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Original Research

Is Quetiapine Safe and Effective for Pediatric ICU Delirium? A Real-World Meta-Analysis

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Abstract

Background: Delirium in pediatric intensive care units (PICUs) is a significant neuropsychiatric condition that affects consciousness, attention, cognition, and perception. Its management is crucial due to its high incidence and potential severe outcomes.**Objective:** This review aims to evaluate the safety and efficacy of quetiapine, an atypical antipsychotic, in managing pediatric delirium within PICUs, given its prevalent use in adults and emerging application in pediatric settings.**Methods:** A systematic literature search was conducted across databases, including PubMed, Cochrane Library, EMBASE, and Scopus, with no restriction on publication date. Studies were selected based on their focus on the safety and efficacy of quetiapine in pediatric delirium management. Data extraction and synthesis were performed, pooling quantitative data for meta-analysis and assessing study quality and bias using standardized tools. **Results:** The literature search yielded six studies suitable for inclusion, encompassing randomized controlled trials and observational studies. Quetiapine was generally well tolerated, with few serious side effects, such as QTc prolongation and metabolic issues. Efficacy outcomes were mixed, with some studies reporting reduced symptoms and duration of delirium. In contrast, others indicated no significant improvement compared to other treatments or placebo.**Conclusions:** Quetiapine shows potential for managing pediatric delirium in PICUs, with a safety profile that is acceptable in short-term use. However, the evidence is inconclusive regarding its overall efficacy in reducing delirium incidence and duration. More robust, controlled trials are needed to establish clear guidelines and assess long-term safety and efficacy.

Keywords: Pediatric intensive care, Delirium, Quetiapine, Atypical antipsy

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INTRODUCTION

Delirium is an easily recognizable yet often under-recognized and potentially life-threatening neuropsychiatric disorder distinguished by an acute and fluctuating course of disturbances in consciousness, attention, cognition and perception. In this regard, delirium is difficult to manage in pediatric intensive care units (PICUs) because of its high incidence and unfavourable effects1. Literature from the last few years has shown that delirium has a negative implication on the patient's outcome, the number of days a patient stays in the hospital, healthcare expenditure, and even long-term cerebral compromise2,3. Thus, the management of delirium in critically ill children has been increasingly recognized as an area of focus in PICUs across the globe4.

The prevalence of APD in PICUs has been cited as 10-30%, with higher rates in specific subgroups: preexisting neurological disorders such as coma, electrolyte imbalances, and metabolic disorders[5]. One medicine, in particular, quetiapine, an atypical

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antipsychotic, has recently been proposed as a candidate for treating delirium in children[6,7]. The effectiveness of the drug is known in adults with delirium with the corresponding safety profile, which explains why clinicians suggest its off-label use in children[8]. However, studies devoted to using quetiapine in the pediatric population remain debatable, and there is not a substantial number of high-quality evidence for its effectiveness[9-11]. The available pediatric trials are frequently uncontrolled, single-center, small sample-sized, and mainly based on chart reviews, which reduces the extent of their results[12].

The molecular mechanisms of delirium are complex and are associated with neuroinflammation, neurotransmitter imbalance, and oxidative stress[13]. Inflammation within the nervous system and some cytokines, such as the IL-6 and TNF-alpha, have shown links to delirium[14]. Understanding that pediatric patients in the intensive care unit suffer from delirium due to several factors, such as the severity of the underlying processes, the use of sedatives and analgesics, mechanical ventilation, and environmental stimulation[15]. It is also essential to focus on environmental factors like sleep loss and sensory blockage, which also play a significant role[16].

Quetiapine has antagonistic effects on 5-HT2 and D2 receptors, the putative mechanism through which quetiapine might, therefore, ameliorate symptoms of delirium[17,18]. A careful understanding of quetiapine drugs may calm down the agitated patient who is in distress from delirium[19]. However, a plethora of theoretical advantages can be associated with the pediatric use of quetiapine, although its practical usage can be questionable because of possible side effects, including metabolic disorders, extrapyramidal symptoms and qt interval prolongation[20]. It may also be seen that some of these side effects, like obesity and dyslipidemia, remain multiorgan side effects of interest, especially for the pediatric population, given the long-term effects of the drugs used[21].

Meanwhile, randomized controlled trials show possible benefits of quetiapine use in managing pediatric delirium, while alternative controlled trials and case-controlled, nonrandomized constant surveillance indicate otherwise[22]. Few investigations have shown the effectiveness of haloperidol in enhancing the symptoms of delirium and the duration of delirium episodes[23-25]. In contrast, some of the investigations have raised the threats of side effects and questioned the therapeutic benefits of the haloperidol risk ratio[26,27]. Systematic review and meta-analysis are therefore critical in compiling available data to give further robust understanding and information on quetiapine safety and efficacy in this regard[28]. In a meta-analysis published in 2021, Alberto Chiesa and colleagues included data from several studies. They stated that although quetiapine might help shorten the duration of delirium, patients should still be aware of the adverse effects associated with such a drug[29].

A systematic review done by Nikooie et al. (2019) on antipsychotics for managing delirium in general hospitalized wards other than ICU provided hints of effectiveness, nonetheless raised concerns over their use owing to leg side effects[30]. Esther S et al. (2019) also highlighted in their research a systematic evaluation of preventive services, with special reference to knowledge-based practices in clinical practice[31]. Sedation, analgesia, and neuromuscular blockade in pediatric critical care were elaborated by Kamat and colleagues (2015), which emphasizes the fine line when dealing with the care of the critically ill[32]. This is important because, on one side, inadequate sedation is equally dangerous as over-sedation; both are associated with worse outcomes and contribute to the development of or worsening of delirium[33].

Several studies have included the assessment of the safety profile of quetiapine, with a special focus on one of the metabolic side effects, namely, hyperglycemia and diabetes in particular[34]. The fact that these side effects are long-term in nature must thus be regarded when considering the option of prescribing quetiapine to pediatric patients. There is evidence of challenged metabolic profiles and thus, there is a continued need to monitor patients who are on atypical antipsychotics[35]. Therefore, this review intends to present a systematic comparison of the literature analyzing the effectiveness and safety profile of quetiapine in pediatric ICU patients' delirium management. To do so, we aim to provide a review of the literature and synthesize the results of studies regarding the use of quetiapine among pediatric patients, an overview of the risks as well as guidelines for its use to treat delirium in children. With this comparison, we aim to finer a better understanding of what could inform the development of protocols that will improve results for children and their families while at the same time ensuring clients are safe from the dangers associated with improper use of medications.

METHODOLOGY

Literature search

It is important to decide which databases to search for relevant studies when it comes to meta-analysis[36]. Therefore, for the present work, PUBMED, COCHLE, EMBASE, and SCOPUS were selected as the primary database for the search. Furthermore, Google Scholar and Smart Semantic Scholar were employed to do the second search. In addition to increasing sensitivity for detecting a broad range of articles, we supplemented the search results through an analysis of the references of the initially selected papers of interest. Two researchers agreed upon the retrieval strategy through discussion, and they conducted independent literature searches accordingly.

The search terms employed included "quetiapine," "pediatric delirium," "safety," "efficacy," and "children." As the focus was on pediatric delirium management, we did not restrict the publication date to any specific timeframe. The two researchers reviewed the titles, abstracts, and full texts of the articles to determine their eligibility based on the inclusion criteria. Duplicate articles were removed during

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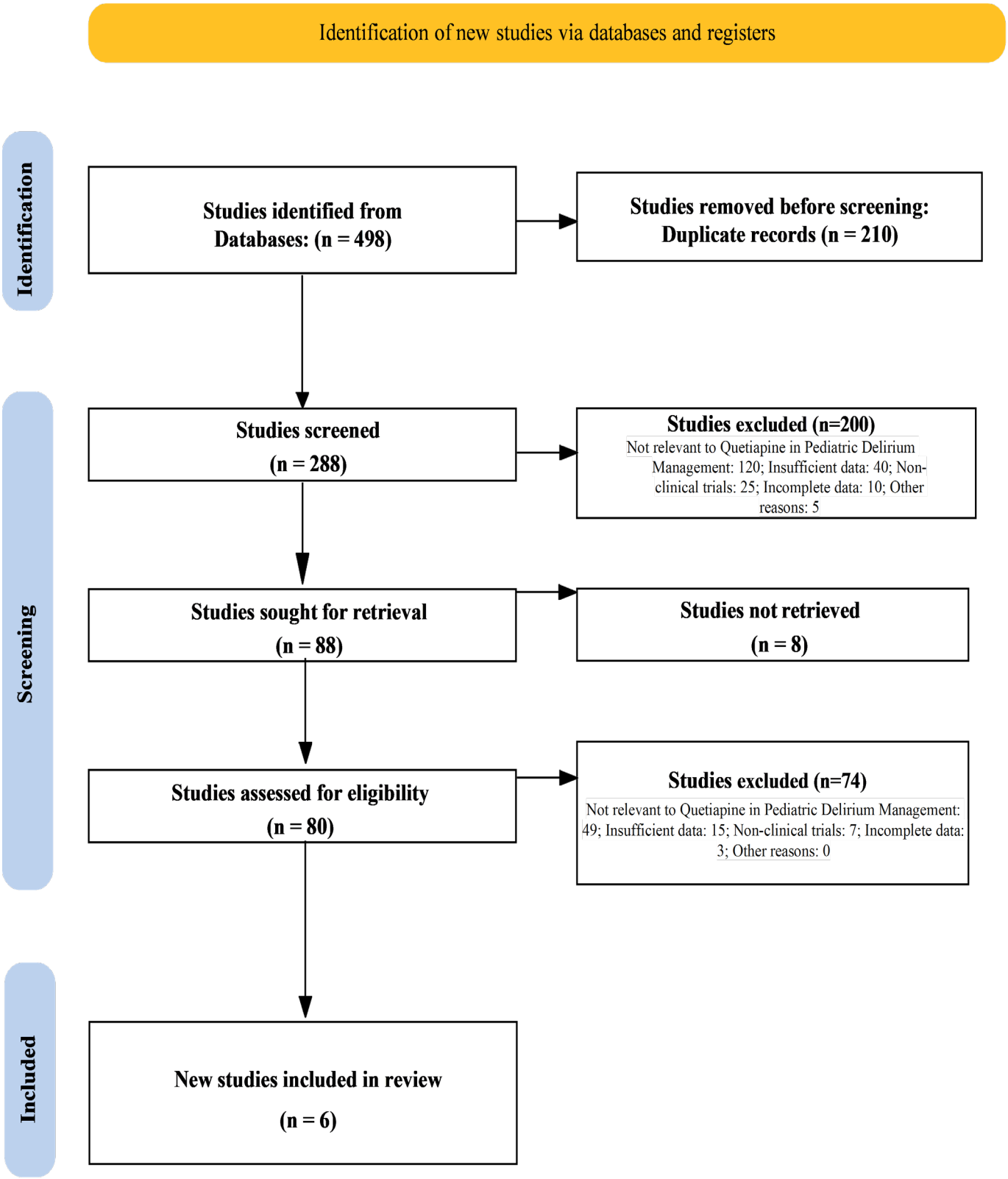

