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Review Article

Haloperidol and QTc Prolongation in Adults With Psychiatric or Behavioral Indications: A Systematic Review and Meta-analysis

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Haloperidol and QTc prolongation in adults with psychiatric or behavioral indications: a systematic review and meta-analysis

Running title: Haloperidol and QTc prolongation

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Abstract

Objective: Haloperidol is widely used for agitation, psychosis, and delirium, but concerns remain regarding QTc prolongation and ventricular arrhythmias. We evaluated the association between haloperidol and QTc prolongation in adults with psychiatric or behavioral indications and secondarily summarized clinically relevant proarrhythmic events.

Methods: We conducted a systematic review registered in PROSPERO (CRD420261306215) following PRISMA 2020. Randomized controlled trials and comparative observational studies enrolling adults receiving haloperidol versus placebo, no antipsychotic, or another antipsychotic were included. The primary outcome was QTc prolongation as defined by study authors. A sensitivity analysis assessed QTc ≥500 ms when explicitly reported by study arm. Meta-analyses were performed using odds ratios when appropriate. Risk of bias was assessed with RoB 2 and the Newcastle–Ottawa Scale; certainty was rated with GRADE.

Results: Sixteen unique studies (17 publications; 16,189 participants) were included. In placebo- or no-antipsychotic comparisons (k=3 randomized controlled trials), haloperidol was not associated with a clear difference in QTc prolongation by author-defined thresholds (random-effects OR=1.18, 95%CI 0.83–1.69; I^2=0%). In the sensitivity analysis restricted to QTc ≥500 ms (k=2 randomized controlled trials), evidence was imprecise due to the small number of studies, low event frequency, and wide confidence interval (OR=1.00, 95%CI 0.38–2.65). Clinically relevant proarrhythmic events were infrequent and usually not reported by study arm or yielded double-zero data, precluding quantitative synthesis.

Conclusions: In placebo-controlled trials conducted in intensive care settings, haloperidol did not show an increase in QTc prolongation by author-defined criteria. Evidence for QTc ≥500 ms remains limited by imprecision, and clinically relevant proarrhythmic events were rare and inconsistently reported.

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Introduction

Haloperidol, a first-generation antipsychotic introduced into clinical practice in the late 1950s, has been used for decades to manage psychosis and agitation in adults and remains widely used worldwide, as reflected by its inclusion in essential medicines lists.[1,2] In hospital practice, including delirium and intensive care unit (ICU) settings, its use also remains common.[3,4] However, its clinical utility is tempered by an important cardiovascular safety concern: prolongation of the corrected QT interval (QTc), a marker of delayed ventricular repolarization associated with potentially life-threatening ventricular arrhythmias, including torsades de pointes (TdP), ventricular fibrillation, and sudden cardiac death.[5]

Critically ill patients are particularly vulnerable to acquired long QT, as multiple predisposing factors often coexist, including medical comorbidity, bradycardia, electrolyte abnormalities, and polypharmacy.[5,6] In this setting, prolonged QTc is common and has been associated with both clinical factors and medications frequently encountered in routine practice.[6]

Although antipsychotics as a class have been linked to arrhythmic risk in community populations, including an increased risk of sudden cardiac death,[7,8] the evidence specific to haloperidol remains heterogeneous across populations, doses, and routes of administration. In schizophrenia, real-world electrocardiographic studies have shown variable QTc effects across antipsychotic agents, including haloperidol.[9] In hospitalized older adults receiving inpatient haloperidol, longitudinal QTc changes have also been described, with some patients progressing into abnormal ranges.[3] By contrast, in higher-risk settings—particularly ICU care and intravenous exposure—case reports and case series have described TdP associated with intravenous haloperidol, especially at high doses and/or when QTc exceeds 500 ms.[10] In critically ill patients, intravenous haloperidol has also been examined in relation to electrocardiographic markers associated with arrhythmic risk.[11] At the same time, observational data suggest that the relationship between QTc prolongation and hard clinical outcomes may be affected by residual confounding and by differences in event definition and ascertainment.[5,12]

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Taken together, these inconsistencies leave an important clinical gap: the comparative effect attributable to haloperidol on QTc remains uncertain, and it is still unclear to what extent QTc changes translate into clinically relevant proarrhythmic outcomes across different routes of administration, exposure intensities, treatment durations, and baseline risk profiles.

Accordingly, this systematic review aimed to evaluate, in adults treated for psychiatric or behavioral indications, the association between haloperidol use and (a) QTc prolongation, as defined by study authors, and (b) clinically relevant proarrhythmic events, compared with other antipsychotics or with no antipsychotic exposure. We conducted a systematic review and meta-analysis of randomized controlled trials and comparative cohort studies, with quantitative synthesis when appropriate and structured risk-of-bias assessment to support clinically relevant conclusions.

Methods

Study design and registration

We conducted a systematic review with meta-analysis of comparative studies in accordance with PRISMA 2020. The protocol was prospectively registered in PROSPERO (CRD420261306215). As prespecified, randomized controlled trials and comparative cohort studies evaluating adults treated with haloperidol for psychiatric or behavioral indications were eligible.

Information sources and search strategy

We systematically searched PubMed (MEDLINE), Embase.com, and LILACS from database inception, with no language or date restrictions. The search strategy combined controlled vocabulary and free-text terms related to haloperidol, QT interval, QT prolongation, torsades de pointes, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death, together with methodological filters for clinical trials and cohort studies.

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The electronic search was run on February 16, 2026. Full database-specific strategies, including search terms, Boolean operators, and platform-specific syntax, are provided in Appendix S1.

Eligibility criteria

We included randomized controlled trials (parallel-group or crossover designs with an adequate washout period) and comparative cohort studies, whether prospective or retrospective. We excluded case reports, case series, cross-sectional studies, case-control studies, pharmacovigilance or spontaneous reporting studies, studies based exclusively on administrative databases or registries without clinical confirmation of outcomes, preclinical or in vitro studies, and systematic reviews; the latter were used only to identify potentially relevant references.

Eligible studies enrolled adults aged 18 years or older treated with haloperidol for psychiatric or behavioral indications, including schizophrenia or psychosis, bipolar disorder or mania, acute agitation, in-hospital or ICU delirium, and other behavioral disturbances. Studies conducted exclusively in pediatric or adolescent populations were excluded, as were studies in which haloperidol was used solely for non-psychiatric indications, such as perioperative antiemetic prophylaxis.

The exposure of interest was haloperidol administered by any route (oral, intramuscular, or intravenous), at any dose and duration, provided that drug-specific data could be extracted. Eligible comparators included other antipsychotics and/or no antipsychotic exposure, such as placebo, usual care, or no use. Studies without a concurrent comparator were excluded.

We considered studies conducted in any care setting in which haloperidol was used for psychiatric or behavioral indications in adults, including ICUs, general wards, emergency departments, psychiatric units, and outpatient care.

Unit of analysis and handling of multiple publications

The unit of inclusion was the unique study rather than the individual publication. When multiple publications arose from the same trial or cohort, they

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were grouped as a single study for eligibility assessment, PRISMA counting, data extraction, and risk-of-bias assessment. In these cases, the primary publication was used for methodological description and risk-of-bias assessment, while secondary publications were used only as complementary sources for specific outcomes when they contributed additional information.

