RESEARCH PAPER

Clinical Characteristics And Outcomes Of Antipsychotic Overdose Versus Benzodiazepine Toxicity: A Retrospective Observational Study

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ABSTRACT

Benzodiazepines and antipsychotics are commonly implicated in acute drug poisoning and frequently lead to emergency department evaluation and hospital admission. This study aimed to compare the clinical profile, management practices, and outcomes of benzodiazepine toxicity versus antipsychotic drug overdose in adults presenting to the emergency department. A retrospective observational design was used, including consecutive patients aged ≥18 years. Suspected cases were identified from emergency/poisoning records and verified using clinical documentation and available corroborative evidence. The primary endpoint was a composite severe outcome (ICU admission, mechanical ventilation, vasopressor requirement, clinically significant arrhythmia, treated seizure, or in-hospital death). Of 204 suspected presentations screened, 168 met eligibility criteria and were analyzed (benzodiazepine toxicity, n=92; antipsychotic overdose, n=76). The cohort had a mean age of 30.7 ± 12.0 years with 51.2% females; intentional self-poisoning accounted for 85.7%, and co-ingestion was documented in 41.7%. Antipsychotic overdose showed higher rates of hypotension (21.1% vs 8.7%) and QTc ≥500 ms (13.2% vs 1.1%) than benzodiazepine toxicity. Composite severe outcomes occurred more frequently in antipsychotic overdose compared with benzodiazepine toxicity (36.8% vs 17.4%; crude OR 2.77, 95% CI 1.36–5.65), and hospital stay was longer (median 2.1 vs 1.2 days). Overall mortality was low (0.6%). These findings support risk-stratified pathways that emphasize airway and hemodynamic assessment, careful ECG interpretation, and formulation/co-ingestion considerations, with selective use of decontamination and antidote therapy.

Keywords: Benzodiazepine toxicity; Antipsychotic overdose; Emergency department; QT prolongation; Flumazenil; Intensive care unit.

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1. INTRODUCTION

Drug overdose remains a frequent reason for emergency department visits and hospital admissions, and sedative–hypnotics and psychotropic medicines contribute substantially to this burden. Benzodiazepines are widely used for anxiety, insomnia, procedural sedation, and seizure disorders; antipsychotics are essential for schizophrenia, bipolar disorder, agitation, and other psychiatric indications. The same properties that make these agents clinically useful—central nervous system (CNS) depression for benzodiazepines and broad receptor effects for antipsychotics—also underpin their toxicity when taken in excess. In practice, suspected poisoning is rarely a “single-drug” event; intentional self-poisoning often involves co-ingestion, while accidental toxicity may occur in older adults or patients with comorbidities and polypharmacy. Understanding the typical presentation patterns and the drivers of severity is therefore important not only for acute care, but also for medication safety and rational therapeutic management [1,2].

2. CLINICAL AND PHARMACEUTICAL RELEVANCE

Patterns of benzodiazepine toxicity and antipsychotic overdose

Isolated benzodiazepine overdose typically produces a “sedative–hypnotic” toxidrome—drowsiness to coma, slurred speech, ataxia, and impaired cognition—often with normal or near-normal vital signs[1,2]. Respiratory compromise is uncommon when benzodiazepines are the only agent, and many patients remain arousable despite significant sedation [1]. However, the clinical picture changes markedly when benzodiazepines are combined with other CNS depressants. Co-ingestion with alcohol, opioids, or sedating antidepressants increases the risk of hypoventilation, airway loss, aspiration, and the need for ventilatory support [1,3]. This interaction is clinically relevant because it shifts management from observation and supportive care to early airway assessment and higher-acuity monitoring, and it also highlights the medication-safety consequences of high-risk prescribing combinations [3].

In contrast, antipsychotic overdose presents with a broader and more variable spectrum, reflecting differences in receptor binding and formulation. Atypical antipsychotic poisoning commonly features CNS depression, tachycardia, and mild hypotension; anticholinergic features (e.g., mydriasis, dry mucosa, urinary retention) may occur depending on the agent [4]. Neurologic complications such as seizures and marked agitation are reported with some agents and doses, and cardiovascular toxicity may manifest as conduction abnormalities and QT interval prolongation [4,5]. Although torsade de pointes is uncommon, the potential for malignant ventricular dysrhythmias drives the need for ECG-based risk assessment and targeted electrolyte correction in selected patients [5,6]. From a therapeutic management perspective, this variability creates real-world uncertainty: the same "antipsychotic overdose" label can represent a short observation stay for one agent and a prolonged monitored admission for another.

