Association Between Psychoactive Medications and Delirium in Hospitalized Patients: A Critical Review

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Psychoactive medications are often reported as delirium risk factors in hospitalized patients, and delirium induced by medication is potentially avoidable. The authors critically reviewed the evidence for a role of medications in delirium etiology. Only a few positive associations were noted. Use of psychoactive medications, considered together as a single variable, and use of opioids increased the risk of delirium. Data were scarce and sometimes conflicting, and methodological limitations were often present. The suspected association between psychoactive drugs and delirium cannot be unambiguously confirmed with current epidemiological evidence. The interpretation of these results must take into account the limitations of published studies, which should be addressed in future research. (Psychosomatics 2005; 46:302–316)

Delirium is a frequent psychiatric syndrome in hospitalized patients in medicine, surgery, intensive care, geriatrics, and oncology services, with incidence ranging from 7% to 87%.[1–8] Methodological differences in study design, as well as in the criteria used to assess delirium status and characteristics of the populations studied, partly explain this variation. Furthermore, not all studies addressed the fluctuating nature and the sudden emergence of delirium by enhancing sensitivity of detection by performing more frequent assessments of delirium status, for instance.

Risk factors for delirium identified mostly in patients in surgical and medical services but also in oncology and intensive care patients include prior/present cognitive impairment,[6,8–13] metabolic abnormalities,[4,6,8,9,11,14] use of psychoactive medications,[4,9,10,13–15] and advanced age.[10,11,13] Among the numerous risk factors for delirium, very few appear to be consistent.[16] Still, commonly prescribed psychoactive medications, such as opioid analgesics, benzodiazepines, and corticosteroids, are repeatedly identified as significant contributors to delirium.[17–22]

Delirium is typically multifactorial in etiology, and a medication in isolation may not cause delirium, but the cumulative effect of medication(s) plus other risk factors (e.g., advanced age, infection, metabolic abnormalities, etc.) may lead to delirium. Risk factors such as hearing, visual, or cognitive impairment are modifiable, but only modest change is possible, and the interventions are rather onerous.[3] On the other hand, risk associated with specific drug classes can be specifically targeted in the therapeutic management of patients, for example, by reducing the medication and/or choosing an alternative medication.

Data about drug-induced delirium have been collected through numerous case reports but from fewer prospective or retrospective studies. Case reports are regularly pub-

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lished to document adverse effects of new molecules, but they do not permit determination of the frequency and importance of adverse effects such as delirium. On the basis of case reports, most drug classes and countless individual drugs have been implicated in secondarily causing psychotic symptoms and/or cognitive impairment.[23,24]

A second method of examining involvement of medication in delirium induction is to review individual cases and to identify, for each case, potential causes for delirium according to defined criteria, ensuring that important causal characteristics were present before delirium occurred (for instance, ensuring that drug exposure preceded delirium onset).[9] According to these studies, psychoactive medications appear to be a frequent cause of delirium, as they were involved in the etiology of 15%–75% of delirium cases (Table 1).[9,14,25–30] However, drugs were a definite delirium cause in only 2%–14% of delirium cases in the studies that included a *definite cause* category in the analysis.[9,25,30] More specifically, opioids, corticosteroids, and benzodiazepines were major contributors to delirium in several studies (Figure 1), although quantifying this effect by using data from studies that examined medication in terms of a potential delirium cause is difficult. Other medications, such as anticholinergics, nonsteroidal anti-inflammatory agents (NSAIDs), and chemotherapeutic agents, were also identified as causes of delirium.

A major limitation of this method is the lack of a control group; thus, the number of patients in which potential

TABLE 1. Characteristics of Eight Case-Series Studies of Medication Involvement in Delirium Etiology

Study	Subjects	Total N	N With Delirium	Delirium Criteria	Prospective Study Design	Causal Criteria Specified	Proportion of Delirium Cases With Medication Involvement[a]
Breitbart et al. 2002[26]	Oncology patients	101	101	DSM-IV	Yes	No	Corticosteroids: 27.7%, opioids: 58.4%
Morita et al. 2001[29]	Oncology patients	237	153	DSM-IV	Yes	Yes	Medication (all)[b]: 25%, opioids: 21%, psychotropics: 4%, others: 4%
Tuma and DeAngelis 2000[30]	Oncology patients age ≥18 years	140	140	DSM-III-R	Yes	Yes	Medications (all): 64%[c], anticholinergics: 6%, anticonvulsants: 6%, antihistamines: 4%, benzodiazepines: 24%, corticosteroids: 21%, histamine type 2 antagonists: 19%, opioids: 54%
Brauer et al. 2000[25]	Surgery patients age ≥50 years	571	54	Confusion Assessment Method	Yes	Yes	Medications (all): 35%[d]
Lawlor et al. 2000[14]	Oncology patients	104	71	DSM-IV	Yes	Yes	Psychoactive medications (all)[e]: 75%, opioids: 76%, nonopioids: 21%
O'Keeffe and Lavan 1999[28]	Geriatrics patients	225	94	Delirium Assessment Scale	Yes	Yes	Drug toxicity (all)[f]: 15%
Olofsson et al. 1996[27]	Oncology patients	705	90	Delirium Rating Scale	No	No	Psychotropic medications[g]: 19%, chemotherapy: 8%, corticosteroids: 5.5%, opioids:13%
Francis et al. 1990[9]	Medicine patients age ≥70 years	229	50	DSM-III-R	Yes	Yes	Medications (all): 50%[h], anticholinergics: 14%, benzodiazepines: 14%, nonsteroidal anti-inflammatories: 6%, opioids: 18%

[a]If proportions were not reported in the original article, they were calculated for comparison purposes by dividing the number of cases in which the particular medication was associated with delirium by the number of delirium cases.

[b]Medications included opioids (morphine, buprenorphine, pentazocine, fentanyl), psychotropics (haloperidol, prochlorperazine, promethazine, methylphenidate, hydroxyzine, phenobarbiturate), and others (ketamine, carbamazepine, lidocaine, digitalis, betamethasone, metoclopramide).

[c]Medications (opioids, corticosteroids, benzodiazepines, histamine type 2 antagonists, antihistamines, anticholinergics, or anticonvulsants) were identified as a definite, probable, possible, or contributory cause. Medications were identified as a definite cause in 4% of cases.

[d]Medications (e.g., sedatives, hypnotics, narcotics, anticholinergics) were identified as a definite, probable, possible, or comorbid cause. Medications were identified as a definite cause in 2% of cases.

[e]Psychoactive medications included opioids (in subcutaneous morphine equivalents daily doses) and nonopioids (methylphenidate hydrochloride, methotrimeprazine, anticholinergics, selective serotonin reuptake inhibitors, theophylline, tricyclics, benzodiazepines, haloperidol decanoate).

[f]Drug toxicity was defined according to the definition of Francis et al.[9]

[g]Psychotropic medications included benzodiazepines and anticholinergic agents and excluded opioids, corticosteroids, and chemotherapy (methotrexate, cytarabine, cytokines).