Study selection and data extraction

Two reviewers independently screened records in two stages: title/abstract screening followed by full-text assessment. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

Data were independently extracted by two reviewers using a standardized form. Extracted variables included study characteristics, population features, exposure details, comparator characteristics, outcome definitions, QTc correction method, reported effect measures, adjustment variables in observational studies, and funding or conflicts of interest when reported. Study authors were not contacted for missing data.

Outcomes

The primary outcome was QTc prolongation, or long QTc, according to each study's definition. We accepted definitions based on absolute QTc thresholds (e.g., >450, >470, or >500 ms) and/or increases from baseline (e.g., ≥30 or ≥60 ms). Whenever possible, this outcome was extracted as a binary event per patient.

Secondary outcomes included torsades de pointes, sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death occurring during treatment or within 30 days after discontinuation, according to the time window reported by each study.

We also performed a prespecified sensitivity analysis restricted to studies that explicitly reported QTc ≥500 ms (or >500 ms, according to the original wording) by study arm. Only studies with directly extractable and comparable data for this threshold were included.

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Risk of bias and data synthesis

Risk of bias was independently assessed by two reviewers, with discrepancies resolved by consensus. We used the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the Newcastle–Ottawa Scale (NOS) for cohort studies.

Quantitative analyses were performed in Jamovi version 2.6.44. Meta-analysis was conducted when at least two studies reported the same outcome with sufficiently comparable definitions and data. Although the protocol allowed the use of risk ratios or odds ratios for dichotomous outcomes, we consistently reported odds ratios (ORs) with 95% confidence intervals (95%CIs) to maintain uniformity across the primary and sensitivity analyses, given the low event frequency and the structure of the available data. Forest plots were reproduced in R (base graphics and metafor package) to generate publication-ready figures; pooled estimates were verified against the Jamovi outputs.

Random-effects models were used for the primary analysis when appropriate and technically stable. For the sensitivity analysis restricted to QTc ≥500 ms, a fixed-effect model was accepted because of the small number of studies and the absence of estimable heterogeneity.

Double-zero studies were excluded from the primary meta-analysis because they did not contribute comparative information and were summarized descriptively in the Supplementary Material. In studies with multiple haloperidol arms sharing the same comparator, haloperidol arms were combined to avoid double-counting the control group. For cohort studies, the most adjusted estimate available was prioritized. When quantitative synthesis was not feasible, we performed a structured narrative synthesis.

Additional analyses

Subgroup analyses were prespecified according to route of administration, dose or exposure intensity, treatment duration, clinical setting, indication, and study design. However, these analyses were performed only when sufficient information and adequate comparability were available. Because reporting was heterogeneous

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and directly comparable data were limited, route, dose, and duration were ultimately explored mainly in descriptive form.

Formal assessment of publication bias was planned only when at least 10 studies contributed to the same outcome. Because this threshold was not met, no formal evaluation of small-study effects was performed.

Certainty of the evidence was assessed using the GRADE approach for the critical outcomes of QTc prolongation, QTc ≥500 ms, and, when possible, clinically relevant proarrhythmic events.

Results

Study selection

The search identified 246 records through electronic databases. After removal of 15 duplicates, 231 records underwent title and abstract screening, and 189 were excluded.

Forty-two reports were sought for full-text assessment; two could not be retrieved, and 40 were assessed for eligibility. Ultimately, 16 unique studies, reported in 17 publications, were included (Figure 1). One publication represented a secondary analysis of a trial already included and was used only as a complementary source for QTc data extraction rather than counted as a separate study. Overall, the included studies contributed 16,189 participants.

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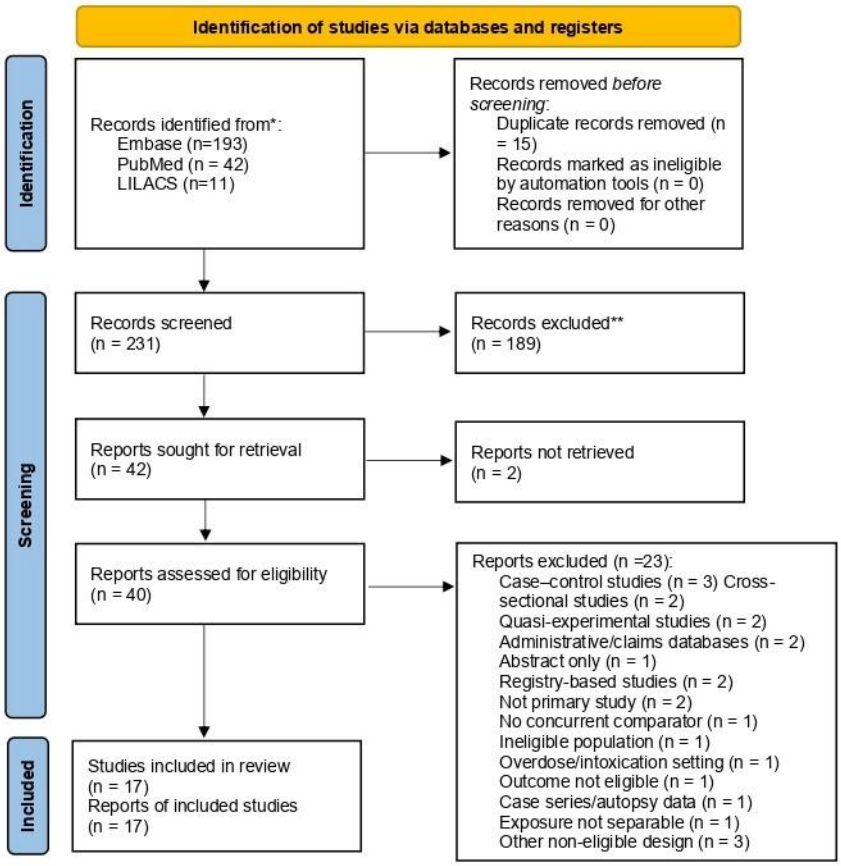


Figure 1. PRISMA 2020 flow diagram of study selection. The diagram summarizes the processes of identification, screening, eligibility assessment, and study inclusion. Sixteen unique studies, reported across 17 publications, were included.

Characteristics of the included studies

Of the 16 included studies, 10 were randomized controlled trials and 6 were comparative observational studies. Experimental evidence was concentrated largely in hospitalized patients, particularly in the ICU, where intravenous haloperidol predominated. By contrast, studies outside the ICU more often

evaluated intramuscular or oral administration, mainly in psychiatric, general inpatient, or geriatric populations. A summary of the general characteristics is presented in Table 1, whereas the full details of the trials and observational studies are shown in Tables S1 and S2.

