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Systematic review

Safety of Intravenous Sedative Agents Used in the Management of Acute Psychiatric Emergencies: A Systematic Review

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Abstract

Background: Acute psychiatric emergencies require intravenous sedation when agitation prevents safe assessment and treatment. Rapid calming requires attention to clinically important respiratory, cardiovascular, and neurological adverse effects and associated clinical consequences. This review evaluated the safety of intravenous sedatives used for acute agitation, including evidence relevant to psychiatric emergency practice. **Methods:** Original studies published by 31/05/2026 were examined in a narrative synthesis. Intravenous findings were distinguished from intramuscular results, and overlapping publications were identified. Randomized comparisons were considered alongside observational safety cohorts, with mixed diagnostic populations interpreted as indirect data. **Results:** Nine original reports represented eight underlying studies. Droperidol produced more sustained sedation than lorazepam, while midazolam provided faster early sedation in another randomized comparison. Active airway management occurred in three midazolam recipients in that trial. Adding droperidol or olanzapine to midazolam shortened sedation time without a statistically detected increase in overall adverse events. Intravenous olanzapine cohorts reported respiratory depression, hypoxia, and hypotension, with differences in outcome definitions and denominators. Evidence did not establish a consistently safest regimen. **Conclusions:** Respiratory compromise and hemodynamic instability remain central safety concerns during intravenous management of acute agitation. Individualized treatment, repeated clinical assessment, physiological monitoring, and immediate airway support are essential in monitored settings, while conclusions specific to primary psychiatric diagnoses remain limited by heterogeneous study populations.

Keywords: Acute agitation; psychiatric emergencies; intravenous sedation; droperidol; midazolam; olanzapine; adverse events; systematic review.

Introduction

Acute agitation is a time-sensitive behavioral presentation associated with psychiatric illness, substance exposure, and disturbed cognition, requiring assessment of both immediate danger and underlying disease (1). Initial management emphasizes respectful communication, reduction of environmental stimulation, and verbal de-escalation to establish cooperation and limit coercive interventions (2). Medical assessment remains essential because hypoxia, metabolic disturbance, intoxication, withdrawal, and neurological illness also produce agitation that resembles a primary psychiatric emergency (3).

Medication becomes relevant when severe agitation persists, cooperation is absent, or immediate behavioral control is necessary to permit essential care (4). The therapeutic goal is adequate calming that preserves clinical assessment and meaningful patient participation (4,5). Antipsychotics address psychosis-associated agitation, whereas benzodiazepines have particular roles in withdrawal and stimulant-related presentations, making the presumed cause central to medication selection (4,5).

Safety assessment extends beyond the proportion of patients who become calm because sedation introduces respiratory, cardiovascular, and neurological risks alongside its therapeutic effects (4,6). A systematic review and meta-analysis identified important differences in calming efficacy and adverse-event profiles across commonly used agents, with rapid midazolam sedation accompanied by concerns about oxygen saturation (6).

Intravenous administration permits rapid drug delivery and dose titration, creating a distinct clinical context from oral treatment or intramuscular injection. A previous review focused specifically on intravenous medications and identified heterogeneous prospective evidence, variable outcome measurements, and limited statistical power for uncommon serious complications (7). Safety interpretation requires

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attention to outcome definitions, observation periods, concurrent medications, and whether reported denominators represent individual patients or repeated drug administrations. Its findings demonstrated that evidence for individual intravenous drugs differed substantially in quantity and methodological strength, precluding straightforward conclusions across the entire drug class (7).

The present review focuses on respiratory compromise, hemodynamic instability, cardiac conduction abnormalities, extrapyramidal reactions, and serious adverse outcomes following intravenous treatment of acute agitation. The objective is to characterize the safety of intravenous sedative regimens relevant to acute psychiatric emergencies, assess the balance between rapid calming and treatment-related harm, and identify limitations affecting application to patients with primary psychiatric diagnoses.

