and inherited channelopathies, such as Brugada syndrome or long QT syndromes, remain important considerations, especially in younger patients or those with a personal or family history of syncope, sudden cardiac death, or unexplained seizures. Metabolic and electrolyte abnormalities form another critical component of the differential. Disturbances such as hypomagnesemia and hyperkalemia can destabilize myocardial conduction and repolarization, thereby facilitating ventricular ectopy and sustained dysrhythmias. These derangements may occur as primary problems or secondary to renal failure, medication effects, dehydration, or acid–base disturbances. Accordingly, rapid assessment of electrolytes and acid–base status is essential, not only to evaluate for sodium channel blocker toxicity but also to identify reversible precipitants that may require immediate correction to prevent recurrent arrhythmia. Within the toxicologic domain, sodium channel blockade represents an especially high-risk mechanism that can mimic or compound other arrhythmogenic conditions. The differential diagnosis for sodium channel blockade toxicity includes a broad range of pharmaceuticals and xenobiotics. Commonly implicated medications include first-generation antihistamines, which may produce slow conduction and QRS widening in overdose, as well as several antipsychotics and phenothiazines that can disrupt cardiac conduction and repolarization. Antispasmodics and chloroquine are additional considerations, particularly when exposure history suggests access to these agents. Class IA and IC antiarrhythmics are classic causes of sodium channel blockade with severe proarrhythmic potential in overdose. Cocaine and local anesthetics are also important causes, as both can produce rapid-onset cardiotoxicity and ventricular dysrhythmias. Finally, certain antidepressants outside the tricyclic class—most notably venlafaxine—have been associated with toxicity that can include sodium channel–blocking features and malignant arrhythmias. Given this breadth, diagnostic reasoning should integrate ECG findings, hemodynamic status, clinical context, and exposure history to distinguish toxicologic sodium channel blockade from ischemic, structural, congenital, and electrolyte-mediated causes, while recognizing that these conditions may coexist and mutually exacerbate risk [24][25][26].

Prognosis

The prognosis of sodium channel blocker toxicity is heterogeneous and depends on the specific agent, dose, co-ingestions, timeliness of intervention, and the presence of early markers of severe cardiotoxicity such as QRS widening, malignant ventricular dysrhythmias, refractory hypotension, or severe acidemia. Tricyclic antidepressant (TCA) overdose has long been recognized as a high-risk poisoning due to its combined sodium channel blockade and additional anticholinergic and adrenergic effects, which together can precipitate rapid clinical deterioration. Similarly, toxicity from Class I antiarrhythmics carries particularly grave implications; reported data indicate that Class I antiarrhythmic toxicity is associated with substantially higher mortality (22.5%) compared with other drugs (1%).[14] This disparity reflects the potent electrophysiologic actions of these agents, their narrow therapeutic indices, and their capacity to provoke profound conduction slowing and fatal ventricular arrhythmias. Despite these risks, outcomes can be excellent when poisoning is recognized early and treated aggressively. Prompt identification of sodium channel blockade on electrocardiography, timely initiation of sodium bicarbonate therapy when indicated, and rapid escalation of supportive measures (including airway management, vasopressor support, seizure control, and advanced rescue strategies when required) can arrest progression and allow complete recovery. The reversibility of many cases is an important counseling point: the toxic effects are often transient and concentration-dependent, so successful stabilization and supportive care over the period of redistribution and metabolism can lead to full neurologic and cardiovascular restoration. Prognosis is therefore strongly time-sensitive, and delays in recognition—particularly when initial symptoms are nonspecific—can convert a potentially reversible exposure into a fatal event. Clinical trajectories may also be influenced by preventable physiologic amplifiers of toxicity, such as hypoxia and metabolic acidosis, which can worsen sodium channel blockade and raise arrhythmic risk. Consequently, prognosis improves most consistently in systems that facilitate rapid triage, early ECG interpretation, and coordinated toxicology-guided management. While high mortality is associated with certain high-potency agents and severe presentations, many patients can fully recover from sodium channel blocker toxicity with early identification and appropriate treatment, underscoring the critical importance of rapid intervention and vigilant monitoring.[14]

Complications

Complications of sodium channel blocker toxicity are primarily driven by the convergence of cardiotoxicity, central nervous system dysfunction, and secondary metabolic derangements. Hemodynamic instability is among the most common and most dangerous sequelae, ranging from mild hypotension to profound shock. Patients may develop bradycardia due to depressed myocardial excitability and conduction, or tachycardia when anticholinergic or sympathomimetic coeffects are prominent. In severe cases, compromised contractility and malignant dysrhythmias progress to cardiogenic shock, with poor end-organ perfusion and escalating lactate production. Without rapid reversal and supportive therapy, this can culminate in cardiovascular collapse and cardiac arrest. Respiratory complications often occur in parallel. Depressed mental status, seizure activity, or medication-induced respiratory depression can lead to hypoventilation, hypoxia, and aspiration, each of which further destabilizes cardiopulmonary physiology. Encephalopathy may present as confusion, agitation, delirium, or coma, reflecting direct neurotoxicity as well as hypoxic–ischemic injury in advanced cases. Neurologic complications may include recurrent seizures and, at the extreme end of severity, status epilepticus. Persistent seizure activity is particularly hazardous because it amplifies metabolic acidosis and catecholamine surge, thereby worsening myocardial oxygen demand and potentiating sodium channel blockade—mechanistically linking neurologic toxicity to further cardiac deterioration. Additional complications may arise from the treatment itself if not carefully monitored, such as electrolyte shifts and alkalemia during bicarbonate therapy, which can increase arrhythmia susceptibility if potassium and ionized calcium are not maintained within safe ranges. Ultimately, the most severe and feared complication is death, typically resulting from refractory ventricular dysrhythmias, irreversible shock, or hypoxic injury following cardiopulmonary arrest. The broad scope of these complications underscores why early recognition, continuous monitoring, and proactive correction of physiologic derangements are central to safe management [26].