Table 1. General characteristics of the included studies

Characteristic	**Randomized controlled trials (n=10)**	**Comparative observational studies (n=6)**
Total participants	3,919	12,270
Setting (n studies)	ICU (7/10)	Hospital/geriatrics/psychiatry (4/6); ICU (1/6); mixed (1/6)
Haloperidol route (n studies)	IV or IV-predominant (7/10); IM (2/10); oral (1/10)	IV (1/6); oral (2/6); IM (0/6); mixed/NR (3/6)
Comparators (n studies)	Placebo/no antipsychotic (7/10); active antipsychotic (3/10)	Quetiapine (1/6); other antipsychotics (3/6); no antipsychotic exposure (2/6)
Primary outcome (n studies)	QTc prolongation (author-defined) (8/10); QTc ≥500 ms as safety threshold (2/10)	QTc prolongation/SQTP (5/6); "critical" QTc threshold (1/6)
Reporting of major clinical events	Rare and inconsistently reported by arm; descriptive synthesis only	Rare and inconsistently reported by arm; descriptive synthesis only

Note: Sixteen unique studies reported in 17 publications were included. One publication corresponded to a secondary analysis of an already included trial and was not counted as an independent study. Full study-level detail is provided in Tables S1 and S2. ICU, intensive care unit; SQTP, severe QTc prolongation.

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QTc measurement and outcome definitions

Substantial heterogeneity was observed in both the measurement and definition of QTc prolongation. Studies used 12-lead electrocardiograms, monitor strips, serial recordings, or ECGs obtained at the clinician's discretion, and applied different correction formulas, including Bazett, Fridericia, Framingham, and Hodges; in some studies, the correction formula was not reported. Because definitions of prolonged QTc were not standardized, the primary analysis was based on QTc prolongation as defined by study authors, with a separate sensitivity analysis restricted to the strict threshold of QTc ≥500 ms.

Primary outcome: QTc prolongation as defined by study authors

Three randomized controlled trials comparing haloperidol with placebo or no antipsychotic provided sufficiently comparable data for meta-analysis of the primary outcome. In absolute terms, QTc prolongation occurred in 82/1,706 patients (4.8%) receiving haloperidol and in 52/1,338 patients (3.9%) receiving placebo or no antipsychotic. In the pooled analysis, haloperidol was not associated with a statistically significant difference in the risk of QTc prolongation (random-effects model: OR, 1.18; 95%CI, 0.83-1.69; I^2=0%) (Figure 2). Study-level details are presented in Table S7.

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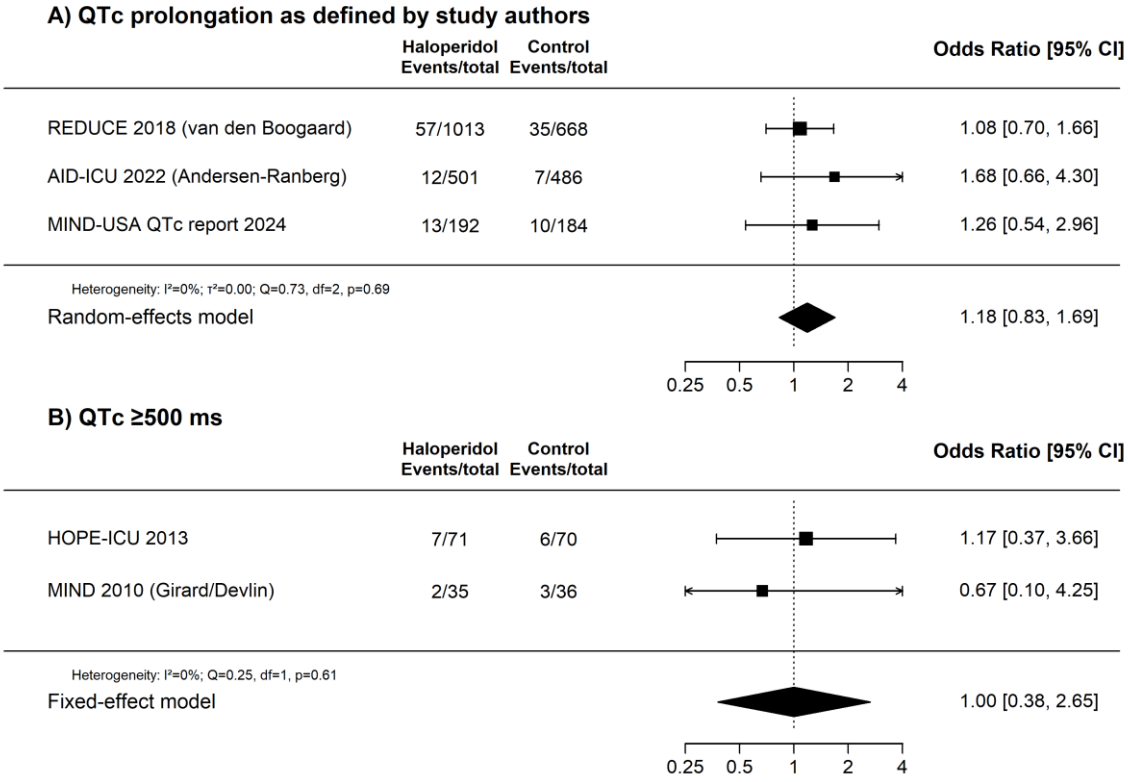


Figure 2. Forest plots of randomized controlled trials comparing haloperidol versus placebo/no antipsychotic. Panel A shows QTc prolongation as defined by study authors and was pooled using a random-effects model (DerSimonian-Laird). Panel B shows the sensitivity analysis restricted to QTc ≥500 ms and was pooled using a fixed-effect model. Squares represent study-level odds ratios, with size proportional to inverse-variance weight; horizontal lines represent 95% confidence intervals; diamonds represent pooled estimates. The x-axis is displayed on a logarithmic odds-ratio scale. Arrows indicate confidence intervals extending beyond the plotting range. CI, confidence interval; OR, odds ratio; QTc, corrected QT interval.

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Sensitivity analysis: QTc ≥500 ms

Two randomized controlled trials with placebo comparators provided directly extractable data for QTc ≥500 ms. In absolute terms, events occurred in 9/106 patients (8.5%) in the haloperidol group and 9/106 patients (8.5%) in the comparator group. In this analysis, the pooled estimate showed no difference between haloperidol and the comparator group (OR, 1.00; 95%CI, 0.38-2.65; I^2=0%) (Figure 2), although the confidence interval remained wide, reflecting limited precision.

QTc ≥500 ms in active-comparator studies

In studies with active comparators, no QTc ≥500 ms events occurred in either arm (double-zero studies). These studies (Miceli 2010, Harvey 2004, and Harrigan 2004) enrolled non-ICU populations receiving intramuscular or oral haloperidol and comparators (ziprasidone, lorazepam, or other antipsychotics), with small sample sizes and short observation windows. The absence of events in both arms is itself a clinically relevant finding, as it suggests that, in these lower-risk settings and with the doses and routes studied, the absolute risk of QTc ≥500 ms was very low for all treatments compared. However, because double-zero cells contribute no comparative information, these studies were excluded from the primary quantitative analysis and are summarized descriptively in Table S7C of the Supplementary Material.

Clinically relevant proarrhythmic events

Clinically relevant proarrhythmic events—including torsades de pointes, sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death—were rare. In most studies, these outcomes were not reported separately by study arm, were reported only as aggregated events, or did not occur in either group. Accordingly, a robust meta-analysis was not feasible, and these outcomes were summarized descriptively.

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Route, dose, and duration of exposure

The strongest comparative evidence came from ICU studies, which predominantly involved intravenous haloperidol. Studies evaluating intramuscular or oral administration were fewer, generally included smaller samples, and often focused on intermediate electrocardiographic outcomes. In observational studies, dose, route, and treatment duration were inconsistently or incompletely reported, precluding formal subgroup analyses or meta-regression. These variables were therefore summarized descriptively.

