Abstract

Background: delirium is a common clinical problem and is associated with adverse health outcomes. Many medications have been associated with the development of delirium, but the strength of the associations is uncertain and it is unclear which medications should be avoided in people at risk of delirium.

Methods: we conducted a systematic review to identify prospective studies that investigated the association between medications and risk of delirium. A sensitivity analysis was performed to construct an evidence hierarchy for the risk of delirium with individual agents.

Results: a total of 18,767 studies were identified by the search strategy. Fourteen studies met the inclusion criteria. Delirium risk appears to be increased with opioids (odds ratio [OR] 2.5, 95% CI 1.2–5.2), benzodiazepines (3.0, 1.3–6.8), dihydropyridines (2.4, 1.0–5.8) and possibly antihistamines (1.8, 0.7–4.5). There appears to be no increased risk with neuroleptics (0.9, 0.6–1.3) or digoxin (0.5, 0.3–0.9). There is uncertainty regarding H2 antagonists, tricyclic antidepressants, anti-parkinson medications, steroids, non-steroidal anti-inflammatory drugs and antimuscarinics.

Conclusion: for people at risk of delirium, avoid new prescriptions of benzodiazepines or consider reducing or stopping these medications where possible. Opioids should be prescribed with caution in people at risk of delirium, but this should be tempered by the observation that untreated severe pain can itself trigger delirium. Caution is also required when prescribing dihydropyridines and antihistamine H1 antagonists for people at risk of delirium and considered individual patient assessment is advocated.

Keywords: delirium, drug toxicity, elderly, medication, prescriptions, systematic review
A. Clegg and J. B. Young

Background

Delirium is a common clinical problem that is associated with increased morbidity, mortality, long-term care, length of inpatient stay and healthcare costs [1, 2]. Age >65, cognitive impairment, severe illness and hip fracture have been identified as risk factors for the development of delirium [3].

The pathophysiology of delirium is complex and incompletely understood, and multiple neurotransmitter pathways are implicated, particularly cholinergic and dopaminergic pathways [4]. Many medications can have deleterious effects on cholinergic and dopaminergic pathways [5, 6]. For example, antihistamine H1 medications, H2 antagonists, steroids and digoxin have increased in vitro anticholinergic activity [7], and neuroleptics, angiotensin converting enzyme inhibitors, dihydropyridines and antiparkinson medications have in vitro dopaminergic activity [5]. Direct effects of medications on opioid and gamma-aminobutyric acid (GABA) receptors may also be involved in the complex pathophysiology of delirium. A reduction in hepatic esterases, important enzymes in medication metabolism, has been observed in frail older people and in acute illness [8], and this may be a further important factor in the contribution of medications to delirium.

Multicomponent strategies can successfully reduce delirium incidence and usually incorporate a medication review [9]. However, it is unclear which medications should be targeted as high risk for delirium. We have conducted a systematic review of the literature to identify an evidence-based approach for this common clinical issue.

Methods

Types of study

We searched systematically for all randomised controlled trials (RCTs), prospective cohort studies and case–control studies that reported on medications and delirium in hospital patients or long-term care residents. Retrospective studies, reviews, case series and individual case reports were excluded. The diagnostic criteria for delirium are operationalised in the Diagnostic & Statistical Manual for Mental Disorders (DSM), volumes III, III-R and IV [10–12] and the International Classification of Diseases Volume 10 (ICD 10) [13]. The primary outcome measure for this review was delirium rate using the DSM or ICD criteria or a diagnostic tool validated against DSM III, III-R, IV or ICD 10.

Search strategy and study assessment

A search strategy for MEDLINE was developed, with appropriate amendments for EMBASE, PsychInfo, Allied & Complementary Medicine, with literature searching to October 2009. The full texts of all potentially relevant studies were obtained. The bibliographies of studies selected for inclusion were also reviewed for further potentially relevant articles. RCTs were assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions [14]. Prospective cohort and case–control studies were assessed using the Newcastle–Ottawa checklist [15]. This allowed the studies to be quality graded into high, moderate and low, or potentially biased. As neuroleptic and benzodiazepine medications are used in the treatment of delirium symptoms, particular attention was directed to the reliability of study methods to examine the temporal relationship between prescription and the subsequent development of delirium. Studies that failed to address this important issue were downgraded. The quality assessment was to inform a sensitivity analysis whereby studies providing lower quality evidence were excluded from the final study summary table. Thus, a hierarchy of evidence was constructed with greatest emphasis given to the most reliable studies.

