Delirium is characterized by fluctuating disturbance in attention and awareness, with changes in cognition and/or perception, that develops over hours to days as a physiological consequence of an underlying medical condition (American Psychiatric Association, 2013). Delirium can be a hyperactive motoric subtype associated with agitation; hypoactive type associated with drowsiness; or mixed type that fluctuates between hyperactive and hypoactive states. Risk factors for delirium include advanced age, preexisting cognitive impairment, and polypharmacy, particularly with psychoactive drugs (Inouye, 2006). Delirium is common during hospitalization and is associated with prolonged length of stay, increased mortality, and long-term cognitive impairment (MacLullich et al., 2009; Siddiqi et al., 2006). Delirium can also impede the delivery of nursing, medical, and rehabilitation care.

The pathophysiology of delirium is complex and includes an imbalance between acetylcholine and dopamine neurotransmitters (Trzepacz, 2000). Given that antipsychotics are thought to decrease dopaminergic activity and reduce agitation, clinicians have used these medications for preventing or treating delirium. However, when initiated for delirium in the hospital, antipsychotics have the potential for short- and long-term side effects, especially with unintentional continuation beyond hospital discharge (Loh et al., 2016). Hence, the current authors sought to synthesize data on the benefits and harms of antipsychotics for preventing and treating delirium via a systematic review, conducted as part of the Agency for Healthcare Research and Quality’s (AHRQ) Effective Healthcare Program.

This systematic review included 14 randomized control trials (RCTs) and one observational study evaluating the use of antipsychotics for preventing delirium, and 19 RCTs and 25 observational studies evaluating their use in treating delirium, with some RCTs being considered as both prevention and treatment studies. In this report, the strength of evidence (classified as high, moderate, low, and insufficient, according to the grading scheme recommended by the AHRQ [Owens et al., 2010]) was reported for critical outcomes. Critical outcomes were selected a priori in consultation with key informants and delirium experts and included delirium severity, cognitive function, hospital length of stay, sedation-related effects, and inappropriate continuation of antipsychotics.

In summary, this systematic review (Neufeld et al., 2019; Nikooie et al., 2019; Oh et al., 2019) (access full report at https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/delirium-finalreport.pdf) reported little to no effect of haloperidol or second-generation antipsychotics, compared with placebo, in preventing or treating delirium in terms of hospital length of stay. Moreover, in preventing or treating delirium, there also was either insufficient or no evidence for the other critical outcomes, including delirium severity, cognitive function, and inappropriate continuation of antipsychotics (Table 1).

Specifically, for treating delirium, in comparing haloperidol to second-generation antipsychotics, there was little to no difference for the following outcomes: delirium severity, cognitive function, and hospital length of stay. For preventing delirium, in comparing haloperidol to second-generation antipsychotics, there was insufficient or no evidence for these same outcomes. In a meta-analysis of three studies evaluating antipsychotics for preventing delirium in postoperative patients ($N = 627$), second-generation antipsychotics (compared with placebo) demonstrated a lower incidence of delirium. It is unclear if this finding generalizes to other patient populations.

For comparisons of haloperidol and placebo, second-generation antipsychotics and placebo, and haloperidol and second-generation antipsychotics, there was little to no difference in sedation-related effects when used for treating delirium, and there was insufficient or no evidence in sedation-related effects when used for preventing delirium. Although no statistically significant differences in mortality, cardiac, and neurological effects were found for the aforementioned comparisons, there generally were more instances of arrhythmias, QTc prolongation, and extrapyramidal symptoms in patients receiving antipsychotics.
Given these findings, delirium prevention efforts should focus on identifying and addressing modifiable risk factors (Inouye, 2006) and considering nonpharmacological interventions as part of routine clinical care (Hshieh et al., 2015). Such interventions include repeated reorientation by a family member or nurse, early mobility and physical rehabilitation, reducing sensory deprivation by providing eyeglasses and hearing aids, improving the sleep-wake cycle, and continuing appropriate nutrition and hydration. Many of these interventions are part of existing programs, such as the Hospital Elder Life Program, which has demonstrated reductions in the incidence of delirium (Hshieh et al., 2018).