Risk of bias and certainty of the evidence

Among randomized controlled trials, risk of bias was generally low or raised some concerns. Among observational studies, overall methodological quality was generally moderate. Certainty of the evidence was rated as moderate for the primary outcome of QTc prolongation as defined by study authors, low for the analysis restricted to QTc ≥500 ms, and very low or insufficient for clinically relevant proarrhythmic events.

Discussion

In this systematic review and meta-analysis, which included 16 comparative studies (10 randomized trials and 6 cohort studies), haloperidol was not associated with a statistically significant increase in QTc prolongation compared with placebo or no antipsychotic in the pooled experimental evidence. The overall effect for QTc prolongation, as defined by study authors, was small and compatible with no clinically meaningful difference (OR, 1.18; 95%CI, 0.83-1.69), whereas the stricter analysis restricted to QTc ≥500 ms was imprecise because of the small sample size and the low event frequency (OR, 1.00; 95%CI, 0.38-2.65). Consistently, clinically relevant proarrhythmic events were rare and, when reported, did not allow robust quantitative synthesis. Overall, the currently available comparative safety signal rests more on intermediate electrocardiographic outcomes than on major clinical arrhythmic events.

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These findings are broadly consistent with major ICU trials, in which haloperidol was administered under relatively strict monitoring and discontinuation criteria. In AID-ICU, treatment interruption due to QTc prolongation was uncommon and only slightly more frequent with haloperidol than with placebo, supporting the view that in a closely monitored setting, clinically relevant electrical toxicity is uncommon and may be manageable with standard mitigation strategies such as treatment interruption and correction of reversible causes.[13] Similarly, in the prespecified QTc analysis derived from MIND-USA, day-to-day QTc changes were minimal, and the adjusted effect of haloperidol on next-day QTc did not differ from placebo.[14] The primary MIND-USA report also showed no clinical benefit of haloperidol over placebo for delirium within a protocol that incorporated QTc safety thresholds and dose titration, thereby limiting sustained exposure in patients at higher electrical risk.[15] Evidence from REDUCE further suggests that the incremental QTc risk attributable to haloperidol may be small when patients are appropriately selected and stopping rules are enforced.[16] Likewise, the post hoc analysis by Duprey et al. found similar baseline and maximum QTc values, as well as comparable proportions of QTc ≥500 ms, between haloperidol and placebo.[17] The pilot trial by Al-Qadheeb et al. also reported comparable rates of QTc-related treatment discontinuation between groups.[18] In a pragmatic ICU agitation cohort, intravenous haloperidol did not appear to carry a greater QTc burden than intravenous olanzapine, again suggesting that any observed differences may depend heavily on comparator choice, patient profile, and baseline risk.[19]

At the same time, part of the observational literature suggests that haloperidol-associated arrhythmic risk may become more apparent in selected high-risk settings. In hospitalized adults, Shao et al. reported a low overall prevalence of critical QTc prolongation and no torsades de pointes, yet haloperidol remained an independent predictor of QTc prolongation alongside established risk factors such as hypokalemia and overdose.[20] In a large multicenter overdose cohort, haloperidol was associated with a higher likelihood of severe QT prolongation, reinforcing the importance of exposure intensity and physiological stressors in modifying risk.[21] Real-world ECG-based data have similarly shown a

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meaningful incidence of severe QTc prolongation, a dose-response relationship between hypokalemia severity and severe QTc prolongation, and a marked increase in ventricular arrhythmic risk once QTc exceeds 500 ms.[22] In that same cohort, the combination of high-risk antipsychotic exposure and hypokalemia appeared to produce synergistic increases in risk, underscoring that the safety profile of haloperidol depends not only on the drug itself but also on the accumulation of patient-level vulnerabilities, including age, renal and cardiac dysfunction, electrolyte imbalance, and polypharmacy.[22] In particularly susceptible populations, such as patients receiving hemodialysis, an active-comparator new-user analysis found a higher 1-year risk of sudden cardiac death with oral haloperidol than with chlorpromazine, suggesting that in settings of extreme baseline vulnerability, the risk-benefit balance may differ from that observed in ICU trials.[23] By contrast, studies using more definitive outcome ascertainment, such as autopsy-confirmed sudden cardiac death in patients with dementia, have not consistently identified an association with oral haloperidol.[24] Taken together, these differences between randomized and real-world evidence are clinically plausible: trials typically exclude patients with marked baseline QT prolongation, impose dose limits and stopping rules, and monitor patients closely, whereas observational studies capture broader comorbidity, more variable prescribing, and longer windows for event detection.

This review has several strengths, including its comparative design, the inclusion of both randomized and observational evidence, and the formal assessment of both risk of bias and certainty of the evidence. These features allow a clearer distinction between the moderate-certainty evidence for QTc prolongation as defined by study authors and the lower-certainty evidence for QTc ≥500 ms and clinically relevant proarrhythmic outcomes. Several limitations should also be acknowledged. First, there was substantial heterogeneity in QTc definition and measurement, including differences in correction formulas, monitoring methods, time windows, and thresholds. Second, although terms related to QTc prolongation and arrhythmias were included in the search strategy, these outcomes are frequently reported as secondary or safety endpoints in psychiatric studies and

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may not be described in the title or abstract of potentially relevant articles; accordingly, some eligible studies may not have been identified by the search, and this should be considered a source of potential selection bias. Third, the evidence base was dominated by ICU studies using intravenous haloperidol, which limits generalizability to psychiatric, outpatient, or non-ICU settings and to oral or intramuscular administration. Fourth, although subgroup analyses by route of administration, dose, and treatment duration were prespecified as potential moderators, these analyses could not be performed as planned: the small number of studies contributing to each comparison, the heterogeneity in exposure reporting, and the low event frequency precluded formal subgroup analyses or meta-regression with adequate statistical power. Fifth, study authors were not contacted for missing data, which may have prevented the recovery of potentially relevant outcome information. Sixth, clinically relevant arrhythmic events were inconsistently reported and were often not available by study arm. Seventh, observational studies were subject to residual confounding and non-standardized exposure characterization, limiting the evaluation of important effect modifiers such as dose, hypokalemia, renal dysfunction, and polypharmacy.

