Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study*

John W. Devlin, PharmD; Russel J. Roberts, PharmD; Jeffrey J. Fong, PharmD; Yoanna Skrobik, MD; Richard R. Riker, MD; Nicholas S. Hill, MD; Tracey Robbins, RN; Erik Garpestad, MD

Objective: **To compare the efficacy and safety of scheduled quetiapine to placebo for the treatment of delirium in critically ill patients requiring as-needed haloperidol.**

Design: **Prospective, randomized, double-blind, placebo-controlled study.**

Setting: **Three academic medical centers.**

Patients: **Thirty-six adult intensive care unit patients with delirium (Intensive Care Delirium Screening Checklist score ≥4), tolerating enteral nutrition, and without a complicating neurologic condition.**

Interventions: **Patients were randomized to receive quetiapine 50 mg every 12 hrs or placebo. Quetiapine was increased every 24 hrs (50 to 100 to 150 to 200 mg every 12 hrs) if more than one dose of haloperidol was given in the previous 24 hrs. Study drug was continued until the intensive care unit team discontinued it because of delirium resolution, therapy ≥10 days, or intensive care unit discharge.**

Measurements and Main Results: **Baseline characteristics were similar between the quetiapine (n = 18) and placebo (n = 18) groups. Quetiapine was associated with a shorter time to first resolution of delirium of 1.0 (interquartile range [IQR], 0.5–3.0) vs. 4.5 days (IQR, 2.0–7.0; $p = .001$), a reduced duration of delirium of 36 (IQR, 12–87) vs. 120 hrs (IQR, 60–195; $p = .006$), and less agitation (Sedation-Agitation Scale score ≥5) of 6 (IQR, 0–38) vs. 36 hrs (IQR, 11–66; $p = .02$). Whereas mortality (11% quetiapine vs. 17%) and intensive care unit length of stay (16 quetiapine vs. 16 days) were similar, subjects treated with quetiapine were more likely to be discharged home or to rehabilitation (89% quetiapine vs. 56%; $p = .06$). Subjects treated with quetiapine required fewer days of as-needed haloperidol of 3 [(interquartile range, 2–4) vs. 4 days (IQR, 3–8; $p = .05$)]. Whereas the incidence of QTc prolongation and extrapyramidal symptoms was similar between groups, more somnolence was observed with quetiapine (22% vs. 11%; $p = .66$).**

Conclusions: **Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation. Future studies should evaluate the effect of quetiapine on mortality, resource utilization, post-intensive care unit cognition, and dependency after discharge in a broader group of patients. (Crit Care Med 2010; 38: 000–000)**

Key Words: delirium; quetiapine; haloperidol; antipsychotic; drug therapy; treatment; critical care; intensive care unit; randomized controlled trial; outcomes

Delirium, characterized by fluctuations in mental status such as inattention, disorganized thinking, hallucinations, disorientation, and altered level of consciousness, is a frequent occurrence in the intensive care unit (ICU) (1–3). Because it is associated with higher mortality, a longer duration of mechanical ventilation and greater healthcare costs, recent ICU guidelines recommend that ICU patients be routinely screened for delirium (4–9). Once identified, many strategies to treat critically ill patients with delirium have been proposed, including reversal of any causative factors, environmental modification, and various sleep-promotion strategies (10, 11). These interventions are often not successful in resolving delirium, and patients frequently are treated with psychoactive medications (12).

To date, there are no published double-blind, randomized, placebo-controlled trials to establish the efficacy or safety of any antipsychotic medication in the management of delirium in the ICU (13). Limited evidence from uncontrolled studies and extensive clinical experience support the use of intravenous haloperidol in agitated ICU patients (9, 14, 15). Use of haloperidol, however, is often limited because of adverse events, including QTc interval prolongation, Torsades de Pointes, hypotension, and extrapyramidal symptoms (9, 16, 17).

Atypical antipsychotic agents such as olanzapine, quetiapine, and risperidone have replaced older neuroleptic agents such as haloperidol in the treatment of psychiatric conditions, such as schizophrenia, because of their more favorable

*See also p. XXX.

From the Northeastern University School of Pharmacy (JWD, RJR), Boston, MA; Massachusetts College of Pharmacy (JJF), Worcestor, MA; Department of Critical Care Medicine, Masionneuve Rosemont Hospital (YS, JH), Montreal, Quebec; Department of Critical Care Medicine, Maine Medical Center (RRR, TR), Portland, ME; Division of Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center (NSH, EG), Boston, MA.

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For information regarding this article, E-mail: j.devlin@neu.edu

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safety profile (18, 19). Small controlled studies have suggested that these atypical agents may be as effective as haloperidol for the treatment of delirium in hospitalized patients, but few of these studies have included ICU patients, incorporated a placebo arm or a dose-titration strategy, and none has been blinded (20–30).

