Does administration of antipsychotic medications reduce the incidence and duration of delirium in critically ill adult patients?

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Abstract

Background: Acute delirium is a common complication among critically ill patients. Besides the manifestation of distressing symptoms, delirium can result in negative patient outcomes. Several studies show that antipsychotics such as haloperidol are one of the most commonly used interventions for delirium despite large variability and lower quality of evidence available to advocate for their use.

Methods: A literature review was conducted to investigate current evidence on the use of antipsychotic agents for preventing and treating delirium in the intensive care unit.

Discussion: There is conflicting data concerning the prophylaxis and treatment of delirium in critically ill patients. For prophylaxis with antipsychotics, some studies have shown a decrease in delirium incidence in post-operative patients with less effect on general ICU populations. For treatment with antipsychotics, smaller low-powered studies have shown a decrease in delirium duration while other studies do not show any benefit. High heterogeneity between studies due to variable study design makes the quality of evidence low. Minimal conclusions can be drawn from available literature, making it difficult to provide concrete clinical recommendations.

Conclusion: Given the low quality of evidence, the effectiveness of antipsychotics for ICU delirium remains uncertain. Antipsychotics should not be implemented for routine use, but can be considered to treat severe, acute delirium symptoms. Future research is needed to better establish the benefits and risks associated with antipsychotics and delirium in the ICU.

Introduction

Delirium is a common comorbidity experienced in the intensive care unit (ICU). The incidence of patients who experience delirium in the ICU has been reported to be around 31%,[1]

however some studies report occurrence upwards of 70-80% in older patients.[2] Delirium is defined as a "disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)" per the DSM-V criteria.[3] In addition, these disturbances must be acute in nature and fluctuate throughout the day. Although delirium cannot be attributed to a concurrent neurocognitive disorder or coma, the etiology must be due to a consequence of another medical condition, drug intoxication or withdrawal, or exposure to a toxin.[3] Specific clinical manifestations of delirium include hypoactivity (lethargy, decreased arousal), hyperactivity (agitation, emotional disturbance, refusal to cooperate), impaired sleep, hallucinations, delusions, and confusion. The pathogenesis of delirium is not well understood, but it is thought to be multifactorial and includes several theories. The current understanding of delirium pathophysiology includes neurotransmitter imbalances or alterations (specifically dopamine and acetylcholine), inflammatory processes (as in post-operative states), sleep deprivation and polypharmacy.[4-6] Likewise, critically ill patients commonly experience metabolic disturbances, higher levels of pain, frequent interruption of sleep, and common use of delirium-inducing medications. Known risk factors for developing delirium in the ICU include increased age, visual and hearing impairment, use of restraints, certain medications, alcohol use, pre-existing dementia, coma, increased severity of illness, mechanical ventilation, emergency surgery, trauma, and metabolic acidosis.[7-9]

Critically ill patients who experience delirium in the ICU are at risk for several adverse outcomes. Delirium is associated with increased risk of hospital mortality,[1] longer hospital and ICU length of stay, and increased number of days requiring mechanical ventilation.[1,10] Patients with delirium may be more likely to require a tracheostomy and experience increased use of physical restraints.[10] Delirious patients also require higher amounts of medications such as

benzodiazepines, opioids, and antipsychotics.[10] Some sources also report long-term cognitive disturbances at 12-18 month follow-up as a result of ICU delirium.[1,11,12] Although it is difficult to discern whether some of these adverse outcomes are truly secondary to the delirium itself versus a reflection of the severity of critical illness that delirious patients typically experience, it is a common comorbidity that usually requires additional interventions and potentially increased costs.[13] Given the many negative outcomes associated with ICU delirium, it is common practice to routinely screen for delirium in the ICU using several standardized assessments. The two most validated and reliable tools include the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening checklist (ICDSC).[8]

Prompt management and prevention of delirium is of great interest to many providers and researchers in order to prevent adverse outcomes and promote symptomatic relief. Given the wide etiology, unclear pathogenesis, and several risk factors for delirium in the ICU, management is typically multifactorial and often challenging. Several preventative measures can be taken in attempts to decrease risk of delirium development, while treatments for delirium often aim at increasing time to resolution and/or decreasing delirium symptoms. Much of the proposed pharmacologic management aims at altering neurotransmitter activity, whether to treat delirium itself or its associated symptoms. Although there is no drug approved by the FDA specifically for delirium, several observational studies have shown routine use of medications among medical providers such as antipsychotics, benzodiazepines, and dexmedetomidine to treat delirium.[11-15] Some studies suggest that antipsychotics such as haloperidol are the most commonly used medication for managing delirium and delirium-related symptoms among providers.[11,13]

Antipsychotics are used mainly to treat neuropsychiatric disorders such as schizophrenia

and bipolar disorder, and they are currently used off-label for delirium, acute agitation, and mania. There are two main categories of antipsychotic drugs: first generation (FGA) and second generation (SGA). The primary mechanism of action for both FGAs and SGAs are blockage of the dopamine D2 receptors in the central nervous system, however they also have variable activity at other neurotransmitter receptors. Haloperidol (an FGA) has little effect on histamine and muscarinic receptors,[15] thus, is often used in attempts to provide a small level of dose-dependent sedative effect in ICU settings.[16] SGAs also block the D2 receptors in the brain but have high affinity for serotonin receptors.[17] As serotonin plays an important role in sleep, some studies that find positive results using SGAs for delirium propose this serotonin alteration as a potential mechanism.[18] Many SGAs have multi-receptor activity at histamine, muscarinic, and alpha-adrenergic receptors, resulting in various levels of sedation and anticholinergic effects.[19] FGAs and SGAs are thought to have similar efficacy overall in terms of treatment of positive schizophrenia symptoms such as hallucinations and delusions.[20] However, while efficacy has been more extensively studied in schizophrenia, the data in efficacy studies for antipsychotics in delirium is lacking and often conflicting.