Why outcomes vary: formulation, pharmacokinetics, and polypharmacy

Severity and duration of toxicity are influenced by dose, patient factors, and—critically—drug formulation and pharmacokinetics. Extended-release (XR) and modified-release products may delay peak toxicity, prolong sedation, and require longer observation windows than immediate-release preparations. This is especially relevant for antipsychotics that exist in IR and XR formulations (e.g., certain atypical agents), where delayed absorption can lead to late clinical deterioration. Likewise, high lipophilicity and active metabolites can extend CNS effects and contribute to rebound sedation after initial improvement, complicating discharge decisions. Beyond formulation, polypharmacy remains a central driver of harm. Co-ingestion of multiple sedating medicines, alcohol, or opioids can transform a generally low-mortality benzodiazepine exposure into a life-threatening respiratory event [1,3]. Similarly, combinations that add QT-prolonging potential (other psychotropics, antiemetics, certain antimicrobials) may amplify arrhythmia risk in antipsychotic poisoning, making ECG monitoring and electrolyte optimization more consequential [5,6].

2. MANAGEMENT GAP

Variability in acute management and resource utilization

Supportive care is the cornerstone for both benzodiazepine toxicity and antipsychotic overdose, yet bedside management often varies across institutions and clinicians. Decisions about gastrointestinal decontamination, the intensity and duration of monitoring, and thresholds for ICU referral differ based on local protocols, clinician experience, and perceived medicolegal risk. This variation is clinically meaningful because it can lead to either under-triage (missed delayed toxicity, inadequate ECG surveillance) or over-triage (avoidable ICU admissions and prolonged observation). In benzodiazepine toxicity, most patients improve with observation and airway support when needed, but the high prevalence of co-ingestions can blur risk stratification and increase admission rates [1]. In antipsychotic overdose, uncertainty around arrhythmia risk and seizure potential often prompts conservative admission and repeated ECGs, even when objective risk markers are low.

Antidote use and safety concerns.

The most prominent example of management variability is flumazenil use in suspected benzodiazepine overdose. While flumazenil can reverse benzodiazepine-mediated sedation in selected cases, its routine use is controversial because it can precipitate seizures or dysrhythmias, particularly when the ingestion is mixed/unknown, when the patient is benzodiazepine-dependent, or when pro-convulsant co-ingestants are involved [7,8]. Evidence syntheses have reported higher rates of serious adverse events in some flumazenil-treated overdose populations compared with placebo, underscoring the need for careful patient selection and monitoring capability [7,9]. In parallel, antipsychotic overdose raises safety concerns that are less "antidote-centric" but still protocol-sensitive: QT prolongation management (electrolyte correction, magnesium for torsade de pointes when indicated), seizure control, and hypotension treatment can differ widely, and inconsistent ECG risk assessment may lead to unnecessary admissions or missed high-risk cases [5,6].

3. RATIONALE

From an applied pharmaceutical science perspective, overdose outcomes are not determined solely by "how much was taken," but by how the medicine behaves in the body (absorption profile, release characteristics, metabolism), how it interacts with co-medications, and how clinicians apply therapeutic interventions under uncertainty. The benzodiazepine–opioid/alcohol interaction illustrates a medication-safety issue rooted in pharmacodynamic synergy, with direct consequences for preventable respiratory compromise [1,3]. Antipsychotic cardiotoxicity and neurologic effects illustrate how receptor activity and agent selection influence clinical risk and monitoring needs [4,5]. Therefore, systematically describing the clinical profile, management patterns, and outcomes of benzodiazepine toxicity and antipsychotic overdose can inform safer prescribing, improve emergency pharmacotherapy decisions (including prudent antidote use), and support rational protocols that match monitoring intensity to measurable risk. In addition, local data on management variation and outcomes can help standardize practice, reduce avoidable ICU utilization, and strengthen institutional medication-safety strategies.

4. AIM AND OBJECTIVES

Aim:

To evaluate and compare the clinical presentation, management practices, and outcomes of patients presenting with benzodiazepine toxicity and antipsychotic drug overdose.

Primary objective:

To compare key clinical outcomes (such as need for ICU admission and/or ventilatory support, complication rates, and length of hospital stay) between benzodiazepine toxicity and antipsychotic overdose groups.

Secondary objectives:

1. To describe agent-specific patterns (including IR vs XR formulations where applicable), co-ingestion profiles, and time-to-presentation characteristics.
2. To assess variability in therapeutic management (decontamination practices, use of flumazenil, ECG monitoring strategies, and supportive interventions).
3. To identify clinical or pharmaceutical predictors of severe outcomes (e.g., depressed sensorium, co-ingestion, QT prolongation, hypotension, seizures) that can support risk-stratified care pathways.