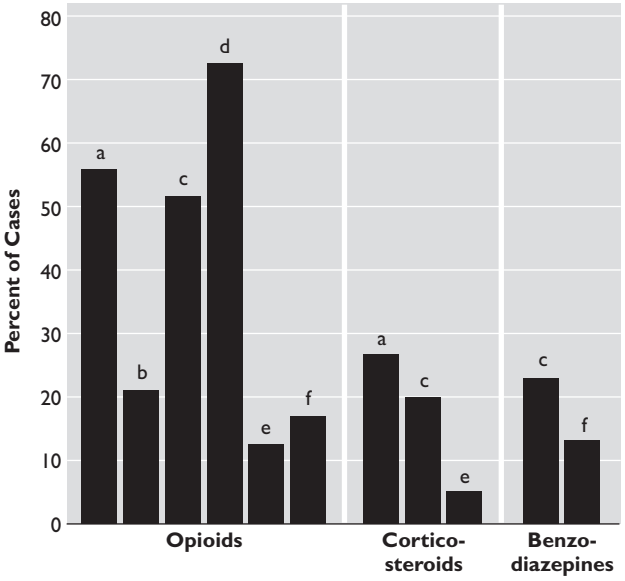
[h]Medication was identified as a definite, probable, possible, or comorbid cause. Medications were identified as a definite cause in 14% of cases.

delirium causes were identified and who became delirious cannot be compared with the number of patients in which the same potential delirium causes were present but who never became delirious. Nevertheless, this design can provide possible directions for ulterior prospective epidemiological studies.

A third approach in investigation of drug-induced delirium is to conduct prospective observational studies—cohort studies and nested case-control studies—examining the contribution of medication, among other factors, to an increase (or decrease) in the risk of delirium. Nested case-control studies are case-control studies conducted in a well-defined cohort. Observational studies can allow for the control of potential confounders to a greater extent, compared with case reports and case series, although to a lesser extent than in randomized controlled trials, which for ethical reasons can obviously not be used to study the propensity of drugs to cause delirium.

To our knowledge, neither meta-analyses nor systematic reviews examining specifically the relationship between psychoactive drug exposure and risk of delirium in hospitalized patients have been carried out. The objectives of the study reported here were to 1) summarize the available evidence and 2) identify potential methodological shortcomings of studies examining the relationship between exposure to psychoactive medications and risk of delirium in hospitalized patients.

FIGURE 1. Delirium Cases Potentially Caused by Opioids, Corticosteroids, and Benzodiazepines in Six Case-Series Studies



[a]Breitbart et al. 2002[26]
[b]Morita et al. 2001[29]
[c]Tuma and DeAngelis 2000[30]
[d]Lawlor et al. 2000[14]
[e]Olofsson et al. 1996[27]
[f]Francis et al. 1999[9]

METHOD

Source of Data

A computerized search for English-language journal articles in MEDLINE (January 1975–October 2003) was performed by using Medical Subject Headings (MeSH) and free text search terms related to both delirium and medication (Figure 2).

Three search strings were combined by using the Boolean operator "AND." Case reports and studies about delirium tremens were excluded from the results (*case report* as a MeSH term, *"delirium tremens"* in any field). The MEDLINE database was last accessed on October 20, 2003. In addition, articles were identified by checking references of pertinent articles and through personal communication with colleagues.

Study Selection and Data Extraction

Since obviously no randomized trial has examined the propensity of psychoactive drugs to cause delirium, we selected all prospective observational studies (cohort and nested case-control studies) that examined medication as a risk factor for delirium. The inclusion criteria for studies were 1) selection of hospitalized patients; 2) assessment of delirium with a validated delirium diagnostic instrument, operationalized diagnostic criteria (DSM criteria), or formal psychiatric assessment; and 3) provision of enough statistical data to compare psychoactive medication users with nonusers (estimates of relative risk, Student t tests). Using a standardized form, two reviewers independently evaluated the potential eligible studies. Disagreements were resolved by consensus. If no consensus was reached, the opinion of a third reviewer was decisive. We extracted reported statistics with 95% confidence intervals (CIs) or p values if CIs were not provided or could not be computed by using the available data.

Criteria Used to Appraise Studies

We systematically reviewed the information included in the studies selected according to five groups of criteria: sample and power, the independent variable (medication

exposure), the dependent variable (delirium), control of confounding, and statistical analyses (Figure 2). These criteria were to a large extent based on recommendations for evaluation of observational studies.[31–35] Additional details are available upon request.

