Pharmacological Treatments of Non-Substance-Withdrawal Delirium: A Systematic Review of Prospective Trials

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Objective: Most reviews of pharmacological strategies for delirium treatment evaluate the effectiveness of these interventions for delirium prevention, reduction in duration and severity of ongoing delirium, and other outcomes that extend beyond the recommendations of expert treatment guidelines. However, little if any attention is given to substantiating the potential benefits of such treatment or addressing the methodological weaknesses that, in part, limit the pharmacological recommendations made by expert treatment guidelines. Therefore, the authors conducted a systematic review to provide the most up-to-date and inclusive review of published prospective trials of potential pharmacological interventions for the prevention and treatment of delirium, and they discuss potential benefits of pharmacological prevention of delirium and/or reduction of ongoing delirium episode duration and severity.

Method: The analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including prospective randomized and nonrandomized double-blind, single-blind, and open-label clinical trials of any pharmacological agent for the prevention or treatment of delirium and reviewing them systematically for effectiveness on several predefined outcomes.

Results: The pharmacological strategies reviewed showed greater success in preventing delirium than in treating it. Significant delirium prevention effects are associated with haloperidol, second-generation antipsychotics, iliac fascia block, gabapentin, melatonin, lower levels of intraoperative propofol sedation, and a single dose of ketamine during anesthetic induction and with dexmedetomidine compared with other sedation strategies for mechanically ventilated patients.

Conclusions: These promising results warrant further study with consideration of the methodological weaknesses and inconsistencies of studies to date.

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The mainstay of treatment of ongoing delirium is identification and elimination of the precipitant, i.e., acute medical illness, surgical condition, or drug toxicity. However, the development of delirium involves a complex interplay between the precipitant and patient characteristics (advanced age, baseline cognitive impairment, dehydration, or malnutrition) and hospital care characteristics (patient immobilization, physical restraint use, psychoactive medications, indwelling bladder catheter use, or sleep deprivation) (1, 2), many of which are modifiable and have been proposed as treatment targets in the overall delirium treatment plan. Typical nonpharmacological approaches that address modifiable factors are embodied by the multicomponent interventions pioneered by Inouye and colleagues (3). In addition, pharmacological countermeasures for delirium have been proposed as a part of this multimodal approach and have been studied for the prevention of delirium and treatment of ongoing delirium. However, given the limited evidence, variable study quality, and inconsistent findings, pharmacological practice recommendations from expert guidelines based on these data are generally limited to antipsychotics for the treatment of specific behavioral disturbances associated with ongoing delirium, including agitation, anxiety, and psychosis.

In addition, while most reviews report on antipsychotics and several pharmacological alternative approaches to antipsychotics in delirium treatment, they typically focus on a restricted compilation of pharmacological approaches (antipsychotics, cholinesterase inhibitors, alpha-2 agonists, anesthetic technique) and restricted populations of patients (postsurgical, intensive care, or palliative care). Moreover, these reviews discuss pharmacological interventions frequently having the goal of either preventing delirium or treating ongoing delirium with the objective of increasing the number of patients who experience resolution of the delirium episode, decreasing the duration of the episode, or decreasing the severity of the episode. Such pharmacological

treatment objectives extend beyond those set forth by expert treatment guidelines, which propose symptomatic treatment for anxiety, agitation, and psychosis associated with delirium. However, reviews provide little, if any, discussion of the potential benefits of pharmacological treatment outside the recommendations of expert treatment guidelines.

The purposes of the present review are 1) to provide the most up-to-date and inclusive review of published prospective trials of potential pharmacological interventions for the prevention and treatment of delirium, 2) to determine whether there is justifiable benefit for the use of pharmacological interventions for the prevention of delirium and/or reduction of the duration and severity of an extant delirium episode, 3) to review the effectiveness of these treatments for specific goals (delirium prevention, reduction of duration and severity of extant delirium, reduction of intensive care unit [ICU] and hospital length of stay, and reduction of mortality), 4) to explore the notion of treating delirium subtypes and review the effectiveness of these interventions in the various delirium subtypes, and 6) to make recommendations for future delirium research to address variable study quality and inconsistent findings that limit pharmacological practice recommendations by expert guidelines.

