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Which medications to avoid in people at risk of delirium: a systematic review

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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

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.

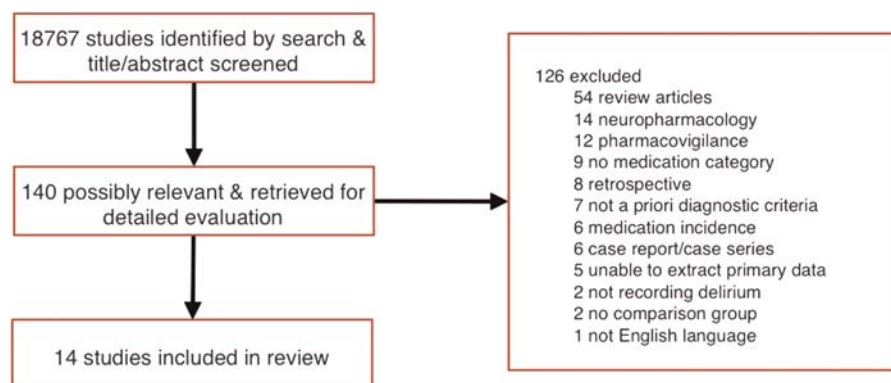


Figure 1. PRISMA flowchart

Table 1. Study summary characteristics

Study	Study design	Year	Country	Healthcare setting	Sample size	Age (mean, SD)	Patients with cognitive impairment/dementia included/excluded	Delirium cases (n)	Diagnostic criteria	Study quality
Agostini <i>et al.</i> [17]	PC	2001	USA	General Medicine	426	80.3 (5.6)	Severe dementia excluded	21	CAM	Moderate
Flacker <i>et al.</i> [18]	PC	1998	USA	General Medicine	67	86.2 (6.5)	Included	20	CAM	Potentially biased
Foy <i>et al.</i> [19]	PC	1995	Australia	General Medicine	418	70.2 (6.8)	Excluded	21	DSM III	Moderate
Gustafson <i>et al.</i> [20]	PC	1988	Sweden	Orthopaedics	111	79.3	Included	68	DSM III	Low
Kalisvaart <i>et al.</i> [21]	RCT	2005	Netherlands	Orthopaedics	430	79.6	Severe dementia excluded	68	DSM IV	High
Kim <i>et al.</i> [22]	RCT	1996	USA	ICU	111	65.9 (10.7)	Included	28	DSM III-R	Low
Lackner <i>et al.</i> [23]	RCT	2008	USA	Long-term care	50	89.2 (1.0)	Included	1	CAM	Low
Marcantonio <i>et al.</i> [24]	CC	1994	USA	Mixed surgical	1341	73 (8)	Included	91	CAM	Moderate
Morrison <i>et al.</i> [25]	PC	2003	USA	Orthopaedics	541	Not given	Included	87	CAM	Moderate
Pandharipande <i>et al.</i> [26]	PC	2006	USA	ICU	198	55.5 (17.0)	Included	Unclear	CAM-ICU	Moderate
Pisani <i>et al.</i> [27]	PC	2009	USA	ICU	304	75	Included	239	CAM-ICU	Moderate
Santos <i>et al.</i> [28]	PC	2005	Sweden	Orthopaedics	34	82.9 (6.3)	Included	19	CAM	Potentially biased
Schor <i>et al.</i> [29]	PC	1992	USA	General Med/Surgery	325	80.5	Included	91	DSM III	Moderate
van der Mast <i>et al.</i> [30]	PC	1999	Holland	Cardiac surgery	296	63	Included	40	DSM III-R	Low

RCT, randomised controlled trial; PC, prospective cohort study; CC, case-control study; CAM, confusion assessment method; DSM, Diagnostic and Statistical Manual of Mental Disorders, Version III, III-R (Revised) or IV.

Heterogeneity in study populations and methods precluded meta-analysis.