From a clinical standpoint, these findings suggest that in adults with ICU delirium or agitation treated with usual haloperidol regimens under structured safety protocols, haloperidol does not appear to confer a clear increase in QTc prolongation compared with control. In the ICU context specifically, intravenous haloperidol is frequently used for delirium management, and the available trial evidence—largely derived from this setting—indicates that clinically relevant QTc toxicity is uncommon when standard precautions are applied, including baseline electrocardiographic screening, dose titration, and predefined discontinuation thresholds. This conclusion is broadly consistent with large-scale pharmacovigilance data, which suggest that serious arrhythmic outcomes attributable to haloperidol, such as torsades de pointes or sudden cardiac death, are rare in absolute terms in real-world populations, even if relative risk may be increased in high-risk subgroups. The rarity of these events in both trial and pharmacovigilance contexts reinforces that the primary clinical concern is not a

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high background rate of arrhythmia, but rather the amplification of risk in patients with accumulating vulnerabilities—particularly severe QTc prolongation exceeding 500 ms, hypokalemia, renal impairment, and concomitant QT-prolonging medications. This supports a risk-stratified monitoring strategy focused on baseline QTc, electrolyte disturbances, cardiac and renal comorbidity, and concomitant QT-prolonging medications, rather than intensive uniform monitoring for all patients. This interpretation is consistent with recommendations to implement standardized hospital strategies aimed at preventing torsades de pointes and improving consistency in QTc surveillance.[25] Future comparative studies should prioritize standardized outcome definitions, including QTc ≥500 ms and ΔQTc; report clinically relevant arrhythmic events by study arm with adequate follow-up; specifically address high-risk populations such as patients receiving hemodialysis or those with severe hypokalemia, heart failure, or renal impairment; and provide enough detail to support analyses by dose and route of administration.[22,23]

In conclusion, the available comparative evidence suggests that haloperidol, particularly in ICU settings and when used within structured safety protocols, is not associated with a significant increase in QTc prolongation compared with placebo or no antipsychotic. However, certainty decreases when the analysis is restricted to QTc ≥500 ms, and the available data remain insufficient to estimate the risk of major proarrhythmic events with precision. Real-world evidence indicates that risk may be amplified in the presence of modifiable factors—especially hypokalemia—and in populations with very high baseline vulnerability, supporting a clinical approach centered on comprehensive risk assessment, correction of reversible factors, and targeted monitoring. These findings should not be interpreted as evidence of absence of risk in patients with marked baseline QTc prolongation, uncorrected electrolyte abnormalities, severe renal impairment, or concomitant exposure to multiple QT-prolonging drugs.

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Disclosure

The authors declare no conflicts of interest related to this work for the last 3 years.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Material. Additional extracted data and analytic decisions are available from the corresponding author upon reasonable request.

Author contributions

JUC contributed to conceptualization, methodology, study selection, data extraction, risk of bias assessment, formal analysis, and writing—original draft.
MCAA contributed to study selection, data extraction, risk of bias assessment, and writing—review and editing.
KTRC contributed to study selection, data extraction, data curation, and writing—review and editing.
CACA contributed to methodology, formal analysis, interpretation of results, and writing review and editing.
PALB contributed to investigation, validation, interpretation of results, and writing—review and editing.
MCME contributed to conceptualization, methodology, supervision, formal analysis, project administration, and writing—review and editing.
All authors have read and approved the final submitted version and take public responsibility for all aspects of the work.

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Supplementary Material

Supplementary tables

Table S1. Detailed characteristics of the randomized controlled trials

Study (year)	Country	Design	Setting	Population/indication	N (Halo/Comp/Total)	Haloperidol (route/dose/ duration)	Comparator	QTc assessment	QT correction	Definition of QTc prolongation	QTc time window
Reade et al. 2009	Australia	Randomized open-label pilot RCT	ICU medical-surgical	Mechanical ventilation; extubation delayed by agitated delirium	10 / 10 / 20	IV infusion 0.5–2 mg/h; optional 2.5 mg loading dose; according to clinical need	Dexmedetomidine infusion 0.2–0.7 µg/kg/h	QTc assessed every 8 h during infusion; comparison with baseline QTc	NR (correction formula not specified)	Abnormal QTc >0.440 s (440 ms); analysis also included values "longer than baseline" during infusion	During infusion (ICU)
Harrigan et al. 2004	United States (multicenter /industry)	Prospective randomized study (6 arms) with metabolic inhibition	Stable psychosis (clinical/research setting)	Psychotic disorders; steady state on antipsychotic treatment	27 / (other antipsychotics) / approximately 164	Oral 15 mg/day (steady state)	Thioridazine, ziprasidone, quetiapine, olanzapine, risperidone (± CYP inhibitors)	ECG: mean of 9 ECGs around the expected Tmax, measured on 3 consecutive days, during monotherapy steady state and with a metabolic inhibitor	Baseline-corrected QTc (primary measure; preferred over Bazett because of bias at extreme heart rates)	Clinical outlier: QTc >500 ms (not observed); also evaluates the mean change in baseline-corrected QTc	At steady state near Cmax (and with metabolic inhibition)
Harvey et al. 2004	United States	Randomized crossover	Clinical research	Volunteers with schizophrenia; IM administration for	12 (crossover)	IM 7.5 mg single dose (crossover;	IM lorazepam	Serial 12-lead ECGs before and	Bazett (QTb), Fridericia	Outliers: QTc ≥450/480/500 ms;	0–6 h after IM administration

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		trial; active comparator	unit (no-ICU)	agitation		after a placebo day)	4 mg (crossover)	after injection for up to 6 h; computerized measurement by a blinded technician	(QTf), and individualized correction (QTii) based on QT = QT/RR^a	ΔQTc ≥30/60/75 ms (according to CPMP recommendations)	
van den Boogaard et al. 2018 (REDUCE)	Netherlands	Multicenter double-blind, placebo-controlled RCT (3 arms)	21 ICUs	Critically ill patients without delirium; high risk; expected ICU stay ≥2 days	350 (1 mg) + 732 (2 mg) / 707 / 1789	IV 1 mg every 8 h or IV 2 mg every 8 h (started within ≤24 h of ICU admission; up to day 28, ICU discharge, or delirium)	Placebo (NaCl 0.9%) every 8 h	Daily adverse event: "QTc-time prolongation" measured by 12-lead ECG or monitor strip; maximum QTc (median [IQR]) and n (%) with prolongation were reported	Bazett (monitor strip or 12-lead ECG)	QTc-time prolongation (definition/threshold not explicitly stated in the appendix; reported as an event count)	During ICU prophylaxis
Miceli et al. 2010	NR (multicenter)	Randomized single-blind RCT (active comparator)	Non-ICU (psychiatry)	Schizophrenia/schizoaffective disorder; 2 IM injections	27 / 31 / 58 treated (59 assigned)	IM 7.5 mg and 10 mg (2 injections separated by 4 h; single-blind)	IM ziprasidone 20 mg and 30 mg	Serial 12-lead ECGs (day 0 and day 1); centrally read by a blinded reviewer; QT measured in lead II	QTc = QT/(RR^b); b derived from lnQT vs lnRR regression using all baseline data (regression-based correction)	Outliers: QTc ≥450/≥480/≥500 ms; ΔQTc ≥30/≥60/≥75 ms; QTc prolongation defined as ≥480 ms (ICH)	Tmax after each injection
Andersen-Ranberg et al. 2022	Multicenter (Europe;	Multicenter placebo-	ICU	Adults with delirium in the ICU due to an acute	510 / 490 / 1000	IV 2.5 mg 3 times/day +	Placebo	QTc monitored	NR (local	Withdrawal/discontinuation	During the ICU stay / recurrent