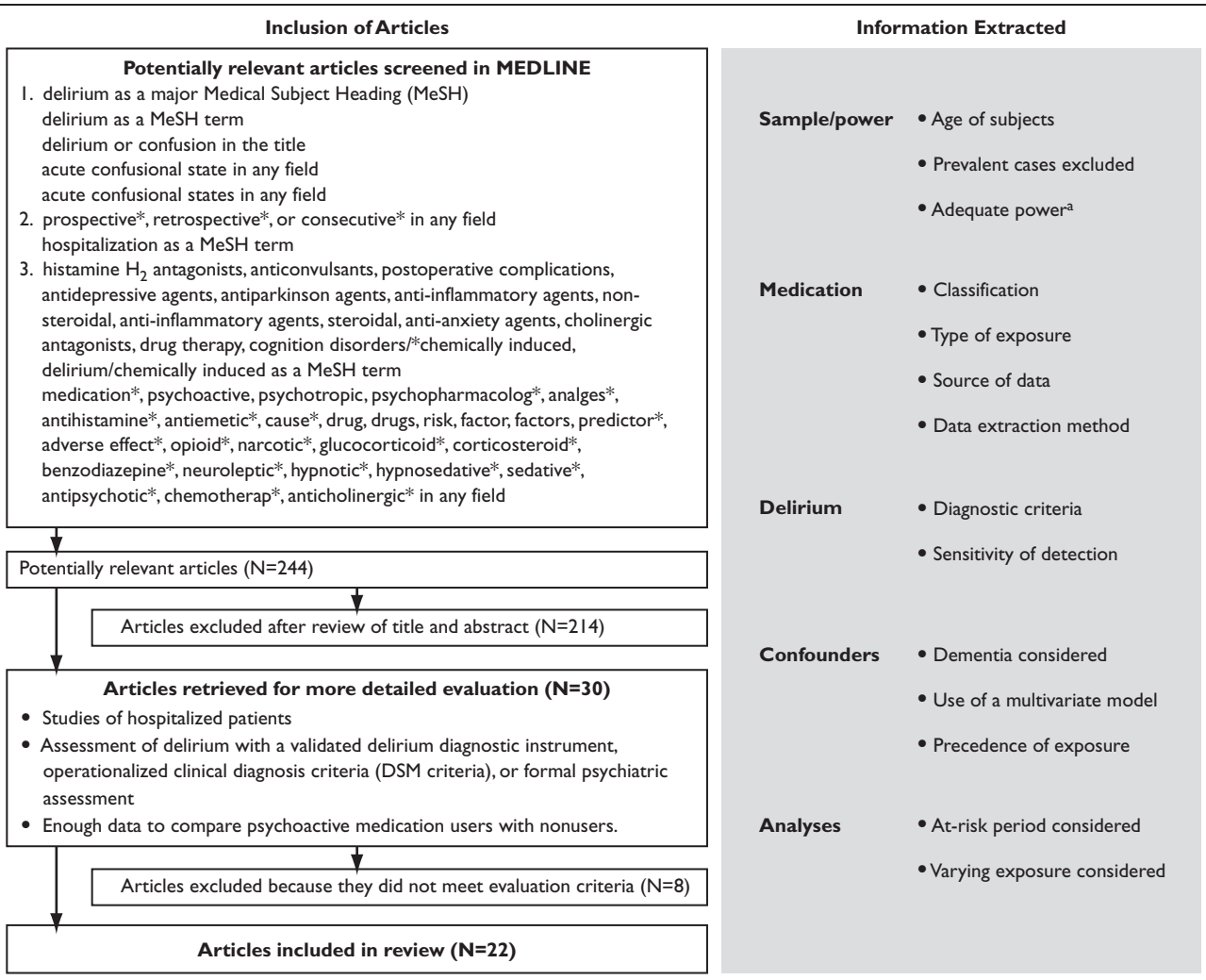
Data Synthesis

Because of important clinical heterogeneity (different psychoactive drug types) and methodological heterogeneity (differences in study types, effect measures, assessments of exposure, types and windows of exposure, confounding factors controlled for, missing data), the data from studies included in the review could not be pooled, and a detailed systematic review was performed.

RESULTS

Of the 244 potentially relevant articles identified in our search, 30 were considered in depth for inclusion, but eight

FIGURE 2. Article Retrieval Procedure and Information Extracted From Studies of the Association Between Psychoactive Medications and Delirium



[a] Given missing frequencies (missing tables of frequencies, missing data for variables with nonsignificant associations) that could not be determined from the data presented in the original articles, a standard assessment of power could not be performed. We calculated the power of studies to observe an odds ratio of 3.0 by using their sample size and delirium prevalence, for a conservative probability of exposure in controls (50%) and for independent and unequal case and control groups, had the designs and analyses been uniform. The minimal detectable odds ratio was calculated by assuming an alpha level of 0.05 (two-sided) and a power of 80%. Studies having a power of less than 80% to observe an odds ratio greater than 3.0 were arbitrarily determined to present a potential lack of power.

TABLE 2. Description and Quality Assessment of Studies Included in a Systematic Review of the Association Between Psychoactive Medications and Delirium in Hospitalized Patients

Study Type and Study	Subjects, N Cases/N Controls, Incidence of Delirium	Diagnosis of Delirium	Medication Exposure		Positive Findings[a]	Factors Adjusted for or Matched
			Medications, Source of Medication Data, Method of Data Extraction	Type and Window of Medication Exposure		
Cohort studies						
Ljubisavljevic and Kelly 2003[47]	Oncology patients; 19/103; 16%	Delirium criteria: Confusion Assessment Method; daily assessment 7 days/week; enhanced detection methods: evening evaluation	Benzodiazepines, corticosteroids, opioids (no details for individual agents); source of data not specified; no details about data extraction	Cumulative daily dose at admission (benzodiazepines, opioids)[b]; study ensured that medication exposure preceded delirium	None	N.A.
Schuurmans et al. 2003[45]	Surgery patients age ≥70 years; 18/74; 20%	Delirium criteria: DSM-IV; assessment at irregular intervals; enhanced detection methods: screening procedure	Psychoactive medications (no details for individual agents); data from patient/relative interview; data extracted by research nurse	Use of medication prehospitalization; study ensured that medication exposure preceded delirium	None	N.A.
Morrison et al. 2003[12]	Surgery patients; 87/454; 16%	Delirium criteria: Confusion Assessment Method; daily assessment 5 days/week; enhanced detection methods: delirium key word search, interview with hospital staff	Opioids (no details for individual agents); data from medical records; no details about data extraction	Cumulative daily dose in the 24 hours predelirium (cases) versus highest dose on postoperative days 1–3 (control subjects); study ensured that medication exposure preceded delirium	Opioids dose <10 mg[c]: relative risk = 5.4, 95% CI = 2.4–12.3	All variables with $p<0.15$ in univariate comparisons
Fann et al. 2002[8]	Oncology patients; 49/41; 54%	Delirium criteria: Delirium Rating Scale; assessment three times per week; enhanced detection methods: delirium key word search, interview with hospital staff	Benzodiazepines, opioids (no details for individual agents); data from medical records; no details about data extraction	Use of medication pretransplantation; study ensured that medication exposure preceded delirium	None	N.A.
Wakefield 2002[51]	Male geriatrics patients age ≥65 years; 16/111; 14%	Delirium criteria: Neelon-Champagne Confusion Scale; daily assessment on days 1–8; no enhanced detection methods	Psychoactive medications (no details for individual agents); data from medication records; no details about data extraction	Use of medication at admission; not specified whether study ensured that medication exposure preceded delirium	None	N.A.
Dubois et al. 2001[4]	Intensive care patients age ≥18 years; 38/160; 19%	Delirium criteria: formal psychiatric criteria; assessment at irregular intervals; enhanced detection method: screening procedure	Antipsychotics, benzodiazepines, corticosteroids, opioids; partial details for antipsychotics, benzodiazepines, opiods; source of data not specified; no details about data extraction	Cumulative daily dose (benzodiazepines, opioids)[d], mean dose in delirium phase (cases) versus mean dose days 1–5 (control subejcts); study did not ensure that medication exposure preceded delirium	Opioids dose 0.01–7.1 mg: odds ratio = 7.8, 95% CI = 1.76–34.4; opioids dose 7.2–18.6 mg: odds ratio = 9.2, 95% CI = 2.17–39.0; opioids dose 18.7–331.6 mg: odds ratio = 6.0, 95% CI = 1.41–25.4	All variables with $p<0.15$ in univariate comparisons