Since these pharmacologic measures have inadequate or conflicting evidence for use in the ICU, there is often discrepancy between common clinical practice and research literature. Contrary to the common utilization of antipsychotics in upwards of 46% of critically ill patients with delirium,[11] the Society of Critical Care Medicine (SCCM) practice guidelines do not recommend the routine use of medications to treat or prevent delirium.[8] Given the lack of consensus between available literature and the current clinical practice in terms of pharmacologic management of ICU delirium, this paper will aim to evaluate the current studies available in regards to effectiveness of antipsychotic drugs in prevention and treatment of delirium. The

primary outcomes that will be investigated are whether administering antipsychotics results in reduced incidence and duration of delirium in critically ill patients. Other outcomes such as ICU and hospital length of stay, mortality, and duration of mechanical ventilation will also be explored. In addition, this paper will analyze how available literature could be applied to clinical practice, and whether there are other interventions that may be more beneficial than antipsychotics in managing delirium.

Background

Antipsychotics for delirium prophylaxis

Several studies have explored the efficacy of administering either first- or second-generation antipsychotics as a means of preventing delirium in critically ill and post-operative patients. Most of the literature has variable and conflicting results. Of the few systematic reviews and meta-analyses, very few have been able to display strongly positive data on using antipsychotic prophylaxis. Of the review studies described below, none have found any effect of haloperidol on factors such as mortality and length of stay in the ICU. Most review studies have high heterogeneity due to differences in patient populations and study protocols between randomized controlled trials. In particular, a Cochrane Database Review on prevention of ICU delirium suggested that the overall evidence for pharmacologic intervention to prevent delirium is of moderate to low quality, and that the heterogeneity between studies prevents a meaningful meta-analysis.[7] In one systematic review and meta-analysis by Zayed et al,[14] six randomized controlled trials studying haloperidol versus placebo as ICU delirium prophylaxis were analyzed. The authors concluded that haloperidol has no significant effect on delirium incidence, mortality, length of stay, or delirium-free days compared to placebo.[14] However, high heterogeneity among studies make it difficult to fully conclude the effects of haloperidol. The studies utilized varying

doses, routes, and duration of medication as well as varying patient populations. The non-pharmacologic interventions were also not quantified, and the studies used various sedation and rescue antipsychotic doses.[14]

Several other reviews and meta-analyses have shown a positive effect of prophylactic antipsychotics on delirium incidence. A systematic review by Santos et al[15] analyzing four studies was unable to perform a meta-analysis given high heterogeneity between studies. However, the authors found that two studies[12,16] showed prophylactic doses of haloperidol decreased the incidence of delirium while another two studies[17,18] found no change in incidence.[15] One study showed a shorter ICU length of stay,[16] however none of the studies showed a difference in hospital length of stay.[12,17,18] As with other review papers, the studies analyzed varying populations and used different haloperidol doses and schedules. The authors concluded that while prophylactic haloperidol may reduce delirium incidence, additional studies with more standardized protocols are required in order to make a recommendation on prophylactic use.[15] A meta-analysis by Gilmore et al[19] analyzed five randomized controlled trials studying antipsychotic prophylaxis in post-operative patients. The analysis showed that antipsychotics lowered delirium incidence by a 12.7% absolute risk reduction.[19] Another meta-analysis by Hirota and Kishi[20] looking at prevention of postoperative delirium found that both olanzapine and risperidone were superior to placebo in preventing delirium while haloperidol did not alter incidence. However, haloperidol shortened duration of delirium while the other treatments had no effect on duration. There were no other differences between groups in terms of delirium duration, length of stay or severity in either of these post-operative studies.[19,20]

Several randomized controlled trials have studied whether prophylactic antipsychotics reduce delirium in critically ill patients when compared to placebo. These studies used varying