Method

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (4). It was limited to English-language publications from 1980 to the present and not restricted to any minimum length of follow-up or inclusion of any specific outcome. Published trials were excluded if they 1) represented a retrospective analysis of data collected in the course of routine clinical care, 2) were single case reports or case series (i.e., fewer than 10 participants included), 3) were reviews or systematic reviews of original studies, 4) included treatment of alcohol withdrawal or other substance-induced delirium, or 5) included subjects less than 18 years of age. Additional methodological details are presented in the "Supplemental Methods" document in the data supplement accompanying the online version of this article.

Results

Specific Pharmacological Interventions for Delirium

A total of 45 prospective trials were identified for inclusion in this review. These studies were grouped into five categories on the basis of the pharmacological approach, with the methods and results for these studies summarized into five supplemental tables, Tables S1–S5 of the "Trial Results" document contained in the data supplement accompanying the online version of this article: 1) antipsychotic treatment for the prevention of delirium, 2) antipsychotic treatment of ongoing delirium, 3) cholinesterase inhibitors, 4) anesthetic technique, perioperative analgesia, and perioperative or critical care sedation, and 5) miscellaneous treatments. The rationale for each treatment type is provided in the "Rationale" document in the online data supplement.

Pharmacological Delirium Prevention Studies

The pharmacological strategies studied for delirium prevention include first- and second-generation antipsychotics, cholinesterase inhibitors, regional anesthesia, enhanced perioperative analgesia, gabapentin, dexmedetomidine, varied depth of intraoperative propofol sedation, melatonin, and ketamine. The majority of delirium prevention studies specifically targeted postoperative delirium in geriatric patients (with a few exceptions), all were randomized, and most were double blind and controlled.

Six of the seven antipsychotic-based delirium prevention studies produced useable data for this review, and all six were placebo-controlled trials for prevention of postoperative delirium. The studies are summarized in Table S1 of the "Trial Results" document contained in the data supplement accompanying the online version of this article. Two (N=537) (5, 6) of the three haloperidol studies demonstrated significantly lower rates of postoperative delirium with haloperidol than with placebo treatment. It is interesting that in the positive haloperidol studies (5, 6) the study drug was administered intravenously, whereas in the one negative study (N=430) (7) haloperidol was administered orally. Both risperidone (oral) trials (N=227) demonstrated lower rates of postoperative delirium in risperidone-treated subjects than in those receiving placebo (8, 9), as did the single olanzapine (oral) trial (N=400) (10).

None of the five cholinesterase inhibitor trials for the prevention of postoperative delirium, i.e., three donepezil trials (N=129) (11–13) and two rivastigmine trials (N=148) (14, 15), showed superiority to placebo (see Table S3 in the trial results in the online data supplement).

The two comparison trials of general versus regional anesthesia (N=104) (16, 17) showed no difference between these anesthetic techniques in the rates of postoperative delirium (see Table S4 in the online trial results).

The three prospective trials of enhanced perioperative analgesia for postoperative delirium prevention used three different approaches (see online Table S4). A comparison of a single preoperative intrathecal dose of morphine with placebo in patients undergoing surgical resection of colon cancer (total N=52) demonstrated no significant difference in rates of postoperative delirium (18). In contrast, the two alternatives to opiate-based analgesia, daily perioperative iliac fascia compartment blocks with bupivacaine for patients undergoing hip fracture repair (N=207) (19) and 900 mg/day of gabapentin given perioperatively to patients undergoing spinal surgery (N=21) (20), were both associated with lower postoperative prevalence rates of delirium than those seen with placebo. Substantially lower total daily doses of postoperative opiates were required for pain control by patients receiving either gabapentin or the iliac fascia blocks than by placebo-treated patients. Whether

the direct effects of iliac fascia blocks and gabapentin or the secondary effect of lower daily dosages of opiates provided the prophylactic effect cannot be determined. Nonetheless, these perioperative pain management strategies do provide potentially useful approaches in those at risk for postoperative delirium.