Galanakis et al. 2001[6]	Surgery patients age ≥60 years; 25/80; 24%	Delirium criteria: Confusion Assessment Method; daily assessment on days 1–7; enhanced detection method: interview with hospital staff	Psychoactive medications (no details on individual agents); data from medication records; no details about data extraction	Use of medication preadmission; study ensured that medication exposure preceded delirium	None	N.A.
Litaker et al. 2001[13]	Surgery patients age ≥50 years; 57/443; 11%	Delirium criteria: DSM-IV; daily assessment on days 1–4; enhanced detection methods: delirium key word search, screening procedure	Benzodiazepines, opioids (no details on individual agents); data from current medication list; no details about data extraction	Use of medication in preoperative period; study ensured that medication exposure preceded delirium	Opioid use: odds ratio = 2.7, 95% CI = 1.4–5.3	All variables with $p<0.15$ in univariate comparisons
Dai et al. 2000[53]	Surgery patients age ≥65 years; 36/665; 5%	Delirium criteria: DSM-IV; assessment at irregular intervals; enhanced detection methods: delirium key word search, screening procedure	Psychoactive medications; details provided for individual agents; source of data not specified; no details about data extraction	Use of medication[e] during hospitalization; not specified whether study ensured that medication exposure preceded delirium	Psychoactive medication use: odds ratio = 6.56, 95% CI = 1.53–28.17	All variables with $p<0.15$ in univariate comparisons
Martin et al. 2000[54]	Medicine-surgery patients age ≥65 years; 28/128; 18%	Delirium criteria: Confusion Assessment Method; daily assessment; enhanced detection methods: delirium key word search, screening procedure	Psychoactive medications, anticholinergics, antipsychotics, benzodiazepines, histamine type 2 (H_2) antagonists, opioids (no details on individual agents); source of data not specified; no details about data extraction	Use of medication predelirium (cases) versus during hospitalization (control subjects); study ensured that medication exposure preceded delirium	Number of psychoactive medications: odds ratio = 1.23, 95% CI = 1.01–1.49	All variables with $p<0.10$ in univariate comparisons
Henon et al. 1999[46]	Stroke patients age ≥40 years; 49/153; 24%	Delirium criteria: DSM-IV; assessment at irregular intervals; no enhanced detection methods	Psychoactive medications (no details on individual agents); source of data not specified; no details about data extraction	Use of medication during hospitalization; study did not ensure that medication exposure preceded delirium	None	N.A.
Lynch et al. 1998[55]	Surgery patients age ≥50 years; 34/327; 9%	Delirium criteria: Confusion Assessment Method[f]; daily assessment on days 1–3; enhanced detection methods: delirium key word search, screening procedure	Opioids (no details on individual agents); data from medical records; no details about data extraction	Cumulative daily dose on day with delirium (cases) versus dose for corresponding day (control subjects); study did not ensure that medication exposure preceded delirium	None	N.A.
Inouye and Charpentier 1996[56]	Medicine patients age ≥70 years; 35/161; 18%	Delirium criteria: Confusion Assessment Method; assessment every 48 hours on days 1–9; enhanced detection methods: delirium key word search, interview with hospital staff	Psychoactive medications, anticholinergics, anticonvulsants, antiemetics, antipsychotics, benzodiazepines, H_2 antagonists, opioids (no details on individual agents); data from medical records; data extracted by trained researchers	Use of medication[g] on days 1–9 ≤24 hours predelirium (cases) and days 1–9 (control subjects); study ensured that medication exposure preceded delirium	More than three psychoactive medications added: relative risk = 2.9, 95% CI = 1.6–5.4	11 variables optimal for four axes based on selection criteria (clinical relevance: relative risk≥1.5, $p<0.10$)

TABLE 2. *Continued*

Foy et al. 1995[48]	Medicine patients age 60 years; 21/397; 5%	Delirium criteria: DSM-III-R; assessment every 48–72 hours on days 1–10; enhanced detection methods: delirium key word search, interview with hospital staff	Benzodiazepines (details provided for individual agents); data from interviews with patients; no details about data extraction	Use of medication 5 days preadmission; study ensured that medication exposure preceded delirium	None	N.A.
Marcantonio et al. 1994[11]	Surgery patients age ≥50 years; 78/798; 9%	Delirium criteria: Confusion Assessment Method[f]; daily assessment on days 2–5; enhanced detection methods: delirium key word search, screening procedure	Psychoactive medications (no details about individual agents); source of data not specified; no details about data extraction	Use of medication[e] during preoperative period; study ensured that medication exposure preceded delirium	None	N.A.
Inouye et al. 1993[44]	Medicine patients age ≥70 years; 27/80; 25%	Delirium criteria: Confusion Assessment Method; daily assessment; enhanced detection methods: delirium key word search, interview with hospital staff	Anticholinergics, benzodiazepines, opioids (no details about individual agents); data from medical records; no details on data extraction	Use of medication[h] at admission; study ensured that medication exposure preceded delirium	None	N.A.
Schor et al. 1992[10]	Medicine-surgery patients age ≥65 years; 91/200; 31%	Delirium criteria: Delirium Symptom Interview; daily assessment on days 1–14; enhanced detection methods: delirium key word search, interview with hospital staff	Anticholinergics, antipsychotics, benzodiazepines, corticosteroids, H_2 antagonists, nonsteroidal anti-inflammatories, opioids (no details on individual agents); data from nursing medication records; no details on data extraction	Use of medication[i] predelirium (cases) versus during hospitalization (control subjects); study ensured that medication exposure preceded delirium	Antipsychotic use: odds ratio = 4.48, 95% CI = 1.82–10.45; opioid use: odds ratio = 2.54, 95% CI = 1.24–5.18	All variables with $p<0.10$ after adjustment for age and sex
Francis et al. 1990[9]	Medicine patients age ≥70 years; 50/176; 22%	Delirium criteria: DSM-III-R; assessment every 48 hours; enhanced detection methods: delirium key word search, interview with hospital staff	Psychoactive medications, anticholinergics (no details on individual agents); data source not specified, no details on data extraction	Use of medication during hospitalization; study did not ensure that medication exposure preceded delirium	Psychoactive medication use: odds ratio = 3.9, 95% CI = 1.4–10.8	All variables with $p<0.05$ in univariate comparisons
Rogers et al. 1989[49]	Surgery patients age ≥60 years; 13/33; 28%	Delirium criteria: DSM-III; one assessment on day 4; no enhanced detection methods	Psychoactive medications, opioids (details provided for individual psychoactive medications); data from medical records; data extraction by blinded researchers	Use of medication[j] during postoperative days 1–4; study did not ensure that medication exposure preceded delirium	Psychoactive medication use: odds ratio = 12.2, 95% CI = 2.4–60.8	Nine variables selected on the basis of data distributions and univariate comparisons

Gustafson et al. 1988[50]	Surgery patients age ≥65 years; 68/43; 61%	Delirium criteria: DSM-III; assessment at irregular intervals; enhanced detection method: screening procedure	Anticholinergics, antiparkinsonians, antidepressans, antipsychotics, benzodiazepines (no details on individual agents); data source not specified; no details on data extraction	Use of medication during hospitalization; study did not ensure that medication exposure preceded delirium	None	N.A.
Nested case-control studies						
Duppils and Wikblad 2000[52]	Surgery patients age ≥65 years; 45/45[k]; 20%	Delirium criteria: DSM-IV; assessment at irregular intervals; enhanced detection method: screening procedure	Psychoactive medications (no details on individual agents); data from medical records; no details on data extraction	Use of medication at admission; study ensured that medication exposure preceded delirium	None	N.A.
Marcantonio et al. 1994[15]	Surgery patients age ≥50 years; 91/154; —	Delirium criteria: Confusion Assessment Method[f]; daily assessment on days 2–5; enhanced detection methods: delirium key word search, screening procedure	Anticholinergics, benzodiazepines, opioids (details provided for individual benzodiazepines and opioids); data from nursing dedication records; data extracted by blinded and trained researchers	Use of medication[l] in 24 hours predelirium (cases) versus corresponding period (control subjects); study ensured that medication exposure preceded delirium	Benzodiazepine use: odds ratio = 3.0, 95% CI = 1.3–6.8	Seven independent preoperative risk factors identified elsewhere[11] from multivariate analyses