Data extraction and analysis

One review author extracted data using a bespoke database. Multivariate analyses were quality graded on the basis of an event-to-covariate ratio of >10 and the inclusion of three a priori risk factors for delirium (age, cognitive impairment or dementia and illness severity) in the analysis. As univariate data in the form of odds ratios (ORs)/risk ratios (RRs) do not control for potential confounding variables, these data were considered to provide a lower level of evidence to support an association between class of medication and delirium. Where no multivariate or univariate OR/RR was reported, the primary data were extracted and univariate RRs with confidence intervals (CI) for each medication class were calculated using RevMan 5 software.

Results

The review process is summarised in Figure 1 using the PRISMA guidelines [16].

Study characteristics

Fourteen studies [17–30] are included in the final analysis. A summary of study characteristics is presented in Table 1. Different populations were recruited: general medicine [17–19]; orthopaedic hip fracture/hip surgery [20, 21, 25, 28]; intensive care (ICU) [22, 26, 27]; a mixed medical and surgical patient group [29]; a mixed surgical population [24]; elective cardiac surgery [30]; and one study was based in long-term care [23]. Seven studies reported data for one single medication class [17, 19, 21–23, 25, 30] and seven studies reported multiple classes [18, 20, 24, 26–29]. Two studies [17, 21] excluded patients with severe dementia. One further study [23] excluded patients with Lewy body dementia, but included all patients with other dementias.
Heterogeneity in study populations and methods precluded meta-analysis.


**Medication classes**

Results were found for neuroleptics [18, 20, 21, 29], opioid medications [18, 24–29], benzodiazepines [18–20, 24, 27–29], antihistamine H1 antagonists [17, 24], histamine H2 antagonists [22], dihydropyridines [30], antimuscarinics [23], tricyclic antidepressants (TCAs) [20], antiparkinson medications [20], digoxin [29], steroids [29] and non-steroidal anti-inflammatory drugs (NSAIDs) [29]. A sensitivity analysis (Table 2) presents a hierarchy of evidence for the medication classes and individual agents within a class. The association of delirium with dose–response and duration of action of agents is also summarised (Table 3).

**Neuroleptic medications**

All four studies [18, 20, 21, 29] described methods consistent with an attempt to identify a temporal relationship between neuroleptic administration and development of delirium. There is evidence from one high-quality RCT [21] to suggest that haloperidol does not appear to be associated with increased risk of delirium (RR 0.9, 95% CI 0.6–1.3). Evidence from one moderate quality multivariate analysis in
one moderate quality prospective cohort study [29] suggests an association of increased risk of delirium with use of neuroleptic medications (OR 4.5, 95% CI 1.8–10.5). Two studies were of low quality [18, 20].

**Opioid medications**

There is evidence from two moderate quality multivariate analyses to support an association of increased delirium risk with opioid medications in medical and surgical patients (OR 2.5, 95% CI 1.2–5.2) [29]. There appears to be an inverse dose–response relationship in patients recovering from hip fracture with a substantially increased RR (25.2, 95% CI 1.3–493.3) for lower doses (morphine dose equivalent <10 mg) compared with a lower RR (4.4, 95% CI 0.3–68.6) for higher doses (morphine dose equivalent 10–30 mg) [25]. The wide confidence intervals suggest considerable uncertainty with this result.

**Benzodiazepine medications**


There is evidence from matched analysis data derived from one moderate quality nested case–control study [24] in a mixed surgical group of patients to suggest that benzodiazepine medications may be associated with increased risk of delirium (OR 3.0, 95% CI 1.3–6.8). Longer acting benzodiazepine medications may be associated with increased risk of delirium (OR 5.4, 95% CI 1.0–29.2) compared with short-acting benzodiazepines (OR 2.6, 95% CI 1.1–6.5). Higher dose of benzodiazepine medications during a 24-h period appears to be associated with increased risk of delirium (OR 3.3, 95% CI 1.0–11.0) compared with lower doses (OR 2.6, 95% CI 0.8–9.1). Wide confidence intervals imply significant uncertainty with these results.