Methods

This review was structured according to PRISMA 2020 and addressed adults receiving intravenous medication for acute agitation relevant to psychiatric emergency care (Fig 1). Eligible designs comprised randomized trials and prospective or retrospective observational cohorts. Psychiatric and undifferentiated agitation studies formed the principal evidence stratum; mixed-indication hospital cohorts provided supplementary safety evidence. Studies limited to intramuscular or oral administration, elective anesthesia, procedural sedation, routine ventilator sedation, pediatric populations, and isolated case reports were excluded. Mixed-route studies contributed only separately identifiable intravenous findings.

PubMed, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials were searched from inception for publications available by 31/05/2026. Search concepts combined agitation, aggression, psychiatric emergency, rapid tranquilization, intravenous administration, sedation, and adverse events. Drug terms included benzodiazepines, midazolam, lorazepam, antipsychotics, droperidol, haloperidol, olanzapine, ketamine, propofol, dexmedetomidine, chlorpromazine, and valproate. Controlled vocabulary and free-text terms were adapted to each database. Reference lists of relevant reviews and included reports were examined for additional studies. Database-specific strategies and actual execution dates were retained for reproducibility.

Two authors independently screened titles and abstracts after duplicate removal and subsequently assessed potentially eligible full texts. Each author applied the same eligibility criteria, and disagreements were resolved through discussion. Reasons for full-text exclusion were recorded by report. Publications describing the same trial population were linked before synthesis, preventing duplicate participant counting. The selection record distinguished database records, retrieved reports, and underlying studies within the PRISMA flow diagram.

Two authors independently extracted study design, setting, participant characteristics, agitation etiology, medication, dose, comparator, monitoring period, and safety outcomes using a standardized form. Outcomes included oxygen desaturation, respiratory depression, airway intervention, hypotension, bradycardia, arrhythmia, corrected QT prolongation, extrapyramidal reactions, and death. Sedation time and rescue medication requirements were extracted as secondary outcomes. Event definitions and patient-based or administration-based denominators were preserved exactly as reported for each regimen. Patient-level and dose-level outcomes were tabulated separately, and temporal association following treatment was distinguished from evidence establishing a medication-induced adverse reaction.

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Risk of bias was evaluated independently using RoB 2 for randomized comparisons and design-appropriate Joanna Briggs Institute checklists for observational studies. Assessments considered confounding, participant selection, outcome measurement, missing data, and selective reporting. Findings were synthesized narratively by medication and safety domain because clinical populations, interventions, follow-up periods, and adverse-event definitions differed substantially.

Results

Richards et al. randomized 202 agitated emergency department patients to intravenous lorazepam or droperidol, with substance-related presentations predominating and psychiatric illness accounting for 20 participants. Droperidol produced better sedation after the initial five minutes, and repeat dosing occurred more frequently with lorazepam, illustrating differences in treatment exposure relevant to safety interpretation (8). In Knott et al., 153 patients received intravenous midazolam or droperidol, with 11 and 10 adverse events reported, respectively. Three midazolam recipients required active airway management, including one intubation, despite similar overall event counts between groups (9).

Chan et al. studied 336 adults receiving titrated intravenous midazolam after droperidol, olanzapine, or placebo . Antipsychotic adjuncts shortened median sedation time by four and five minutes, respectively, without statistically detected differences in adverse-event profiles (10). Taylor et al. randomized 349 patients and demonstrated faster sedation with midazolam-droperidol than either droperidol or olanzapine alone, alongside fewer additional medication requirements. Overall adverse-event rates did not differ statistically, although the trial was primarily designed around sedation effectiveness rather than exclusion of uncommon serious harm (11).

The methamphetamine subgroup report from the same trial included 92 patients and therefore represented overlapping evidence rather than an additional independent cohort. Adverse events occurred in 7/34 combination recipients, 2/30 droperidol recipients, and 6/28 olanzapine recipients; oxygen desaturation was the most frequent event. These subgroup counts show respiratory events across regimens without establishing comparative safety superiority in a small diagnostic subset (12).