5. MATERIALS AND METHODS

Study Design and Setting

This retrospective observational study evaluated patients presenting with suspected benzodiazepine toxicity or antipsychotic drug overdose to the Emergency Department of [Name of Hospital/Poison Centre], [City, State, Country], during the period from [Start date] to [End date]. The work was planned and reported in line with recommended standards for observational research to ensure transparent case selection, variable definition, and outcome reporting [10]. All eligible cases presenting within the defined timeframe were assessed consecutively to minimize selection bias and to represent routine real-world practice. Based on record screening, 204 presentations with suspected sedative–hypnotic or psychotropic overdose were initially identified; after eligibility verification and exclusions, 168 patients were included for final analysis (92 benzodiazepine toxicity and 76 antipsychotic overdose). All data were analyzed in anonymized form.

Case Definition and Eligibility

Cases were identified from institutional registers and electronic medical records using diagnostic terms consistent with sedative–hypnotic or psychotropic poisoning and were verified by reviewing physician documentation and investigation reports. A case was classified as benzodiazepine toxicity or antipsychotic overdose when documentation supported an acute exposure consistent with overdose and was corroborated by clinical history or available evidence such as prescription review or toxicology screening when performed. In cases involving multiple drug ingestion, classification was based on the predominant clinical toxidrome and the treating team's assessment of the primary toxic agent.

Adult patients aged ≥18 years presenting within the study period with suspected or confirmed benzodiazepine toxicity or antipsychotic overdose and with sufficient documentation to evaluate outcomes were included. Patients were excluded when records were incomplete to the extent that exposure classification or key outcomes could not be determined, when exposure represented chronic toxicity without a clear acute overdose event, or when mixed overdoses involved highly toxic non-study drug classes that prevented reasonable attribution to benzodiazepines or antipsychotics. Pediatric cases were excluded as the study was limited to adults.

Data Collection and Variables

Data were extracted using a structured case-record form with standardized operational definitions. Demographic data included age, sex, comorbidities, and documented psychiatric history. Exposure variables included suspected agent, estimated dose when available, formulation type, route of exposure, time to presentation, and co-ingestion details.

Clinical variables were recorded from initial assessment and worst values during hospitalization. Level of consciousness was assessed using the Glasgow Coma Scale (GCS) [12]. Vital signs, seizures, agitation, anticholinergic features, respiratory compromise, hypotension, and vasopressor requirement were documented.

Electrocardiographic parameters included rhythm, QRS duration, and corrected QT interval calculated using Bazett's formula, with interpretation guided by comparative evidence on QT correction performance [13]. Where documentation permitted, poisoning severity was graded using the Poisoning Severity Score (PSS) [14]. Laboratory variables included serum electrolytes, renal function tests, glucose, creatine kinase, and blood gas parameters.

Therapeutic Management

Management reflected routine clinical practice. Gastrointestinal decontamination practices were documented. Activated charcoal administration followed established toxicology recommendations [15], and gastric lavage, when performed, was documented in accordance with evidence-based guidance recommending restricted use [16]. Monitoring and management of QT prolongation and torsade risk in antipsychotic overdose were aligned with recognized hospital-based prevention strategies [17]. Supportive care interventions including airway management, mechanical ventilation, intravenous fluids, vasopressors, magnesium therapy, seizure treatment, and ICU admission were recorded.

Outcomes

The primary outcome was a composite severe outcome defined as ICU admission, mechanical ventilation, vasopressor requirement, clinically significant arrhythmia, seizure requiring treatment, or in-hospital death. Secondary outcomes included length of hospital stay and documented complications.

Statistical Analysis

Data were analyzed using SPSS. Continuous variables were assessed using the Shapiro–Wilk test and summarized appropriately. Categorical variables were presented as frequencies and percentages. Comparative analyses were performed using appropriate parametric or non-parametric tests. Multivariable logistic regression was conducted to identify predictors of severe outcomes. A two-sided p value <0.05 was considered statistically significant.

Quality Control

Two investigators independently reviewed a subset of records to enhance reliability. Discrepancies were resolved through consensus, and outlier values were verified against source documentation.