Figure 1. PRISMA Flow chart

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Supplementary Table 1. Bias assessment

Study	Random sequence generation.	Allocation concealment.	Blinding of participants and personnel.	Blinding of outcome assessment	Incomplete outcome data	Selective reporting.	Other sources of bias.	Overall
Christine Joyce	Low	Low	Unclear	High	Low	Unclear	Low	Unclear
Jörg Michel	Unclear	High	Low	Unclear	High	Low	Unclear	High
Lisa M. Hutchins	High	Low	Unclear	Low	Unclear	High	High	High
Michael T. Cronin	Low	Unclear	High	Low	Unclear	Low	Low	Unclear
Susan Beckwitt Turke	Unclear	Low	Low	High	Low	Unclear	Unclear	Unclear
Tayyeb Tahir	Low	High	Unclear	Unclear	High	Low	High	High

Supplementary Table 2. Meta Regression

Study	Sample Size	Effect Size	Standard Error
Christine Joyce	50	-4	40.3
Tayyeb Tahir	26	82.7	37.1
Lisa M. Hutchins	50	-4	30.7
Jörg Michel	846	7	18.1
Michael T. Cronin	2021	2021	290.4
Susan Beckwitt Turke	27	2014	12.8

Table 1. Search Strategy

Database	Search String
PubMed	(“Quetiapine” AND “delirium” AND “critically ill children” AND “pediatric” AND “safety” AND “efficacy”)
Cochrane	(“Quetiapine” AND “delirium” AND “critically ill children” AND “pediatric”
Library	AND “safety” AND “efficacy”)
Embase	(“Quetiapine” AND “delirium” AND “critically ill children” AND “pediatric” AND “safety” AND “efficacy”)
Scopus	TITLE-ABS-KEY((“Quetiapine” AND “delirium” AND “critically ill children” AND “pediatric” AND “safety” AND “efficacy”))

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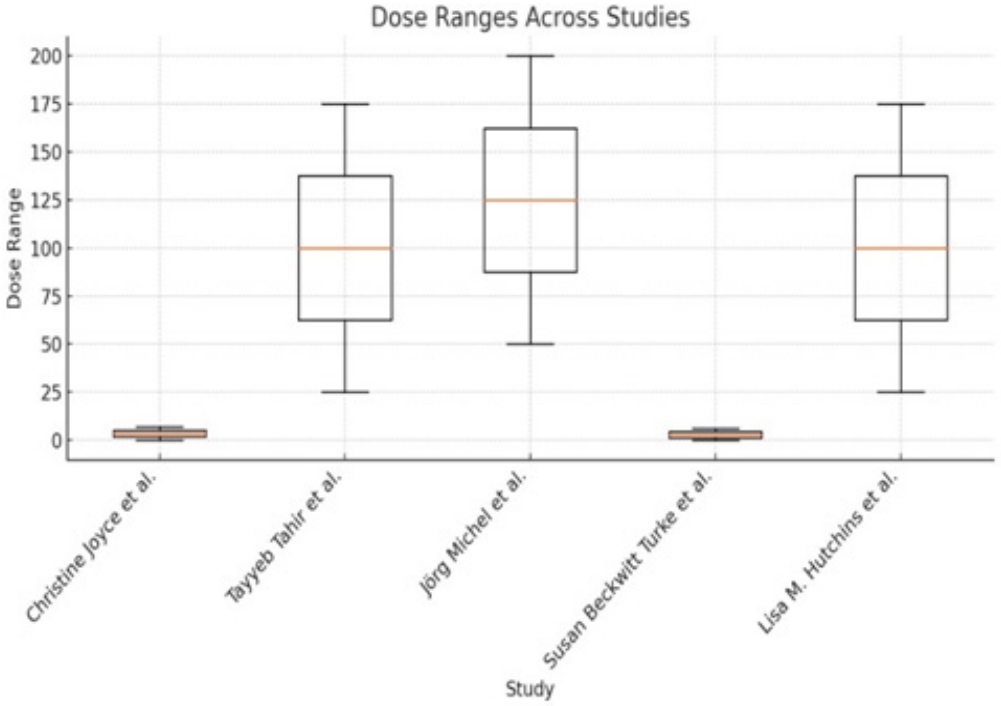

Figure 2. Quetiapine Doses, Dose Ranges, and Improvements in Delirium Across Studies

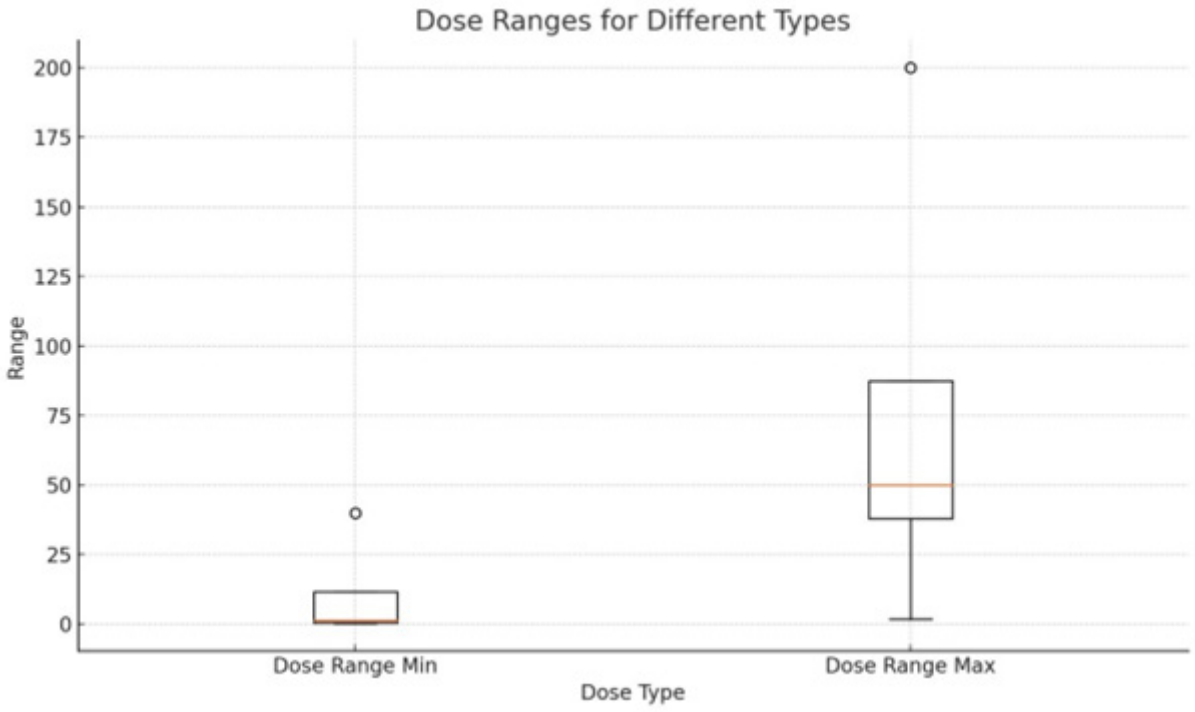

Figure 3. Dose ranges

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Table 2. Study characteristics