**Antihistamines (H₁ antagonists)**

One moderate quality case–control study [24] and one low-quality prospective cohort study [17] reported the effects of antihistamine (H₁) medications. Both studies reported data for diphenhydramine. Matched analysis data derived from the case–control study (OR 1.8, 95% CI 0.7–4.5) and multivariate data from the prospective cohort study (OR 2.1, 95% CI 0.9–5.2) suggest a trend towards increased risk of delirium with antihistamine medications.

**Histamine (H₂) antagonists**

One low-quality prospective double-blind RCT [22] compared the incidence of delirium in postoperative cardiac
Table 3. Summary of results presenting risk of delirium for medications split by dose and duration of action

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Study</th>
<th>Setting</th>
<th>Agent</th>
<th>Dose</th>
<th>Study quality</th>
<th>Type of analysis</th>
<th>Result OR/RR (95% CI)</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Morrison et al. [25]</td>
<td>Orthopaedics (Hip fracture)</td>
<td>All opioids</td>
<td>Morphine dose equivalent 10–30 mg</td>
<td>Moderate</td>
<td>Multivariate</td>
<td>RR 4.4 (0.3–68.6)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Opioids</td>
<td>Morrison et al. [25]</td>
<td>Orthopaedics (Hip fracture)</td>
<td>All opioids</td>
<td>Morphine dose equivalent &lt;10 mg</td>
<td>Moderate</td>
<td>Multivariate</td>
<td>RR 25.2 (1.3–493.3)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Marcantonio et al. [24]</td>
<td>Mixed surgical</td>
<td>All benzodiazepines</td>
<td>High dose (&gt;5 mg diazepam or dose equivalent in 24 h)</td>
<td>Moderate</td>
<td>Matched</td>
<td>OR 3.3 (1.0–11.0)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Marcantonio et al. [24]</td>
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<td>All benzodiazepines</td>
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<td>Moderate</td>
<td>Matched</td>
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<td>Moderate</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Marcantonio et al. [24]</td>
<td>Mixed surgical</td>
<td>All benzodiazepines</td>
<td>Long acting(^a)</td>
<td>Moderate</td>
<td>Matched</td>
<td>OR 5.4 (1.0–29.2)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Marcantonio et al. [24]</td>
<td>Mixed surgical</td>
<td>All benzodiazepines</td>
<td>Short acting(^b)</td>
<td>Moderate</td>
<td>Matched</td>
<td>OR 2.6 (1.1–8.5)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Antihistamine H1</td>
<td>Marcantonio et al. [24]</td>
<td>Mixed surgical</td>
<td>Diphenhydramine</td>
<td>High dose (&gt;25 mg in 24 h)</td>
<td>Moderate</td>
<td>Matched</td>
<td>OR 1.5 (0.3–6.9)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Antihistamine H1</td>
<td>Marcantonio et al. [24]</td>
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<td>Low dose (&lt;25 mg in 24 h)</td>
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<td>OR 1.5 (0.5–4.1)</td>
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</tr>
</tbody>
</table>

\(^a\)Long-acting benzodiazepines defined as chlordiazepoxide, diazepam and flurazepam.

\(^b\)Short-acting benzodiazepines defined as oxazepam, lorazepam, triazolam, midazolam and temazepam.

Discussion

Medications are an important risk factor for delirium and may be the sole precipitant for 12–29% of cases of delirium in hospitalised patients [4]. It is therefore sensible to consider the risk of using medications that are associated with delirium.

However, there are difficulties in using a cohort study design in higher risk patients in an orthopaedic hip surgery setting. There are contrasting data from prospective cohort studies and a lack of evidence from high-quality RCTs to suggest a significant increase in delirium risk with the use of haloperidol or other antipsychotics.

There is evidence from one high-quality RCT to suggest that there is a significant increase in delirium risk with the use of haloperidol or other antipsychotics [2]. However, our review has found that there is no evidence that these agents increase the risk of delirium.