Three RCTs [21–23] presented estimates of effect size with confidence intervals or *P* values. Six prospective cohort studies [18, 25–27, 29, 30] presented the results of multivariate analyses. Three of the multivariate analyses were of moderate quality [25, 26, 29] and three low quality [18, 27, 30]. One nested case-control study [24] performed a matched analysis of control variables. Six prospective cohort studies [17–20, 28, 29] performed univariate analyses.

Medication classes

Results were found for neuroleptics [18, 20, 21, 29], opioid medications [18, 24–29], benzodiazepines [18–20, 24, 27–29], antihistamine H_1 antagonists [17, 24], histamine H_2 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

Table 2. Evidence hierarchy table summarising the risk of delirium with different medication classes and different agents within a class of medications

Medication class	Study	Setting	Agent	Type of analysis	Result OR/RR (95% CI)	Evidence quality
Neuroleptic	Kalisvaart <i>et al.</i> [21]	Orthopaedic (hip surgery)	Haloperidol	RCT	RR 0.9 (0.6–1.3)	High
	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All neuroleptics	Multivariate	OR 4.5 (1.8–10.5)	Moderate
Opioid	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All opioids	Multivariate	OR 2.5 (1.2–5.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	All opioids	Matched	OR 1.4 (0.5–4.3)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Fentanyl	Multivariate	OR 1.2 (1.0–1.5)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Morphine	Multivariate	OR 1.1 (0.9–1.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Meperidine (pethidine)	Matched	OR 2.7 (1.3–5.5)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Morphine	Matched	OR 1.2 (0.6–2.4)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Fentanyl	Matched	OR 1.5 (0.6–4.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Oxycodone	Matched	OR 0.7 (0.3–1.6)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Codeine	Matched	OR 1.1 (0.4–3.6)	Moderate
Benzodiazepine	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	Matched	OR 3.0 (1.3–6.8)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Lorazepam	Multivariate	OR 1.2 (1.1–1.4)	Moderate
	Pandharipande <i>et al.</i> [26]	ICU	Midazolam	Multivariate	OR 1.7 (0.9–3.2)	Moderate
Antihistamine (H ₁)	Marcantonio <i>et al.</i> [24]	Mixed surgical	Diphenhydramine	Matched	OR 1.8 (0.7–4.5)	Moderate
Dihydropyridine	van der Mast <i>et al.</i> [30]	Cardiac surgery	Nifedipine	Multivariate	OR 2.4 (1.0–5.8)	Low
H ₂ Antagonist	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All H ₂ antagonists	Univariate	OR 1.4 (0.8–2.5)	Low
Cardiac glycoside	Schor <i>et al.</i> [29]	Mixed medicine/surgery	Digoxin	Univariate	OR 0.5 (0.3–0.9)	Low
Steroid	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All steroids	Univariate	OR 0.5 (0.2–1.7)	Low
NSAIDs	Schor <i>et al.</i> [29]	Mixed medicine/surgery	All NSAIDs	Univariate	OR 0.4 (0.1–1.5)	Low
Tricyclic antidepressant	Gustafson <i>et al.</i> [20]	Orthopaedic (hip fracture)	All tricyclic antidepressants	Univariate	RR 1.7 (1.4–2.1)	Very low
Antiparkinson	Gustafson <i>et al.</i> [20]	Orthopaedic (hip fracture)	Antiparkinson	Univariate	RR 1.3 (0.9–1.7)	Very low

Following a sensitivity analysis, only higher quality evidence has been included for each class of medication where possible.

H₁, histamine 1 receptor; H₂, histamine 2 receptor; NSAID, non-steroidal anti-inflammatory drug; TCA, tricyclic antidepressant; ICU, intensive care unit; RR, risk ratio; OR, odds ratio; CI, confidence interval.

