

Systematic Review Snapshot

Clinical Synopsis

TAKE-HOME MESSAGE

According to limited evidence, emergency physicians should avoid meperidine and consider prescribing oxycodone to elderly patients when narcotics are indicated for pain control.

METHODS

DATA SOURCES

MEDLINE, EMBASE, PsychInfo, and Allied & Complementary Medicine from 1966 through October 2009 were used; bibliographies of selected studies were reviewed for additional relevant articles.

STUDY SELECTION

Randomized controlled trials, prospective cohort studies, and case-control studies that reported on medications and delirium in hospitalized patients or long-term care residents were included. Delirium was defined by the *Diagnostic and Statistical Manual for Mental Disorders (DSM)*, *International Classification of Diseases, 10th Revision (ICD-10)*, or a diagnostic tool validated against the *DSM, Third Edition*; *DSM, Third Edition, Revised*; *DSM, Fourth Edition*; or *ICD-10*.

DATA EXTRACTION AND SYNTHESIS

A single author extracted data. Lower-quality evidence was excluded from the final study summary table. Multivariate analyses were quality graded on the basis of an event-to-covariate ratio exceeding 10 and the inclusion of 3 delirium risk factors: age, dementia, and illness severity. Outcomes were reported as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs).

Which Medications Are Associated With Incident Delirium?

EBEM Commentator

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Results

Risk of acute delirium.

Medication	Patient Population	Study Design (95% CI)	Effect Size (95% CI)
Haloperidol	Hip surgery	Randomized controlled trial	RR 0.9 (0.6–1.3)
Neuroleptic medications	Mixed medical/surgical	Prospective cohort	OR 4.5 (1.8–10.5)
Meperidine	Surgical	Nested case control	OR 2.7 (1.3–5.5)
Oxycodone	Surgical	Nested case control	OR 0.7 (0.3–1.6)
Parenteral morphine dose equivalent <10 mg during 24 h	Orthopedic surgery	Prospective cohort	RR 25.2 (1.3–493.3)
Parenteral morphine dose equivalent 10–30 mg during 24 h	Orthopedic surgery	Prospective cohort	RR 4.4 (0.3–68.6)

RR, Relative risk; OR, odds ratio.

Fourteen studies, including 3 randomized controlled trials, were included, but because of heterogeneity in study populations and methods, meta-analysis was not conducted. The mean age of subjects in 12 studies was more than 65 years, and no trial was based in the ED. The only high-quality randomized controlled trial to evaluate a single medication evaluated haloperidol in hip surgery patients and observed no association with incident delirium. One moderate-quality multivariate analysis of a prospective cohort observed an increased risk of delirium with neuroleptic medications

(OR 4.5). Among opioids, meperidine was more highly associated with delirium than other narcotic alternatives (OR 2.7; moderate quality). On the other hand, oxycodone in a mixed population of surgical patients had no association with delirium (moderate quality). When opioids were evaluated as a class in postoperative orthopedic patients, an inverse relationship was observed between the dose and the risk of delirium, with a higher risk for lower doses (parenteral morphine dose equivalent <10 mg for the 24 hours preceding the incident delirium or the highest 24-hour dose

received during the first 3 postoperative days for nondelirious patients; RR 25.2; moderate quality) than for higher doses (morphine dose equivalent 10 to 30 mg; moderate quality). However, as observed by the review authors, the wide CIs imply considerable uncertainty about the association of narcotic dosing with incident delirium. There was insufficient evidence to assess the risk of delirium with administration of antihistamines (H1 or H2 antagonists), steroids, nonsteroidal anti-inflammatory drugs, digoxin, tricyclic antidepressants, oxybutynin, or antiparkinsonian medications.

Commentary

Emergency providers are faced with the dual responsibilities of delirium recognition among the myriad diagnostic possibilities presenting as cognitive dysfunction and avoidance of precipitating delirium by prescribing higher-risk medications. One challenge is that emergency physicians do not recognize delirium in 75% of patients with the disease.^{1,2} Another challenge is that physicians are often unaware of which medications are associated with incident delirium in susceptible populations. Beers criteria were developed to identify potentially inappropriate medications for geriatric patients.³ Beers criteria are imperfect for application in the emergency department (ED) because the criteria were not developed in conjunction with emergency medicine experts, were not based on ED populations, and may not be valid for the single doses often prescribed in the ED.⁴ Nonetheless, up to 29% of geriatric patients arrive in the ED when already receiving at least 1 Beers-defined inappropriate medication and 12.6% are prescribed one while there.^{5,6}

The most compelling evidence identified in this systematic review was

for opioid analgesia: avoid meperidine, oxycodone should be considered among the safest agents, and lower opioid doses in surgical patients may paradoxically increase the risk of delirium. Meperidine has been one of the most commonly prescribed Beers-defined potentially inappropriate medications in the ED setting.⁶ The pathophysiology for the inverse relationship between opioid doses and delirium has not yet been well described but may be the result of impaired use of patient-controlled analgesia, ineffective communication of pain scores, or more likely a multifactorial problem compounded by the effects of acute pain on central nervous system dopaminergic and cholinergic neurotransmitter pathways.⁷ The potential for bias in the remainder of the evidence is too great to permit confident recommendations for other classes of medications, including benzodiazepines, antihistamines, steroids, nonsteroidal anti-inflammatory drugs, antidepressants, cardiac glycosides, and antiparkinsonian agents. No other medication classes were evaluated.

The systematic review authors did not elaborate on 2 other potential sources of bias. Six of the 14 trials used the Confusion Assessment Method and 2 more used the Confusion Assessment Method-ICU to define the presence or absence of delirium. Some have argued that these instruments are better to screen for, rather than diagnose, delirium.⁸ Furthermore, one of the key confounding variables to concurrently precipitate and complicate the diagnosis of delirium is dementia, a condition that is also poorly recognized by both inpatient and outpatient providers. The authors do not detail the methods to define dementia, which is critical to the interpretation of their multivariate models.

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8. Laurila JV, Pitkala KH, Strandberg TE, et al. Confusion Assessment Method in the diagnostics of delirium among aged hospital patients: would it serve better in screening than as a diagnostic instrument? *Int J Geriatr Psychiatry.* 2002;17:1112-1119.

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