Martel et al. described 713 intravenous olanzapine recipients, including 245 treated for agitation, providing supplementary evidence from a mixed-indication emergency population. Hypoxia occurred in 74 patients and major respiratory complications in 15, with the latter category including airway stimulation or repositioning and intubation (13). Cole et al. prospectively evaluated parenteral olanzapine, with 295 intravenous recipients among 784 participants overall. Respiratory depression occurred in 11 intravenous recipients, representing 3.7%, and two underwent intubation, with observational treatment selection restricting causal interpretation (14).

Hunt et al. evaluated 1,247 intravenous olanzapine administrations in 252 hospitalized patients, with 104 administrations associated with at least one adverse drug event. Hypotension was the most frequently identified complication, and the predominance of intensive care administration limited direct applicability to primary psychiatric emergencies (15). Dragonetti et al. studied 304 inpatients receiving 1,214 administrations and reported vital-sign adverse effects after 7.41% of doses, increasing to 15.23% for doses exceeding 5 mg (16). Extensive concurrent medication exposure complicated attribution, and administration-based rates were not directly comparable with patient-based respiratory outcomes (14-16).

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The data set comprised nine original reports representing eight underlying studies, including four randomized trials and four observational studies (8-16). Mixed etiologies, overlapping publications, and divergent safety definitions prevented a defensible pooled adverse-event estimate. No cross-study ranking was calculated from these clinically heterogeneous, non-equivalent estimates. Tables 1 and 2 summarize study characteristics and the principal reported safety findings while preserving the original denominators.

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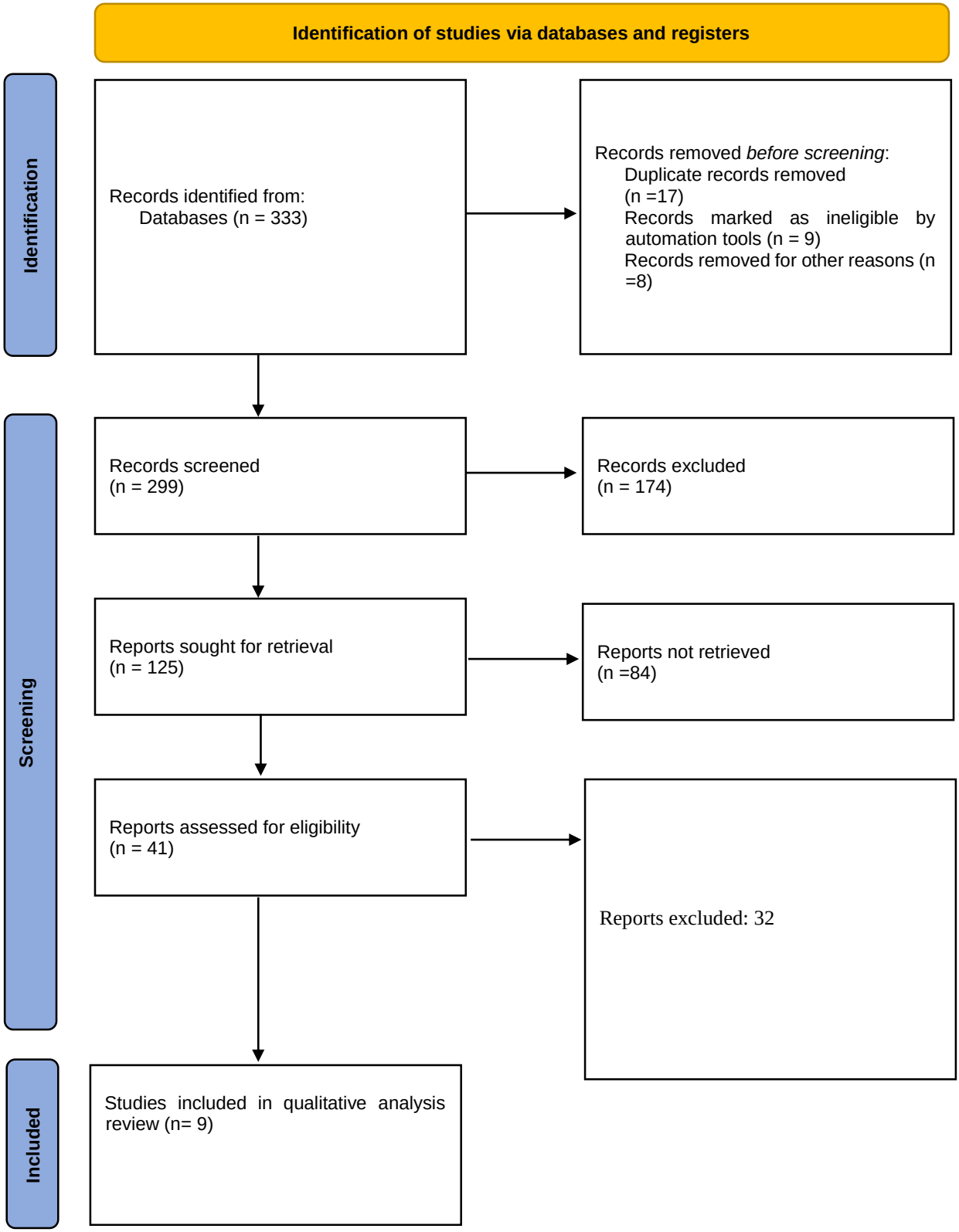