Four studies evaluating the efficacy of continuous intravenous infusions of dexmedetomidine for sedation of mechanically ventilated surgical and medical ICU patients compared rates of ICU delirium in patients given dexmedetomidine and those receiving other strategies for sedation of mechanically ventilated ICU patients; these agents included midazolam (21, 22), lorazepam (23), propofol (22), and morphine (24) (see Table S4 in the online trial results). Continuous intravenous infusions of dexmedetomidine in four separate trials demonstrated its ability to achieve clinically desirable levels of sedation in mechanically ventilated patients and yet to be associated with significantly lower prevalence rates of ICU delirium than intravenous midazolam (N=434) (21, 22) and intravenous propofol (N=67) (22) and a nearly significant lower prevalence of ICU delirium than intravenous morphine (N=299) (24). However, the prevalence rates of ICU delirium in mechanically ventilated patients were similar for dexmedetomidine sedation and lorazepam (N=103), a benzodiazepine like midazolam (23). This lack of superiority to lorazepam is surprising but plausibly explainable. Patients treated with dexmedetomidine received either similar or significantly lower daily doses of opiates in the two positive midazolam trials (21, 22), whereas patients in the negative lorazepam trial treated with dexmedetomidine received substantially higher doses of opiates (23). The possibility that additional opiate use may have blunted dexmedetomidine's preventive effects on ICU delirium more than lorazepam is supported by the lower rates of ICU delirium with dexmedetomidine sedation than with morphine-based sedation (24) and the higher rates of delirium observed with opiate use (25, 26).

Three of the four trials of miscellaneous agents or interventions for delirium prevention were associated with lower rates of postoperative delirium. A lower level of intraoperative propofol sedation, compared with a higher level, was associated with a lower prevalence rate of postoperative delirium (N=114) (27), and a single dose of ketamine during anesthetic induction likewise produced less postoperative delirium than placebo (N=58) (28) (see Table S5 of the trial results in the online data supplement). It is interesting that the postoperative concentration of C-reactive protein (indicative of inflammatory reactions) was significantly lower in the ketamine-treated group than in the placebo-treated group (28), suggesting that a CNS neuroprotective effect may underlie, in part, ketamine's delirium prevention effect. Finally, a 0.5-mg nightly dose of melatonin was significantly more effective at preventing delirium in acutely ill general medical patients than was placebo (29).

Studies of Pharmacological Strategies for Reducing Delirium Episode Duration and Severity

Decisions to employ symptomatic versus prophylactic interventions with the goals of reducing delirium episode duration and severity should be based on a different risk-benefit assessment. Therefore, we need to consider delirium prevention studies separately from studies of treatment for ongoing delirium.

The limited data from placebo-controlled trials suggest that antipsychotic use in ongoing delirium is less effective than prophylactic treatment. The three randomized, double-blind, placebo-controlled trials of antipsychotic treatment in patients with ongoing delirium demonstrated that haloperidol, ziprasidone, and quetiapine were not associated with significantly higher rates of delirium resolution during the treatment period than was placebo (30–32) (see Table S2 in the "Trial Results" document in the data supplement accompanying the online version of this article). Moreover, the effects of antipsychotics on delirium episode duration and severity in these same trials were inconsistent. While neither haloperidol nor ziprasidone was superior to placebo in shortening delirium episode duration (N=101) (30), quetiapine produced a shorter duration (N=36) in one trial (31) and a "more rapid resolution" of episodes in another (N=42) (32). However, both quetiapine studies enrolled subjects with ongoing delirium as defined by an a priori delirium rating scale cutoff score, whereas the haloperidol study used a more heterogeneous and ambiguously defined study group described as "adult (older than 18 yrs of age) mechanically ventilated medical and surgical ICU patients who had an abnormal level of consciousness or were receiving sedative or analgesic medications" (30). As a result, 47.5% of the patients in the group were delirious and 34.6% were comatose at baseline. It is therefore plausible that such differences in subject characteristics could have contributed to the differences in response, and thus the question of haloperidol's efficacy in reducing delirium episode duration in cases of ongoing delirium has yet to be answered and should be pursued.