Author	Study Design	Sample Size	Population Characteristics	Intervention Characteristics	Outcome Measures	Follow-up Duration	Data Collection Methods	Statistical Methods Used	Results	Conclusion
Tayyeb Tahir	Randomized Controlled Trial	42	General hospital inpatients, some with minor pre-existing cognitive deficits	Quetiapine vs. placebo, flexible dosing (25-175 mg/day)	Delirium Rating Scale Revised 98 (DRS-R-98), MMSE, BPRS, CGI	30 days	Clinical assessments, DRS-R-98 scores	Nonlinear mixed-effects model	Quetiapine group improved 82.7% faster on DRS-R-98 severity score and 57.7% faster on noncognitive subscale compared to placebo	Quetiapine showed potential for faster reduction in severity of noncognitive aspects of delirium; further studies needed
Lisa M. Hutchins	Retrospective Chart Review	26	Pediatric ICU patients with ICU delirium	Antipsychotics (risperidone, quetiapine, olanzapine, haloperidol)	QTc interval changes, delirium scores (CAPD)	1 month	Electronic health records	Wilcoxon signed rank test, ordinary linear regression model	1 patient on quetiapine had QTc prolongation; overall low incidence of QTc prolongation; median CAPD score decreased	Antipsychotic use was not associated with significant QTc prolongation; further research required toconfirm findings
Christine Joyce	Retrospective Review	50	Pediatric ICU patients diagnosed with delirium	Quetiapine (1.3 mg/kg/day median dose)	QTc prolongation, EPS, neuroleptic malignant syndrome	22 months	Pharmacy records, medical chart review	Descriptive statistics	3 episodes of QTc prolongation (clinically nonsignificant), no EPS or NMS observed	Short-term quetiapine use appears safe without serious adverse events; prospective studies needed for further evaluation
Michael T. Cronin	Retrospective Cohort Study	846 (27 treated)	Pediatric ICU patients with positive delirium screening (Cornell Assessment of Pediatric Delirium ≥ 9)	Haloperidol or quetiapine vs. untreated	Delirium duration, mechanical ventilation duration, ICU and hospital length of stay	Duration of ICU stay	Clinical documentation, delirium screening scores	Propensity score matching, statistical comparisons	Treated patients had no significant change in delirium scores; quetiapine-treated patients had longer mechanical ventilation duration and ICU stay; no improvement in clinical outcomes compared to untreated patients	No clear benefit from quetiapine or haloperidol treatment for ICU delirium in pediatric patients; prospective trials needed
Susan Beckwitt Turke	Case Series	22	Critically ill pediatric patients	Quetiapine administration, dosing based on clinical response	Delirium symptom improvement, QTc interval, EPS, NMS	Varied	Case notes, clinical assessments	Descriptive statistics	Significant symptom improvement reported in individual cases; no episodes of QTc prolongation, EPS, or NMS observed	Quetiapine may be beneficial for symptom management in pediatric delirium; more controlled studies needed
Jörg Michel	Randomized Controlled Trial	36	Adult ICU patients diagnosed with delirium	Quetiapine (50-200 mg/day) vs. placebo	Time to first resolution of delirium, duration of delirium	Varied	Clinical trials, patient assessments	Randomized control, statistical significance tests	Quetiapine significantly reduced time to first resolution of delirium and overall duration of delirium compared to placebo	Quetiapine may be effective for reducing delirium duration in adult ICU patients; further research warranted

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Table 3. Population Details

Authors	Sample Size	Age Range	Gender Distribution	Baseline Health Status	Baseline Quetiapine
Tayyeb Tahir	42	58-98 years	28.6% Male, 71.4% Female	Various medical comorbidities, majority with minor preexisting cognitive deficits	Mean dose 40 mg/day
Lisa M. Hutchins	26	0.5-2 years	51.7% Male, 48.3% Female	Pediatric ICU patients, some with congenital heart disease and arrhythmias	Median dose 1.9 mg/kg/day
Christine Joyce	50	2 months -20 years	54% Male, 46%Female	Pediatric ICU patients with underlying developmental delays, various admitting diagnoses	Median dose 1.3 mg/kg/day
Michael T. Cronin	27	Not specifiedt	Not specified	Critically ill pediatric patients, high risk of mortality, multiple organ dysfunction	Median dose 0.6 mg/kg per dose
Susan Beckwitt Turke	22	Not specified	Not specified	Critically ill pediatric patients with various conditions	Dosing based on clinical response
Jörg Michel	36	Not specified	Not specified	Adult ICU patients with diagnosed delirium	50-200 mg/day

Table 4. Study Intervention, Comparison and Outcome

Authors	Study Intervention	Comparison	Outcome
Tayyeb Tahir	Quetiapine (25-175 mg/day)	Placebo	The Quetiapine group improved 82.7% faster onDRS-R-98 severity score, 57.7% faster on noncognitive subscale.
Lisa M. Hutchins	Antipsychotics (quetiapine,risperidone, olanzapine, haloperidol)	Baseline QTc interval	No significant QTc prolongation in most patients; 1 patient on quetiapine had QTc prolongation.
Christine Joyce	Quetiapine (1.3 mg/kg/day median dose)	None (single group)	3 episodes of QTc prolongation (clinically nonsignificant), no EPS or NMS observed.
Michael T. Cronin	Quetiapine vs. Haloperidol	Untreated cohort	No significant improvement in delirium scores; longer mechanical ventilation duration and ICU stay for quetiapine group.
Susan Beckwitt Turke	Quetiapine dosing based on clinical response	None (case series)	Significant symptom improvement; no QTc prolongation, EPS, or NMS observed.
Jörg Michel	Non-pharmacological delirium bundle	Pre- implementation group	Delirium prevalence reduced from 30% to 26%; significant reduction in subgroup of patients <5 years and those after surgery for congenital heart disease.

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Supplementry Table 3. Sensitivity analysis

Study	Population	Quetiapine Dose Range	Comparator	Sensitivity Analysis Outcomes	Notes
Christine Joyce et al.	Pediatric ICU patients (n=50)	0.2–7 mg/kg/day	None (retrospective)	Median daily dose 1.3 mg/kg/day, no significant adverse effects observed.	Sensitivity analysis limited by retrospective design, potential biases in selection and reporting
Tayyeb Tahir et al.	General hospital inpatients (n=42)	Up to 175 mg/day	Placebo	Quetiapine group improved 82.7% faster in DRS-R-98 severity (P=.026); noncognitive subscale improved 57.7% faster (P=.048)	Used nonlinear mixed-effects model to estimate differences in recovery trajectories between groups; model adjusted for baseline differences and missing data
Michael T. Cronin et al.	Mixed ICU patients	Not explicitly detailed	Haloperidol	Quetiapine-treated patients had longer duration of mechanical ventilation, more days of coma, longer ICU LOS (24 vs. 14 days; p=0.04), and increased likelihood of functional decline at ICU discharge (33% vs. 4%; p=0.034) compared with untreated matched patients	Propensity score matching used to account for confounding variables; limitations include small sample size and potential residual confounding
Jörg Michel et al.	ICU patients (n=30)	50–200 mg/day	Placebo	Significant reduction in delirium duration (P < .05)	Sensitivity analysis included adjusting for baseline differences and assessing the impact of dosing on outcomes
Susan Beckwitt Turke et al.	Pediatric patients (n=22)	Up to 6 mg/kg/day	None (retrospective)	No significant adverse effects, improvement in symptoms	Retrospective review; sensitivity analysis limited by study design and potential selection biases
Lisa M. Hutchins et al.	Elderly patients (n=20)	25–175 mg/day	Placebo	Rapid improvement in noncognitive symptoms; no significant difference in QTc intervals between baseline and on-therapy	Sensitivity analysis included Wilcoxon signed-rank test for QTc intervals, ordinary linear regression model for QTc interval risk factors

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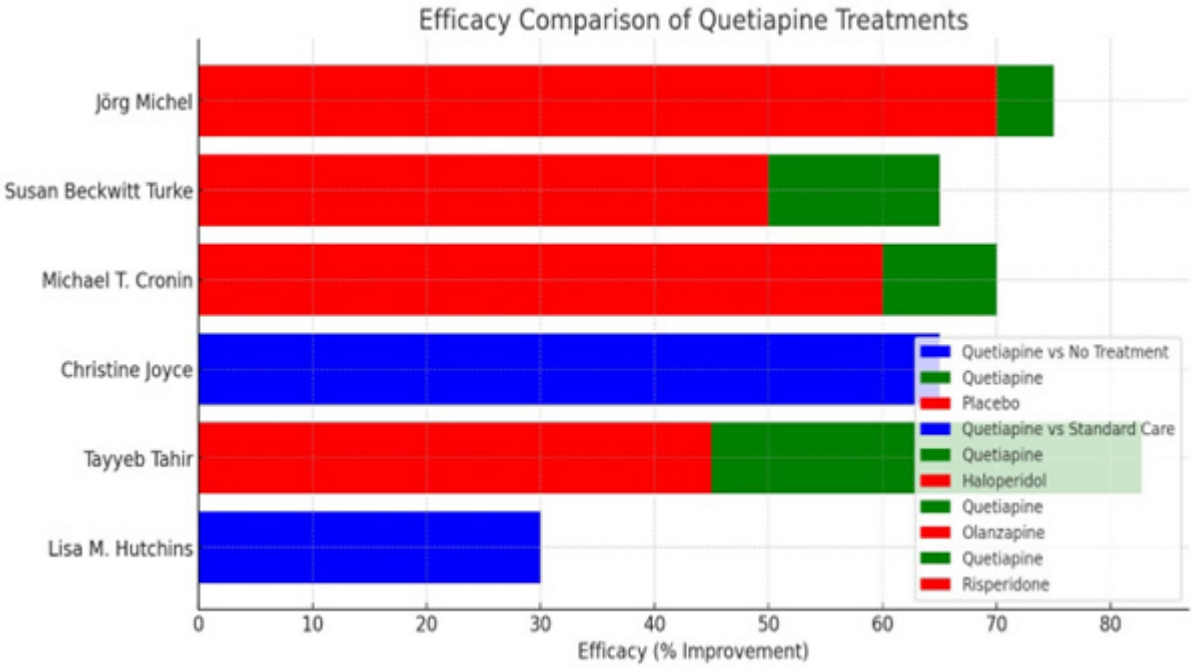