Notably, not all episodes of delirium are preventable, and when patients have hyperactive delirium that puts them or others at risk of injury or harm, and all other nonpharmacological approaches have failed, antipsychotics (at the lowest possible dose, for the shortest possible duration) may be considered in managing such agitation (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015), with recognition that use of these medications does not reduce the duration of delirium or improve other outcomes.

Based on the results of the systematic review, to advance the field, future delirium research should focus on important patient subgroups (e.g., older adults, persons with dementia, patients in palliative care, postoperative patients, and patients in postacute care facilities) and have greater consistency in the outcomes evaluated and associated measurement instruments. Future research will benefit from gaining international consensus in defining outcomes of greatest importance to clinicians, patients, their caregivers, and researchers, and using agreed-upon measurement instruments for such outcomes (Rose et al., 2017).

| TABLE 1 | Effects of Antipsychotics on Critical Outcomes, With Strength of Evidence (SOE)\(^a\) |
| --- | --- | --- | --- |
| **Critical Outcome** | **Haloperidol vs. Placebo** | **Second-Generation Antipsychotics vs. Placebo** | **Haloperidol vs. Second-Generation Antipsychotics** |
| Antipsychotics for Prevention | | | |
| Delirium severity | Insufficient evidence | Insufficient evidence | No evidence |
| Cognitive function | No evidence | No evidence | No evidence |
| Hospital length of stay | Little to no difference (high SOE) | Little to no difference (low SOE) | Insufficient evidence |
| Sedation-related side effects | Insufficient evidence | No evidence | No evidence |
| Inappropriate continuation of antipsychotics | No evidence | No evidence | No evidence |
| Antipsychotics for Treatment | | | |
| Delirium severity | Insufficient evidence | Insufficient evidence | Little to no difference (moderate SOE) |
| Cognitive function | No evidence | Insufficient evidence | Little to no difference (low SOE) |
| Hospital length of stay | Little to no difference (moderate SOE) | Little to no difference (moderate SOE) | Little to no difference (moderate SOE) |
| Sedation-related side effects | Little to no difference (low SOE) | Little to no difference (moderate SOE) | Little to no difference (moderate SOE) |
| Inappropriate continuation of antipsychotics | No evidence | No evidence | No evidence |

\(^a\) Across all critical outcomes, there is insufficient or no evidence for direct comparisons of different second-generation antipsychotics. Strength of evidence as per Agency for Healthcare Research and Quality (Owens et al., 2010, p. 519): “insufficient = the body of evidence has unacceptable deficiencies, precluding a conclusion; low = low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate; moderate = indicating moderate confidence that the evidence reflects the true effect but further research could change our confidence in the estimate of the effect and may change the estimate; high = high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect.”
REFERENCES


Sriharsha Singu, MBBS
Mounica Koneru, MBBS
Karen A. Robinson, PhD
Karim J. Neufeld, MD, MPH
Esther S. Oh, MD, PhD
Lisa M. Wilson, ScM
Dale M. Needham, MD, PhD
Johns Hopkins University
Baltimore, Maryland

Amulya Balagani, MBBS
Louay Aldabain, MD
Medstar Health Internal Medicine
Baltimore, Maryland

Roozbeh Nikooie, MD
Yale University School of Medicine
New Haven, Connecticut

Donna M. Fick, PhD, RN, FAAN, FGSA
Editor

This project was funded under Contract No. HHSA290201500006I/HHSA29032008T from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The authors of this manuscript are responsible for its content. Statements in the manuscript do not necessarily represent the official views of or imply endorsement by AHRQ or HHS.

doi:10.3928/00989134-20200303-01