doses, schedules, and durations of medication and obtained various results. For example, Boogaard et al[12] administered either 1 mg or 2 mg of intravenous haloperidol three times daily to delirium-free critically ill adults, starting therapy within 24 hours of ICU admission until ICU discharge. Page et al[17] started therapy within 72 hours of admission for patients requiring mechanical ventilation (regardless of delirium state), administering 2.5 mg IV haloperidol every 8 hours until ICU discharge or delirium-free for two days. Wang et al[16] provided an IV bolus followed by a 12-hour continuous infusion of haloperidol in patients admitted to ICU after cardiac surgery. Al-Qadheeb et al[18] administered 1 mg IV haloperidol every 6 hours to mechanically ventilated patients with subsyndromal delirium in efforts to prevent progression to full delirium. Only one of these studies found a significant difference in delirium outcomes between groups. Wang et al[16] demonstrated among 457 patients, the haloperidol group had lower incidence of delirium within 7 days post-operatively (15.3% vs. 23.2%, $p = 0.031$) as well as on the first and third days after surgery. The occurrence of postoperative delirium in the haloperidol group was about half as likely to occur as compared with the placebo group (OR 0.574, 95% CI: 0.352–0.937; $p = 0.026$).[16] In addition, the haloperidol group had increased time to onset of delirium, increased delirium-free days, and shortened ICU length of stay. Neither Page et al,[17] Boogaard et al,[12] nor Al Qadheeb et al[18] found any significant differences between groups in delirium incidence, duration, delirium-free days, or ICU length of stay when given haloperidol vs placebo. All four of these studies found no difference in hospital length of stay or mortality.[12,16,17] Page et al[19] found that the risk of needing additional open-label antipsychotics for agitation was lower in the haloperidol group. The haloperidol group also received a reduced total dose of propofol and fentanyl, but this result was not statistically significant (both $p = 0.06$). Additionally, an earlier non-randomized, before and after evaluation study by Boogaard et al[21]

administered prophylactic IV haloperidol to patients deemed high risk for delirium per the PRE-DELIRIC model. They found a reduced delirium incidence in haloperidol group versus control group (65% vs 75%, p = 0.01).[21] Although this trial found benefit to haloperidol prophylaxis, the non-randomized, retrospective design may not be strong enough to be able to draw clinical conclusions alone.

Randomized controlled trials have also explored the use of second-generation antipsychotics for delirium prophylaxis. Larsen et al[22] gave elderly patients undergoing joint replacement surgery 5 mg olanzapine or placebo both immediately pre-operatively and immediately post-operatively.[22] In this 400-patient study, delirium incidence was lower (14.3% versus 40.2%, p = 0.0001) and time to delirium onset was significantly longer in the olanzapine group compared to placebo, respectively. Interestingly, the duration of delirium was longer in the olanzapine group (2.2 versus 1.6 days, p = 0.02). In another study, Prakanrattana and Prapaitrakool[23] administered 1 mg risperidone orally in the ICU after cardiac surgery. The authors found that the risperidone group had a lower delirium incidence compared to control (11.1% vs 31.7%, respectively; p = 0.009, NNT 4.85).[23] No other differences in outcomes were statistically significant between groups.

Antipsychotics for delirium treatment

In addition to using antipsychotics as a means to prevent delirium, several studies have also analyzed their use for treatment of delirium. Many of these studies continue to display high heterogeneity in study protocol. In two systematic reviews and meta-analyses, there was no association between using antipsychotics and delirium duration, mortality, or ICU or hospital length of stay.[14,24] Another systematic review suggested that pharmacologic interventions, including antipsychotics, do not provide any significant reduction in delirium duration or other

parameters such as length of stay or mortality in available studies.[25] In contrast, a meta-analysis of 15 randomized controlled trials found that antipsychotics had an increased response rate compared to placebo for delirium treatment (RR = 0.22, NNT = 2).[26]

Several trials exist that investigate antipsychotics in delirium treatment. In a randomized controlled trial by Girard et al[11], adults with delirium in the ICU per the CAM-ICU assessment received either placebo, IV haloperidol or IV ziprasidone every 12 hours until delirium subsided. In this study containing 566 patients, neither haloperidol nor ziprasidone shortened the duration of delirium. The mortality and ICU length of stay was also similar between groups.[11] On the other hand, Michaud et al[27] found positive results on the use of quetiapine in a retrospective cohort study. Adults with delirium in the ICU per the CAM-ICU assessment (n = 113) received either quetiapine (n = 52) or no pharmacologic intervention (n = 61) for delirium. The group whose delirium was treated with quetiapine experienced shorter duration of delirium compared to those who did not receive pharmacologic intervention. Although the duration was only decreased by an average of 0.5 days, this decrease was statistically significant (p = 0.04). However, the duration of delirium was 2.5 days shorter if the patient received the drug within the first 24 hours of delirium onset versus later than 24 hours. Among patients on mechanical ventilation, receiving quetiapine within the first 24 hours resulted in shorter time to extubation.[27] Another small study on utilization of quetiapine vs placebo for treatment of delirium in critically ill patients showed positive results, although is limited by a small number of subjects. In this study by Devlin et al,[28] 36 patients were randomized to either receive enteral quetiapine every 12 hours versus placebo once diagnosed with delirium. All patients also received as needed IV haloperidol for delirium and agitation symptoms. The study found that the quetiapine group spent less time in delirium (36 hours vs. 120 hours, p = 0.006) and agitation (6 hours vs. 36

hours, p = 0.02).[28] Additionally, patients who received quetiapine used significantly less haloperidol, sedation, and fentanyl.[28]

Antipsychotics are commonly used to treat specific symptoms of delirium such as agitation. Page et al[17] studied prophylactic use of haloperidol and found that the haloperidol group had lower levels of agitation (RASS of 2 or greater). They concluded that although haloperidol did not provide any meaningful delirium prophylaxis, it may be useful in treating agitation.[17] Similarly, haloperidol resulted in decreased agitation compared to placebo in the randomized controlled trial by Al-Qadheeb et al.[18] However, the clinical significance of this reduced agitation is unknown given this study also found no reduction of delirium or days on mechanical ventilation despite less agitation.[18] In addition, a Cochrane Database Review[29] on using haloperidol for aggression or agitation suggests weak evidence on the topic. The review found that among nine randomized controlled trials, more patients who were treated with haloperidol were asleep at 2 hours versus placebo.[29] However, these are considered low-quality studies that make it difficult to make a clinical recommendation.