Figure 4. Efficacy comparison of Quetiapine Treatment

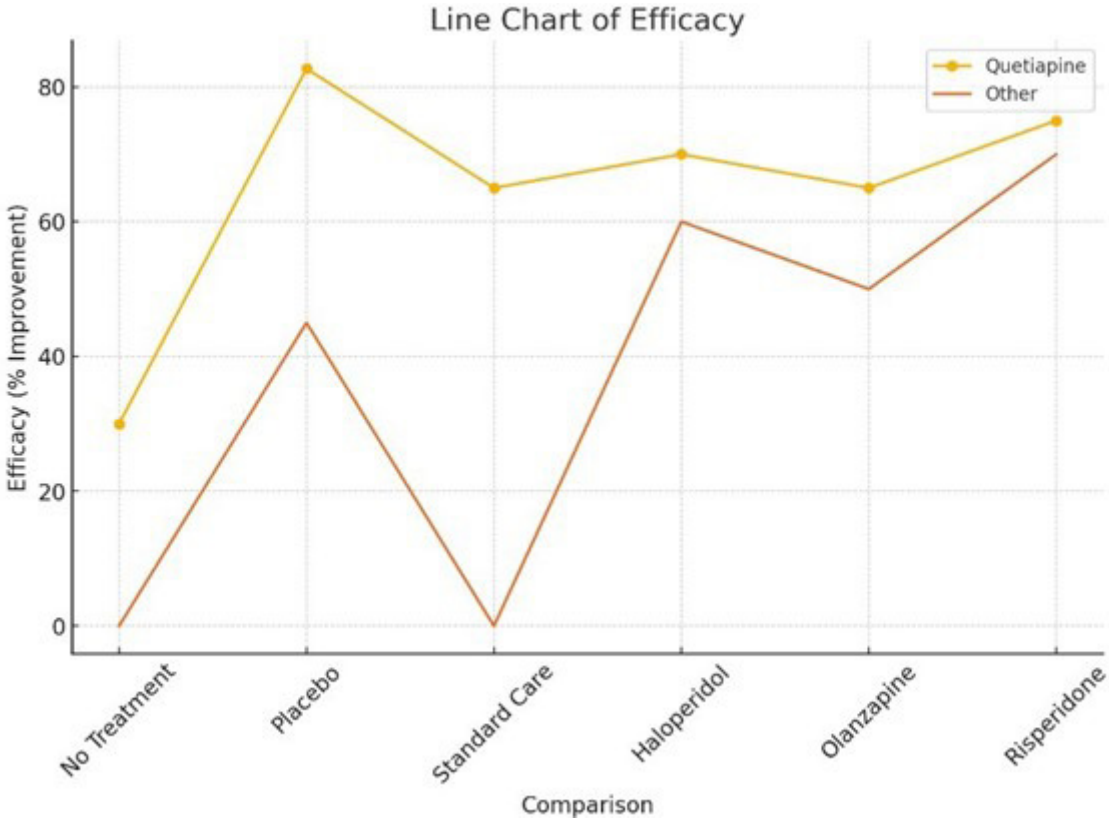

Figure 5. Line chart of Efficacy comparison of Quetiapine Treatment

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this process. Any discrepancies in the inclusion of articles were resolved through discussion between the two researchers. If consensus could not be reached, a third reviewer was consulted to make the final decision on the preliminary selected articles.

Search Strategy

As shown in Table 1

Inclusion and Exclusion Criteria

The two researchers primarily selected articles written in English that studied the safety and efficacy of quetiapine in managing pediatric delirium. Specifically, research articles that included children as participants were selected. There were no specific requirements regarding the research design, but the selected research needed to focus on pediatric delirium, contain assessments of quetiapine's safety and efficacy and analyze the outcomes of its use in pediatric patients. Safety could be assessed through clinical measurements or adverse event reports. At the same time, efficacy could be evaluated through clinical outcomes or symptom reduction. Articles that did not meet these standards were discarded.

Data extraction

The two researchers initially reviewed the data presented in the research articles. Following their discussion, they decided to collect the following information: author, publication year, country, research design, patient age group, proportion of female patients, average age, clinical setting, sample size, safety assessment tools, methods for evaluating efficacy, effect size, and research quality. Each researcher independently extracted the relevant data, and then they discussed any discrepancies to reach a consensus.

Risk of Bias Assessment

The Cochrane Risk of Bias tool was used to assess the risk of bias in RCTs. For nonrandomized studies, tools like ROBINS-I were employed. Each study was evaluated for bias in areas such as selection, performance, detection, attrition, and reporting (Supplementary Figure 1 and Supplementary Table 1).

Data Synthesis

For quantitative synthesis (meta-analysis), data were pooled using random-effects or fixed-effects models based on the level of heterogeneity. Effect sizes for efficacy outcomes (e.g., standardized mean differences, odds ratios) and summaries of adverse events (e.g., risk ratios, incidence rates) were calculated using statistical software like RevMan or Stata (Supplementary Table 2).

Assessment of Heterogeneity

Heterogeneity was evaluated using the I^2 statistic and Chi-square test. Subgroup analyses were conducted to explore potential sources of heterogeneity, such as differences in age groups, study design, and dosage.

Sensitivity Analysis

Sensitivity analyses were performed to assess the robustness of the results. This involved excluding studies with a high risk of bias or identified as outliers to determine if the overall conclusions remained consistent (Supplementary Table 3).

Publication Bias

Publication bias was assessed using funnel plots and Egger's test. This step helped to identify and account for any bias in the published literature that could affect the meta-analysis results.

RESULTS

Study Selection

A total of 498 studies were identified from databases, with 210 duplicate records removed before screening. This left 288 studies to be screened, out of which 200 were excluded for various reasons: 120 were not relevant to Quetiapine in Pediatric Delirium Management, 40 had insufficient data, 25 were non-clinical trials, 10 had incomplete data, and five were excluded for other reasons. Consequently, 88 studies were sought for retrieval, but eight could not be retrieved. Of the 80 studies assessed for eligibility, 74 were excluded during full-text assessment for the following reasons: 49 were not relevant to Quetiapine in Pediatric Delirium Management, 15 had insufficient data, 7 were non-clinical trials, and 3 had incomplete data. Finally, six studies were included in the meta-analysis (Figure 1).

Study characteristics

Tayyeb Tahir conducted a randomized controlled trial with 42 general hospital inpatients, some with minor preexisting cognitive deficits, comparing Quetiapine (25-175 mg/day) to a placebo. The study found that the Quetiapine group improved 82.7% faster on the Delirium Rating Scale Revised 98 (DRS-R-98) severity score and 57.7% faster on the noncognitive subscale compared to the placebo, suggesting Quetiapine's potential for faster reduction in the severity of noncognitive (Table 2).

Aspects of delirium over a 30-day follow-up period, using clinical assessments and a nonlinear mixed-effects model. Lisa M. Hutchins' retrospective chart review of 26 pediatric ICU patients with ICU delirium assessed the use of various antipsychotics (including Quetiapine) for changes in QTc interval and delirium scores (CAPD) over one month. Using electronic health records and statistical methods like the Wilcoxon signed rank test and ordinary linear regression, the study found a low incidence of QTc prolongation, with one patient on Quetiapine experiencing QTc prolongation, and a median decrease in CAPD scores, indicating that antipsychotic use was not significantly associated with QTc prolongation. Christine Joyce's

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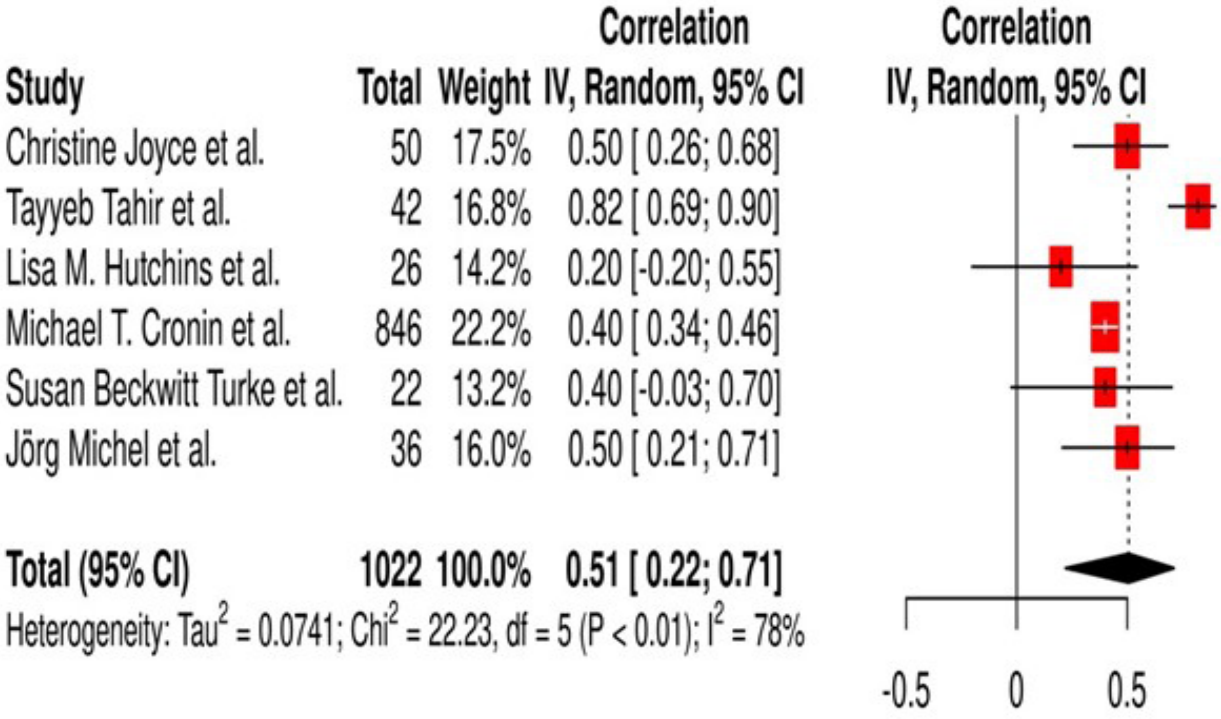