Figure 1: PRISMA flow chart

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Table 1. Characteristics of the original reports

Report	Design and population	Intravenous treatment
Richards, 1998	Randomized trial; 202 ED patients; predominantly stimulant-related agitation	Lorazepam versus droperidol (8)
Knott, 2006	Randomized trial; 153 adults; psychiatric illness, intoxication, or both	Midazolam or droperidol, 5 mg repeated every five minutes (9)
Chan, 2013	Randomized trial; 336 agitated ED patients	Droperidol 5 mg, olanzapine 5 mg, or placebo, followed by titrated midazolam (10)
Taylor, 2017	Randomized trial; 349 agitated ED patients	Midazolam 5 mg-droperidol 5 mg versus droperidol 10 mg or olanzapine 10 mg (11)
Yap, 2017	Methamphetamine subgroup; 92 participants from Taylor trial	Same randomized regimens; overlapping population (12)
Martel, 2016	Retrospective ED cohort; 713 patients, including 245 with agitation	Olanzapine; mixed indications (13)
Cole, 2017	Prospective ED cohort; 295 IV recipients among 784 total participants	Olanzapine; IV findings extracted separately (14)
Hunt, 2021	Retrospective inpatient cohort; 252 patients; 1,247 administrations	Olanzapine; predominantly intensive care administration (15)
Dragonetti, 2025	Retrospective inpatient cohort; 304 patients; 1,214 administrations	Olanzapine 1-20 mg; mixed hospital population (16)

Table 2. Reported outcomes and interpretation

Report	Finding	Interpretation
Richards	Repeat doses: lorazepam 40 versus droperidol 8	Efficacy finding; limited adverse-event detail in abstract (8)
Knott	Adverse events: midazolam 11 versus droperidol 10; three midazolam recipients required airway management	Event counts and airway severity differed (9)
Chan	No statistically detected adverse-event difference across three groups	Equivalent safety was not established (10)
Taylor	No statistically detected overall adverse-event difference	Faster combination sedation did not establish superior safety (11)
Yap	Any adverse event: 7/34 combination, 2/30 droperidol, 6/28 olanzapine	Desaturation predominated; subgroup overlapped parent trial (12)
Martel	Hypoxia: 74/713; major respiratory complications: 15/713	Mixed indications; complications included airway maneuvers and intubation (13)
Cole	IV respiratory depression: 11/295; IV intubation: 2/295	Patient-based outcomes; observational comparison (14)
Hunt	At least one adverse event: 104/1,247 administrations	Administration-based rate; hypotension most frequent (15)
Dragonetti	Vital-sign adverse effects: 7.41% of doses; 15.23% above 5 mg	Dose association confounded by concurrent medications (16)