[a]Positive findings are those in which the association between medication exposure and the occurrence of delirium is significant ($p<0.05$). Unless specified otherwise, estimates of relative risk compare medication users versus nonusers. If not provided in the original article, relative risk estimates and 95% confidence intervals (CIs) were calculated from raw data in the original article. If neither 95% CIs nor p values were provided in the original article, 95% CIs were calculated from raw data in the original article.

[b]For corticosteroids, exposure was defined as use (yes/no) on admission.

[c]Reference dose presented in the original article was >30 mg morphine; 0 mg (no opioid exposure) was assimilated to the low-dose category.

[d]For antipsychotics and corticosteroids, exposure was defined as use (yes/no) during the intensive care unit stay.

[e]In addition, the mean number of medications for delirious versus nondelirious patients was compared.

[f]The diagnosis of delirium was made either with the Confusion Assessment Method or on the basis of delirium key words in both the medical record and hospital's nursing intensity index (MEDICUS) on the same day.

[g]The variables were the addition of two or more psychoactive medication types or the addition of more than three psychoactive medication types during the 24–48 hours before the onset of delirium.

[h]In addition, the study assessed the number of admission medications as a continuous variable.

[i]For anticholinergics, in addition to a dichotomous exposure, the total number of standard doses received by each patient was tallied as a continuous variable.

[j]For opioids, exposure was defined as receiving more than 80 mg of morphine equivalents over the 4 postoperative days. The reference category was defined as receiving less than 80 mg.

[k]The 45 matched control subjects were selected among 180 nondelirious patients.

[l]For benzodiazepines and anticholinergics, the low-dose variable was defined as one standard therapeutic dose or less, and the high-dose variable was defined as a higher amount, given in either single or multiple doses.

were excluded because they did not meet the inclusion criteria[36–43] (Figure 2). Twenty-two studies[4,6,8–13,15,44–56] met all inclusion criteria. Agreement between the two reviewers for study eligibility was high ($\kappa = 0.91$). Among the 22 studies, 20 were cohort studies[4,6,8–13,44–51,53–56] and two were nested case-control studies, one[52] matching a control group of nonconfused patients to delirium patients within the study and the other[15] deriving samples of affected patients and control patients from the patients in a cohort study that was also included in the review[11] (Table 2).

Thirteen studies were conducted in surgical (N = 11) or medical-surgical (N = 2) services. Others were conducted in medicine (N = 4), oncology (N = 2), geriatrics (N = 1), stroke (N = 1), and intensive care populations (N = 1). The number of delirium cases per study varied from 13 to 91, and the total number of patients from 46 to 701. Delirium incidence ranged from 5% to 61%.

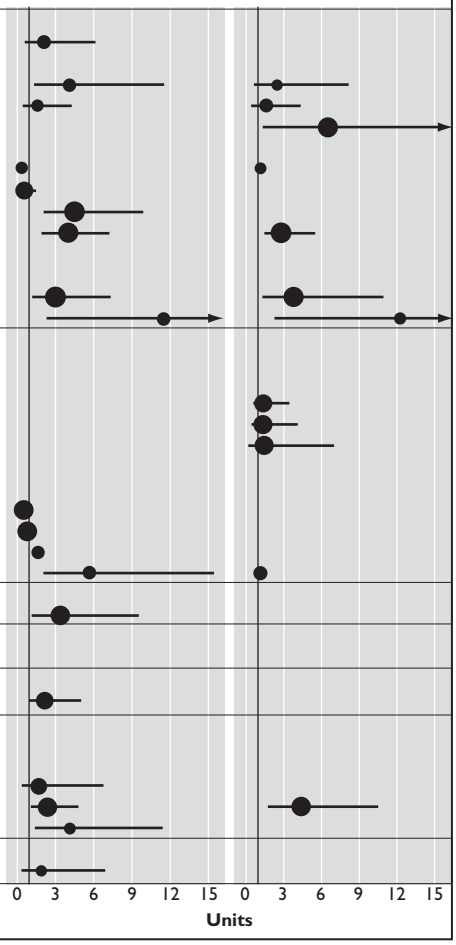
Study Appraisal

Sample and Power Most studies (N = 17) restricted the sample to elderly patients, generally age 50 years or older (Table 2). In several studies (N = 15), the mean age of the subjects was above 70 years.[6,9,10,12,15,44–46,48,50–54,56] Most studies (N = 16) excluded prevalent delirium cases.[4,6,10–13,15,44,45,48,51–56] On the basis of our simple and indulgent analysis of power, 11 studies had a potential lack of power to detect associations.[6,8,44,45,47–52,54]

Medication Psychoactive drugs studied included anticholinergics, anticonvulsants, antiparkinsonians, antiemetics, antidepressants, antipsychotics, benzodiazepines, corticosteroids, histamine type 2 (H_2) antagonists, NSAIDs, and opioid analgesics. Six studies[4,12,15,48,49,53] provided at least

FIGURE 3. Effect Estimates For Studies of the Association Between Psychoactive Medications and Delirium, by Type of Medication[a]