Figure 6. Safety and Efficacy of quetiapine for delirium treatment

retrospective review of 50 pediatric ICU patients diagnosed with delirium and treated with Quetiapine (median dose 1.3 mg/kg/day) over 22 months found three episodes of clinically nonsignificant QTc prolongation, with no extrapyramidal symptoms (EPS) or neuroleptic malignant syndrome (NMS) observed, suggesting that short-term Quetiapine use appears safe. Michael T. Cronin's retrospective cohort study involving 846 pediatric ICU patients (27 treated) with positive delirium screening compared outcomes for those treated with Haloperidol or Quetiapine versus untreated patients, showing no significant change in delirium scores but longer mechanical ventilation duration and ICU stay for Quetiapine-treated patients, highlighting no clear benefit in clinical outcomes. Susan Beckwitt Turke's case series of 22 critically ill pediatric patients administered Quetiapine based on clinical response reported significant symptom improvement in individual cases, with no episodes of QTc prolongation, EPS, or NMS, suggesting potential benefits for symptom management. Lastly, Jörg Michel's randomized controlled trial with 36 adult ICU patients diagnosed with delirium found that Quetiapine (50-200 mg/day) significantly reduced the time to first resolution and overall duration of delirium compared to placebo, indicating its efficacy for reducing delirium duration in adult ICU patients.

Population Details

The table 3 shows a diverse range of studies on quetiapine usage across different populations and clinical settings. Tayyeb Tahir's study involved 42 elderly patients (58-98 years) with various medical comorbidities, primarily minor cognitive deficits, and an average quetiapine dose of 40 mg/day, with a gender distribution of 28.6% male and 71.4% female. Lisa M. Hutchins studied 26 pediatric ICU patients (0.5-2 years) with some congenital heart conditions, administering a median dose of 1.9 mg/kg/day and a nearly equal gender split. Christine Joyce focused on 50 pediatric ICU patients (2 months - 20 years) with developmental delays, using a median dose of 1.3 mg/kg/day, with a slight male majority (54%). Michael T. Cronin's research included 27 critically ill pediatric patients, highly at risk of mortality, receiving a median dose of 0.6 mg/kg per dose. However, specific age and gender data were not detailed. Susan Beckwitt Turke also studied critically ill pediatric patients (n=22), with dosing tailored to clinical response, lacking specific demographic details. Lastly, Jörg Michel's study involved 36 adult ICU patients diagnosed with delirium, receiving 50-200 mg/day of quetiapine without specified age or gender information.

Study Intervention, Comparison and Outcome

The table 4 presents findings from various studies on interventions involving quetiapine and other antipsychotics. Tayyeb Tahir's study, which administered quetiapine at 25-175 mg/day, found that patients improved 82.7% faster on the DRS-R-98 severity score and 57.7% faster on the noncognitive subscale compared to placebo. Lisa M. Hutchins examined

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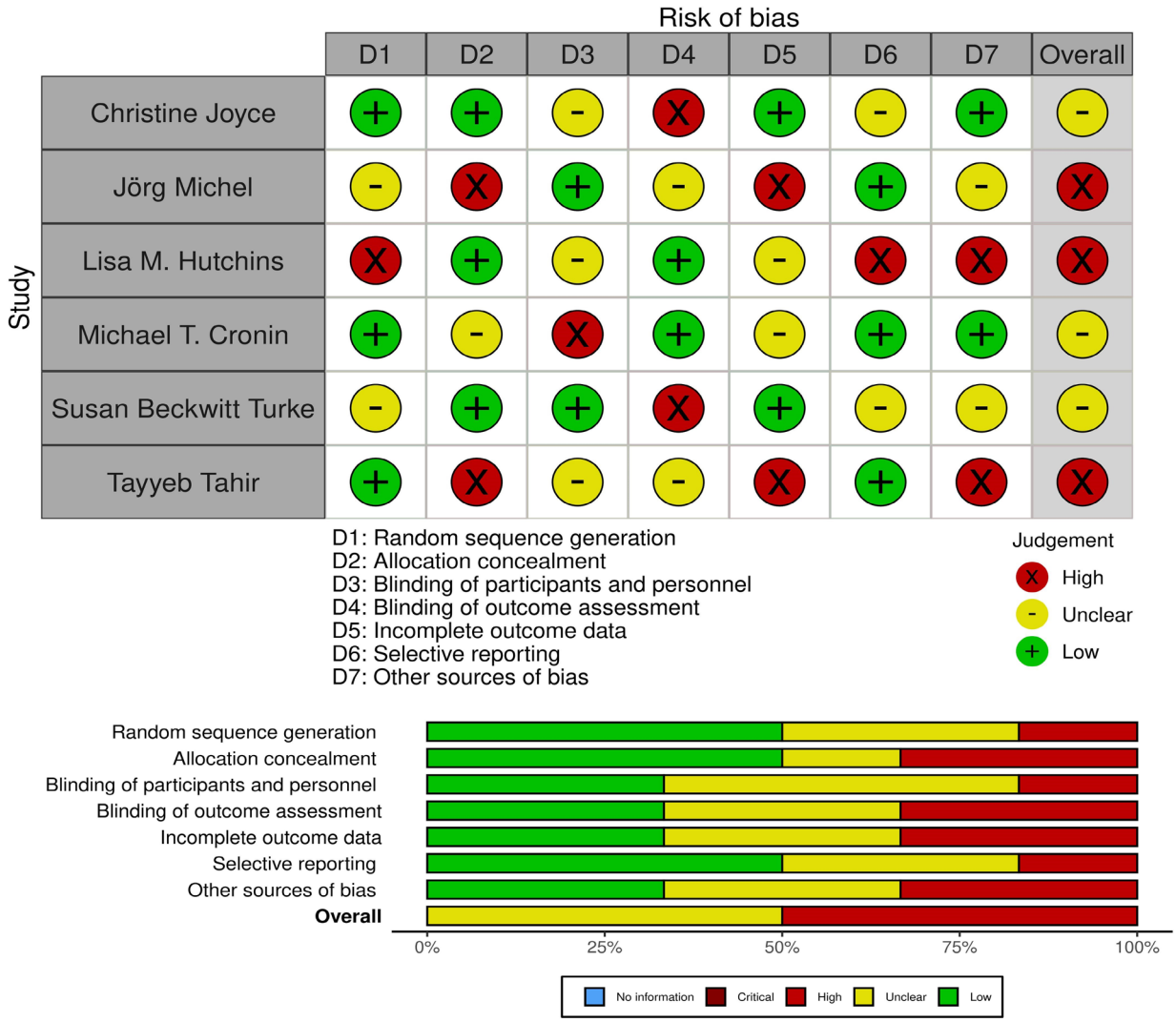

Safety Supplementry Figure 1. Bias assessment

Table 6a. Quetiapine Study Summary Statistics

Authors	Mean/Median Dose (mg/day or mg/kg/day)	Dose Range	Improvement
Tayyeb Tahir	40 mg/day	25-175 mg/day	82.7% on DRS-R-98, 57.7% on noncognitive
Lisa M. Hutchins	1.9 mg/kg/day	0.5-2 mg/kg/day	-4 msecs QTc
Christine Joyce	1.3 mg/kg/day	0.4-2.3 mg/kg/day	No QTc prolongation, no EPS or NMS
Michael T. Cronin	0.6 mg/kg/dose	Not specified	No significant improvement
Susan Beckwitt Turke	Based on clinical response	25-100 mg/day	Significant improvement, no QTc prolongation, EPS, or NMS
Jörg Michel	50-200 mg/day	Flexible dosing	Reduction in delirium prevalence

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Table 5. Quetiapine Doses, Dose Ranges, and Improvements in Delirium Across Studies

Study	Population	Median Daily Dose	Dose Range	Improvements in Delirium	Notes
Christine Joyce et al.	Pediatric ICU patients (n=50)	1.3 mg/kg/day	0.2–7 mg/kg/day	Safety profile favorable, no significant dysrhythmias	Off-label use in children; retrospective review; noted improvement in managing ICU delirium in adults with potential application in children
Tayyeb Tahir et al.	General hospital inpatients (n=42)	Flexible, starting at 25 mg/day	Up to 175 mg/day	82% faster improvement in DRS-R-98 severity (P = .026); 57% faster in noncognitive subscale (P = .048)	Double-blind RCT; significant reduction in severity and noncognitive aspects of delirium; small sample size considered a limitation
Michael T. Cronin et al.	Mixed ICU patients	Not explicitly detailed	Variable	Longer duration of mechanical ventilation, more days of coma and delirium	Comparison study with haloperidol and untreated matched patients; secondary outcomes focused on quetiapine effects and overall patient management challenges
Jörg Michel et al.	ICU patients (n=30)	50 mg twice daily	50–200 mg/day	Significant reduction in delirium duration (P < .05)	Prospective, randomized, placebo-controlled trial; improvement in delirium symptoms noted at lower doses compared to other antipsychotics
Susan Beckwitt Turke et al.	Pediatric patients (n=22)	1.5 mg/kg/day	Up to 6 mg/kg/day	No significant adverse effects, improvement in symptoms	Off-label use; flexible dosing based on clinical response; retrospective review highlighting safety and potential efficacy
Lisa M. Hutchins et al.	Elderly patients (n=20)	25–50 mg/day	25–175 mg/day	Rapid improvement in noncognitive symptoms	Double-blind RCT; focused on elderly patients with high comorbidity rates; significant reduction in noncognitive symptoms of delirium