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(AID-ICU)	coordinated from Denmark)	controlled, double-blind RCT		condition		2.5 mg PRN (max 20 mg/day) during delirium in the ICU		according to local practice; treatment discontinued if QTc prolongation was documented	practice; no standardized formula reported)	criterion: QTc prolongation defined according to local ward practice	episodes (up to discharge)
Girard et al. 2010 (MIND)	United States	Placebo-controlled RCT (3 arms)	ICU	ICU delirium; mechanical ventilation common	35 / 36 (placebo) / 101 total (including ziprasidone n = 30)	5 mg per dose (solution 1 mg/mL) initially; alternative IM 0.5 mL if without enteral access (max 8 IM doses). A second dose at 12 h if QTc <500; then every 6 h with adjustments (q8h/q12h) according to resolution; up to day 14	Placebo (and ziprasidone)	Safety: baseline QTc <500 ms required for dose 2 (at 12 h); subsequent doses every 6 h; discontinue if QTc >500 ms	NR	Safety event: QTc >500 ms (causing discontinuation)	Up to 14 days or ICU discharge
Page et al. 2013 (HOPE-ICU)	United Kingdom (multicenter)	RCT placebo-controlled	ICU	Critically ill patients; delirium/coma in the ICU	71 / 70 / 141 analyzed (142 randomized)	IV 2.5 mg every 8 h; maximum 14 days	Placebo (saline)	Continuous ECG monitoring plus daily 12-lead ECG; if QTc >500 ms, treatment was temporarily withheld and reversible	NR	QTc >500 ms (criterion for discontinuation; also baseline exclusion if QTc >500 ms)	During ICU treatment (up to 14 days)

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								causes were corrected; treatment was restarted at 50% dose when QTc <500 ms			
Al-Qadheeb et al. 2016/2017 (pilot SSD→delirium)	United States	Double-blind, placebo-controlled RCT (pilot)	3 ICUs (academic)	Mechanically ventilated patients with subsyndromal delirium (ICDSC 1–3)	34 / 34 / 68	IV 1 mg per dose (total daily dose 4 mg); slow IV push; up to delirium onset, ICU discharge, 10 days, or an adverse event	Placebo	QTc measured by nursing staff every 6 h on the monitor; if potentially prolonged, it was confirmed with a 12-lead ECG	NR	Potential QTc prolongation: QTc ≥500 ms or ΔQTc ≥60 ms vs baseline; if confirmed on a 12-lead ECG → exclusion/withdrawal	During the ICU stay (up to 10 days)
Girard et al. 2018 (MIND-USA)	United States (16 centers)	Multicenter double-blind, placebo-controlled RCT (3 arms)	ICU medical-surgical	ICU delirium with respiratory failure/shock	192 / 184 (placebo) / 566 total (including ziprasidone n = 190)	IV: <70 years 2.5 mg initially; ≥70 years 1.25 mg; then every 12 h (≈10:00/22:00) with titration (double/half); maximum 10 mg per administration and 20 mg/day; up to 14 days or ICU discharge	Placebo (and ziprasidone)	QTc monitoring: before each dose (BID) by telemetry; if telemetry suggested QTc ≥550 ms, it was confirmed with a 12-lead ECG; if ECG QTc was ≥550 ms, treatment was held and reversible causes were corrected	Bazett (telemetry; reported in the prespecified QTc analysis of MIND-USA)	Safety threshold: QTc ≥550 ms (for eligibility and for holding doses)	Until delirium resolution, ICU discharge, or 14 days

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Note: Trials are presented as unique studies. When multiple publications arose from the same trial, they were grouped for eligibility assessment and methodological description. The primary publication was used for the general study characteristics, whereas secondary publications were used only as complementary sources for specific outcomes when they provided additional information.

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Table S2. Detailed characteristics of the comparative observational studies

Study (year)	Design	Setting	Population/indication	N (Halo/Comp/Total)	Haloperidol (route/dose/duration)	Comparator	QTc assessment	QT correction	Definition of QTc outcome (author)	Adjustments/confounders (if applicable)
Wang/Chang et al. 2024 (Heart Rhythm)	Multicenter retrospective cohort (EMR)	Hospital (mixed)	Adults aged ≥18 years exposed to haloperidol or quetiapine with a baseline and follow-up ECG	2341 / 8832 / 11173	NR in protocolized detail; exposure according to clinical prescribing	Quetiapine	Baseline and follow-up ECG	Bazett (primary analysis); Fridericia (sensitivity analysis)	SQTP = follow-up QTc >500 ms or an increase >60 ms from baseline	Multivariable logistic regression; clinical factors, electrolytes, comorbidities, and concomitant medications
Felton et al. 2018/2019	Retrospective comparative cohort (chart review)	Inpatient geriatric/palliative care	Hospitalized patients aged ≥65 years with delirium during palliative care consultation	100 / 82 / 304	Reported doses 0.5–5 mg; mean scheduled dose 1.4 mg, mean rescue dose 0.5 mg; route not clearly standardized	Non-haloperidol antipsychotics (olanzapine, risperidone, quetiapine) and a no-pharmacologic-treatment group	ECG at clinician discretion; no standardized protocol	NR (an institutional policy was applied to classify QTc)	QTc prolongation = >500 ms in men or >480 ms in women	Univariable comparisons and multivariable models adjusted at least for sex
Castro et al. 2020	Prospective observational cohort with age- and frailty-matched controls	Geriatric hospitalization	Frail adults aged ≥70 years (GFI >3) with delirium	150 / 150 / 300	Oral; mean dose 1.5 mg/24 h; second ECG after ≥2 doses, at the estimated Tmax	Controls without haloperidol	Two ECGs (on admission and during hospitalization); QTc manually validated by trained physicians	Framingham (primary)	Potentially dangerous QTc = QTc >500 ms or an increase >60 ms	Models including age, sex, inflammation, and heart failure; repeated analyses between groups
Bohny et al. 2023 (Frontiers in Psychiatry)	Retrospective naturalistic descriptive cohort	Non-ICU hospital setting (multiple services)	Adults with delirium (hyperactive, hypoactive, or mixed)	10 / 43 / 35 / 14	Monotherapy or combination therapy; doses expressed as haloperidol equivalents (eH); overall antipsychotic exposure was low	Pipamperone / haloperidol + pipamperone / no antipsychotic	Baseline ECG (ECGa) and ECG during delirium (ECGb, under higher exposure)	Bazett	CQP = QTc >470 ms in men or >480 ms in women	Primarily descriptive analyses and between-group comparisons; limited multivariable adjustment
Spellmann et al. 2018	Prospective naturalistic observational study (monotherapy)	Psychiatry	Patients with schizophrenia/schizophrenia-spectrum disorders treated with different antipsychotics	10 haloperidol / other antipsychotics / 199 total	Monotherapy; dose NR in this table; 5-week follow-up	Other antipsychotics in monotherapy	Baseline QTc and weekly QTc for 5 weeks	NR in the verified excerpt	QTc prolongation = ≥450 ms in men / ≥470 ms in women; it also explored prediction of QTc	Mixed models with clinical/genetic covariates; useful as a comparative descriptive

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									>420 ms	study, but not as a clean paired haloperidol-vs-control comparison
Wang et al. 2021/2022 (IV olanzapine vs IV haloperidol)	Retrospective comparative cohort	ICU (tertiary academic center)	Adults in the ICU with agitation treated with IV antipsychotics	96 / 96 / 192	IV; usual initial dose 2–5 mg (non-older adults) or 0.25–0.5 mg (older adults); additional doses according to response; recommended maximum 40 mg/24 h	IV olanzapine	Pre/post QTc when available within the safety analysis	Hodges	QTc prolongation = QTc >500 ms and/or a change >60 ms from baseline	Multivariable logistic regression for the primary clinical outcome; QTc comparison as a safety outcome was mainly descriptive