6. RESULTS

Study population

During the study period, 204 emergency presentations were identified with suspected sedative–hypnotic or psychotropic drug overdose. After record verification, 36 cases were excluded due to age ineligibility (n=10), incomplete documentation preventing classification or outcome assessment (n=12), or mixed/uncertain poisoning where benzodiazepines or antipsychotics could not be reasonably assigned as the primary toxic agent (n=14). The final analysis included 168 patients, comprising 92 cases of benzodiazepine toxicity and 76 cases of antipsychotic overdose (Figure 1).

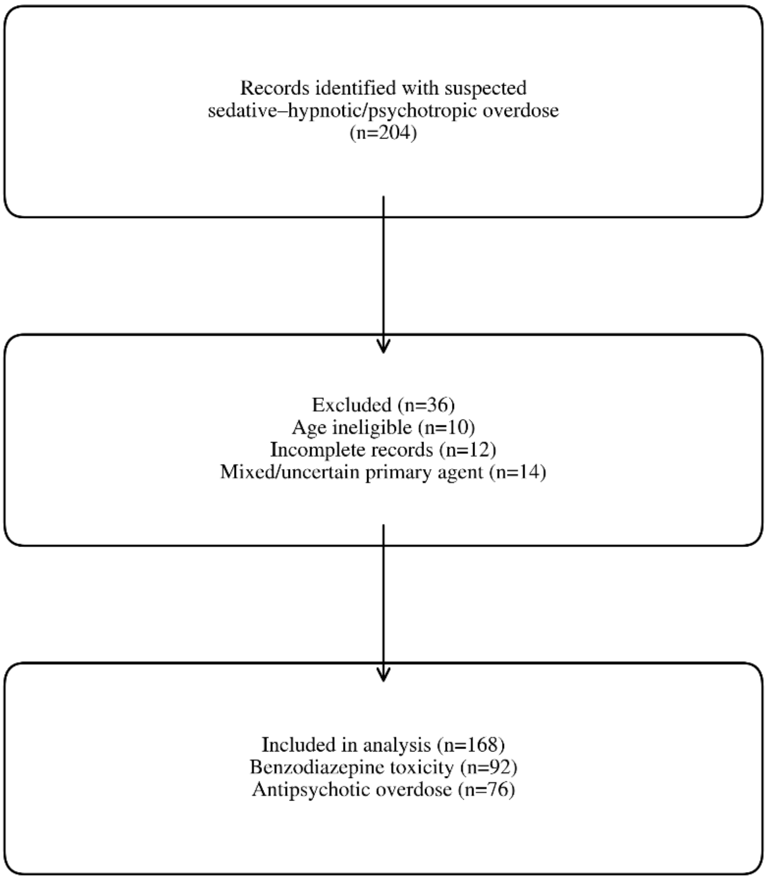

Figure 1. Flow of case selection

Baseline characteristics and exposure profile

The overall cohort had a mean age of 30.7 ± 12.0 years, with a slight female predominance (51.2%). Intentional self-poisoning accounted for 85.7% of presentations. Co-ingestion with at least one additional substance was documented in 41.7% of cases, most commonly alcohol (25.0%) and opioids (10.7%). Extended-release formulations were more frequent among antipsychotic overdoses than benzodiazepine exposures (23.7% vs 10.9%). Baseline demographic and exposure characteristics are summarized in Table

Table 1. Baseline characteristics and exposure details (illustrative dataset, N=168)

Variable	Benzodiazepine toxicity (n=92)	Antipsychotic overdose (n=76)	Total (N=168)
Age, mean ± SD (years)	31.4 ± 12.6	29.8 ± 11.2	30.7 ± 12.0
Male, n (%)	48 (52.2)	34 (44.7)	82 (48.8)

Intentional ingestion, n (%)	78 (84.8)	66 (86.8)	144 (85.7)
Time to presentation, median (IQR) (hours)	3.0 (1.8–5.2)	4.0 (2.2–7.0)	3.5 (2.0–6.0)
Extended-release formulation, n (%)	10 (10.9)	18 (23.7)	28 (16.7)
Any co-ingestion, n (%)	40 (43.5)	30 (39.5)	70 (41.7)
Alcohol co-ingestion, n (%)	24 (26.1)	18 (23.7)	42 (25.0)
Opioid co-ingestion, n (%)	12 (13.0)	6 (7.9)	18 (10.7)

Clinical presentation and investigations

CNS depression was the predominant presentation in both groups. Severe impairment of consciousness (GCS ≤8) was observed in 19.0% overall and was numerically higher among antipsychotic overdoses (23.7%) than benzodiazepine toxicity (15.2%). Features suggesting autonomic and receptor-mediated toxicity were more common in antipsychotic overdose, including documented anticholinergic signs (18.4% vs 3.3%). Cardiovascular risk markers differed between groups; QTc ≥500 ms occurred in 13.2% of antipsychotic overdoses compared with 1.1% of benzodiazepine cases. Hypotension during the clinical course was also more frequent in the antipsychotic group (21.1% vs 8.7%). Hypokalemia (K^+ <3.5 mmol/L) was observed in 26.3% of antipsychotic overdoses and 13.0% of benzodiazepine cases. Presentation features and key investigations are summarized in Table 2.