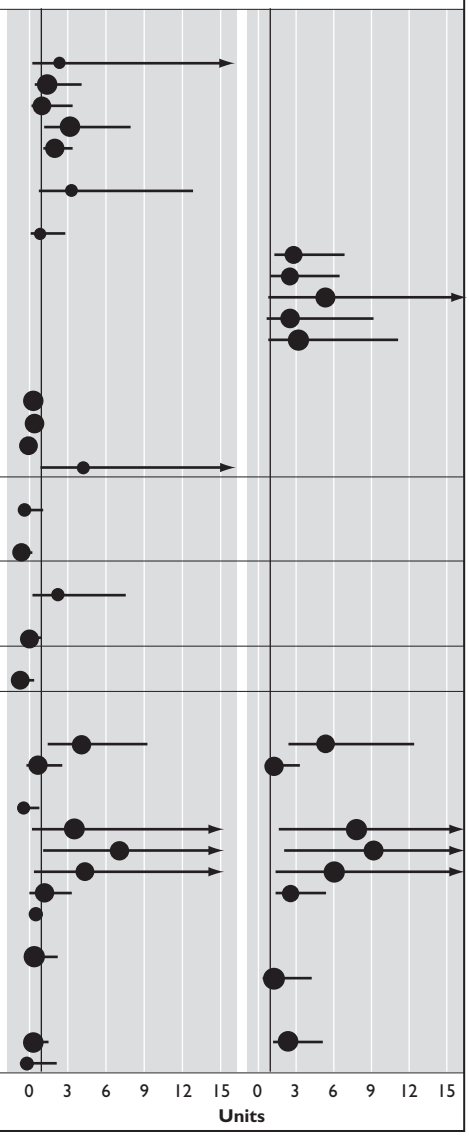
Study	Year	Medication and Variable Examined	Crude Estimate	95% CI	Adjusted Estimate	95% CI
Any psychiatric medication						
Schuurrnans et al. (45)	2003	Use	2.2	0.77–6.18		
Wakefield (51)	2002	Use	—			
Galanakis et al. (6)	2001	Use	4.18	1.50–11.62	2.53	0.79–8.04
Duppils and Wikblad (52)	2000	Use	1.6	0.61–4.30	1.63	0.61–4.3
Dai et al. (53)	2000	Use	—		6.56	1.53–28.17
Dai et al. (53)	2000	Mean N used	—	p<0.001(t test)		
Martin et al. (54)	2000	N used, continued	0.4		1.23	1.01–1.49
Hénon et al. (46)	1999	Use	0.82	0.42–1.62		
Inouye and Charpentier (56)	1996	2+ medications added	4.5	2.1–9.9		
Inouye and Charpentier (56)	1996	>3 medications added	4.0	2.1–7.3	2.9	1.6–5.4
Marcantonio et al. (11)	1994	Mean N used	—			
Marcantonio et al. (11)	1994	Use	—			
Francis et al. (9)	1990	Use	3.1	1.3–7.3	3.9	1.4–10.8
Rogers et al. (49)	1989	Use	11.7	2.33–58.47	12.2	2.4–60.8
Anticholinergics						
Martin et al. (54)	2000	Use	—			
Inouye and Charpentier (56)	1998	Use	—			
Marcantonio et al. (15)	1994	Use	—		1.5	0.6–3.4
Marcantonio et al. (15)	1994	1 dose	—		1.5	0.5–4.1
Marcantonio et al. (15)	1994	>1 dose	—		1.5	0.3–6.9
Inouye et al. (44)	1993	Use	—			
Inouye et al. (44)	1993	N used, continued	—			
Schor et al. (10)	1992	Use	0.7	0.38–1.18		
Schor et al. (10)	1992	Continued	0.95	0.88–1.24		
Francis et al. (9)	1990	Use	1.8	0.8–3.9		
Gustafson et al. (50)	1988	Use	5.8	2.17–15.57	1.2	0.98–1.47
Anticonvulsants						
Inouye and Charpentier (56)	1996	Use	3.6	1.3–9.8		
Antidepressants						
Gustafson et al. (50)	1988	Use	Infinite			
Antiemetics						
Inouye and Charpentier (56)	1996	Use	2.3	1.1–5.1		
Antipsychotics						
Dubois et al. (4)	2001	Use	—			
Martin et al. (54)	2000	Use	—			
Inouye and Charpentier (56)	1996	Use	1.9	0.5–6.9		
Schor et al. (10)	1992	Use	2.51	1.26–5.02	4.48	1.82–10.45
Gustafson et al. (50)	1988	Use	4.3	1.61–11.60		
Antiparkinsonians						
Gustafson et al. (50)	1988	Use	2.1	0.63–6.96		



partial details about which individual agents were included in the medication variables. In only two studies[49,53] was the "grouped psychoactive medications" variable explicitly defined a priori. Most studies (N = 18) examined medication as a dichotomous variable (use: yes/no) for a particular window of exposure. Windows of exposure varied widely between studies (Table 2). Data on medications were obtained from nursing charts or medical/medication records in one-half of the studies (N = 11). Most studies did not specify the precise manner in which medication data were

FIGURE 3. Effect Estimates For Studies of the Association Between Psychoactive Medications and Delirium, by Type of Medication[a] (continued)

Study	Year	Medication and Variable Examined	Crude Estimate	95% CI	Adjusted Estimate	95% CI
		Benzodiazepines				
Ljubisavljevic and Kelly (47)	2003	Mean dose	—	p=0.63 (t test)		
Fann et al. (8)	2002	Use	2.5	0.39–29.30		
Dubois et al. (4)	2001	0.01–0.68 mg/day	1.6	0.58–4.19		
Dubois et al. (4)	2001	0.69–1.82 mg/day	1.1	0.36–3.45		
Dubois et al. (4)	2001	1.83–14.75 mg/day	3.3	1.31–8.04		
Litaker et al. (13)	2001	Use	2.1	1.26–3.53		
Martin et al. (54)	2000	Short-acting use	—			
Martin et al. (54)	2000	Long-acting use	3.4	0.89–12.93		
Inouye and Charpentier (56)	1996	Use	—			
Foy et al. (48)	1995	Use	1.0	0.3–3.0		
Marcantonio et al. (15)	1994	Use	—		3	1.3–6.8
Marcantonio et al. (15)	1994	Short-acting use	—		2.6	1.1–6.5
Marcantonio et al. (15)	1994	Long-acting use	—		5.4	1.0–29.2
Marcantonio et al. (15)	1994	1 dose	—		2.6	0.8–9.1
Marcantonio et al. (15)	1994	>1 dose	—		3.3	1.0–11.0
Inouye et al. (44)	1993	Use	—			
Inouye et al. (44)	1993	N used, continued	—			
Schor et al. (10)	1992	Use	0.42	0.26–0.71		
Schor et al. (10)	1992	Short-acting use	0.53	0.32–0.89		
Schor et al. (10)	1992	Long-acting use	0.12	0.03–0.50		
Gustafson et al. (50)	1988	Use	4.4	0.93–20.70		
		Corticosteroids				
Ljubisavljevic and Kelly (47)	2003	Use	0.75	0.27–2.06		
Dubois et al. (4)	2001	Use	—			
Schor et al. (10)	1992	Use	0.41	0.14–1.25		
		Histamine Type 2 Antagonists				
Martin et al. (54)	2000	Use	3.3	1.28–8.58		
Inouye and Charpentier (56)	1996	Use	—			
Schor et al. (10)	1992	Use	1.23	0.75–2.03		
		Nonsteroidal Anti-inflammatories				
Schor et al. (10)	1992	Use	0.39	0.11–1.38		
		Opioids				
Ljubisavljevic and Kelly (47)	2003	Mean dose	—	p=0.94 (t test)		
Morrison et al. (12)	2003	<10 mg/day	5.1	2.51–10.41	5.4	2.4–12.3
Morrison et al. (12)	2003	10–30 mg/day	1.7	0.76–3.64	1.4	0.6–3.3
Morrison et al. (12)	2003	>30 mg/day	—			
Fann et al. (8)	2002	Use	0.8	0.3–1.8		
Dubois et al. (4)	2001	0.01–7.1 mg/day	4.7	1.22–18.3	7.8	1.76–34.4
Dubois et al. (4)	2001	7.2–18.6 mg/day	8.1	2.16–30.5	9.2	2.17–39.0
Dubois et al. (4)	2001	18.7–331.6 mg/day	5.4	1.4–20.5	6	1.41–25.4
Litaker et al. (13)	2001	Use	2.24	1.16–4.34	2.7	1.4–5.3
Martin et al. (54)	2000	Continued	1.6			
Lynch et al. (55)	1998	Mean dose	—	p=0.50 (t test)		
Inouye and Charpentier (56)	1996	Use	1.6	0.8–3.2		
Marcantonio et al. (15)	1994	Use	—		1.4	0.5–4.3
Inouye et al. (44)	1993	Use	—			
Inouye et al. (44)	1993	N used, continued	—			
Schor et al. (10)	1992	Use	1.46	0.88–2.41	2.54	1.24–5.18
Rogers et al. (49)	1989	>80 mg/4 days	0.8	0.23–3.15		