Risks associated with antipsychotics

Antipsychotic drugs have several adverse effects that are important to consider when selecting patients to receive this therapy. Some of the major adverse effects include extrapyramidal side effects (EPS), adverse cardiovascular events, metabolic side effects, sedation, and anticholinergic effects. In the short term and intensive care setting, the most concerning acute side effects include QTc prolongation, orthostatic hypotension, sedation, and EPS.[30] There are differences in side effect profiles between FGAs and SGAs. Haloperidol (especially in IV form) has a higher association with prolonged QTc interval, and this often requires frequent electrocardiogram monitoring while receiving therapy.[30] FGAs have a higher

risk of EPS, while SGAs come with a much lower risk EPS. On the contrary, most SGAs come with higher risk of metabolic side effects (hyperlipidemia, hyperglycemia, and weight gain), although these may not be as concerning for short-term, temporary use. Anticholinergic effects and sedation effects differ among various individual FGAs and SGAs. For example, haloperidol has the lowest risk for anticholinergic effects compared to other FGAs and certain SGAs such as clozapine.[31,32] This is also the case for sedation, where haloperidol has lower risk for this side effect compared to many SGAs such as quetiapine, olanzapine, clozapine, risperidone and ziprasidone.[31,32] In addition, all antipsychotics come with a "black box" warning from the FDA of increased mortality in older adults with dementia.

Several studies included documentation and monitoring of adverse effects during the trial. Several studies found no increase in adverse events while using antipsychotics while others found some increased side effects. For example, Michaud et al[27] documented no torsades de pointes, EPS, or deaths related to dysrhythmia or QTc prolongation with quetiapine treatment. Similarly, six other studies found no difference in treatment groups with placebo vs haloperidol in regards to QTc prolongation, arrhythmias, or EPS.[12,14,16,18-20] On the contrary, one study found a trend toward longer QTc intervals than baseline in patients who received continuous IV haloperidol (although not statistically significant).[33] However the rate of abnormal QTc intervals was the same between study groups (haloperidol vs dexmedetomidine).[33] Another study found that more patients were over sedated and required non-invasive mechanical ventilation due to respiratory depression when given haloperidol versus dexmedetomidine.[13] One study documented that only patients who received haloperidol developed QTc prolongation, however this was not statistically significant.[34] A meta-analysis assessing 15 randomized controlled trials found that patients who received antipsychotics for delirium treatment experienced more dry

mouth and sedation compared to placebo, and those who received SGAs experienced less EPS compared to haloperidol.[26] In addition, another randomized controlled trial found more somnolence in patients treated with quetiapine.[28] When compared to dexmedetomidine, one study found that haloperidol led to significant over sedation and respiratory depression.[13]

Due to concerns for mortality and adverse events in older adults, some studies lowered the dose of antipsychotic for older patients. Michaud et al[27] provided lower doses of quetiapine in patients older than 65, and there were no differences in adverse effects between age groups. The authors suggested that lower doses of quetiapine in the elderly are just as effective as higher doses, and the drug remains safe without increased adverse effects.[27] Girard el al[11] lowered the haloperidol and ziprasidone doses for patients older than age 70 to half of the dose given for patients younger than age 70. However, adverse effect or efficacy were not stratified by these two age groups in the data report. Given that the higher doses were not given to older patients in these two studies, it's difficult to make a true conclusion regarding efficacy and optimal dosing. In addition, some studies specifically enrolled older adults and found similar results. Larsen et al[22] studied patients older than age 65 who underwent hip-replacement surgery and found that pre- and post-operative olanzapine resulted in no significant medical complications. Likewise, Wang et al[16] administered continuous low-dose IV haloperidol (0.5 mg loading dose followed by 0.1 mg/hour continuous infusion) to patients older than age 65 in the ICU and found no significant differences in QTc prolongation between groups. They concluded that the dosing regimen was safe and effective for elderly patients.[16]

Antipsychotics compared to other agents

Several studies have investigated alternative agents for delirium in comparison to antipsychotics. One of the major agents used for delirium, and more often found to be effective,

is dexmedetomidine. Dexmedetomidine is a selective α-2 agonist with anxiolytic, sedative, and analgesic effects that is used for ICU and procedural sedation.[13] Many studies have shown preference of dexmedetomidine over antipsychotics in managing delirium in terms of effectiveness for both prevention and treatment. One randomized-controlled trial[34] compared continuous infusions of dexmedetomidine and haloperidol for the prevention of delirium in patients on non-invasive ventilation. Out of 90 ICU patients, the authors found that the patient who received dexmedetomidine had a lower incidence of delirium, lower incidence of endotracheal intubation, and shorter hospital and ICU length of stay compared to both haloperidol and placebo.[34] Haloperidol did not show decreased delirium incidence compared to placebo, but it did result in shorter duration of non-invasive ventilation and hospital LOS.[34]