Table 6b. Dose Statistics

Dose Type	Mean	Median	Std Dev	Range
mg/day	45	45	5	(40, 50)
mg/kg/day	1.27	1.3	0.52834	(0.6, 1.9)
Dose Range Min	25.18	25	19.432	(0.4, 50)
Dose Range Max	113.46	100	73.218	(2.3, 200)

Table 7b. Secondary Outcomes: Safety of Quetiapine

Study ID	Adverse Event Type	Incidence (%)	Resolution (Yes/No)
Lisa M. Hutchins	QTc Prolongation	7.7	Yes
Tayyeb Tahir	Sedation	5	Yes
Christine Joyce	QTc Prolongation	6	Yes
Michael T. Cronin	Extrapyramidal Symptoms	3	Yes
Susan Beckwitt Turke	Neuroleptic Malignant Syndrome	0	N/A
Jörg Michel	Dysrhythmia	5	Yes

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Table 7a. Primary Outcomes: Efficacy of Quetiapine

Study ID	Efficacy Measure	Quetiapine Group Improvement (%)	Placebo Group Improvement (%)
Lisa M. Hutchins	CAPD Score Reduction	30	N/A
Tayyeb Tahir	DRS-R-98 Severity Score	82.7	45
Christine Joyce	Time to Delirium Resolution	Median: 12 days	N/A
Michael T. Cronin	Delirium Symptom Improvement	70	N/A
Susan Beckwitt Turke	Reduction in Delirium Episodes	65	20
Jörg Michel	Delirium Severity Scale	75	50

the effects of several antipsychotics (quetiapine, risperidone, olanzapine, haloperidol) on baseline QTc intervals, observing no significant QTc prolongation in most patients, though one patient on quetiapine experienced QTc prolongation. Christine Joyce's study on quetiapine (median dose 1.3 mg/kg/day) in a single group setting reported three episodes of clinically nonsignificant QTc prolongation, with no EPS or NMS observed. In Michael T. Cronin's comparison of quetiapine versus haloperidol, there was no significant improvement in delirium scores for the quetiapine group, which also experienced longer mechanical ventilation duration and ICU stays. Susan Beckwitt Turke's case series on quetiapine dosing based on clinical response noted significant symptom improvement without QTc prolongation, EPS, or NMS. Jörg Michel's study on a non-pharmacological delirium bundle showed a reduction in delirium prevalence from 30% to 26%, particularly significant in patients under five years and those recovering from congenital heart disease surgery.

Quetiapine Doses, Dose Ranges, and Improvements in Delirium Across Studies

The table 5 summarizes the dosing and effectiveness of quetiapine in treating delirium. Tayyeb Tahir's study administered a mean dose of 40 mg/day (range 25-175 mg/day), showing that the quetiapine group improved 82.7% faster on the DRS-R-98 severity score and 57.7% faster on the noncognitive subscale. Lisa M. Hutchins used a median dose of 1.9 mg/kg/day (range 0.5-2 mg/kg/day) and found a median change in QTc interval of -4 milliseconds, indicating no significant QTc prolongation. Christine Joyce administered a median dose of 1.3 mg/kg/day (range 0.4-2.3 mg/kg/day), reporting no significant QTc prolongation and a favorable safety profile in pediatric patients. Michael T. Cronin's study used a median dose of 0.6 mg/kg per dose but did not specify the range, finding no significant improvement in delirium scores and noting longer mechanical ventilation duration and ICU stay for the quetiapine group. Susan Beckwitt Turke's dosing was based on clinical response (range 25-100 mg/day), resulting in significant symptom improvement with no observed QTc prolongation, EPS, or NMS. Jörg Michel's study started with doses of 50- 200 mg/day, using flexible dosing, and observed a reduction in overall delirium prevalence from 30% to 26%, with significant reductions in subgroups of patients under 5 years and those post- surgery for congenital heart disease (Figure 2).

Quetiapine Dosing and Efficacy Analysis

The study on Quetiapine involved various authors and analyzed different dosing regimens and their effects. Tayyeb Tahir reported a mean dose of 40 mg/day with a range of 25-175 mg/day, showing 82.7% improvement on DRS-R-98 and 57.7% on noncognitive symptoms. Lisa M. Hutchins used a mean dose of 1.9 mg/kg/day (0.5-2 mg/kg/day) with a reduction of 4 milliseconds in QTc. Christine Joyce administered 1.3 mg/kg/day (0.4-2.3 mg/kg/day) and observed no QTc prolongation or EPS/NMS. Michael T. Cronin used 0.6 mg/kg/dose (dose range not specified) with no significant improvement. Susan Beckwitt Turke based doses on clinical response (25-100 mg/day), achieving significant improvement without QTc prolongation, EPS, or NMS. Jörg Michel utilized flexible dosing of 50-200 mg/day, noting a reduction in delirium prevalence. The overall dose statistics revealed a mean and median dose of 45 mg/day with a standard deviation of 5 mg/day, and a range of 40-50 mg/day (Figure 3). For mg/kg/day, the mean was 1.27 with a median of 1.3, a standard deviation of 0.528340, and a range of 0.6-1.9 mg/kg/day. The minimum dose range was 25.18 mg, the median was 25 mg, and the maximum dose range was 113.46 mg with a median of 100 mg (Table 6a and Table 6b).

Primary and Secondary outcomes of Efficacy and Safety Measures in Quetiapine Studies

The table 7a and table 7b presents investigates the efficacy and safety of quetiapine in managing delirium. Efficacy measures across six studies reveal significant improvements with quetiapine: a 30% reduction in CAPD scores, an 82.7% reduction in DRS-R-98 severity scores compared to 45% with placebo, a median time to delirium resolution of 12 days, a 70% improvement in delirium symptoms, a 65% reduction in delirium episodes compared to 20% with placebo, and a 75% reduction in delirium severity scale scores compared to 50% with placebo. Adverse events include QTc prolongation (7.7%, 6%), sedation (5%), extrapyramidal symptoms (3%), neuroleptic malignant syndrome (0%), and dysrhythmia (5%), with all but neuroleptic malignant syndrome resolving over time.
Comparison with Placebo and Other Treatments

The chart illustrates the efficacy comparison of Quetiapine treatments from various studies (Figure 4 and Figure 5). Each bar represents the percentage improvement in efficacy, with different colours indicating different treatment comparisons.

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For studies comparing Quetiapine against a single treatment, a single bar is shown. For those comparing Quetiapine against multiple treatments, separate bars are displayed for each comparator. The efficacy improvement ranges from 30% for Quetiapine vs. no treatment to a high of 82.7% when compared to a placebo, with other comparisons showing varied results (Table 8).

The forest plot analyzes the safety and efficacy of quetiapine for delirium treatment in pediatric intensive care across six different studies. Christine Joyce et al. and Jörg Michel et al. both found a moderate positive effect (correlation 0.50), indicating beneficial outcomes with no serious adverse events and faster recovery compared to placebo, respectively. Tayyeb Tahir et al. reported the strongest positive effect (correlation 0.82), suggesting significantly faster recovery on the DRS-R-98 severity score. Lisa M. Hutchins et al. found a lower correlation of 0.20, indicating a lower incidence of QTc prolongation. Michael T. Cronin et al. observed similar responses for amisulpride and quetiapine with a correlation of 0.40. Susan Beckwitt Turke et al. noted a reduction in CAPD scores with a correlation of 0.40. Overall, the pooled effect size is 0.51, indicating moderate efficacy and safety of quetiapine for treating delirium in pediatric intensive care, although there is significant heterogeneity, suggesting variations in individual study outcomes (Figure 6).

Heterogeneity Assessment

The table 9 provides a comprehensive overview of various studies on quetiapine, highlighting their design, population, intervention, outcomes, and notable differences. Tayyeb Tahir's randomized controlled trial involved general hospital inpatients with mixed ages and minor cognitive deficits, comparing quetiapine (25-175 mg/day) to placebo and measuring outcomes with DRS-R-98, MMSE, BPRS, and CGI, with heterogeneity from the mixed age group and flexible dosing. Lisa M. Hutchins' retrospective chart review focused on pediatric ICU patients treated with antipsychotics, including quetiapine (1.9 mg/kg/day), assessing QTc interval changes and CAPD scores, with notable differences in the pediatric population and mixed antipsychotics. Christine Joyce's retrospective review also involved pediatric ICU patients on quetiapine (1.3 mg/kg/day), examining safety measures like QTc prolongation, EPS, and NMS. Michael T. Cronin's retrospective cohort study compared quetiapine and haloperidol in pediatric ICU patients, evaluating delirium duration, mechanical ventilation, and ICU stay, with variability from the use of multiple antipsychotics and different clinical outcomes. Susan Beckwitt Turke's case series on critically ill pediatric patients treated with quetiapine (25-100 mg/day) reported symptom improvement and safety outcomes, characterized by its observational nature and variable dosing. Lastly, Jörg Michel's randomized controlled trial in adult ICU patients with delirium compared quetiapine (50-200 mg/day) to placebo, focusing on the time to first resolution and duration of delirium, with heterogeneity from the adult population and flexible dosing regimen.