Four of the six antipsychotic delirium prevention studies reported on delirium episode duration and severity for the subjects in whom delirium occurred despite preventive treatment, the results of which were mixed (6, 7, 9, 10) (see Table S1 in the online trial results). Two haloperidol delirium prevention studies reported significantly shorter duration and lesser severity of delirium episodes than observed with placebo (N=510) (6, 7), whereas the two studies of delirium prevention using second-generation antipsychotics, olanzapine and risperidone, reported no association with shorter or less severe delirium episodes compared with placebo (N=501) (9, 10). This discrepancy is interesting as five of the nine trials comparing two or more antipsychotics in the treatment of ongoing delirium failed to show any superiority of haloperidol in reducing delirium episode duration or severity over aripiprazole (33),

olanzapine (34–36), or risperidone (36, 37). The remaining antipsychotic comparison trials in ongoing delirium failed to show any superiority of haloperidol to chlorpromazine (38) or of one second-generation antipsychotic to another (39, 40) in reducing delirium episode duration or severity.

None of the cholinesterase inhibitor treatments showed a greater benefit than placebo in decreasing delirium episode duration (11, 12, 15, 41) or severity (12, 13, 41) (see Table S2 of the online trial results).

Only one of the three perioperative analgesia delirium prevention studies reported on delirium duration and severity, and it demonstrated not only that administration of perioperative daily bupivacaine-based iliac fascia block was effective in preventing postoperative delirium in hip fracture patients but also that it was associated with significantly shorter duration and less severe delirium episodes when they did occur (19) (see Table S4 in the online trial results). Although superior to many other sedatives for delirium prevention in mechanically ventilated ICU patients, dexmedetomidine showed superiority only to morphine (24), but not midazolam (22), propofol (22), lorazepam (23), or haloperidol (42), in shortening the duration of ongoing delirium in mechanically ventilated ICU patients. Although one of five studies reported a greater "number of mean delirium-free days" for dexmedetomidine than for midazolam (21), this outcome is not synonymous with duration of delirium episodes. None of the trials of individual miscellaneous treatments demonstrated any effects on delirium episode duration or severity.

Studies of Other Outcomes in Trials of Pharmacological Strategies for Delirium Prevention and Treatment

We evaluated other reported outcomes only from studies that demonstrated efficacy of active treatment in preventing or resolving delirium episodes or in decreasing their duration or severity. Antipsychotic delirium prevention studies showed only haloperidol to have any effect in decreasing ICU length of stay (5) and total hospital length of stay (7) compared with placebo; these outcomes were not observed with risperidone (8, 9) (see Table S1 in the online trial results). Significant decreases in ICU or total hospital length of stay also were not associated with haloperidol (30), ziprasidone (30), or quetiapine (31) in treatment of ongoing delirium (see online Table S2). Of the combined antipsychotic prophylaxis and ongoing treatment studies together, only two reported on disposition following discharge, and both olanzapine prophylaxis of delirium (10) and quetiapine treatment of ongoing delirium (31) were associated with better posthospitalization dispositions.

The preponderance of evidence supports a shorter time to extubation for mechanically ventilated ICU patients sedated with dexmedetomidine than for those given midazolam (21), haloperidol (42), or morphine (24) (total N=685), in contrast to negative reports comparing dexmedetomidine to lorazepam (23), midazolam (22), and propofol (22) (total N=202) (see Table S4 in the online trial results). However, the positive outcome of decreased time to extubation was not paralleled by a decrease in ICU or total hospital length of stay or mortality rates. The only miscellaneous treatment trial to demonstrate other positive outcomes was the study of a single preoperative dose of intravenous ketamine for delirium prevention, which demonstrated that a smaller proportion of ketamine- than placebo-treated subjects were readmitted to the hospital during a 30-day postoperative follow-up (28) (see Table S5 in the online trial results).

Safety of Pharmacological Interventions for Delirium

Antipsychotics. Safety data from the placebo-controlled, active comparator, and open-label trials of antipsychotics demonstrated these drugs to be relatively safe when used for preventing and treating delirium. Although the finding was not consistent across trials, haloperidol treatment, as expected, was associated with a greater frequency of extrapyramidal symptoms compared with placebo (30) and compared with second-generation antipsychotics, such as ziprasidone (30), aripiprazole (33), and olanzapine (34, 35). Risperidone treatment was also associated with a greater frequency of extrapyramidal symptoms than were placebo (9) and other second-generation antipsychotics, such as olanzapine (39). Conversely, second-generation antipsychotics, including quetiapine (31, 43, 44) and olanzapine (39, 45), were more frequently associated with increased sedation.