[a]Estimates from Litaker et al.[13] and Inouye and Charpentier[56] are relative risks. All other estimates are odds ratios. Student t tests p values for variables from Dai et al.,[53] Ljubisavljevic and Kelly,[47] and Lynch et al.[55] are also presented. Adjusted effects are adjusted for different variables in each study. In the graphs, estimates from studies with a potential lack of power are represented as smaller. Nonsignificant results were not systematically reported in all studies. Except for Morrison et al.,[12] in which the reference dose of opioids is >30 mg morphine, estimates of relative risk compare drug users versus nonusers.

collected, but in three studies,[15,49,56] the data extractors were trained researchers and/or were blinded to the patient's delirium status or to the study hypothesis (Table 2). Only one study identified the individual drugs examined and had medication data extracted from nursing records by trained researchers who were blinded to the study hypothesis.[15]

Delirium In most studies (N = 18) delirium was diagnosed by using either the Confusion Assessment Method or operationalized DSM criteria (DSM–III, DSM–III–R, DSM–IV). Delirium assessments were generally performed on a regular basis—at least three times a week (Table 2). In most studies, at least one action had been taken to enhance sensitivity of delirium detection (Table 2). Only two studies performed continuous monitoring of symptoms.[4,45]

Control of Confounding Delirium risk factors are numerous and inconsistent. Besides dementia/cognitive impairment, there are few established confounding variables to control for. In all studies data related to cognitive impairment of the subjects were extracted. Definition of the variable varied widely between studies, as did the measurement technique used, which ranged from evidence of dementia noted in the patient's medical chart to the use of diagnostic instruments such as the Informant Questionnaire of Cognitive Decline in the Elderly[57] or the Mini-Mental State Examination.[58] For cohort studies, adjustment in multivariate models was performed by entering only the variables found to be significant in univariate comparisons at various levels of significance (range = 0.05–0.15) (Table 2). Variables used for adjustment varied widely between studies. One of the two nested case-control studies[52] matched six baseline variables (including cognitive impairment), and the other[15] used a multivariate model that adjusted for all potential confounders (including cognitive impairment). Only one[15] of the two studies stratified the analysis by matching factors. In 14 studies, actions were taken to ensure that the medication exposure preceded delirium emergence, for instance by requiring that the drug was present at least 24 hours before onset of delirium[56] or recording medication exposures for the 24 hours before delirium for new-onset cases and for the same 24-hour postoperative period for control subjects[15] (Table 2).

Analyses Statistical analyses featured direct relative risk calculation in two studies.[13,56] One study used proportional hazards regression analyses.[44] Most studies used odds ratio calculations that compared delirium cases with control subjects on medication exposure without taking into account the length of follow-up. Student t tests were used in three studies.[47,53,55] Medication exposure was not examined as a time-dependent covariate in any study.

Risk of Delirium Associated With Psychoactive Medications

Grouped psychoactive medications Eleven studies examined risk of delirium with psychoactive medications as a group (Figure 3).[6,9,11,45,46,49,51–54,56] Definitions of this variable were far from uniform between studies, ranging from "medications categorized by a pharmacist as high, moderate, low, or no risk for contributing to the development of delirium"[51] to a list of 26 potentially psychoactive drugs[53] to "17 classes of psychoactive medications (including sedative-hypnotics, narcotics, anticholinergics, and H_2-blockers)".[56] Positive results were found in five studies.[9,49,53,54,56] Exposure to psychoactive medications increased the risk of delirium in all five studies (range of adjusted estimates = 1.23–12.2). Nonsignificant results were not always reported (Figure 3).

Anticholinergics Seven studies examined anticholinergic medications.[9,10,15,44,50,54,56] All had negative results (Figure 3). Nonsignificant results were not systematically reported.

Anticonvulsants One study examined risk associated with anticonvulsant medication.[56] Positive results were found (unadjusted relative risk = 3.6, 95% CI = 1.3–9.8) (Figure 3). The variable was not entered in multivariate analyses, because it did not meet the authors' selection criteria for inclusion (Table 2).

Antidepressants The one study that examined risk associated with antidepressants had positive results (p = 0.005), although all subjects were exposed to the drug of interest (odds ratio = infinite).[50]

Antiemetics One study examined antiemetics and found positive results (unadjusted relative risk = 2.3, 95% CI = 1.1–5.1)[56] (Figure 3). The variable was not entered in multivariate analyses, because it did not meet the authors' selection criteria for inclusion (Table 2).

Antipsychotics Five studies examined risk associated with antipsychotic medications.[4,10,50,54,56] Two studies found positive results (adjusted odds ratio = 4.48, 95% CI = 1.82–10.45;[10] unadjusted odds ratio = 4.3, 95% CI = 1.61–11.60[50]) (Figure 3). Nonsignificant results were not systematically reported.

Antiparkinsonians The one study that examined risk of delirium associated with antiparkinsonians had negative results.[50]

Benzodiazepines Eleven studies examined benzodiazepines.[4,8,10,13,15,44,47,48,50,54,56] Four studies found positive results: risk associated with a dose range of 1.83–14.75 mg/day (unadjusted odds ratio = 3.3, 95% CI = 1.31–8.04);[4] risk associated with use of benzodiazepines (unadjusted odds ratio = 2.1, 95% CI = 1.26–3.53);[13] risk associated with use of benzodiazepines (adjusted odds ratio = 3.0, 95% CI = 1.3–6.8) and with use of short-acting benzodiazepines (adjusted odds ratio = 2.6, 95% CI = 1.1–6.5);[15] and risk associated with use of benzodiazepines (unadjusted odds ratio = 0.42, 95% CI = 0.26–0.71), with use of short-acting benzodiazepines (unadjusted odds ratio = 0.53, 95% CI = 0.32–0.89), and with use of long-acting benzodiazepines (unadjusted odds ratio = 0.12, 95% CI = 0.03–0.50)[10] (Figure 3). Nonsignificant results were not systematically reported.