Of the six atypical antipsychotics currently available in the United States, quetiapine (Seroquel Astra-Zeneca, Wilmington, DE) has several advantages that may be especially useful when treating delirium in the ICU, including a predominate antihistaminic mechanism of action, a short half-life that facilitates dose titration, a low propensity to alter the QTc interval, and very rare reports of extrapyramidal symptom effects (31). We hypothesized that quetiapine, administered on a scheduled basis and titrated to effect, will lead to a faster resolution of delirium in critically ill adults (12). Therefore, we conducted this randomized, placebo-controlled trial to evaluate the efficacy and safety of the addition of quetiapine to as-needed intravenous haloperidol in critically ill patients with delirium.

MATERIALS AND METHODS

This prospective, randomized, double-blind, placebo-controlled trial was conducted at three academic hospitals: Tufts Medical Center, Boston, MA; Maine Medical Center, Portland, ME; and Maisonneuve-Rosemont Hospital, Montreal, Quebec. The Institutional Review Boards at each institution approved the study. From April 2006 to August 2008, adult patients admitted to the medical and surgical ICU at each institution with delirium diagnosed (Intensive Care Delirium Screening Checklist [ICDSC] ≥4) by the primary care team, had an order for as-needed haloperidol, and were tolerating enteral nutrition (≥20 mL/hr for at least 12 hrs) were evaluated for the study (Appendix 1) (32). Study exclusion criteria were extensive and are presented in Table 1.

Subjects were assigned in blocks of four to one of the two groups in a 1:1 ratio by means of a computer-generated random number table. A different randomization schedule was used at each site and treatment allocation was known only to the investigational pharmacist at each site. At the time of enrollment, the following baseline demographics were collected: age, gender, admitting diagnosis, ICDSC score, sedative and analgesia use in the previous 24 hrs, level of sedation, QTc interval, location before ICU admission, number of days of ICU admission before study admission, and intubation status. The Multiple Organ Dysfunction Score and Acute Physiology and Chronic Health Evaluation II score was obtained at both ICU admission and study randomization (33, 34).

Table 1. Study exclusion criteria

History of irreversible cognitive dysfunction (e.g., dementia) based on a review of the patient record
Admitted with a primary neurologic condition or injury (e.g., intracranial hemorrhage, active seizure)
History of hepatic encephalopathy or end-stage liver disease (Childs-Pugh class B or worse)
Actively withdrawing from alcohol
Treatment with an antipsychotic agent in the 30 days before ICU admission
Current treatment with dexmedetomidine or a neuromuscular blocker
Current treatment with an agent having either the potential to affect quetiapine concentrations (e.g., phenytoin) or increase the risk for QTc prolongation (e.g., erythromycin or any class Ia, Ic, or III antiarrhythmic)
Baseline QTc interval ≥500 msec
Pregnancy
Non-English speaking
Presence of a condition preventing delirium assessment (e.g., coma, severe hearing disability)
Prognosis considered hopeless
Informed consent could not be obtained from the legally authorized representative

ICU, intensive care unit.

Level of sedation was assessed using the Sedation-Agitation Scale (SAS) (35). Critical care nurses at each institution underwent formalized educational training regarding the use of the SAS and are required to document it in the ICU flow sheet at least every 4 to 6 hrs in all patients. Agitation was defined as a SAS score ≥5, and a sedation level of "deeply sedated" was defined as a SAS score ≤2. Somnolence was defined as decrease in the SAS score ≥1 in the absence of the administration of sedative in those patients with a SAS score ≤4. Delirium was assessed during the study using the ICDSC, with a score ≥4 of the eight components being considered equivalent to a diagnosis of delirium (Appendix 1) (32). To be considered assessable, the patients had to be awake with a SAS score ≥3. If a patient was found to have a SAS score ≤2, the delirium assessment was deferred and repeated every 2 hrs until the patient had a SAS score ≥3. Delirium assessments were completed by the subject's bedside nurse at baseline and during every nursing shift. The ICDSC was used at all three institutions before the start of the study. All critical care nurses underwent formal education regarding the ICDSC consisting of both clinical case-based scenarios and didactic presentations (36, 37).

The QTc interval was measured at least every 12 hrs and documented in the subject's flow sheet. The criteria used to define QTc interval prolongation (>60 msec above baseline or >450 msec for males and >470 msec for females) was based on established guidelines from the Committee for Proprietary Medicinal Products (38, 39). Signs of extrapyramidal symptoms were monitored daily and, if thought to be present, were evaluated by one of the investigators using the Simpson-Angus Scale within 1 hr and then every 12 hrs thereafter (40). All subject-initiated episodes of device removal were routinely documented in the subject's flow sheet.