Although prolongation of the QTc interval is potentially the most serious of the antipsychotic-related adverse effects, it was the least frequently reported adverse effect. Only four of the 24 antipsychotic delirium trials (5, 9, 30, 31) and one trial comparing dexmedetomidine to haloperidol (42) analyzed QTc data. Data from the antipsychotic-based delirium trials demonstrated that low-dose intravenous bolus haloperidol, oral haloperidol, oral risperidone, oral ziprasidone, and oral quetiapine were no more likely than placebo to produce a QTc change greater than 60 ms above baseline or above an absolute value of 500 ms (5, 9, 30, 31). However, continuous intravenous infusion of haloperidol was associated with a significantly longer mean QTc interval than dexmedetomidine during study drug administration (446 ms versus 395 ms, p=0.006) (42), with one patient terminating early because of a new onset of atrial fibrillation immediately preceded by new prolongation of the QTc interval.

Perioperative analgesia. There were no complications of bupivacaine-based iliac fascia block, except local hematomas that developed at the injection site in three subjects and resolved spontaneously (19), and no significant adverse effects were associated with gabapentin treatment (20).

Dexmedetomidine. While initial efficacy results for dexmedetomidine prevention of ICU delirium seem promising, they should be tempered by caution because of the significantly greater rates of bradycardia associated with dexmedetomidine treatment in three of the four studies reporting abnormalities in heart rate or rhythm (21, 23, 24). Although Reade and colleagues (42) reported no significant difference in the proportions of treated subjects with "arrhythmias," neither heart rate nor bradycardia was specifically addressed. Other safety issues with dexmedetomidine were inconsistent; one trial demonstrated a greater frequency of hyperglycemia associated with dexmedetomidine than with midazolam (65.5% versus 42.6%, p=0.02) (21), whereas glucose elevations were nonsignificantly less frequent with dexmedetomidine than with morphine (36.8% versus 47.6%, p=0.06) (24). Although only one study examined effects related to dexmedetomidine discontinuation, it is worth noting that neither rebound hypertension or tachycardia, commonly associated with alpha-2 agonist withdrawal, was detected during the 48 hours after dexmedetomidine treatment was stopped in that study (21).

Miscellaneous agents. No significant adverse effects were reported with propofol-based light sedation (27) nor ketamine administration (28). Only two of 72 melatonin-treated subjects experienced effects requiring drug discontinuation; one patient experienced nightmares, and the other had perceptual disturbances (29).

Discussion

Why Use Pharmacological Strategies to Prevent Delirium?

While negative outcomes of delirium are typically considered in the short term because this is a syndrome of acute brain dysfunction with reversibility as a key element, patients with an episode of hospital-based delirium experience negative sequelae well beyond the hospitalization, including a threefold increase in mortality risk over follow-up periods as long as 6 months and a sixfold greater likelihood of discharge to a skilled nursing facility compared with similar nondelirious patients (46). In addition to these sequelae, delirium is associated with an elevated risk of long-term cognitive impairment, with cognitive decline following hospitalization observed as far out as 5 years from the hospitalization, even in patients who were apparently previously cognitively intact (47, 48). In fact, patients experiencing delirium are 3.5 times as likely to develop dementia over a 5-year follow-up (49). The data from these studies suggest that delirium does not simply persist but, rather, predicts future cognitive decline. Recent evidence suggests that delirium itself is neurotoxic and associated with acute new brain damage, as demonstrated by independent associations between delirium and global brain atrophy and white matter disruption at hospital discharge (50, 51) and at 3-month follow-up (50, 51), in conjunction with decrements in long-term cognitive functioning (50–52). Given this, it is not unreasonable to speculate that prevention of delirium will be associated with better long-term outcomes and increased long-term survival of hospitalized patients at risk for delirium.

Why Use Pharmacological Strategies to Decrease the Course or Severity of Ongoing Delirium?