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Table S3. Reported clinically relevant proarrhythmic events

Study	Design	Comparator	TdP	VT/VF / "ventricular arrhythmia"	Sudden death	Comment
AID-ICU 2022	RCT	Placebo	NR	**Ventricular arrhythmia:** 5/501 vs 4/486	NR	"Ventricular arrhythmia" is reported as an aggregate outcome (does not separate TdP/VT/VF).
MIND-USA 2018	RCT	Placebo / ziprasidone	Reports 2 cases in the haloperidol arm (uncertain attribution)	NR	NR	The report does not allow unambiguous arm-level estimation of "trial drug–related" events.
MIND 2010	RCT	Placebo / ziprasidone	NR	"No ventricular arrhythmias after initiation" (no counts reported)	NR	Qualitative statement; no n/N provided.
Felton 2018/19	Cohort	NHAP / non-pharmacologic	"No TdP"	NR	NR	Double-zero/NR for major events.
Bohny 2023	Cohort	No antipsychotic (and others)	"No TdP"	NR	NR	Double-zero/NR for major events.
Wang/Chang 2024	Cohort	Quetiapine	NR	Reports an association between SQTP and VA/SCD within the drug-exposed group	Reports SCD within the analysis	No direct HAL vs QTP comparison is provided for the clinical event (based on available extraction).

Note: Because of the low event frequency, incomplete arm-level reporting, and the presence of studies with no events in either group, these outcomes were summarized descriptively and were not pooled quantitatively. TdP, torsades de pointes; VT, ventricular tachycardia; VF, ventricular fibrillation; NR, not reported.

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Table S4. Haloperidol route, dose, and duration of exposure

Study	Design/setting	HAL route	HAL dose (as reported)	Exposure duration/time window	Comment (relevant for interpretation)
REDUCE 2018	RCT ICU	IV	1 mg every 8 h or 2 mg every 8 h	Prophylaxis during the ICU stay	QTc outcome "as defined by study authors" in a sub-sample / per-protocol analysis.
AID-ICU 2022	RCT ICU	IV	2.5 mg every 8 h + PRN (max 20 mg/day)	During ICU delirium	QTc definition "according to local practice."
MIND-USA 2018	RCT ICU	IV	Protocolized regimen (haloperidol vs ziprasidone vs placebo)	During delirium	"Dose held" because of QTc (operational protocol threshold).
MIND 2010	RCT ICU	IV	Protocolized	During delirium	Reports QTc >500 ms by arm.
HOPE-ICU 2013	RCT ICU	IV	2.5 mg every 8 h	Up to 14 days/discharge	Reports QTc >500 by arm.
Al-Qadheeb pilot	RCT ICU	IV	1 mg every 6 h	Up to 10 days/discharge	QTc defined using a threshold / ΔQTc.
Reade 2009	RCT ICU	IV	Infusion 0.5–2 mg/h	During mechanical ventilation	Open-label.
Miceli 2010	RCT no-ICU	IM	7.5 mg and 10 mg (2 injections)	Hours after injection	Focused on QTc / outliers; major events were rare.
Harvey 2004	RCT no-ICU	IM	7.5 mg (crossover)	0–6 h after IM administration	Small sample; no major events.
Harrigan 2004	Trial no-ICU	Oral	15 mg/day	Steady-state	Pharmacologic focus; continuous QTc / outliers.
Castro 2020	Geriatric cohort	(NR / low dose)	mean 1.5 mg/24 h	Baseline ECG + second ECG	Matched control; events were rare.
Felton 2018/19	Geriatric/palliative cohort	NR	NR	Hospitalization	Non-protocolized ECG.
Bohny 2023	Cohort no-ICU	NR	HAL equivalent ~1.2 mg/day	During delirium	Clinical ECG; defines CQP.
Wang/Chang 2024	Cohort EMR	NR	NR	Baseline ECG + follow-up ECG	Comparator: quetiapine; SQTP defined as >500 / Δ>60.
Wang IV 2021/22	Cohort ICU	IV	NR	QTc in a pre/post sub-sample	Sub-sample limits effect-modifier analyses.
Spellmann 2018	Prospective observational	Oral (NR)	NR	5 weeks	Weekly QTc; not designed for events.

Note: This table is presented for descriptive purposes. Clinical heterogeneity and incomplete exposure reporting precluded formal effect-modification analyses by route, dose, or duration.

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Table S5. Risk of bias of the randomized controlled trials (RoB 2)

Study	D1	D2	D3	D4	D5	Global	Brief justification (1–2 lines)
REDUCE 2018 (JAMA)	Low	Low	Some concerns	Low	Some concerns	Some concerns	Double-blind trial; QTc was reported as a "safety event" in a sub-sample/per-protocol analysis → possible selection/incompleteness of the set analyzed for that outcome.
AID-ICU 2022 (NEJM)	Low	Low	Low	Low	Low	Low	Multicenter, double-blind, placebo-controlled design; QTc treated as a safety outcome. The "according to local practice" definition introduces variability, but blinding reduces differential bias.
MIND-USA 2018 (NEJM)	Low	Low	Low	Low	Low	Low	Large multicenter double-blind trial (3 arms). QTc was managed per protocol (hold/withhold) and recorded systematically.
MIND 2010 (CCM)	Low	Low	Low	Low	Some concerns	Low	Three-arm pilot trial; QTc >500 ms was reported by arm. Safety prespecification was less detailed than in larger trials → minor concern in D5.
HOPE-ICU 2013 (Lancet RM / NIHMS)	Low	Low	Low	Low	Low	Low	Double-blind placebo-controlled trial; reports QTc >500 ms by arm as an adverse/safety event.
Al-Qadheeb 2016/2017 (pilot SSD→delirium)	Low	Low	Low	Low	Low	Low	Double-blind pilot trial; defines QTc prolongation and reports events by arm (including criteria such as ≥500 ms and/or ΔQTc).
Reade 2009 (Critical Care)	Some concerns	High	Some concerns	Low	Some concerns	High	Open-label trial: high risk of co-interventions and differential clinical decisions; QTc is an objective measure, but clinical management may vary between arms.
Miceli 2010 (Clin Ther, IM)	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Single-blind randomized design, but details of concealment/implementation were sometimes incomplete (NR). QTc was measured by ECG → objective assessment.
Harvey 2004 (crossover)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns	Crossover design: possible carryover if washout/design does not ensure independence for events; reporting of allocation/concealment may also be limited (NR).
Harrigan 2004 (multi-arm)	Low	Some concerns	Low	Low	Some concerns	Some concerns	Randomization was robust but the trial was open-label; QTc is usually an objective measure (sometimes centrally/standardly read), but safety reporting was not always the paper's primary outcome.

Note: Risk of bias was assessed for the primary outcome of this review (QTc prolongation). Trials were evaluated as unique studies; secondary publications arising from the same trial were

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not assessed independently.