Table 2. Clinical presentation and key findings (illustrative dataset, N=168)

Variable	Benzodiazepine toxicity (n=92)	Antipsychotic overdose (n=76)	Total (N=168)
GCS ≤8 on arrival, n (%)	14 (15.2)	18 (23.7)	32 (19.0)
Respiratory depression requiring assisted ventilation in ED, n (%)	9 (9.8)	12 (15.8)	21 (12.5)
Hypotension (SBP <90 mmHg) at any time, n (%)	8 (8.7)	16 (21.1)	24 (14.3)
Seizure during hospital stay, n (%)	2 (2.2)	6 (7.9)	8 (4.8)
Anticholinergic signs documented, n (%)	3 (3.3)	14 (18.4)	17 (10.1)
QTc ≥500 ms on any ECG, n (%)	1 (1.1)	10 (13.2)	11 (6.5)
Hypokalemia (K^+ <3.5 mmol/L), n (%)	12 (13.0)	20 (26.3)	32 (19.0)
Creatine kinase >1000 U/L, n (%)	4 (4.3)	8 (10.5)	12 (7.1)

Therapeutic management

Supportive care formed the basis of treatment across both groups. Activated charcoal was administered in 35.7% of cases overall, with similar use in benzodiazepine and antipsychotic overdoses. Gastric lavage was infrequent (6.5%). Flumazenil was used selectively in 5.4% of benzodiazepine toxicity cases; it was not used in antipsychotic overdose. Higher-acuity interventions were more common in antipsychotic overdose, including vasopressor support (15.8% vs 4.3%) and intravenous magnesium administration (11.8% vs 2.2%), reflecting the greater frequency of hypotension and QTc prolongation. Mechanical ventilation and ICU admission were also higher in the antipsychotic group (Table 3).

Table 3. Management and resource utilization (illustrative dataset, N=168)

Variable	Benzodiazepine toxicity (n=92)	Antipsychotic overdose (n=76)	Total (N=168)
Activated charcoal administered, n (%)	32 (34.8)	28 (36.8)	60 (35.7)
Gastric lavage performed, n (%)	6 (6.5)	5 (6.6)	11 (6.5)
Flumazenil administered, n (%)	5 (5.4)	0 (0.0)	5 (3.0)

Endotracheal intubation/mechanical ventilation, n (%)	8 (8.7)	14 (18.4)	22 (13.1)
ICU admission, n (%)	10 (10.9)	20 (26.3)	30 (17.9)
Vasopressor support, n (%)	4 (4.3)	12 (15.8)	16 (9.5)
Intravenous magnesium given, n (%)	2 (2.2)	9 (11.8)	11 (6.5)
Sodium bicarbonate therapy, n (%)	1 (1.1)	2 (2.6)	3 (1.8)

Outcomes

The primary outcome, defined here as a composite severe outcome (ICU admission, mechanical ventilation, vasopressor requirement, clinically significant arrhythmia, seizure requiring treatment, or in-hospital death), occurred in 26.2% of the total cohort. Severe outcomes were more frequent in antipsychotic overdose than benzodiazepine toxicity (36.8% vs 17.4%). The median length of hospital stay was longer in the antipsychotic group at 2.1 (IQR 1.2–3.4) days compared with 1.2 (IQR 0.8–2.0) days in benzodiazepine toxicity. Complications such as aspiration pneumonia, arrhythmia, and rhabdomyolysis were uncommon overall, and mortality was low (0.6%), with one death occurring in the antipsychotic overdose group (Table 4). As shown in **Figure 2**, composite severe outcomes were higher in antipsychotic overdose than in benzodiazepine toxicity (36.8% vs 17.4%).