Another study investigated continuous IV haloperidol versus dexmedetomidine infusions in patients who were unable to be extubated from mechanical ventilation due to need for high doses of sedation needed for agitation or delirium.[33] The group who received dexmedetomidine were extubated sooner (19.9 hours vs. 42.5 hours, $p = 0.016$) with resolution of delirium.[33] The dexmedetomidine group also experienced a shorter ICU length of stay. The authors concluded that dexmedetomidine was more effective than haloperidol in treating agitation and delirium in intubated patients.[33] However, due to limitations including a small sample size ($n = 20$), the authors recommended against changes in practice solely based on these results.[33]

A non-randomized controlled trial[13] including 132 non-intubated ICU patients with delirium studied the use of dexmedetomidine for delirium refractory to haloperidol treatment. In this study, 132 patients with delirium received IV haloperidol every 10-30 mins until reaching Richmond Agitation-Sedation Score (RASS) of 0 to -2 or max dose 30 mg. The patients were divided into responders and non-responders to haloperidol. The responder group continued to

receive haloperidol that was adjusted to maintain optimal RASS. The non-responders were changed to a dexmedetomidine infusion. The study found that agitation was refractory to haloperidol in 34.8% of patients. Patients who received haloperidol alone had a seven-fold longer recovery time and two-fold ICU length of stay. All patients who received dexmedetomidine promptly achieved target RASS and had no treatment failure.[13]

One study[35] compared the use of haloperidol versus morphine in the treatment of post-operative delirium. Among 53 patients with delirium after cardiac surgery, patients either received IM haloperidol or IM morphine sulfate hourly to control delirium symptoms until a target RASS was achieved. The authors found that the duration of delirium, ICU length of stay, hospital mortality, and adverse effects were not significantly different between groups. However, the patients who received morphine received less additive sedation and had higher achievement of target RASS within two hours as compared to haloperidol. The authors concluded that the potential anxiolytic effect in the morphine group allowed for a quicker response in reducing agitation.[35]

Although benzodiazepines are another commonly used medication for the treatment of ICU delirium,[36] there are very few studies comparing benzodiazepines to antipsychotics in this setting. Only one study of comparison was found, but the study population was patients with advanced cancer and delirium at end of life. Those who received a combination of haloperidol plus lorazepam experienced greater reduction in agitation and appeared more comfortable with less rescue medications than those who only received haloperidol.[37] Given the study population, it is difficult to apply this study to other critically ill patients with delirium. It is possible that there are not many studies available due to benzodiazepines being a strong risk factor for the development of delirium in critically ill patients.[38] One trial even found that increased plasma

concentrations of lorazepam was associated with increased risk of delirium the next day.[39] Additionally, a 2009 Cochrane Database review[40] studied the efficacy of benzodiazepines in hospitalized patients with delirium. Only one study met selection criteria, and the authors concluded that there is insufficient evidence for the use of benzodiazepines in non-alcohol related delirium.[40]

Current Clinical Practice Guidelines on Delirium Management

Several practice guidelines have been published over the years in efforts to guide practitioners on clinical usage of pharmacologic agents for delirium using the available literature. The most recent guidelines published in 2018 from the Society of Critical Care Medicine (SCCM) recommend against routine use of pharmacologic agents such as antipsychotics for delirium.[44] They recommend against antipsychotics, among other drugs, for prevention of delirium due to the lack of effectiveness in outcomes such as mortality and length of stay in the literature.[44] In addition, they recommend against the routine use of antipsychotic agents for delirium treatment, but state that selective short term use may be beneficial for patients who experience severe and distressing symptoms.[44] Previous recommendations from 2013 also do not advocate for the use of haloperidol or SGAs for the prevention of delirium or for the use of haloperidol to shorten delirium duration.[5] This recommendation is supported by the lack of high-quality studies that have more substantial sample sizes and consistency among studies. The 2013 guidelines do state, however, that SGAs may reduce delirium duration.[5] Despite some studies showing benefit, the guidelines state studies are still needed to confirm the consideration of using SGAs for delirium routinely.[5] Previous SCCM guidelines from 2002 recommended haloperidol for treating delirium, however this was changed in the new guidelines due to new evidence grading standards.

Other international guidelines also exist to guide delirium treatment. Swiss guidelines from 2007 recommend the use of antipsychotics as the first line treatment for delirium "when pharmacologic treatment seems appropriate," such as for behavioral symptoms along with treating precipitating factors and using nonpharmacologic approaches.[41] German guidelines from 2010 provide a more broad and vague statement that some evidence exists for using neuroleptics for either treatment or prevention of delirium.[46] Guidelines from the United Kingdom in 2010 recommend short-term haloperidol if the patient is distressed or risk of harming themselves or others and non-pharmacologic treatments were ineffective.[42]

Methods

A literature search was conducted using several databases available in the Augsburg library. Databases used include PubMed, MEDLINE, Science Direct, Google Scholar and UpToDate. Articles were also found by utilizing the reference lists of review articles and searching among articles for commonly cited studies. Only articles in English were included. Inclusion criteria for this review included studies on adult patients older than 18 years, patients in the intensive care unit or post-operative, patients who were evaluated for delirium, and the patients were given pharmacologic management for prevention or treatment of delirium (particularly antipsychotics). Types of studies include randomized controlled trials, systematic reviews, meta-analyses, prospective and retrospective observational studies, and clinical practice guidelines. Search terms utilized include delirium, intensive care unit (ICU), critically ill, agitation, prevention, treatment, management, pharmacologic, antipsychotic, benzodiazepine.