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

Six of the seven studies investigating benzodiazepines described methods consistent with an attempt to identify a temporal relationship between medication prescription and delirium [18–20, 24, 27, 29]. Two studies [19, 24] assessed a dose–response relationship for benzodiazepines. Two studies [24, 29] assessed delirium rates with short-acting versus long-acting 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

Medication class	Study	Setting	Agent	Dose	Study quality	Type of analysis	Result OR/RR (95% CI)	Evidence quality
Opioids	Morrison <i>et al.</i> [25]	Orthopaedics (Hip fracture)	All opioids	Morphine dose equivalent 10–30 mg	Moderate	Multivariate	RR 4.4 (0.3–68.6)	Moderate
	Morrison <i>et al.</i> [25]	Orthopaedics (Hip fracture)	All opioids	Morphine dose equivalent <10 mg	Moderate	Multivariate	RR 25.2 (1.3–493.3)	Moderate
Benzodiazepines	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	High dose (≥ 5 mg diazepam or dose equivalent in 24 h)	Moderate	Matched	OR 3.3 (1.0–11.0)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	Low dose (≤ 5 mg diazepam or dose equivalent in 24 h)	Moderate	Matched	OR 2.6 (0.8–9.1)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	Long acting ^a	Moderate	Matched	OR 5.4 (1.0–29.2)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	All benzodiazepines	Short acting ^b	Moderate	Matched	OR 2.6 (1.1–8.5)	Moderate
Antihistamine H ₁	Marcantonio <i>et al.</i> [24]	Mixed surgical	Diphenhydramine	High dose (≥ 25 mg in 24 h)	Moderate	Matched	OR 1.5 (0.3–6.9)	Moderate
	Marcantonio <i>et al.</i> [24]	Mixed surgical	Diphenhydramine	Low dose (≤ 25 mg in 24 h)	Moderate	Matched	OR 1.5 (0.5–4.1)	Moderate

H₁, histamine H₁ receptor; RR, risk ratio; OR, odds ratio.^aLong-acting benzodiazepines defined as chlorthalidoxepoxide, diazepam and flurazepam.^bShort-acting benzodiazepines defined as oxazepam, lorazepam, triazolam, midazolam and temazepam.

surgery patients treated with cimetidine versus ranitidine and found no significant difference ($P < 0.05$) in rates of delirium for patients prescribed either medication. One moderate quality prospective cohort study [29] reported univariate data that indicated a small, non-significant trend towards increased delirium risk with H₂ antagonists (OR 1.4, 95% CI 0.8–2.5).

Medication classes with data from single studies

One low-quality prospective cohort study of cardiac surgery patients [30] reported multivariate data for nifedipine and suggested increased risk of delirium (OR 2.4, 95% CI 1.0–5.8). Univariate data from one moderate quality study [29] suggest that digoxin (OR 0.5, 95% CI 0.3–0.9) does not appear to be associated with significant risk of delirium. Univariate data from one low-quality prospective cohort study [20] suggests that tricyclic antidepressants (TCAs) may be associated with increased risk of delirium (RR 1.7, 95% CI 1.4–2.1). Univariate data from the same low-quality study suggest that there is no significant association between antiparkinson medications and delirium (RR 1.3, 95% CI 0.9–1.7) [20]. There is uncertainty regarding the association of steroids (OR 0.5, 95% CI 0.2–1.7) [29] and NSAIDs (OR 0.4, 95% CI 0.1–1.5) [29] with delirium. One low-quality RCT [23] compared oxybutinin with placebo and found no significant difference in delirium rates between the two study arms ($P < 0.05$). There was only one case of delirium recorded in this study and firm conclusions should not be drawn from this result.

Discussion

Medications are an important risk factor for delirium and may be the sole precipitant for 12–39% of cases of delirium [4]. It is therefore sensible to conduct a drug review for patients at risk of delirium. Ideally, such a review should be informed by an evidence base that identifies those agents at highest associated risk for delirium. However, our review has found that there is a paucity of data from higher quality prospective studies for a number of classes of medication. Of note is the general absence of *a priori* power calculations to inform sample size estimates 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 attendant risk of excluding some relevant studies. Only cautious inferences are therefore possible.

There is evidence from one high-quality RCT to suggest no increased incidence of delirium with the use of haloperidol in higher risk patients in an orthopaedic hip surgery setting. There are contrasting data from prospective cohort studies to suggest the presence of an association between the use of neuroleptics and increased risk of delirium. However, there are difficulties in using a cohort study

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 dihydropyridines 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, dihydropyridines 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.

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