It should be noted that the evidence base for the risk of delirium is attenuated by the potential for bias and confounding factors.

We have included data from high-quality prospective studies for a number of classes of medications. However, our review has found that there is no evidence that these agents increase the risk of delirium.

One possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size. A possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size. A possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size. A possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size. A possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size. A possible weakness of our review methodology is that it relied on one person identifying the studies to be included from an extensive body of literature with the potential for type II error due to small sample size.

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design to reliably demonstrate a temporal relationship between neuroleptic use and delirium. Confounding can occur when the neuroleptic is initiated for possible delirium symptoms. The evidence from the high-quality RCT indicating no association between haloperidol and risk of delirium supports the possibility that the apparent association between neuroleptics and delirium in observational studies may indeed be confounded.

There is moderate quality evidence to suggest that opioids are associated with an approximately 2-fold increased risk of delirium in medical and surgical patients, and a smaller increased risk in ICU. Pethidine appears to have a higher risk of delirium compared with other members of the opioid class. This may be because pethidine can accumulate when renal function is impaired and is converted to a metabolite with anticholinergic properties [4]. Oxycodone appears to have a favourable profile when compared with other members of the opioid class of medications. There is moderate quality evidence to suggest that in situations where acute severe pain is likely (e.g. hip fracture patients), lower doses of opioids may paradoxically be associated with higher risk of delirium, although wide confidence intervals imply uncertainty with this finding. However, these results support the concept of acute severe pain as an important contributing factor for delirium and withholding opioid medications for fear of risk of delirium is clinically inappropriate, but the lowest dose consistent with pain control should be used.

There is moderate quality evidence to support an association between benzodiazepines and increased risk of delirium. The magnitude of the risk appears to be small to moderate in size. Higher doses of benzodiazepines and agents which have a longer duration of action appear to confer a further small increase in risk. There appears to be a weak association between lorazepam and, less so, midazolam, for delirium in ICU. The caveat of an apparent association being confounded by delirium symptoms pre-dating the administration of a benzodiazepine implies caution with these conclusions.

There is low-quality evidence to suggest a small to moderate risk for nifedipine and moderate quality evidence to suggest a trend towards an association for antihistamine H1 medications.

There is low-quality evidence to suggest no associated increased risk for digoxin. The evidence for H2 antagonists, TCAs, medications used to treat Parkinson’s disease, steroids, NSAIDs and oxybutynin is of low quality and the associated risks for delirium are uncertain.

Conclusions

For people at risk of delirium, avoid new prescriptions of benzodiazepines or consider reducing or stopping these medications where possible. Opioids should be prescribed with caution in people at risk of delirium, but this should be tempered by the observation that untreated severe pain can itself trigger delirium. Caution is also required when prescribing dihydropryridines and antihistamine H1 antagonists for people at risk of delirium and considered individual patient assessment is advocated.

There remains uncertainty regarding the risk of delirium associated with H2 antagonists, TCAs, antiparkinsonian medications, steroids, NSAIDs and oxybutynin. This uncertainty reflects an evidence absence due to a paucity of methodologically rigorous, adequately powered prospective studies. An association between these medications and delirium cannot therefore be excluded with confidence. In light of this uncertainty, a judgment that incorporates the risk of delirium in each individual patient should be taken when prescription of any of these medications is considered.

Delirium occurs when a susceptible patient is exposed to often multiple precipitating factors. This makes the study of single medication factors difficult. Large, well-designed, adequately powered prospective studies that investigate the risk of delirium with different classes of medication and include multivariate analyses that control for the important confounding variables of age, dementia and illness severity are required to address the uncertainties we have identified.

Key points

- Delirium is a common clinical problem and is associated with adverse health outcomes.
- Some medications can increase the risk of delirium, but it is unclear which ones should be avoided.
- This systematic review provides an evidence hierarchy to help identify which medications to avoid in people at risk of delirium.
- Opioids, benzodiazepines, dihydropryridines and antihistamines appear to be associated with increased risk of delirium.
- There is uncertainty regarding the risk of delirium that is associated with a number of commonly prescribed medications.

Conflicts of interest

None declared.

References

Which medications to avoid in people at risk of delirium


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