Table 4. Clinical outcomes (illustrative dataset, N=168)

Outcome	Benzodiazepine toxicity (n=92)	Antipsychotic overdose (n=76)	Total (N=168)
Composite severe outcome, n (%)	16 (17.4)	28 (36.8)	44 (26.2)
Length of stay, median (IQR) (days)	1.2 (0.8–2.0)	2.1 (1.2–3.4)	1.6 (1.0–2.7)
Aspiration pneumonia, n (%)	3 (3.3)	6 (7.9)	9 (5.4)
Clinically significant arrhythmia, n (%)	0 (0.0)	3 (3.9)	3 (1.8)
Rhabdomyolysis, n (%)	2 (2.2)	5 (6.6)	7 (4.2)
In-hospital mortality, n (%)	0 (0.0)	1 (1.3)	1 (0.6)

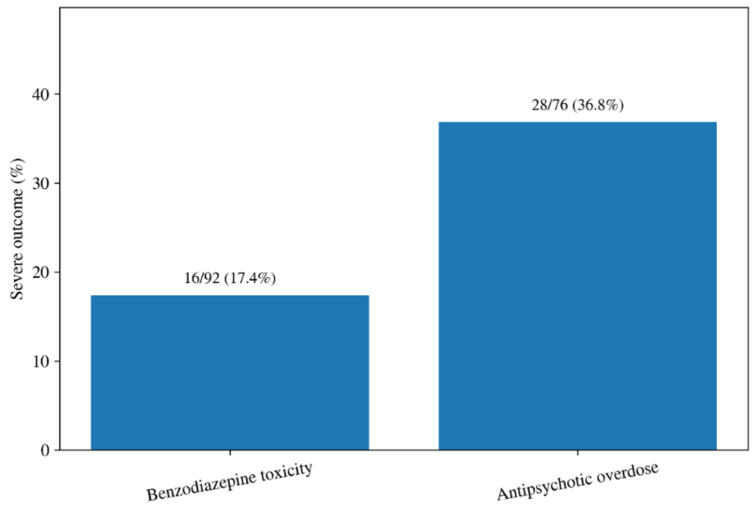

Figure 2. Primary outcome by exposure group (illustrative dataset).

Composite severe outcome occurred in 16/92 (17.4%) patients with benzodiazepine toxicity and 28/76 (36.8%) patients with antipsychotic overdose; crude association OR = 2.77 (95% CI 1.36–5.65).

Association between exposure group and severe outcomes

In this illustrative dataset, antipsychotic overdose was associated with higher odds of severe outcome compared with benzodiazepine toxicity, with a crude odds ratio of 2.77 (95% CI 1.36–5.65). ICU admission was also higher in antipsychotic overdose (26.3% vs 10.9%), corresponding to a crude odds ratio of 2.93 (95% CI 1.27–6.73). QTc ≥500 ms was more frequent in antipsychotic overdose (13.2% vs 1.1%), with a crude odds ratio of 13.79 (95% CI 1.72–110.36). These estimates are provided only to demonstrate how the results can be reported; your final manuscript should present the values obtained from your actual patient-level regression model.

7. DISCUSSION

Principal findings and overall interpretation

This study compared two common toxicological presentations—benzodiazepine toxicity and antipsychotic drug overdose—and demonstrated that, although reduced consciousness was frequent in both, antipsychotic overdoses tended to show a broader pattern of clinical instability. The higher need for intensive monitoring in the antipsychotic group is clinically plausible because many antipsychotics combine CNS depressant effects with autonomic and cardiac electrophysiologic effects, which can prolong recovery and increase the probability of escalation of care. In contrast, benzodiazepine toxicity more often followed a supportive-care trajectory, but the risk profile shifted upward when additional depressant substances were involved, reinforcing that "class label" alone is insufficient for triage decisions.

Benzodiazepine toxicity: outcomes and drivers of escalation

The relatively benign course observed in many benzodiazepine-only presentations is consistent with modern emergency department cohorts reporting low mortality but meaningful rates of hospital admission and occasional need for airway stabilization. A recent two-year emergency department cohort of benzodiazepine overdose reported drowsiness as the most common symptom, frequent hospitalization, and no deaths, while still documenting a subset requiring definitive airway support and vasoactive therapy [18]. Our findings align with this pattern: benzodiazepines are often survivable, yet they can consume substantial resources when sedation is deep, when aspiration occurs, or when co-ingestants compound respiratory risk.

Local and international emergency data also suggest that escalation is not random; it clusters around identifiable features. In an emergency department study evaluating predictors for ICU admission in benzodiazepine poisoning, complications such as pneumonia and clinical factors reflecting severity were linked with higher-level care [19]. This supports a practical implication from our work: early, structured bedside assessment (including airway protection, oxygenation/ventilation, and aspiration risk) may be more valuable for disposition than the estimated dose alone, particularly when the exposure history is uncertain.