Subjects and all study personnel were blinded to the study drug assignment. Subjects were randomized to either quetiapine or placebo tablets that were identical to each other even when crushed. Therapy was initiated at 50 mg every 12 hrs and administered either orally or via a nasogastric/enteral tube. Therapy was titrated upwards on a daily basis by increments of 50 mg every 12 hrs to a maximum dose of 200 mg every 12 hrs if the subject received at least one dose of as-needed haloperidol in the previous 24 hrs (13, 24, 25). Tube feeds held for 30 mins before the administration of each dose of study medication. The feeding tube was then flushed with 25 mL of sterile water before study drug administration. The subject's nurse crushed each study medication dose, mixed it in 10 mL water, and administered the slurry via nasogastric/enteral tube. Feeding tubes were then flushed with 50 mL of sterile water after administration of each dose of the study medication and tube feeds were restarted immediately after study drug administration at the same rate that was used before study drug administration.

All subjects were allowed to receive IV haloperidol 1 to 10 mg administered up to every 2 hrs on an as-needed basis to control symptoms associated with delirium. Nurses were reminded at the start of each shift that there was a 50% chance their patient could be receiving a placebo and that they should administer haloperidol as they would in routine clinical practice. Scheduled IV or oral haloperidol and other antipsychotic medications were not allowed during the study. All prescribing decisions regarding sedation and analgesia therapy were left to the discretion of the subject's intensivist and were not mandated as part of the study.

The study drug was continued until one of the following occurred: (1) the subject was deemed by the attending intensivist, based on their clinical judgment, to no longer demonstrate signs of delirium and, therefore, to no longer require scheduled therapy with an antipsychotic agent; (2) 10 days of therapy had elapsed; (3) ICU discharge occurred; or (4) an adverse event potentially attributable to the study drug occurred that warranted discontinuation of the study drug. Allowing the attending intensivist to discontinue study drug once the subject no longer had signs of delirium was consistent with existing clinical practice in our institutions. In situations in which 10 days of therapy was reached or the subject was ready to transfer out of the ICU while still receiving study drug, the subject's treatment assignment was revealed to the attending intensivist (but not the study team) to help determine the best course of therapy (which could include continued therapy with quetiapine).

Consistent with recent guidelines for the conduct of delirium studies, the primary outcome to evaluate efficacy in this study was time to first resolution of delirium (41). This was defined as the time in hours from administration of the first dose of study drug until an ICDSC ≤3 was first detected. Secondary efficacy outcomes included: total hours in delirium during the study, total hours spent "deeply sedated" (SAS ≤2) or agitated (SAS ≥5), episodes of subject-initiated device removal, use of haloperidol therapy including total dose in milligrams during the study, number of doses, and number of days of therapy, the use of sedatives (converted to midazolam equivalents) and analgesics, duration of study drug administration, average daily and maximum study drug dose, length of mechanical ventilation, duration of both ICU and hospital stay, and hospital mortality (42). The disposition of subjects after hospital discharge was categorized to one of four groups: (1) home; (2) rehabilitation facility; (3) chronic care facility; and (4) death. Measures of safety included total number of adverse and serious adverse events related to study drug administration (using FDA MEDWATCH criteria), episodes of somnolence, incidence of extrapyramidal symptoms, and episodes of QTc interval prolongation.

Given the absence of placebo-controlled studies evaluating the response to antipsychotic therapy in critically ill patients, and the lack of available studies that have measured the effect of antipsychotic therapy on time to resolution of delirium, we extrapolated results from studies in patients not in the ICU demonstrating that delirium resolves in 20% to 60% of patients receiving neuroleptic therapy (21, 23, 28). Therefore, for our study, we assumed that delirium would resolve in 50% of subjects treated with quetiapine during study drug administration and in 10% of subjects treated with placebo. Given these assumptions, we calculated that 24 subjects in each group would provide >80% power to find a significant difference with a Fisher's exact test and a two-sided alpha level of 0.05. Because of slow study enrollment, however, we closed the study early after 36 patients were enrolled.