Table S6. Methodological quality of the observational studies (NOS)

Study	Total NOS	Selection	Comparability	Outcome	Brief justification (2–3 points)
Wang/Chang 2024 (Heart Rhythm)	**7/9**	High	Moderate-high	High	Defines SQTP by ECG (QTc >500 and/or Δ>60); large EMR cohort with baseline and follow-up ECG; residual confounding is possible because of treatment selection (haloperidol vs quetiapine).
Castro 2020 (Age & Ageing)	**7/9**	High	High	Moderate-high	Matched controls (age/frailty) and serial ECGs; clear definition of "dangerous" QTc; rare events → limited precision.
Wang IV 2021/2022 (IV OLZ vs IV HAL)	**6/9**	Moderate	Moderate	Moderate	Retrospective design; concurrent comparator; QTc assessed in a sub-sample with pre/post ECGs → possible selection bias in the subanalysis and residual confounding.
Felton 2018/2019	**5/9**	Moderate	Low-moderate	Moderate	Concurrent comparators; institutional QTc definition; ECGs obtained “at discretion” (non-protocolized) → risk of differential detection.
Bohny 2023 (Frontiers)	**5/9**	Moderate	Low-moderate	Moderate	Requires a baseline ECG close to exposure and an ECG during delirium; between-group comparability is limited without robust adjustment (NR).
Spellmann 2018	**4/9**	Moderate	Low	Moderate	Weekly follow-up and prespecified thresholds; however, between-drug comparisons may not be randomized/adjusted (high confounding risk).

Note: NOS, Newcastle–Ottawa Scale. Assessment focused on group comparability, outcome measurement, and adequacy of follow-up, with emphasis on QTc prolongation.

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Table S7. Study-level detail for the quantitative results of the randomized controlled trials

A. Primary outcome: QTc prolongation as defined by study authors (placebo/no antipsychotic)

Study	Comparator	HAL (events/total)	Control (events/total)	logOR (IC95%)	OR (IC95%)
REDUCE 2018	Placebo	57/1013	35/668	0.075 (−0.357 to 0.508)	1.08 (0.70 to 1.66)
AID-ICU 2022	Placebo	12/501	7/486	0.518 (−0.422 to 1.459)	1.68 (0.66 to 4.30)
MIND-USA (QTc report)*	Placebo	13/192	10/184	0.234 (−0.616 to 1.084)	1.26 (0.54 to 2.96)

B. Strict sensitivity analysis: QTc ≥500 ms (placebo/no antipsychotic)

Study	Comparator	HAL (events/total)	Control (events/total)	logOR (IC95%)	OR (IC95%)
HOPE-ICU 2013	Placebo	7/71	6/70	0.154 (−0.990 to 1.298)	1.17 (0.37 to 3.66)
MIND 2010	Placebo	2/35	3/36	−0.405 (−2.259 to 1.448)	0.67 (0.10 to 4.25)

C. QTc ≥500 ms with active comparator (descriptive supplementary analysis; double-zero)

Study	Active comparator	HAL (events/total)	Active comparator (events/total)	logOR (IC95%)	OR (IC95%)	Comment
Miceli 2010	IM ziprasidone	0/27	0/31	Not estimable	Not estimable	No QTc ≥500 ms events in either arm; summarized descriptively
Harvey 2004	IM lorazepam	0/12	0/12	Not estimable	Not estimable	No QTc ≥500 ms events in either arm; summarized descriptively
Harrigan 2004	Ziprasidone / other antipsychotics	0/27	0/31	Not estimable	Not estimable	No QTc ≥500 ms events in either arm; summarized descriptively

* The MIND-USA value comes from a secondary publication of the same trial (QTc report) and was used only to supplement outcome extraction; it was not counted as an independent study.

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Table S8. Summary of Findings (GRADE)

Outcomes (comparison: haloperidol vs placebo/no antipsychotic)	Risk with control (per 1,000)	Risk with haloperidol (per 1,000)	Relative effect	Participants (studies)	Certainty (GRADE)
QTc prolongation (author-defined)	39	46 (32 to 64)	OR 1.18 (0.83 to 1.69)	3044 (3 RCTs)	⊕⊕⊕◯ Moderate a,b
QTc ≥500 ms (strict threshold)	85	85 (34 to 197)	OR 1.00 (0.38 to 2.65)	212 (2 RCTs)	⊕⊕◯◯ Low c
Ventricular arrhythmia (study-defined; proxy clinical event)	8	10 (3 to 36)	OR 1.21 (0.32 to 4.55)	987 (1 RCT)	⊕◯◯◯ Very low d,e

Note: Certainty of the evidence was assessed using the GRADE approach. Evidence from randomized controlled trials started as high certainty and was downgraded for risk of bias, indirectness, imprecision, inconsistency, and possible publication bias.

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Appendices

Appendix S1. Full electronic search strategies

The search strategies were designed to identify comparative studies evaluating haloperidol use and its association with QTc prolongation and/or clinically relevant proarrhythmic events in adults. Controlled vocabulary and free-text terms were adapted to each database.

Appendix S1A. Search strategy for PubMed (MEDLINE)

("haloperidol"[MeSH] OR haloperidol[tiab] OR haldol[tiab]) AND ("torsades de pointes"[MeSH] OR "torsade de pointes"[tiab] OR "ventricular arrhythmias"[MeSH] OR "ventricular arrhythmia"[tiab] OR "ventricular tachycardia"[tiab] OR "ventricular fibrillation"[tiab] OR "sudden cardiac death"[MeSH] OR "sudden death"[tiab] OR "QT interval"[MeSH] OR "QT prolongation"[tiab] OR "long QT"[tiab]) AND ("Randomized Controlled Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "Cohort Studies"[MeSH] OR cohort[tiab] OR "observational study"[tiab]) AND ("adult"[MeSH] OR adult[tiab]) NOT ("Case Reports"[Publication Type] OR "Case-Control Studies"[Publication Type])

Appendix S1B. Search strategy for Embase.com

('haloperidol'/exp OR haloperidol:ti,ab OR haldol:ti,ab) AND ('torsade de pointes'/exp OR 'torsade de pointes':ti,ab OR 'ventricular arrhythmia'/exp OR 'ventricular arrhythmia*':ti,ab OR 'ventricular tachycardia':ti,ab OR 'ventricular fibrillation':ti,ab OR 'sudden cardiac death'/exp OR 'sudden death':ti,ab OR 'qt interval prolongation'/exp OR 'long qt syndrome'/exp OR 'qt prolongation':ti,ab) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'cohort analysis'/exp OR cohort:ti,ab) AND [humans]/lim AND [adult]/lim NOT ('case report'/exp OR 'case control study'/exp)

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Appendix S1C. Search strategy for LILACS

((MH:Haloperidol OR TW:(haloperidol OR haloperidona OR haldol)) AND (MH:"Arritmias Cardíacas" OR MH:"Torsade de Pointes" OR MH:"Muerte Súbita Cardíaca" OR MH:"Intervalo QT" OR TW:("torsade de pointes" OR "torsades de pointes" OR "taquicardia ventricular" OR "fibrilación ventricular" OR "muerte súbita" OR "prolongación QT" OR "intervalo QT prolongado"))) AND (TW:(cohorte OR estudio de cohorte OR ensayo clínico OR ensayo aleatorio) OR PT:("Clinical Trial" OR "Randomized Controlled Trial")) AND (MH:Adulto OR TW:(adulto*))

BJP PRE-PROOF