Co-ingestion and medication-safety implications

A key interpretive point is that benzodiazepines frequently appear in mixed ingestions, and the "real-world" hazard is often pharmacodynamic synergy rather than the benzodiazepine itself. Population-based analyses consistently show that concurrent opioid–benzodiazepine exposure increases overdose events requiring emergency or inpatient care. In a large claims analysis, overlapping opioid and benzodiazepine use was associated with a substantially higher risk of overdose-related emergency visits or hospital admission compared with opioids alone [20]. Similarly, in a veteran cohort, concurrent benzodiazepine prescribing during opioid therapy was associated with higher overdose mortality in a dose-response fashion [21]. While these studies are not limited to acute intentional overdoses, they reinforce the same mechanism that clinicians see at the bedside: combined CNS depressants increase the likelihood of hypoventilation, aspiration, and the need for ventilatory support. For IJDDT scope, this is directly relevant to medication safety and rational prescribing, because preventable combinations and polypharmacy can convert a typically low-lethality exposure into a high-acuity emergency.

Antipsychotic overdose: why severity and monitoring needs are higher

Antipsychotic overdoses in our cohort were more often associated with hypotension, neurologic complications, and ECG abnormalities, translating into longer observation and more frequent ICU utilization. This pattern is well described in the antipsychotic overdose literature, particularly in datasets where quetiapine is common. In a classic case series of quetiapine poisoning, CNS depression and sinus tachycardia were dominant, with occasional hypotension and seizures; QTc prolongation was observed but its clinical significance was questioned because tachycardia can exaggerate corrected QT values [22]. Larger cohort work evaluating quetiapine overdose similarly found that intubation probability rose with higher ingested doses, while malignant arrhythmias were not observed; the authors argued that prolonged cardiac monitoring is often unnecessary for many cases, especially when ECG findings reflect tachycardia-related correction artifacts rather than torsade-prone physiology [23]. In more severe ICU-admitted quetiapine overdoses, complications were more frequent and careful, sometimes prolonged observation was recommended [24]. Taken together, these studies match the clinical signal seen here: antipsychotic overdose is heterogeneous, and escalation decisions should be driven by physiologic instability and agent characteristics rather than the generic label of "antipsychotic poisoning."

Formulation effects and delayed toxicity

One pharmaceutical factor that should be emphasized is formulation. The presence of extended-release (XR) products can shift toxicity onset and prolong clinical course, which complicates early reassurance and discharge decisions. In a comparative analysis of XR versus immediate-release quetiapine overdoses, XR ingestion was associated with delayed peak sedation and longer recovery compared with immediate-release formulations when sedating co-ingestants were absent [25]. This supports a key practice implication consistent with our findings: when XR exposure is suspected or confirmed, observation windows may need to be extended, and "early improvement" should be interpreted cautiously because deterioration can occur later than expected.

QT prolongation: interpreting risk without over-triaging

QT prolongation is one of the most anxiety-provoking findings in psychotropic overdose care, yet the true risk depends on the drug, the clinical context, and how QT is measured. In a large prospective cohort from the Toxicology Investigators' Consortium, severe QT prolongation was shown to be drug-specific after acute overdose and included associations with several antipsychotics, underscoring that class-wide assumptions are misleading [26]. A more recent prospective cohort focused on acute antipsychotic poisoning identified practical early predictors of prolonged QTc—such as hypotension and particular agents like quetiapine—suggesting that QT risk can often be anticipated from bedside findings and exposure history [27]. For bedside decision-making, several studies support moving beyond "QTc cutoff reflexes." In antipsychotic overdose, assessment using a QT nomogram framework has been proposed to contextualize QT interval against heart rate and reduce false-positive risk labeling in tachycardic patients [28]. The QT nomogram itself has been evaluated against torsade cases and controls and demonstrated strong discriminatory performance for arrhythmogenic risk compared with simple QTc thresholds [29]. This is especially relevant in overdoses, where tachycardia is common and Bazett correction can inflate QTc estimates. A clinical review on drug-induced QT prolongation further emphasizes manual QT measurement and context-based interpretation rather than relying solely on automated ECG outputs [30]. In practical terms, our findings support a balanced approach: ECG screening is reasonable, but prolonged telemetry and ICU admission should be prioritized for patients with clear instability, severe QT prolongation in a high-risk heart-rate context, electrolyte abnormalities, or exposure to higher-risk agents, rather than applied uniformly to all antipsychotic overdoses.