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Discussion

The we found that rapid intravenous calming and medication safety represent related, distinct treatment outcomes, with no consistently safest regimen established across the reviewed reports. The Cochrane benzodiazepine review identified limited, low-certainty data and additional sedation with some combination regimens, reinforcing caution when interpreting faster behavioral control as an overall safety advantage (17). The Cochrane droperidol review supported its effectiveness without establishing freedom from respiratory or cardiovascular harm, particularly given imprecise estimates for uncommon events (18).

Cardiac safety requires distinction between electrocardiographic changes and arrhythmia, rather than treating these outcomes as interchangeable manifestations of toxicity (19). In a large emergency department cohort, one torsades de pointes event occurred among 16,546 droperidol recipients, corresponding to 0.006%, in a patient with multiple risk factors. That mixed-population estimate provides useful context for rare arrhythmias, without constituting an intravenous-only psychiatric risk estimate or demonstrating equivalence between different medications (20). Respiratory surveillance remains equally important because airway events were directly observed in the intravenous randomized and observational evidence (9,13,14).

Patient characteristics and treatment sequence influence observed harm, complicating comparisons based solely on the selected medication (21). A multicenter analysis associated older age, alcohol intoxication, and administration of multiple parenteral sedatives within 60 minutes with increased adverse-event risk, although these observational associations do not establish causation (21). Monitoring intensity also affect detection and therefore observed event frequencies (13,14,21). Neurological tolerability also deserves attention because the Cochrane haloperidol review documented extrapyramidal concerns alongside substantial uncertainty across comparisons (22). A network meta-analysis of emergency tranquilization reported imprecision and predominantly very low confidence in safety estimates, limiting confidence in medication rankings, particularly when transferring intramuscular evidence to intravenous practice (23).

The intravenous olanzapine literature illustrates the importance of separating feasibility from established comparative safety, especially when a medication is administered through an off-label route. Previous synthesis identified encouraging observational findings alongside unresolved questions about optimal use, coadministered sedatives, and respiratory adverse effects (24). The present findings add hemodynamic signals from hospitalized populations, although those cohorts differ from psychiatric emergency patients in illness severity, concurrent medication exposure, and repeated dosing patterns (15,16). The 3.7% respiratory-depression estimate and the administration-based hemodynamic event rates describe different outcomes and populations, rather than interchangeable estimates of a single underlying risk (14-16).

Interpretation also depends on transparent reporting of eligibility, information sources, selection decisions, and the distinction between individual studies and their associated reports, as emphasized by PRISMA 2020 (25). Principal data limitations include heterogeneous diagnoses, inconsistent event definitions, short observation periods, and observational confounding (7,13-16,23). These restrict generalization to primary psychiatric disorders and prevent inference that an absence of statistically significant differences establishes equivalent safety (7,11,23). Future comparisons require standardized respiratory and cardiovascular endpoints, explicit airway-

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intervention reporting, diagnostic subgroup analyses, and follow-up adequate to identify delayed neurological reactions and other clinically important harms.

Conclusion

Intravenous sedatives provide rapid control of severe acute agitation, with safety influenced by medication choice, dose, concurrent treatment, and underlying illness. Respiratory compromise and hemodynamic instability were the clearest recurring concerns. Droperidol-containing regimens offered effective calming, while midazolam exposure required particular attention to airway events. Intravenous olanzapine was associated with respiratory and blood-pressure abnormalities in observational cohorts.

List of abbreviations

Abbreviation	Definition
BETA	Best Practices in Evaluation and Treatment of Agitation
ED	Emergency department
IV	Intravenous
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QT	Electrocardiographic interval encompassing ventricular depolarization and repolarization
RoB 2	Revised Cochrane risk-of-bias tool for randomized trials
SIESTA	Sedation for Acute Agitation in Emergency Department Patients: Targeting Adverse Events

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