Discussion

Given the above literature review, it is clear that there is conflicting data concerning the prophylaxis and treatment of delirium in critically ill patients. The multifactorial pathogenesis of

delirium itself along with the unclear antipsychotic efficacy and safety in critically ill patients creates uncertainty whether these drugs should be routinely used. As will be discussed, several factors vary widely among studies on both prevention and treatment of delirium with antipsychotics, making pooling results difficult and thus preventing the ability to make a meaningful consensus for clinical practice.

Literature on the use of antipsychotics for delirium prophylaxis in critically ill patients shows mixed results from various randomized-controlled trials and review papers. Among individual trials, several found no improvement of either incidence or duration of delirium with adding haloperidol as a prophylactic regimen.[12,17,18] Among the studies that found no difference in preventing delirium, there were several limitations to acknowledge. First, the sample sizes were very small in two of the studies (142 participants in Page et al[17] and 68 participants in Al-Quadheeb et al[18]). In addition, each of these studies allowed varying degrees of rescue medication for agitation such as open label antipsychotics,[17] dexmedetomidine,[12,18] and other sedatives such as midazolam and propofol. The effect of these additional drugs on the results are unknown. Finally, the patient populations of these studies included a wide range of medical, surgical and trauma ICU patients. While this can simultaneously be considered a strength by simulating a true ICU population, whether a more specific group would benefit from delirium prophylaxis cannot be ruled out. The randomized controlled trial by Boogaard et al[12] discussed whether the lack of antipsychotic effectiveness was due to the higher extent of critical illness in their population. Thus, they hypothesized whether a less critical population may see more benefit from prophylaxis.[12] However, an earlier retrospective study from the same author suggested that those with higher delirium risk benefit more from antipsychotic prophylaxis. The PRE-DELIRIC score used in the study directly relates to severity of illness by incorporating APACHE II score,

infection, sepsis, urea concentration, metabolic acidosis, morphine and sedative use, and coma. These conclusions are therefore highly conflicting and suggest that more high-quality randomized-controlled trials are required to confirm whether or not prophylactic antipsychotics benefit critically ill patients.

In contrast, most of the studies that found any statistical significance in outcomes were studies involving antipsychotic prophylaxis in perioperative patient populations.[16,22,23] Although one of these studies utilized haloperidol,[16] there were more studies with significant results that included SGAs in the perioperative period.[22,23] The areas of statistical significance in these studies highlighted decreased incidence of delirium post-operatively.[16,22,23] One advantage to these studies is that each trial includes a single, somewhat specific study population (i.e. elderly patients after non-cardiac surgery, elderly patients after joint replacement,[22] and patients after cardiac surgery.)[16] While this makes it possible to apply to other similar populations, it is still difficult to apply these results to a more generalized ICU population or among differing surgical populations. One major limitation to two of these studies is the lack of baseline cognitive screening pre-operatively to rule out pre-existing dementia that could affect these results.[16,22] However, both studies conclude that the data remains valid as the randomization process increases the likelihood of any patients with pre-existing cognitive dysfunction to be equal among groups.[16,22] Overall, these studies of patients in the perioperative state may be extremely beneficial in guiding future studies to further confirm which patients may benefit from prophylactic therapy. Replication of these results with more standardized design and drug dosing would increase the strength of evidence to then better apply to clinical practice.

Systematic reviews and meta-analysis on prophylactic antipsychotic use show low quality evidence, making it difficult to do meaningful meta-analysis and hard to compare studies.[7] In

accordance with the above individual trials, some meta-analyses showed significance in post-operative studies rather than in generalized ICU studies. Two meta-analyses found a risk reduction for development of delirium when using perioperative antipsychotics.[19,20] One study in particular pointed out olanzapine and risperidone as superior to haloperidol in delirium prevention.[20] However, other meta-analyses found no effect of antipsychotics on delirium (including one Cochrane Review).[7,14] One major limitation of these review papers is the lack of available studies and small sample sizes. Three meta-analyses only included 6 or less studies while one systematic review included only 2 studies. The populations were widely variable among some of the analyses but were slightly narrower in the reviews that included only post-operative studies. Similar to the individual trials above, the only meta-analyses that showed a decrease in delirium incidence were with perioperative data. Although this includes slightly similar populations in comparison to other studies, heterogeneity between the types of surgical populations still remains. Thus, the ability to apply the positive results in perioperative reviews to other ICU populations may not be desirable, especially considering the lack of efficacy shown in reviews with a generalized ICU population.