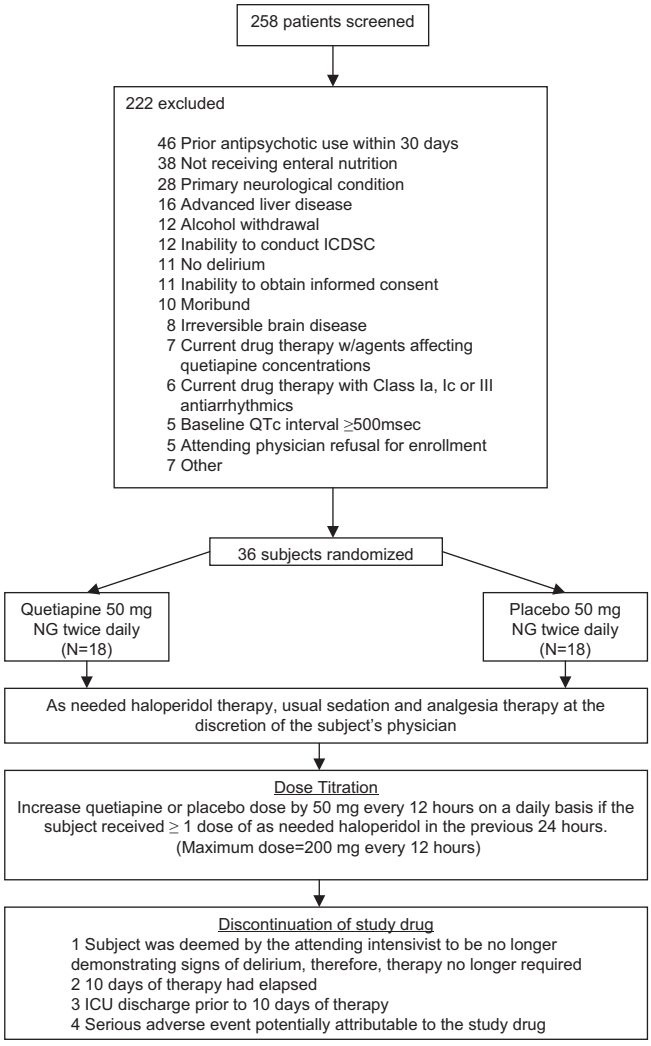

Figure 1. Patient screening, enrollment, and randomization.

Data were analyzed using an intention-to-treat principle. To account for the fact that study drug was discontinued in some subjects before resolution of delirium and before the end of the maximum 10-day treatment period, we chose to compare time to first resolution of delirium between groups by comparing Kaplan-Meier survival curves with a log rank test which allowed for the inclusion of these cases but censored them at the time of cessation of follow up (43). Outcomes were compared using the Mann-Whitney *U* test (expressed as median and IQR or the chi-square test, with the Yates correction when appropriate). Fisher's exact tests were used for categorical data with rare events. For outcomes reported as a percentage of the time study drug was administered, a percentage was first calculated for each subject and then the median percent (IQR) was reported for each group. A $p \leq .05$ was considered significant for all analyses. All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

RESULTS

During the study period, 258 ICU patients were screened and 222 were excluded (Fig. 1). No subjects had informed consent withdrawn. All 36 randomized patients were included in the analysis. Baseline characteristics were not statistically different between the two study groups (Table 2). Overall, most subjects were admitted to a medical ICU service and intubated. Severe sepsis/acute respiratory distress syndrome (42%) were the most common admitting diagnoses.

Table 2. Baseline characteristics[a]

	Quetiapine (n = 18)	Placebo (n = 18)
Age, yrs	62.4 ± 14	63.6 ± 15.3
Male, %	56	56
APACHE II, on admission to ICU	19.7 ± 5.3	21.4 ± 9.2
APACHE II, at study entry	16.8 ± 5.2	16.8 ± 5.1
MODS, on admission to ICU	5.3 ± 2.9	7.1 ± 3.6
MODS, at study enrollment	4.9 ± 2.1	4.1 ± 2.7
ICU type, %		
Medical	72	78
Surgical	28	22
ICU days before enrollment	5 (2–8)	7 (3–11)
Intubated at study entry, %	72	89
Location before ICU, %		
Home	67	50
Another hospital	11	44
Nursing home	6	0
Floor unit	16	6
Admission diagnosis, %		
Sepsis/acute respiratory distress syndrome	39	44
Chronic obstructive pulmonary disease	11	11
Surgery	28	17
Myocardial infarction	16	11
Other	6	17
Sedative, analgesic and haloperidol use in the 24 hrs before randomization		
Midazolam equivalents, mg	5.7 (0–10)	5.7 (0–6)
Fentanyl, μg	0 (0–200)	520 (0–1200)
Haloperidol, mg	3 (0–17)	2 (0–31)
Subjects exposed to a benzodiazepine in the 24 hrs before study randomization, %	22	33
SAS at study entry, %		
3 or 4	72	67
≥5	28	33
ICDSC score at study entry	5 (4–6)	5 (4–6)
Baseline QTc, msec	399 ± 41	412 ± 37

APACHE, Acute Physiology and Chronic Health Evaluation; MODS, Multiple Organ Dysfunction Score; ICU, Intensive Care Unit; SAS, Sedation Agitation Scale; ICDSC, Intensive Care Delirium Screening Checklist.