Decontamination and supportive care: pragmatic expectations

Our management patterns reflect real-world toxicology practice where supportive care dominates and gastrointestinal decontamination is applied selectively. Evidence from quetiapine overdose cohorts suggests that early single-dose activated charcoal may reduce the probability of intubation modestly when administered within a narrow time window, without materially shortening ventilation duration once respiratory failure has occurred [23]. This implies that decontamination may have a role in carefully selected early presenters who can protect the airway, but it should not be expected to reverse severe toxicity once established. The broader message remains that airway management, hemodynamic stabilization, temperature control, and complication surveillance drive outcomes for both exposure groups.

Flumazenil: explaining low use and defining a safe niche

The limited and selective use of flumazenil observed in our cohort is consistent with ongoing clinical caution around seizure precipitation and diagnostic uncertainty in mixed ingestions. However, contemporary evidence also suggests that adverse-event rates vary strongly with patient selection. A poison center's ten-year experience involving a large number of acutely poisoned adults who received flumazenil reported a low seizure frequency, indicating that when clinicians choose cases carefully, serious complications may be uncommon [31]. At the same time, expert toxicology perspectives continue to highlight that flumazenil can be a "treatment or toxin," especially when given to benzodiazepine-dependent patients or those with pro-convulsant co-ingestions [32]. A broader clinical review contrasting empirical "coma cocktail" practices has also argued that antidotes should be used as targeted interventions rather than automatic components of undifferentiated altered mental status management [33]. More recently, bedside experience reports have re-examined the historical hesitancy around flumazenil, proposing that it can be used safely as a diagnostic and therapeutic tool in selected sedative-hypnotic toxicity scenarios when contraindications are actively excluded [34]. For a pharmaceutics and therapeutic management journal, the important takeaway is not that flumazenil should be avoided universally, but that its benefit–risk profile depends on clinical context and that explicit selection criteria can make its use safer and more reproducible across clinicians.

ICU utilization and opportunities for risk-stratified pathways

Because intoxication-related ICU admissions often include a substantial "observation" component, standardizing escalation criteria can improve resource use without compromising safety. A national ICU-registry study designed to predict true ICU treatment need in intoxicated patients found that only a small fraction of ICU admissions ultimately required ICU-specific interventions, and predictors such as respiratory insufficiency, older age, and very low GCS were strongly associated with genuine ICU treatment need [35]. This supports an actionable implication from our findings: integrating drug class, formulation (IR vs XR), physiologic instability, and structured ECG risk interpretation into a disposition pathway could reduce unnecessary ICU admissions while preserving safety for higher-risk presentations.

Strengths and limitations

This study provides a clinically relevant comparison between two common overdose categories using real-world emergency and inpatient care data, with attention to therapeutic practices and outcomes. Nonetheless, the observational design limits causal inference, and reliance on documentation and patient/attendant history may introduce misclassification, particularly in mixed ingestions. Toxicology confirmation was not uniform, and some laboratory or ECG variables may have been missing, potentially affecting predictor modeling. Finally, single-center practices and ICU thresholds may influence generalizability; however, the direction of findings is consistent with multiple toxicology cohorts and pharmacoepidemiologic evidence on co-exposure risk.

Summary of implications

In summary, antipsychotic overdoses more often require escalated monitoring due to hemodynamic effects, delayed toxicity in modified-release exposures, and higher prevalence of QT-related ECG changes, while benzodiazepine toxicity remains largely supportive-care-driven unless compounded by co-ingestion. Evidence supports selective decontamination in early presenters, careful QT interpretation grounded in heart-rate context and accurate measurement, and targeted antidote use particularly flumazenil guided by explicit contraindication screening and standardized protocols.

8. CONCLUSION

This comparative observational study indicates that antipsychotic drug overdose is generally associated with a higher clinical severity and greater need for intensive monitoring and critical care support than benzodiazepine toxicity, largely due to broader receptor-mediated effects such as hypotension, ECG abnormalities (including QT prolongation), and neurologic complications. In contrast, benzodiazepine toxicity most often follows a supportive-care course, but the risk of deterioration increases substantially in the presence of co-ingestion with other CNS depressants, emphasizing the importance of medication-safety vigilance. A structured approach that integrates airway and breathing assessment, hemodynamic evaluation, careful ECG interpretation, and formulation considerations (IR vs XR) can improve triage decisions and avoid unnecessary ICU admissions while maintaining patient safety. Gastrointestinal decontamination should remain selective and time-dependent, and flumazenil should be reserved for carefully selected cases with low seizure risk. Overall, protocol-guided management tailored to drug class and exposure context may enhance outcomes and optimize emergency and critical care resource utilization.

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