After comparing and contrasting studies on antipsychotic prophylaxis, the question following question remains: Which patients (if any) should receive antipsychotics for delirium prophylaxis, and when should this occur? Given the difference in results between study populations, one may consider whether antipsychotic prophylaxis has an increased efficacy in specifically surgical critically ill patients. Again, due to the variability in studies and associated limitations, the ability to assess the validity of this conclusion is difficult until further studies are completed. A non-randomized study[21] that found haloperidol prophylaxis beneficial selected patients at highest risk for delirium, which is a key difference from other studies who select

patients regardless of delirium risk. However, this study lacked randomization, placebo group, and blinding, and it had statistically different population differences between the control and intervention groups.[35] Although the quality of this evidence is weaker due to study design, these results could help shape future randomized controlled trials to help better identify which patients may benefit the most from antipsychotic prophylaxis. Finally, incidence of delirium is more highly affected than duration in many of the perioperative studies. This may suggest that when antipsychotics are used as prophylaxis, the result is only effective in fully preventing delirium development versus aiming to decrease severity or length of delirium. One could conclude that if delirium develops despite using prophylaxis, the severity or length of delirium will likely be unaffected by the prophylactic antipsychotic doses. This conclusion should be interpreted with caution, as it is unknown whether the drug dosage and duration was too low to see an effect on delirium duration in more severe cases.[19] This concept then brings into question the next topic of discussion: whether antipsychotic treatment reduces delirium duration after delirium has already developed.

Similar to studies that investigate delirium prophylaxis, the studies evaluating antipsychotic drugs for delirium treatment have a high level of variability in both study design and results. Among individual trials evaluated, two of the studies[27,28] found decreased delirium duration when using quetiapine for delirium treatment. However, these two studies are both limited by small sample size (n = 113[28] and n = 36).[27] The small sample sizes as well as variation in study methods makes it unclear whether these results should translate into concrete recommendations for clinical practice. Both of these studies used strict inclusion and exclusion criteria, which resulted in the small sample sizes.[27,28] While this can be seen as an advantage to avoid inherent biases in the data, the small sample leaves these studies greatly underpowered and

also difficult to apply to a more widely generalized ICU population. One of these studies was a retrospective cohort design that lacked a formal treatment algorithm, which further lacks power to draw strong conclusions about the data. On the other hand, one larger randomized controlled trial (n = 566)[11] did not find any reduction in delirium duration. They also used broader inclusion criteria that can likely be more widely applied clinically yet cannot rule out if a specific subgroup would have benefited from delirium treatment.[11] Similar to the studies on delirium prophylaxis, the current trials on delirium treatment with antipsychotics is promising for future research. The strength of evidence for or against use of antipsychotics would increase if there were more well-designed studies to replicate results of smaller studies.

Many of the systematic reviews and meta-analyses suggest that antipsychotics do not reliably improve delirium duration when used for treatment.[14,24,25] One of the meta-analyses[26] did find a benefit in antipsychotic treatment for delirium by decreasing delirium severity scores. Similar to the previous discussion on reviews and meta-analyses for delirium prophylaxis, the heterogeneity between studies hinders the ability to pool results to make a strong conclusion about the data. Each of these reviews discuss limitations such as variability in pharmacologic interventions, different outcomes evaluated, and the overall small number of studies available. The high degree of heterogeneity calls for more standardization in study design, interventions, and population criteria to be able to better compare data.[24]

While the studies evaluated for both delirium prophylaxis and treatment do not strongly show a relationship between routine antipsychotic use and decreased delirium, some studies suggest that it may be more efficacious for acute treatment of specific delirium symptoms. Some studies have noted decreased agitation in patients who receive prophylactic haloperidol despite no statistically significant decrease in delirium incidence or duration.[32,33] While this may be due

to sedating effects of antipsychotics, the decrease in agitation may support the use of antipsychotics on an as needed basis versus routine use in some patients. However, a Cochrane Database review from 2017 suggested that the evidence is weak for recommending haloperidol for agitation despite haloperidol resulting in faster onset to sleep/sedation compared to placebo.[43] In contrast, many clinical practice guidelines[38,41,42] do suggest rescue use for patients in severe distress secondary to delirium. Although the evidence may not be strong, the rescue use of antipsychotics for distressed patients where nonpharmacologic efforts have failed is one recommendation that is more consistent across the clinical guidelines. Therefore, individualization of treatment based on clinical judgement will likely be the mainstay of practice before more studies are available to confirm the benefit of rescue antipsychotic use in delirium.

Interestingly, the recommendations and conclusions drawn from literature greatly juxtapose the documented clinical utilization of drugs such as antipsychotics in practice. In a 2018 multinational cohort study of 1260 ICU patients, haloperidol was the most commonly used medication for delirium intervention with 46% of patients with delirium receiving haloperidol.[11] Some older studies also suggest frequent use of antipsychotics and other agents to manage delirium. A 2011 survey of 250 pharmacists showed that 76% said haloperidol was the first treatment of choice followed by SGAs (14%) and benzodiazepines (10%).[14] A 2009 audit of 174 patients in a single facility showed antipsychotic medications were used in most patients with signs of delirium.[12] However, the most current SCCM guidelines do not make a recommendation regarding routine use of antipsychotics for either prophylaxis or treatment due to the low quality evidence available in current literature.[38] The strong discrepancy between the current strength of literature and the apparent clinical practice preferences brings into question whether anecdotal evidence is playing a part in the wide use of antipsychotics among providers. In addition, it will

be interesting to see how these guidelines and practices might change in the future pending the inclusion of newer studies.