[a]Data presented as either mean± SD or median (interqurtile range).

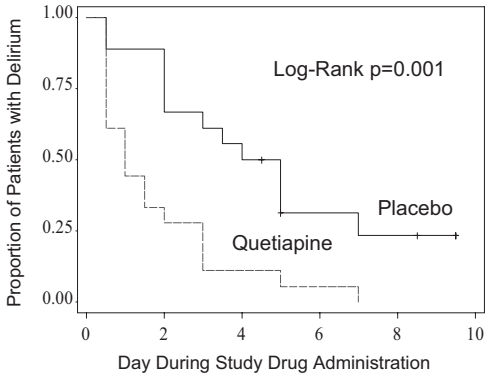

Figure 2. Proportion of patients with first resolution of delirium over time between quetiapine (n = 18) and placebo (n = 18) groups. Both groups of patients were treated using the same as-needed intravenous haloperidol protocol.

The time to first resolution of delirium was shorter with quetiapine therapy than with placebo (median [IQR]: 1.0 [0.5–3.0] vs. 4.5 days [2.0–7.0]; $p = .001$; Fig. 2). During the period of study drug administration, delirium resolved at least once in all quetiapine patients but in only 78% of patients receiving placebo ($p = .05$). Subjects receiving quetiapine also spent fewer hours in delirium (36 [12–87] vs. 120 [60–195]; $p = .006$) and required a shorter duration of study drug therapy (102 [84–168] vs. 186 hrs [108–228], $p = .04$; Table 3). Quetiapine was associated with fewer hours of agitation (SAS ≥5) compared to the placebo group (6 [0–38] vs. 36 [11–66]; $p = .02$). The number of subjects who experienced "deep sedation" (SAS ≤2) or a patient-initiated device removal was not different between groups. Duration of mechanical ventilation, length of ICU and hospital stay, and hospital mortality did not differ between groups (Table 4). However, subjects who received quetiapine were more likely to be discharged from hospital to either home or a rehabilitation facility as opposed to being transferred to a chronic care facility or dying (89 vs. 56%; $p = .06$).

Subjects in the quetiapine group received a shorter duration of haloperidol therapy (3 [2–4] vs. 4 days [3–8]; $p = .05$; Table 5). The total amount and number of doses of haloperidol administered per day during the study was less in the quetiapine group, although this did not reach significance. Subjects in the quetiapine group also received a sedative agent (propofol or a benzodiazepine) on fewer days than placebo-treated subjects (1 [0–3] vs. 4 days [1–9]; $p = .09$). In addition, quetiapine-treated subjects also received fentanyl therapy on fewer days (0 [0–3] vs. 4 days [1–9]; $p = .03$), received a lower daily study drug dose (110 [88–191] vs. 210 mg [116–293]; $p = .01$), and required less up-regulation of the study medication dose (200 [100–313] vs. 375 mg [25–400]; $p = .02$). Two subjects randomized to receive placebo were discontinued from the study by the attending intensivist before the maximum 10-day duration of therapy because their symptoms associated with delirium (primarily severe agitation) could not be controlled with the administration of multiple, high doses of IV haloperidol.

Safety outcomes are presented in Table 6. More subjects treated with quetiapine experienced adverse events, possibly related to the study drug, than those treated with placebo, although this did not reach statistical significance. Five episodes of somnolence and one episode of hypotension were observed that were thought to be possibly related to the administration of quetiapine. No episodes of extrapyramidal symptoms were experienced during the study drug period. The number of subjects with QTc prolongation as determined by >60-msec increase from baseline (39% vs. 44%; $p =$

Table 3. Clinical outcomes during study drug administration[a,b]

	Quetiapine (n = 18)	Placebo (n = 18)	p
Time of study drug administration, hrs	102 (84–168)	186 (108–228)	.04
Time in delirium			
Hours	36 (12–87)	120 (60–195)	.006
Percent[c]	53 (16–67)	69 (58–100)	.02
Number of subjects experiencing delirium recurrence after initial delirium resolution, %	22	44	.29
Time spent agitated, Sedation-Agitation Scale ≥5			
Hours	6 (0–38)	36 (11–66)	.02
Percent[c]	3 (0–22)	21 (8–41)	.03
Time spent deeply sedated, Sedation-Agitation Scale ≤2			
Hours	0 (0–8)	0 (1–2)	.54
Percent[c]	0 (0–8)	0 (0–0)	.39
Subject-initiated device removal			
Number of episodes	8	10	.79
Number of subjects with ≥1 episode, %[d]	17	22	1.0
Reason for discontinuation of study drug, %[d]			
Therapy thought to be no longer required by subject's attending intensivist	44	39	.31
10 days of therapy had elapsed	12	33	
ICU discharge	44	28	
Serious adverse drug event potentially attributable to study drug	0	0	

[a]Median (interquartile range) unless otherwise noted; [b]*p* values calculated using Mann-Whitney *U* test when medians are presented and a Yates-corrected chi-square test when percentages are presented, unless noted otherwise; [c]as the percentage of time subject was administered study drug; [d]*p* value calculated using Fisher's exact test.