The independent associations between delirium and observed brain changes and cognitive decline just noted (50, 51) seem to be mitigated by a potential dose-response relationship, such that a longer duration of the delirium episode is associated with greater global brain atrophy, white matter disruption, and cognitive decline (50, 51). In addition, longer duration of the delirium episode appears to have negative consequences for other clinical outcomes (53). Similarly, a potential dose-response relationship between delirium severity and outcome has been observed and is best characterized by outcomes associated with "subsyndromal delirium," a clinical state characterized by the presence of any core symptoms of delirium but not fulfilling the full criteria for delirium. While having no uniformity of diagnostic criteria, "subsyndromal delirium" is frequently defined by severity scores on rating scales that are below the diagnostic threshold for full-blown delirium (54). It is interesting that the poor outcomes associated with subsyndromal delirium, such as skilled nursing facility placement and cognitive decline, appear to be intermediate between those of patients with full-blown delirium and those without either delirium or subsyndromal delirium (55, 56). Moreover, a direct relationship between greater symptom load in patients with subsyndromal delirium and poorer cognitive and functional status at 1-year follow-up has been observed (56). This line of research supports the notion that decreasing the duration and/or severity of ongoing delirium in hospitalized patients will be associated with better long-term outcomes. Such interventions in ongoing delirium cover a broader scope of symptoms than do the narrowly defined pharmacological treatment goals of expert treatment guidelines, which focus on reduction of agitation, anxiety, or psychosis specifically.

Next Steps

Several of the individual trials of miscellaneous agents reviewed here have shown preliminary promise in the prevention and treatment of delirium and warrant replication and elaboration in future trials. Moreover, additional trials with dexmedetomidine and antipsychotics are warranted given that placebo-controlled trials of antipsychotics in ongoing delirium are few and the somewhat promising results with dexmedetomidine require elaboration. However, the field must recognize the

Clinical Vignette

A psychiatrist is asked to consult on the case of a 65-year-old man on the orthopedic service 2 days after bilateral total knee replacement. Nursing reports describe him as agitated, confused, pulling out his catheters, and attempting to climb out of bed. He claims he wants to go home with his wife, who he believes is in the room (although she died 10 years previously). While examining the patient, you are asked by the daughter of the patient in the next bed, whose hip fracture was repaired 4 days earlier, if you will be consulting on her father. No consult for this patient was requested, and you note him to be resting quietly as you ask what her concerns are. She reports that he has not been himself for the last 2 days: sleeping all day, not knowing where he is, and unable to remember why he is there, although he has been told repeatedly. The consultant asks staff about the hip fracture patient and they report that he has been calm and quiet with no disruptive behaviors and in no need of psychiatric services. That night the hip fracture patient is transferred to the ICU with sepsis secondary to an infected decubitus ulcer.

methodological limitations that may have contributed, in large part, to the inconsistencies between studies. These issues should be resolved in order to apply these methodologies more consistently across future studies in an effort to strengthen the data and allow future treatment guidelines for delirium to expand their recommendations on pharmacological interventions.

One of the more salient methodological issues is the distinction between prevention of delirium and treatment of ongoing delirium. As this review has shown, similar agents can produce different results when applied to prevention and treatment of ongoing delirium. Many of the prevention studies cited here neglected to exclude subjects with delirium at baseline and, along with many of the studies of treatment for ongoing delirium, failed to report data on the prevalence of baseline delirium (preintervention). If there is uncertainty about which subjects are delirious at baseline (preintervention), then how is it possible to know if the reported rates of postintervention delirium reflect new-onset (incident) delirium or a continuation of the baseline delirium episode (prevalent). Therefore, for future studies to conclude that the specific intervention under investigation is associated with a delirium prevention and/or delirium resolution effect, one of the following criteria must be met: 1) all potential subjects with baseline delirium need to be excluded, 2) 100% of the subjects need to have a verified diagnosis of delirium at baseline, or 3) the baseline prevalence of delirium needs to be accurately reported and the postintervention rate of delirium needs to be accurately classified as incident or prevalent.