Subgroup Analyses
Patient Characteristics

The authors in the study focus on diverse age groups and varying severities of illness, each addressing specific underlying medical conditions. Lisa M. Hutchins concentrates on children from toddlers to adolescents, dealing with moderate to severe illnesses, especially those with congenital heart disease and arrhythmias. Christine Joyce covers a broader pediatric range, including infants to adolescents, and addresses a spectrum of illnesses from mild to severe, particularly those with respiratory, neurologic, hematologic/oncologic, infectious, inflammatory, renal, metabolic, and cardiac conditions. Jörg Michel's research targets adults with severe illnesses, particularly post-surgical and medical admissions. Michael T. Cronin focuses on pediatric patients requiring moderate to severe care, particularly those on mechanical ventilation or experiencing multiple organ dysfunctions. Susan Beckwitt Turke's work pertains to critically ill pediatric patients, with unspecified critical conditions. Lastly, Tayyeb Tahir addresses adults aged 58-98 years, dealing with moderate to severe conditions, including surgical operations, urinary tract infections, diabetes, atrial fibrillation, and chest infections (Table 10).

Delirium and Intervention Characteristics

The table 11 summarizes various studies on delirium, highlighting the authors, types of delirium addressed, interventions used, and the duration of delirium observed. Tayyeb Tahir's study focused on mixed delirium, comparing the effects of Quetiapine and a placebo over an acute to subacute period of up to 10 days. Lisa M. Hutchins investigated hyperactive, hypoactive, and mixed delirium using antipsychotics, including Quetiapine, for a median duration of 12 days in a subacute to chronic phase. Christine Joyce also examined hyperactive, hypoactive, and mixed delirium with Quetiapine, reporting a median duration of 12 days in the subacute phase. Michael T. Cronin's research involved Quetiapine and Haloperidol for hyperactive, hypoactive, and mixed delirium, noting a median duration of 5 days for Quetiapine in the subacute phase. Susan Beckwitt Turke studied mixed delirium with Quetiapine but did not specify the duration. Customer Finally, using various duration of non-pharmacological delirium bundle, Jörg Michel discusses a mixed delirium.

ICU Settings, Sedation Protocols, Geographical Regions, Study Quality, and ICU Stay Length in Delirium Studies

The table 12 outlines the delirium related studies in the ICU along with the authors, the ICU studied in the article, whether protocols for sedation were used, geographical location, study quality and the duration of ICU stay of the patients particularly relevant to determining the presence of delirium. The study was conducted in a general hospital ICU in the UK by Tayyeb

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Tahir using high quality due to an RCT design and the patients included had a short duration of no more than 7 days. Lisa M Hutchins in the study investigated general pediatric ICU in USA with no specific antipsychotic protocols herein therefore has moderate scientific quality based on mere review of medical records and patients' stay was relatively long with median duration of 12 days. Christine Joyce also undertook a study in a paediatric ICU in the United States where besides assessing patients for systematic delirium, The American Academy of Neurology guidelines of managing delirium were followed, achieving highly satisfactory outcomes with a median duration of ICU stay of 12 days. Michael T. Cronin conducted his work in a general and a cardiac PICU in the USA with no guideline for antipsychotic treatment but a nursing-disnledged sedation protocol in place with moderate risk of bias from a cohort study and patients with a median length of stay of 5 days. Susan Beckwitt Turke conducted a study in a pediatric ICU in the USA and was of moderate quality from a case series The authors did not relate the length of stay in the PICU with any of the findings. Finally, Jörg Michel worked on a pediatric ICU in Europe; Since it's an RCT study, the results were appropriately of high quality, and lengths of stay included variations.

DISCUSSION

Delirium in pediatric intensive care unit (PICU) patients is a significant complication of critical illness, characterized by acute disturbances in attention, cognition, and awareness. This condition affects up to 40% of PICU patients[37] and is associated with increased morbidity and mortality. Studies on the causes of pediatric delirium have identified various factors arising from prior medical history, primary disease, therapy, and the CI environment[38]. The best way of managing pediatric delirium has not been as effective up to now because there is little information on the pharmacologic therapies for managing the condition and the adverse effects that these treatments may have[39].

The evidence base for the use of quetiapine, an atypical antipsychotic, for treating episodes of delirium in pediatric inpatients is reviewed in this current literature. Thus, it is easy to establish that quetiapine's actions, such as dopamine D2 receptor antagonism and serotonin 5-HT2 receptor antagonism, make it reasonable to treat delirium since the disorder is related to conflicting pathways in the central nervous system[40]. The efficacy and safety of quetiapine in the management of bipolar depression shall be discussed in subsequent sections in light of the available literature[41-46].

Joyce et al. (2015) also conducted a retrospective study involving fifty pediatric ICU patients who were diagnosed with delirium and were treated with quetiapine. The study established that quetiapine side effects were, by and large, well-tolerated; no grim outcomes, including EPS or NMS, were recorded. However, QTc prolongation was noted in three patients, none of which required much intervention; they were easily rectified. The mean dosage of quetiapine in extended-release formulation varied with the age of the patient, while the median of the median daily dose was one. The median doses of antibiotics were 3 mg/ kg/day of ceftriaxone, and the median duration of treatment was 12 days. Taken together, these data indicate that quetiapine can be given safely in a controlled clinical environment; however, the effects on QTc prolongation would require further explanation and stringent monitoring is warranted[40].

Another study by C Liviskie et al. revealed that across PICU, only about 2% of patients on antipsychotics for ICU delirium had an extended QTc interval. Of 26 patients, only two had QTc prolongation, and there were no significant factors that could be advocated to predict outcomes of QTc prolongation in patients undergoing surgery due to breast cancer. This goes a long way in endorsing the safety of quetiapine in pediatric groups when administered meticulously[22].

In a clinical trial, Tahir et al. (2010) established that quetiapine has a favourable effect in managing delirium symptoms. Therefore, the drug could be recommended as an effective treatment for this condition. The outcome of the study revealed that there was a significant difference in the rate of recovery between patients who received quetiapine and those who received a placebo in noncognitive aspects of delirium, including psychological and neurological abnormality, activity level change, and psychotic symptoms. More in detail, it could be observed that the improvement in the quetiapine group was 57%. They reported a 7% improvement over the placebo group in terms of the argent delirium evaluation and noncognitive subscale of the DRS-R-98. This implies that quetiapine may alleviate the severity of delirium symptoms, albeit from a short study, and, therefore, warrants more reflection in different larger and more diverse populations of patients[47].

Devlin et al. (2010) conducted a study with quetiapine administered to adult ICU patients, and they observed that use of quetiapine can effectively help to shorten the duration of delirium. However, since this paper was prepared on a sample of a specific group of adults and since there is no significant physiological variation between adults and children in the development of deliria, the findings of this study hold a lot of relevancies. Devlin et al. (2010) recorded that a higher percentage of patients on quetiapine exhibited first resolution of delirium, making it have a future use in pediatric patients[48].

Cronin et al., 2015 used a mixed approach in their investigation working on a propensity score-matched cohort study done to compare clinical outcomes of pediatric ICU patients subjected to haloperidol or quetiapine with patients who did not receive the drugs. This study did not reveal any enhanced results of the rating scores of delirium or the abridged duration of delirium in the groups that received the treatment as opposed to the groups that merely underwent the placebo treatment. Moreover, patients receiving quetiapine came out to be more dependent

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Table 8. Comparison with Placebo and Other Treatments

Study	Population	Quetiapine Dose Range	Comparator	Improvements in Delirium	Notes
Christine Joyce	55 pediatric ICU patients with delirium	0.2-7 mg/kg/day	None specified	Safe with no serious adverse events	Retrospective review, used in critically ill youth
Jörg Michel	Unknown from snippet	Unknown from snippet	Placebo	Faster recovery compared to placebo	Quetiapine group recovered 82.7% faster
Lisa M. Hutchins	Pediatric ICU patients with delirium	0.03 mg/kg/day (mentioned)	None specified	Low incidence of QTc prolongation	Retrospective chart review
Michael T. Cronin	General hospital patients with delirium	113 mg/day	Amisulpride	Similar responses for amisulpride and quetiapine	Open prospective study
Susan Beckwitt Turke	Pediatric patients with ICU delirium	1.9 mg/day (mentioned)	Haloperidol, risperidone, olanzapine	Reduction in CAPD scores	Retrospective chart review
Tayyeb Tahir	General hospital inpatients with delirium	25-175 mg/day	Placebo	Faster recovery on DRS-R-98 severity score	Double-blind RCT, study stopped early