Table 4. Other clinical outcomes[a,b]

	Quetiapine (n = 18)	Placebo (n = 18)	p
Duration of mechanical ventilation, days	11 (3–19)	11 (4–29)	.67
Duration of intensive care unit stay, days	16 (10–22)	16 (13–32)	.28
Duration of hospitalization, days	24 (11–33)	26 (17–49)	.32
Hospital mortality, %[c]	11	17	1.0
Delirium in the 14-day period after study drug discontinued, or until subject discharged/transferred from hospital[d]			
Subjects with ≥1 day of delirium, %	20	56	.09
Time spent in delirium, %[e]	0 (0–0)	14 (0–47)	.05
Subject placement after hospital discharge, %[c]			
Home/rehabilitation center	89	56	.06
Chronic care facility/another acute care hospital/death	11	44	

[a]Median (interquartile range) unless otherwise noted; [b]*p* values calculated using Mann-Whitney *U* test when medians are presented and a Yates-corrected chi-square test when percentages are presented, unless noted otherwise; [c]*p* value calculated using Fisher's exact test; [d]the duration of subject follow-up after study drug discontinuation was similar between quetiapine(n = 15) (7 [4–10] and placebo (n = 16) (10 days [4–14]) groups ($p = .50$); [e]as the percentage of time, subject was followed-up in 14-day period after study drug was discontinued.

0.74), QTc >500 msec (22% vs. 28%; $p = 1.0$), or other Committee for Proprietary Medicinal Products definitions (50% vs. 72%; $p = 0.31$) was similar between the quetiapine and placebo groups. Torsades de Pointes was not observed in any subjects.

DISCUSSION

This is the first double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of antipsychotics for the treatment of delirium in the ICU. Quetiapine, when dose-escalated to desired effect, may be associated with faster resolution of delirium, reduced time of delirium and agitation, and a more favorable disposition at hospital discharge than patients who receive as-needed intravenous haloperidol therapy alone. Distinct from previous studies, this is the first study to incorporate a placebo arm (with rescue haloperidol in both arms) allowing estimation of a quetiapine treatment effect for delirium in critically ill adults (21–26, 28, 44, 45). Our study also suggests that quetiapine administration to ICU patients with delirium may decrease the need for intravenous haloperidol—an important consideration given the numerous safety concerns associated with its use and recent data suggesting that use of haloperidol may prolong the duration of delirium (9, 44, 46, 47).

The use of an escalating dose of quetiapine may also help to prevent adverse effects and mimics a dosing strategy that may be generalizeable to routine clinical practice. Given the limited information available regarding quetiapine use for ICU delirium when we designed this study, extensive exclusion criteria were incorporated to reduce adverse events, improve safety for enrolled subjects, and reduce confounding from conditions with symptoms that may overlap delirium. Additional testing with less restrictive criteria is required before this approach can be generalized to a wider ICU population.

A validated and reliable delirium screening tool, the ICDSC, was used to identify delirium and measure response to treatment in study patients. This instrument was developed and initially validated at one of the study sites (Maisonneuve-Rosemont Hospital) and, after education, has been used both clinical and research practice at the other two study sites for >4 yrs (32). Given the protocol was developed for all aspects of the study, including study drug dosing and titration, use of haloperidol therapy, clinical monitoring, and study drug discontinuation, we are confident that subjects were managed in a similar fashion at all three study sites. Last, the outcome measures and statistical analysis that we chose are consistent with those used in other ICU clinical studies evaluating the impact of interventions on delirium resolution and patient safety (3, 41, 44, 48, 49).

A number of potential limitations of our study must be considered when evaluating the results. Although adequate to demonstrate a difference in our primary outcome, our sample size was not large enough to reliably detect differences in any of the efficacy or safety outcomes. In addition, the multiple analyses that were completed may have contributed to an inflated type 1 error. Therefore, our investigation should be considered a pilot study. The rigorous study inclusion criteria that we chose lead to only 14% of

Table 5. Medication use during study drug administration[a,b]