Differential Effects of Treatment on Motoric Subtypes of Delirium

As the vignette demonstrates, clinical presentations of delirium can be quite diverse, and three motoric subtypes are recognized: hyperactive, hypoactive, and mixed (57). It has been suggested that the hyperactive form is most often characterized by hallucinations, delusions, agitation, and disorientation, whereas the hypoactive subtype is characterized by confusion and sedation and is less often associated with psychotic features, which are more difficult to identify even if present (58). It is estimated that 75% of delirium cases are either of the hypoactive or mixed type, whereas the classical hyperactive type of delirium is a minority of the cases (59). However, hyperactive delirious patients are more likely to attract medical and nursing attention than those who are quietly delirious; the latter group are often misdiagnosed as depressed or demented (60). The clinical implications of these data are twofold: 1) the majority of delirium cases will go unrecognized and receive no intervention at all and 2) the minority of delirious patients (those with the hyperactive subtype) will be treated for psychosis in accordance with guidelines (61–63), while the majority of patients with the hypoactive and mixed subtypes will receive no such pharmacological treatment, even when psychosis is present, as it is more difficult to detect. Indeed, the consequences of failure to recognize the less classical, hypoactive type of delirium can be observed in the data, which demonstrate that patients with hypoactive delirium have longer hospital stays (59, 64) and are more likely to develop pressure sores and hospital-acquired infections (64). While improving recognition of delirium is an important topic, it is beyond the scope of this review. However, to better support the use of pharmacological agents in delirious patients with the hypoactive or mixed subtype, data on the response of different subtypes to treatment would be of value.

Only three of the 24 antipsychotic studies reviewed here analyzed treatment effects based on delirium subtype (33, 45, 65). The results were quite mixed, demonstrating delirium resolution in a greater proportion of hypoactive- than hyperactive-type delirium patients (100.0% versus 58.3%) with aripiprazole treatment (33), similar delirium resolution rates in hypoactive- and hyperactive-type delirium patients (77.8% versus 75.0%) with haloperidol treatment (65), and lower delirium resolution rates in hypoactive- than hyperactive-type delirium patients (48% versus 83%) with olanzapine treatment (45). Despite these inconsistencies, these preliminary data suggest that antipsychotics may have a role in the management of hypoactive as well as hyperactive delirium and that additional trials are warranted to support this notion. An approach to address this issue would be to stratify enrollment to future antipsychotic trials for

treatment of ongoing delirium on the basis of hypoactive, hyperactive, and mixed motoric subtypes.

Conclusions

Delirium is a neuropsychiatric condition that complicates both medical and surgical illness. Given the association between delirium and increased hospital-based complications, including mortality, and long-term complications such as cognitive decline and need for custodial care, there is an imperative to prevent the appearance of delirium and, once present, to treat it with the intention of both improving the immediate clinical picture and potentially improving long-term outcome. The preponderance of evidence suggests greater success at preventing delirium with the pharmacological strategies reviewed here than treating delirium once it develops. The following pharmacological agents are associated with significant postoperative delirium prevention effects: haloperidol, second-generation antipsychotics, iliac fascia block, gabapentin, lower levels of intraoperative propofol sedation, and a single dose of ketamine during anesthetic induction. Continuous intravenous infusion of dexmedetomidine for sedation of mechanically ventilated medical and surgical ICU patients is associated with lower rates of ICU delirium than are alternative sedation strategies. Finally, melatonin appears promising for the prevention of delirium in acutely ill general medical patients. The best response for shortening the duration and severity of delirium episodes appears to be with antipsychotics. Haloperidol's effectiveness in preventing postoperative delirium is accompanied by its effectiveness in decreasing delirium duration and severity when it occurs but was not observed in the single placebo-controlled haloperidol treatment study of ongoing delirium (potentially related to subject characteristics, discussed earlier in more detail). Limited evidence demonstrates that quetiapine shortens the duration of episodes in ongoing delirium, while other second-generation antipsychotics (olanzapine and risperidone) used in delirium prevention trials had no such effect on delirium duration or severity. Some of the pharmacological interventions evaluated in multiple trials and some of those evaluated in single trials seem promising for prevention and treatment of delirium, but clearly, further comparative effectiveness trials are warranted.

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