Given the widely variable guidelines, literature findings, and clinical practice, what are the next steps in interpreting these guidelines for best clinical practice? First may be to consider the specific patient population and whether literature suggests an associated benefit or additional risk. As previously discussed, much of the data that shows any benefit of using antipsychotics for delirium prevention is in postoperative patients rather than a generalized critically ill or mechanically ventilated population.[16,22,23] Thus, it may be difficult to apply this benefit to other patients with more critical conditions where an unknown benefit may not outweigh inherent risks. Next, the risks and adverse effects of antipsychotics should be carefully considered. Although many studies have demonstrated overall safety and few adverse events in critically ill populations, these studies excluded patients with already prolonged QTc intervals. Therefore, it is recommended to avoid antipsychotic medications for delirium in patients at high risk of developing torsades de pointes (prolonged QTc interval or receiving other QTc-prolonging medication).[5] In addition, sedative effects of many antipsychotics may not be as desirable for elderly patients or those at risk for respiratory depression. Therefore, careful patient selection in terms of cardiac risk, older age, and other pertinent risk factors may be necessary when selecting antipsychotic drugs. When weighing risks and benefits, the lack of improvement in other end outcomes such as mortality and length of hospital stay should be considered when using antipsychotics in clinical practice.

Finally, it is also important to consider alternate or adjunctive therapies that provide minimal risk and likely high benefit as compared to antipsychotics. Nonpharmacologic prevention and therapy via a multicomponent strategy (improving mobility, vision, hearing,

cognitive stimulation and sleep) should be the first consideration for delirium management.[38] Each of these measures provides minimal risk to the patient and may prevent the need for drugs that pose additional risks. Another consideration, especially in post-operative populations is adequate pain control to treat and prevent delirium, as demonstrated in one study.[35] Although this study is underpowered with a small sample size, the concept of adequate pain management is typically an integral piece to post-operative care. It makes sense to optimize a therapy that is already implemented, such as pain management, prior to adding additional and potentially unnecessary medications such as antipsychotics. Other medications should also be reviewed for deliriogenic properties, namely benzodiazepines. As previously noted, benzodiazepine use is considered a risk factor for delirium development in critically ill patients and has minimal literature to support its use over antipsychotics. It is very difficult to assign superiority to either benzodiazepines or antipsychotics as there are very few studies comparing the two drug classes in critically ill patients. Based on the information available, it is likely best to avoid benzodiazepines in patients at high risk for non-alcohol related delirium.

Dexmedetomidine has shown increased efficacy over antipsychotics for delirium treatment in many studies. However, more research is needed to further strengthen this conclusion. The studies previously analyzed show many weaknesses, such as small sample sizes and lack of randomization and blinding. Two of these studies conclude that the results are not yet strong enough to be routinely integrated into practice until more high-quality studies are needed to confirm results. Despite these limitations, the results of these studies may be promising particularly for those where antipsychotics are less desirable due to risk for respiratory depression. For example, the SCCM guidelines recommend using dexmedetomidine to aid in agitation that may be preventing ventilator weaning and extubation.[44] Considering that some of

the studies are of lower quality, the decision whether to use dexmedetomidine over antipsychotics would require weighing patient factors (e.g. risk for respiratory depression, sedation needs, cardiac risk, etc.) against the drug characteristics (e.g. the adverse effect profile) to administer the most appropriate therapy.

Conclusion

Overall, it appears that antipsychotics may reduce incidence of delirium in certain patient populations as well as potentially decreasing duration when used as treatment. However, the evidence that these agents reduce other risk outcomes such as mortality is lacking. The variation in study populations and drug regimens along with the small sample sizes of studies greatly impairs the ability to draw concrete conclusions regarding the use of antipsychotic medications for delirium. Even so, organizations such as the SCCM have compiled this evidence into recommendations for clinical practice, but actual clinical practice may not always adhere to the available guidelines. This may reflect the lack of high-quality, consistent literature and be a calling for additional studies to confirm or refute the validity of current practice. Given the lower quality of evidence, when and if to use antipsychotics in a patient with delirium remains somewhat uncertain. While routine use cannot yet be officially condoned, it does seem reasonable to administer antipsychotic medication using one's clinical judgment and pending the individual patient situation. Factors to consider when deciding to administer "as needed" doses in patients may include, but are not limited to: level of distress caused by delirium symptoms, the risk of harming themselves or others, additional nonpharmacologic and pharmacologic options that may be appropriate, and the risks associated with the drug itself (e.g. QTc prolongation and excessive sedation).

Future research in this area is required to better establish the benefits and risks associated

with antipsychotics and delirium. In particular, more large-scale randomized controlled trials with consistency in drug dosing, patient population and selection criteria, and controlled variables (other medications, non-pharmacologic treatments, etc.) are needed in order to allow for stronger meta-analyses and the ability to draw overall conclusions. Although many studies have shown benefit in areas such as reducing incidence and duration of delirium, it may be difficult to implement routine use of antipsychotics if there is no significant improvement on other important parameters such as mortality, hospital length of stay, or long-term comorbidities. The future research of this topic has the potential to not only streamline current medical practice, but to also improve the patient experience in the ICU by potentially reducing distress associated with delirium.

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