	Quetiapine (n = 18)	Placebo (n = 18)	p
Haloperidol			
Amount per day, mg	1.9 (0.8–3.8)	4.3 (1.2–6.1)	.26
Doses administered per day	0.9 (0.4–1.8)	1.6 (0.5–2.2)	.36
Days when ≥1 dose administered			
Total	3 (2–4)	4 (3–8)	.05
Percent[c]	44 (40–100)	60 (33–80)	.7
Sedative[d,e]			
Amount of midazolam equivalents per day, mg	5.3 (0–42)	26.5 (0.3–74)	.32
Days when ≥1 dose administered			
Total	1 (0–4)	4 (1–9)	.09
Percent[c]	27.7 (0–87.5)	41.7 (10–90)	.74
Subjects ever exposed to a benzodiazepine, %	50	67	.50
Days when ≥1 dose of benzodiazepine administered			
Total	0.5 (0–2)	3 (0–7)	.14
Percent[c]	10 (0–50)	12.7 (0–60)	.48
Fentanyl			
Amount per day, μg	0 (0–65)	170 (14–1089)	.02
Days when ≥1 dose administered			
Total	0 (0–3)	4 (1–9)	.03
Percent[c]	0 (0–60)	70 (17–100)	.07
Study drug			
Daily dose, mg	110 (88–191)	210 (116–293)	.01
Maximum daily dose, mg	200 (100–313)	375 (225–400)	.02

[a]Median (interquartile range) unless otherwise noted; [b]*p* values calculated using Mann-Whitney *U* test when medians are presented and a Yates-corrected chi-square test when percentages are presented, unless noted otherwise; [c]as the percentage of time subject was administered study drug; [d]sedative therapy refers to use of propofol, midazolam, or lorazepam; [e]midazolam equivalents refers to the use of propofol, midazolam, or lorazepam converted to mg of midazolam (42).

Table 6. Safety outcomes during study drug administration[a]

	Quetiapine (n = 18)	Placebo (n = 18)	p
Adverse events[b]	54	69	.29
Study drug-related adverse events[c]	6	2	.39
Subjects who experienced a study drug-related adverse event, %[d]	28	11	.4
Episodes of somnolence	5	2	.56
Subjects experiencing somnolence, %[d]	22	11	.66
Episodes of hypotension	1	0	.79
Subjects experiencing hypotension, %[d]	6	0	1.0
Episodes of EPS	0	0	1.0
Serious study drug-related adverse events[e]	0	0	1.0
Episodes of QTc interval >60 msec above baseline	20	34	.7
Subjects experiencing QTc interval >60 msec above baseline, %[f]	39	44	1.0
Episodes of QTc interval prolongation[g]	30	41	.32
Subjects experiencing QTc prolongation, %[f,g]	50	72	.31
Episodes of QTc interval >500 msec	8	8	1.0
Subjects experiencing QTc interval >500 msec, %[d,f]	22	28	1.0

[a]*p* values calculated using a Yates-corrected chi-square test when percentages are presented, unless noted otherwise; [b]all adverse events experienced by subjects during period of study drug administration; [c]all adverse events possibly or probably related to the study drug; [d]*p* value calculated using Fisher's exact test; [e]all adverse events possibly or probably related to the study drug deemed to be serious and reportable as per FDA MEDWATCH criteria; [f]subjects experiencing ≥1 episode of QTc prolongation are included only once regardless of the number of episodes of QTc prolongation experienced; [g]QTc interval prolongation was defined as >450 msec for males and >470 msec for females.

patients screened for the study actually being enrolled, and thus the external validity of our study may be low.

To accommodate the varying duration of delirium seen in clinical practice, we did not require a minimum duration of study drug treatment, instead allowing the subject's intensivist to discontinue study drug when delirium was thought to have resolved or the subject was ready to transfer from the ICU. Given its fluctuating nature, considering delirium resolved when first noted to be absent may be premature, but it is a reasonable and reproducible event. In addition, study drug may have been discontinued prematurely in subjects with hypoactive delirium, although the optimal way to treat these patients is not well-defined (3, 50–53). Whereas the same "as-needed" haloperidol dosing protocol was used for all study patients, the average dose of haloperidol that was administered was lower than the dose recommended in some guidelines and may reflect increasing safety concerns among clinicians regarding the use of high-dose haloperidol therapy (9, 54). The greater use of haloperidol in patients receiving placebo could have diminished the treatment effect of quetiapine that was observed.

No standard definition for delirium resolution exists in the literature. We chose to use time to first shift without delirium as our primary outcome, consistent with previous efficacy outcomes in delirium clinical trials advocating the use of delirium resolution or response as primary end points (41). Given that delirium waxes and wanes, the appropriateness of using time to first resolution of delirium could be questioned. Whereas patients not tolerating enteral nutrition were excluded from the study, it is possible that absorption of quetiapine could have been compromised in some patients given the numerous gut function abnormalities that occur in the critically ill (55). Whereas more patients randomized to receive quetiapine had a better discharge outcome (i.e., disposition to home or a rehabilitation facility), it is important to note that we did not evaluate post-ICU cognitive function or assess quality of life or ability to complete activities of daily living. Last, the fact we relied on the subject's admission history to rule out irreversible cognitive dysfunction rather than conducting an Informant Questionnaire on Cognitive Decline in the Elderly assessment may have

missed the baseline presence of dementia in some of our subjects.