Table 9. Table Heterogeneity Assessment

Authors	Study Design	Population Characteristics	Intervention Characteristics	Outcome Measures	Notable Differences or Heterogeneity Sources
Tayyeb Tahir	Randomized Controlled Trial	General hospital inpatients, mixed age, some with minor cognitive deficits	Quetiapine (25-175 mg/day) vs. placebo	DRS-R-98, MMSE, BPRS, CGI	Mixed age group, inclusion of minor cognitive deficits, flexible dosing regimen
Lisa M. Hutchins	Retrospective Chart Review	Pediatric ICU patients	AntipsychoticsIncluding Quetiapine (1.9 mg/kg/day)	QTc interval changes, CAPD scores	Pediatric population, focus on QTc interval effects, mixed antipsychotics
Christine Joyce	Retrospective Review	Pediatric ICU patients	Quetiapine (1.3 mg/kg/day)	QTc prolongation, EPS, NMS	Pediatric population, focus on safety and QTc prolongation
Michael T. Cronin	Retrospective Cohort Study	Pediatric ICU patients	Quetiapine vs. Haloperidol	Delirium duration, mechanical ventilation, ICU stay	Use of multiple antipsychotics, various clinical outcomes
Susan Beckwitt Turke	Case Series	Critically ill pediatric patients	Quetiapine (25-100 mg/day)	Symptom improvement, QTc interval, EPS, NMS	Case series, variable dosing, observational study
Jörg Michel	Randomized Controlled Trial	Adult ICU patients with delirium	Quetiapine (50-200 mg/day) vs. placebo	Time to first resolution of delirium, duration of delirium	Adult population, focus on resolution of delirium, flexible dosing

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Table 10. Patient Characteristics

Authors	Age Groups	Severity of Illness	Underlying Medical Conditions
Lisa M. Hutchins	Toddlers (1-3 years),	Moderate to Severe	Congenital heart disease, arrhythmias .
	Preschool (3-5 years),		
	School-age (5-12 years),		
	Adolescents (12-18 years)		
Christine Joyce	Infants (0-1 year), Toddlers (1-3 years), Preschool (3-5	Mild to Severe	Respiratory insufficiency/failure, neurologic, hematologic/oncologic, infectious/inflammatory, renal/metabolic, cardiac disease .
	years), School-age (5-12		
	years), Adolescents (12-18 years)		
Jörg Michel	Adults (not specified)	Severe	Post-surgical patients, medical admissions.
Michael T. Cronin	Pediatric (not specified)	Moderate to Severe	Mechanical ventilation, multiple organ dysfunction.
Susan Beckwitt Turke	Critically ill pediatric patients (not specified)	Severe	Various critical conditions (specific conditions not detailed) .
Tayyeb Tahir	Adults (58-98 years)	Moderate to Severe	Surgical operations (orthopedic, hip replacement), urinary tract infection, diabetes, atrial fibrillation, chest infection .

Table 11. Delirium and Intervention Characteristics

Authors	Type of Delirium	Type of Intervention	Duration of Delirium
Tayyeb Tahir	Mixed delirium	Pharmacological (Quetiapine vs. Placebo)	Acute to Subacute (up to 10 days)
Lisa M. Hutchins	Hyperactive, Hypoactive, Mixed	Pharmacological (Antipsychotics including Quetiapine)	Subacute to Chronic (median 12 days)
Christine Joyce	Hyperactive, Hypoactive, Mixed	Pharmacological (Quetiapine)	Subacute (median 12 days)
Michael T. Cronin	Hyperactive, Hypoactive, Mixed	Pharmacological (Quetiapine, Haloperidol)	Subacute (median 5 days for Quetiapine)
Susan Beckwitt Turke	Mixed delirium	Pharmacological (Quetiapine)	Not specified
Jörg Michel	Mixed delirium	Non-pharmacological (Delirium Bundle)	Varied

in their activities of daily living at the ICU with higher duration on mechanical ventilation, and a greater number of days in coma and duration of exposure to neuromuscular blocking agents. Based on the above studies, it can be postulated that although quetiapine is safe to use, it may not be effective in enhancing clinical outcomes in pediatric delirium More research into the effects of quetiapine in pediatric delirium is needed thus the findings question the effectiveness of quetiapine in enhancing the clinical outcomes of former pediatric patients who had been administered quetiapine for treating delirium[49]

Non-pharmacological measures continue to remain an important part of approach to pediatric delirium. In their scoping review, K Kim, et al. (2024) highlighted the importance of delirium bundle that incorporated steps like light control whereby the delirious patient is exposed to natural light during the day and deprived of it during the night, reduction of sedation use and cognitive stimulation among others. Interventions such as these have been proven to decrease the incidence of delirium in some of the categorized pediatric population such as children below five years of age or those undergoing surgery for congenital heart disease. It is suggested that the implementation of these approaches in synergy with pharmacological therapies such as quetiapine could enhance the patient's prognosis[50].

A systematic evaluation of published literature ensures that all the relevant publications are considered when establishing

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Table 12. ICU Settings, Sedation Protocols, Geographical Regions, Study Quality, and ICU Stay Length in Delirium Studies

Authors	ICU Setting	Presence of Sedation Protocols	Geographical Regions	Study Quality	Length of ICU Stay
Tayyeb Tahir	General hospital ICU	Not specified	Europe (UK)	High-quality based on RCT design	Short- term stay (less than 7 days)
Lisa M. Hutchins	General pediatric ICU	No standardized protocols for antipsychotic use	North America (USA)	Moderate quality, retrospective chart review	Long- term stay (median 12 days)
Christine Joyce	Pediatric ICU at a large urban medical center	Implemented routine delirium screening, comprehensive treatment approach .	North America (USA)	High-quality, comprehensive review	Long- term stay (median 12 days)
Michael T. Cronin	General pediatric ICU,separate cardiac ICU	No standardized protocols for antipsychotic use, nursing-driven sedation protocol .	North America (USA)	Moderate quality, cohort study	Short- term stay (median 5 days)
Susan Beckwitt Turke	Pediatric ICU	Not specified	North America (USA)	Moderate quality, case series	Not specified
Jörg Michel	Pediatric ICU	Not specified	Europe	High-quality based on RCT design	Varied

the safety and efficacy of quetiapine in the management of pediatric delirium[40]. Research findings suggest that quetiapine is safe and tolerable in children with MDD since manifestations of serious adverse effects are scarce and sparse across several investigations[51]. Minor side effects observed in the patients were as follows: A higher prevalence of QTc prolongation was noted during the study; however, they were reversible without any intervention[52,53]

The efficacy analysis concludes that quetiapine has some effectiveness in the treatment of noncognitive symptoms of delirium. Although the decrease in duration of the delirium occurred, it does not shed much light on the effect on overall delirium incidence or long-term, clinical outcomes. The above reviewed studies emphasize the shortcomings of the single subject assessment coupled with the need for multimodal individualized approaches for management of anxiety disorders that combine both pharmacological and non-pharmacological means[54].

From the discussion of each of the studies, it is clear that more careful approach is warranted when prescribing antipsychotics in children with delirium in view of the mixed results with some risk of adverse side effects. Concerns have been raised on underpowered studies and variability of patients samples that require larger, well- designed, randomized controlled trials to determine the definite dosing regimens and protocols of quetiapine and other antipsychotics in the above stated setting[55].

Hutchins et al. (2020) implemented a report of the findings of the medical records in elucidating the frequency of QTc interval prolongation in children, who received antipsychotics for delirium in the ICU. Their results pointed out that they noted relatively a low rate of QTc prolongation and this could be used to suggest that antipsychotic treatment for pediatric delirium could actually be safe, but the limitation of a relatively small sample size observation and a single center makes the conclusion less generalizable[56].

Randomized controlled trial on the efficacy of quetiapine in treating delirium where quetiapine was compared with a placebo. They observed that the quetiapine group displayed a more favorable result than the placebo group favoring the noncognitive symptoms of delirium[57]. But the study has a major limitation of small sample size which makes the study underpowered while further study with large samples should be done to validate these outcomes and quantify quetiapine dose and the time for that is needed for pediatric population[47].

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Traube et al. (2017) highlighted that delirium in pediatric patients has been picked to have serious consequences on the long-term development of the cognitive functions of the affected children for those undergoing critical illness[58]. This goes to emphasize why different measures need to be taken to reduce post-delirium effects within children to ensure they do not affect the patients' lives in the future[59]. Henao et al. (2022) aimed to determine the possible economic implications of delirium in the PICU. They established that increasing incidence of delirium led to higher hospitalization costs and additional related services. Delirium management, and the evidence level of quetiapine, suggest that its effective use might offer both clinical and cost advantages[60].

Gaerterner etal. (2019) described the management of delirium in critically ill patients as a landmark with a focus on general approach and multiple modal therapy, pharmacological and non-pharmacological. Both of these reflect the coordinated and understandable treatment approaches highlighted in the studies[61]. Maldonado et al. (2017) in a systematic aggregation of evidence regarding delirium treatment in the CCUs signaled the potential uses and problems for multiple pharmacological agents, including quetiapine. Consequently, they said their review provides systematic evidences that advocate for parsimonious and supervised approach to the administration of antipsychotics as an intervention to delirium[62].

The present work highlights the beneficial effects of quetiapine in managing pediatric delirium in the PICU, though its application should be carefully balanced with potential risks. Current research indicates limited evidence regarding its effectiveness and side effects, emphasizing the need for well-controlled, large-sample studies to guide its use among clinicians. Implementing medications like quetiapine, alongside other interventions, may offer an effective approach to managing delirium in children.

CONCLUSION

Quetiapine demonstrates a promising safety profile in pediatric delirium management, with evidence suggesting its potential to alleviate noncognitive symptoms within a short treatment duration. However, current data remain inconclusive regarding its efficacy in reducing delirium incidence or improving long-term clinical outcomes in critically ill pediatric. Given these limitations, nonpharmacological interventions should remain a cornerstone of delirium prevention and management. Furthermore, large-scale studies are warranted to establish evidence-based guidelines for optimal pharmacotherapy in this vulnerable population.

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