Treatment of delirium: A review of 3 studies

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Delirium is defined as a disturbance in attention, awareness, and cognition that develops over hours to days as a direct physiological consequence of an underlying medical condition and is not better explained by another neurocognitive disorder.[1] This condition is found in up to 31% of general medical patients and up to 87% of critically ill medical patients. Delirium is commonly seen in patients who have undergone surgery, those who are in palliative care, and patients with cancer.[2] It is associated with increased morbidity and mortality. Compared with those who do not develop delirium, patients who are hospitalized who develop delirium have a higher risk of longer hospital stays, post-hospitalization nursing facility placement, persistent cognitive dysfunction, and death.[3]

Thus far, the management and treatment of delirium have been complicated by an incomplete understanding of the pathophysiology of this condition. However, prevailing theories suggest a dysregulation of neurotransmitter synthesis, function, or availability.[2] Recent literature reflects this theory; researchers have investigated agents that target dopamine or acetylcholine. Below we review some of this recent literature on treating delirium; these studies are summarized in the *Table*[4-6] (*page 36*).

1. Burry L, Mehta S, Perreault MM, et al. Antipsychotics for treatment of delirium in hospitalized non-ICU patients. Cochrane Database Syst Rev. 2018;6:CD005594.

An extensive literature review identified randomized or quasi-randomized trials on the treatment of delirium among non-critically ill hospitalized patients in which antipsychotics were compared with nonantipsychotic medications or placebo, or in which a first-generation antipsychotic (FGA) was compared with a second-generation antipsychotic (SGA).[4]

Study design

• Researchers conducted a literature review of 9 trials that included 727 hospitalized but not critically ill patients (ie, they were not in an ICU) who developed delirium.

• Four trials compared an antipsychotic with a medication from another drug class or with placebo.

• Seven trials compared a FGA with an SGA.

Outcomes

• Although the intended primary outcome was the duration of delirium, none of the included studies reported on duration of delirium. Secondary outcomes were delirium severity and resolution, mortality, hospital length of stay, discharge disposition, health-related quality of life, and adverse effects.

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Researchers have investigated agents targeting dopamine or acetylcholine

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Table

Treatment of delirium: 3 studies

Study	Design	Outcome
Burry et al[4] (2018)	Review of 9 trials that included 727 hospitalized patients with delirium who received an antipsychotic, a medication from another class, or placebo	Compared with nonantipsychotic medications, antipsychotics did not reduce delirium severity. There also was no difference between first- and second-generation antipsychotics
Girard et al[5] (2018)	In a double-blind trial, 566 patients who developed delirium were randomized to receive IV haloperidol, ziprasidone, or placebo	Neither ziprasidone nor haloperidol had an impact on the number of days alive without delirium or coma. There was also no statistically significant difference in 30-day survival, 90-day survival, time to freedom from mechanical ventilation, ICU discharge, ICU readmission, or hospital discharge
Yu et al[6] (2018)	Review of RCTs in which cholinesterase inhibitors were compared with placebo or another drug for treating delirium in patients who were not critically ill. Only one study, which included 15 participants treated with rivastigmine or placebo, met the criteria to be included in the review	The included study did not report on the severity of delirium and lacked statistical power to determine a difference in duration of delirium between the rivastigmine and placebo groups. There was no clear difference between groups in terms of the use of rescue medications, mortality, or early departure from the study

RCTs: randomized controlled trials

• Among the secondary outcomes, no statistical difference was observed between delirium severity, delirium resolution, or mortality.

• None of the included studies reported on hospital length of stay, discharge disposition, or health-related quality of life.

• Evidence related to adverse effects was determined to be very low quality due to potential bias, inconsistency, and imprecision.

Conclusion

• A review of 9 randomized trials did not find any evidence supporting the use of antipsychotics for treating delirium. However, most of the studies included were of lower quality because they were single-center trials with insufficient sample sizes, heterogeneous study populations, and risk of bias.

2. Girard TD, Exline MC, Carson SS, et al; MIND-USA Investigators. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med. 2018;379(26):2506-2516.

Study design

• Researchers used the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) to assess 1,183 patients with acute respiratory failure or shock in 16 medical centers in the United States.[5]

• Overall, 566 patients developed delirium and were randomized in a double-blind fashion to receive IV haloperidol, ziprasidone, or placebo.

• Haloperidol was started at 2.5 mg (age <70) or 1.25 mg (age ≥70) every 12 hours and titrated to a maximum dose of 20 mg/d as tolerated.

• Ziprasidone was started at 5 mg (age <70) or 2.5 mg (age ≥70) every 12 hours and titrated to a maximum dose of 40 mg/d as tolerated.

Outcomes

• The primary endpoint was days alive without delirium or coma. Secondary endpoints included duration of delirium, time to freedom from mechanical ventilation, time to final successful ICU discharge, time

to ICU readmission, time to successful hospital discharge, 30-day survival, and 90-day survival.

• Neither ziprasidone nor haloperidol had an impact on number of days alive without delirium or coma.

• There was also no statistically significant difference in 30-day survival, 90-day survival, time to freedom from mechanical ventilation, ICU discharge, ICU readmission, or hospital discharge.

Conclusion

• This study found no evidence supporting haloperidol or ziprasidone for the treatment of delirium. Because all patients in this study were critically ill, it is unclear if these results would be generalizable to other hospitalized patient populations.

3. Yu A, Wu S, Zhang Z, et al. Cholinesterase inhibitors for the treatment of delirium in non-ICU settings. Cochrane Database Syst Rev. 2018;6:CD012494.

Study design

• A literature review identified published and unpublished randomized controlled trials in English and Chinese in which cholinesterase inhibitors were compared with placebo or another drug for treating delirium in non-critically ill patients.[6]

• Only one study met the criteria to be included in the review. It included 15 participants treated with rivastigmine or placebo.

Outcomes

• The intended primary outcomes were severity of delirium and duration of delirium. However, the included study did not report on the severity of delirium. It also lacked statistical power to determine a difference in duration of delirium between the rivastigmine and placebo groups.

• Secondary outcomes included use of a rescue medication, persistent cognitive impairment, length of hospitalization, institutionalization, mortality, cost of intervention, early departure from the study, and quality of life.

• There was no clear difference between the rivastigmine group and the placebo group in terms of the use of rescue medications, mortality, or early departure from the study. The included study did not report on persistent cognitive impairment, length of hospitalization, institutionalization, cost of intervention, or quality of life.

Conclusion

• This literature review did not find any evidence to support the use of cholinesterase inhibitors for treating delirium. However, because this review included only a single small study, limited conclusions can be drawn from this research.

In summary, delirium is common, especially among patients who are acutely medically ill, and it is associated with poor physical and cognitive clinical outcomes. Because of these poor outcomes, it is important to identify delirium early and intervene aggressively. Clearly, there is a need for further research into short- and long-term treatments for delirium.

References

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6. Yu A, Wu S, Zhang Z, et al. Cholinesterase inhibitors for the treatment of delirium in non-ICU settings. Cochrane Database Syst Rev. 2018;6:CD012494.

Clinical Point

A literature review did not find any evidence to support the use of cholinesterase inhibitors for treating delirium