Quetiapine was well-tolerated during the study with few safety issues. Because subjects were not required to remain in the study for a constant duration (e.g., 10 days), even short-term safety goals may have not been evenly distributed over time. Consistent with the antihistaminic effects of quetiapine, more somnolence was noted in subjects treated with quetiapine. Although this difference did not reach statistical significance, the small size of our study does not preclude that a difference does exist and, therefore, clinicians should closely monitor patients receiving quetiapine for oversedation and attempt to differentiate oversedation from hypoactive delirium. Recently, the U.S. FDA issued a public health advisory regarding a greater risk of cardiovascular and infectious sequelae when atypical antipsychotics were administered to control behavioral symptoms in patients with underlying dementia (44, 56). Whereas patients with dementia were excluded from our study, it is not known whether delirious patients exposed to quetiapine for a short treatment duration (i.e., <2 wks) are at similar risk for these adverse events.

Future studies should evaluate the effect of quetiapine on mortality, duration of ICU and hospital stay, post-ICU cognitive function, dependency after hospital discharge, and safety in a broader group of ICU patients. Studies are also needed to better-evaluate the cost-effectiveness of quetiapine for the treatment of delirium in the ICU. Last, future studies should evaluate whether quetiapine has a role in preventing delirium in the ICU (57). In this double-blind, randomized, controlled trial, scheduled quetiapine added to as-needed intravenous haloperidol achieved a faster time to first resolution of delirium compared to placebo among medical and surgical critically ill patients. Therapy with quetiapine may reduce the duration of delirium and agitation. The results of this pilot investigation support further study of an expanded role of quetiapine for the treatment of delirium in the ICU.

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RIKER SAS					
TIME					
1. Altered level of consciousness Choose **ONE** from A-E. Note: May need to reassess patient if recent administration of sedation therapy					
A. Exaggerated response to normal stimulation SAS = 5, 6, or 7 Score 1 point					
B. Normal wakefulness SAS = 4 Score 0 points					
C. Response to mild or moderate stimulation SAS = 3 Score 1 point (follows commands) **Score 0 if altered level of consciousness related to recent sedation/analgesia**					
D. Response only to intense and repeated stimulation (e.g. loud voice and pain) SAS = 2 ****Stop assessment**		-	-	-	-
E. No response SAS = 1 ****Stop assessment**		-	-	-	-
2. Inattention Score 1 point for any of the following abnormalities: A. Difficulty in following commands OR B. Easily distracted by external stimuli OR C. Difficulty in shifting focus **Does the patient follow you with their eyes?**					
3. Disorientation Score 1 point for any one obvious abnormality: A. Mistake in either time, place or person **Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in? (list examples)**					
4. Hallucinations or Delusions Score 1 point for either: A. Equivocal evidence of hallucinations or a behavior due to hallucinations (Hallucination = perception of something that is not there with NO stimulus) OR B. Delusions or gross impairment of reality testing (Delusion = false belief that is fixed/unchanging) **Any hallucinations now or over past 24 hrs? Are you afraid of the people or things around you? [fear that is inappropriate to clinical situation]**					
5. Psychomotor Agitation or Retardation Score 1 point for either: A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (e.g. pulling IV lines out or hitting staff) OR B. Hypoactive or clinically noticeable psychomotor slowing or retardation **Based on documentation and observation over shift by primary caregiver**					
6. Inappropriate Speech or Mood Score 1 point for either: A. Inappropriate, disorganized or incoherent speech OR B. Inappropriate mood related to events or situation **Is the patient apathetic to current clinical situation (i.e. lack of emotion)? Any gross abnormalities in speech or mood? Is patient inappropriately demanding?**					
7. Sleep/Wake Cycle Disturbance Score 1 point for: A. Sleeping less than four hours at night OR B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) OR C. Sleep ≥ 4 hours during day **Based on primary caregiver assessment**					
8. **Symptom Fluctuation** Score 1 point for: fluctuation of any of the above items (i.e. 1 – 7) over 24 hours (e.g. from one shift to another) **Based on primary caregiver assessment**					
TOTAL ICSDC SCORE (Add 1 – 8)					

A total ICSDC Score ≥ 4 has a 99% sensitivity correlation for a psychiatric diagnosis of delirium

Source: Bergeron N et al. Intensive Care Med 2001; 27:869-64 **Revised July 22 2005**