Patient Education

Prevention remains the most effective strategy for reducing morbidity associated with sodium channel blocker toxicity, particularly because many implicated agents are common in outpatient care and several exposures are avoidable. In the procedural context, clinicians administering local anesthetics should be thoroughly familiar with maximum recommended doses and dose adjustments based on patient factors such as body weight, age, pregnancy, hepatic function, and comorbid cardiovascular disease. Safe injection practices are critical: aspirating before injection helps avoid inadvertent intravascular administration, and incremental dosing with careful patient observation can provide early warning of systemic toxicity. The use of epinephrine-containing formulations of lidocaine, bupivacaine, or other local anesthetics can reduce systemic distribution by promoting local vasoconstriction, thereby increasing the potentially toxic dose threshold and improving procedural safety when appropriately used. Education in clinical settings should reinforce the importance of monitoring immediately after administration, because local anesthetic systemic toxicity can evolve rapidly and requires urgent intervention. In the outpatient setting, patient education should emphasize that sodium channel blocker toxicity can occur with a range of medications, including antidepressants and anticonvulsants, and may result from accidental dosing errors as well as intentional overdose. Patients prescribed higher-risk agents—such as TCAs—should receive clear counseling on dosing, avoidance of duplication, and the dangers of combining sedatives or alcohol with prescribed medications. Families and caregivers should be instructed on safe storage practices, especially in households with children, older adults, or individuals with cognitive impairment. Because self-harm risk is a major driver of severe poisoning, patients with psychiatric illness or those identified as high-risk should be counseled on protective measures, including limiting quantities dispensed, using supervised administration when needed, and promptly seeking mental health support. The overarching message for both clinicians and patients is that prevention—through safe prescribing, safe administration, and safe storage—is the most reliable "treatment," because it reduces the probability of catastrophic exposures that may progress faster than definitive care can be delivered [26].

Enhancing Healthcare Team Outcomes

Optimal outcomes in acute sodium channel blocker toxicity depend on coordinated interprofessional care, as patients often require rapid resuscitation, continuous cardiac monitoring, and complex pharmacologic interventions. Early recognition and stabilization typically begin in the emergency department, where immediate ECG acquisition, airway assessment, and hemodynamic support can be initiated. Many patients with significant toxicity require intensive care unit admission for close monitoring, serial ECGs, frequent laboratory reassessment, and titration of therapies such as sodium bicarbonate infusion and vasopressors. Consultation with a medical toxicologist or coordination with a regional poison control center is especially valuable, as expert guidance can refine differential diagnosis, interpret evolving ECG findings, recommend escalation strategies (e.g., hypertonic saline, lipid emulsion, or extracorporeal support), and assist in anticipating delayed complications. Close collaboration with these resources is crucial in directing management, particularly when co-ingestions or mixed-mechanism toxicities are suspected. Nursing and pharmacy teams are central to safe and timely implementation of treatment. Nursing staff provide continuous clinical surveillance for evolving dysrhythmias, seizures, or decompensation, administer emergent medications, and monitor for complications of therapy such as electrolyte shifts during alkalinization. Pharmacists play a pivotal role in medication reconciliation, identification of high-risk co-ingestions, dosing support for sodium bicarbonate, lipid emulsion, and sedatives, and rapid preparation of infusions under emergent conditions. Effective communication between nursing and pharmacy improves speed and reduces medication error risk during high-acuity care. Additional services are often necessary, including respiratory therapy for ventilatory management, cardiology for complex arrhythmias or uncertainty regarding structural disease, and critical care teams for shock and multisystem support. Finally, psychiatry is essential when poisoning occurs in the context of self-harm: early involvement supports risk assessment, safety planning, and continuity of mental health care after medical stabilization. Across all disciplines, prompt identification and coordinated treatment reduce morbidity and mortality, demonstrating that system-level teamwork is not ancillary but fundamental to improving patient outcomes in sodium channel blocker toxicity [25][26].

Conclusion:

Sodium channel blocker toxicity represents a critical clinical challenge due to its rapid onset, severe cardiotoxicity, and potential for fatal outcomes. The pathophysiology involves profound conduction slowing, metabolic acidosis, and neurologic excitation, creating a vicious cycle that accelerates deterioration. Prognosis hinges on early recognition and intervention: ECG-driven detection of QRS widening and prompt administration of sodium bicarbonate are lifesaving measures. Adjunctive therapies such as hypertonic saline, lipid emulsion, and ECMO provide additional options for refractory cases, while benzodiazepines remain first-line for seizure control. Despite the complexity of management, outcomes can be favorable when treatment is timely and comprehensive. Prevention remains paramount—through meticulous dosing, procedural vigilance, and patient education—given that many exposures are avoidable. Interprofessional collaboration among emergency physicians, toxicologists, pharmacists, and critical care teams is essential to optimize care and reduce mortality. Ultimately, this review underscores that sodium channel blocker toxicity, though formidable, is a reversible condition when addressed with evidence-based strategies and system-level preparedness.

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