Corticosteroids Three studies examined corticosteroids.[4,10,47] Negative results were found in all three studies (Figure 3). Nonsignificant results were not systematically reported.

H_2 Antagonists Three studies examined risk associated with H_2 antagonists.[10,54,56] Positive results were found in one study (for use of H_2 antagonisists: unadjusted odds ratio = 3.3, 95% CI = 1.28–8.58).[54] Nonsignificant results were not systematically reported.

NSAIDs The one study[10] that examined risk associated with NSAIDs found negative results (Figure 3).

Opioids Twelve studies examined opioid analgesics.[4,8,10,12,13,15,44,47,49,54–56] Among the four studies that found positive results,.[4,10,12,13] an increase in the risk of delirium (range of adjusted odds ratios = 2.54–9.2) resulting from opioid exposure was noted in all but one study,[12] in which patients who received low daily cumulative doses of a morphine equivalents (0–10 mg/day) were roughly five times more likely to develop delirium than patients who received more than 30 mg/day (adjusted odds ratio = 5.4, 95% CI = 2.4–12.3) (Figure 3).

DISCUSSION

This systematic review was designed to explore the relationship between psychoactive medications and risk of delirium in hospitalized patients. Some findings deserve attention.

First, few studies have been conducted on this topic. Psychoactive medications are among the potential iatrogenic causes of delirium that can be modified to a certain extent, unlike, for instance, hospital-acquired infections. There should be extensive research on this issue. However, only 22 studies met the relatively broad inclusion criteria for our review. Thirteen of those studies were conducted in surgical or medical-surgical settings. Clearly, more research is needed, especially in medicine, oncology, geriatrics, and intensive care services, where delirium is also a high-incidence problem.

Second, few studies had positive results, and among the associations that were reported, only a few were replicated in independent samples. Psychoactive medications, when grouped as a single variable, significantly increased the risk of delirium after adjustment in five studies (Figure 3). A cumulative/interactive effect between different agents included in the category of psychoactive medications cannot be dismissed. Definitions of psychoactive medications varied between the studies, and only two studies[49,53] provided complete details about which individual drugs had been included in the category and specified that the variable was defined a priori. The possibility of a selective inclusion of medications in order to observe significant results cannot be ruled out. Moreover, some exposures that were examined (e.g., number of hospital medications as a continuous variable, use of more than six medications regularly before admission) are not readily translatable to clinical management of hospitalized patients. Thus it may be more informative to study several drug classes and to study them separately. Among drug classes, benzodiazepines significantly increased the risk of delirium in one study, as did antipsychotics in another study, whereas anticholinergics, anticonvulsants, antidepressants, antiemetics, antiparkinsonians, corticosteroids, H_2 antagonists, and NSAIDs were not significantly associated with delirium in any study. More than one-half of the studies (eight of 12) that examined the effects of opioids on the risk of delirium did not identify a significant association. Among studies with positive findings, a two- to ninefold increase in the risk of delirium was noted (Figure 3). However, the results were inconsistent. Although a significant increase in risk of delirium for patients exposed to doses of more than 18.7 mg/day of morphine equivalents was noted by Dubois et al.,[4] Morrison et al.[12] found that patients who were administered doses of more than 30 mg/day of morphine equivalents had a significantly and markedly *lower* risk of de-

lirium than patients who received doses of less than 10 mg/day. The evidence for an increased risk of delirium associated with psychoactive medications thus appears to be thin. Still, methodological shortcomings could alone account for the negative results.

Third, we found substantial heterogeneity across studies for study setting, sample characteristics, assessment of the independent variable, assessment of the dependent variable, control of confounding, and statistical analysis. This heterogeneity impeded sensible statistical pooling of the results, and hence, a qualitative summary was undertaken.

Fourth, the studies presented methodological limitations. The most frequent limitations were potential lack of power, random error in measurement of medication and delirium, and suboptimal statistical analyses. Future studies examining the association between psychoactive medications and delirium should take into account the following methodological considerations:

1) Samples should be large enough to detect significant associations.

2) Medication data should be extracted from accurate sources by trained researchers blinded to patients' delirium status.

3) Studies should consider separately several drug classes, provide details regarding which individual agents were included in the variables (especially for anticholinergics), and use equivalent dosing when possible.

4) Results for medication variables with nonsignificant associations should be reported.

5) The delirium diagnostic criteria used should be more homogeneous.

6) Patients should be under continuous monitoring for delirium symptoms, and a validated and sensitive instrument should be used for monitoring.

7) Besides dementia/cognitive impairment, other adequately measured, potentially important confounding variables should ideally be taken into account (e.g., medical illness).

8) Studies should take into account the variations in exposure periods and medication doses by using survival analyses with medication as a time-dependent covariate.

The review reported here also has some limitations. A search involving different key words might have resulted in a different group of articles. Notwithstanding this limitation, we believe that the strategies used to retrieve and select articles examining the relation between medication and delirium were efficient. Because of the potential biases inherent in observational research, statistical combination of data from observational studies should be performed with caution.[59] Considering this caveat, as well as the important differences between the studies included in this systematic review, we refrained from performing a formal meta-analysis. Another limitation of this review is that some of its findings might relate only to specific populations (e.g., geriatric patients versus cancer patients versus surgical patients), and the implications of the findings could depend on other risk factors in those specific populations. The effects of other risk factors could be particularly important in studies of surgical populations, and 13 of the 22 studies we reviewed were conducted in surgery or medicine-surgery settings.

In summary, we found that the risk estimates from studies that examined the risk of delirium associated with psychoactive medication exposure were scattered around the null effect (Figure 3), and we therefore conclude that the currently available epidemiologic evidence of an association between psychoactive medications and delirium is rather weak, scarce, and sometimes conflicting. For instance, although opioids have been frequently linked to delirium, it remains unclear whether exposure to these medications enhances or reduces the risk of delirium. For the other types of medications, few have been significantly associated with delirium. Still, the weakness of these associations must be interpreted by taking into account the methodological limitations in the published studies. Hence, the chief priority in research on drug-induced delirium should be to improve the quality of individual studies. Data from future studies that avoid the methodological shortcomings exposed in this article could strengthen the evidence linking psychoactive medications to delirium in hospitalized patients. With the present evidence, one cannot yet conclude that psychoactive drugs do not contribute to causing delirium. In the meantime, physicians should maintain their prescription practices—that is, limit patients' exposure to deliriogenic medications (e.g., benzodiazepines) whenever possible and follow the available treatment guidelines[60,61] until more light is shed on the question. A distinction should also be made between patients who are not yet delirious and those who are delirious. For example, while a benzodiazepine may not cause delirium in many patients, it should clearly be avoided in most patients who are currently delirious.[61]

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