VOLUME 23 · NUMBER 27 · SEPTEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Psychoactive Medications and Risk of Delirium in Hospitalized Cancer Patients

Jean-David Gaudreau, Pierre Gagnon, François Harel, Marc-André Roy, and Annie Tremblay

From the Centre de Recherche en Cancérologie de L'Hôtel-Dieu de Québec; Department of Psychiatry, L'Hôtel-Dieu de Québec; Centre Hospitalier Universitaire de Québec; Faculties of Pharmacy and Medicine and Department of Psychiatry, Faculty of Medicine, Laval University; Maison Michel Sarrazin; and Centre de Recherche Université Laval Robert-Giffard, Québec City, Québec, Canada.

Submitted November 10, 2004; accepted May 9, 2005.

Supported by a grant from the Sociobehavioural Cancer Research Network, funded through the National Cancer Institute of Canada (NCIC) Centre for Behavioural Research and Program Evaluation, with funds from the Canadian Cancer Society. J.-D.G. is the recipient of a Fonds d'Enseignement et de Recherche Award from the Faculty of Pharmacy, Laval University, and of a Canadian Institutes of Health Research-NCIC award from the Strategic Training Program in Palliative Care Research. P.G. is a research scientist of the Canadian Cancer Society through an award from the NCIC, and M.-A.R. is a senior research scientist (Chercheur-Boursier) supported by the Fonds de la Recherche en Santé du Québec (Montreal). M.-A.R. is also the recipient of a Clinical Scientist Award from the Fonds de la Recherche en Santé du Québec.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Pierre Gagnon, MD, L'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, 11 Côte du Palais, Québec City, Québec, Canada G1R 2J6; e-mail: pierre.gagnon@crhdq.ulaval.ca.

0732-183X/05/2327-6712/$20.00

DOI: 10.1200/JCO.2005.05.140

ABSTRACT

Purpose
Psychoactive medications are biologically plausible and potentially modifiable risk factors of delirium. To date, however, research findings are inconsistent regarding their association with delirium. The association between exposure to anticholinergics, benzodiazepines, corticosteroids, and opioids and the risk of delirium was studied.

Patients and Methods
A total of 261 hospitalized cancer patients were followed up with repeated assessments by using the Nursing Delirium Screening Scale for up to 4 weeks for incident delirium. Detailed exposure to psychoactive medications was documented daily. Strengths of association with delirium were expressed as hazard ratios (HRs) in univariate and multivariate analyses by using Cox regression models. All medication variables were coded as time-dependent covariates. Whenever possible, exposure was computed by using cumulative daily doses in equivalents; dichotomous cutoffs were determined.

Results
During follow-up (mean, 8.6 days), 43 patients became delirious (16.5%). Delirium was associated with a history of delirium and the presence of hepatic metastases at admission. Analysis of the effect of medications was performed adjusting for these factors. Patients exposed to daily doses of benzodiazepines above 2 mg (HR, 2.04; 95% CI, 1.05 to 3.97), above 15 mg of corticosteroids (HR, 2.67; 95% CI, 1.18 to 6.03), or above 90 mg of opioids (HR, 2.12; 95% CI, 1.09 to 4.13) had increases in the risks for delirium. We did not observe associations between anticholinergics and risk for delirium.

Conclusion
Exposure to opioids, corticosteroids, and benzodiazepines is independently associated with an increased risk of delirium in hospitalized cancer patients.

J Clin Oncol 23:6712-6718. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Delirium is a common neuropsychiatric complication occurring during hospitalization of cancer patients. In oncology, delirium incidence ranges from 18%[1] to 85%.[2]

Aside from psychoactive medications, there are few established risk factors for delirium in hospitalized patients. In a recent systematic review and meta-analysis, Elie et al[3] identified 61 different risk factors for delirium. From those, aside from medication, 26 risk factors for delirium had been studied in two or more prospective studies. These potential confounding variables of an association between medication and delirium were grouped into broad risk categories including demographics, mental status, medical illness, physical status, laboratory findings, and surgery/anesthesia. Of all variables, dementia/cognitive impairment was the most convincing risk factor for delirium. Other factors such as illness severity and psychoactive medications also seemed to be consistent between studies. Of the most important delirium risk factors, use of psychoactive

medications is one of the few that can be significantly modified with little effort to avoid or alleviate delirium. Therefore, research on this matter is of the utmost importance for effective prevention or treatment of this condition.

An excess of central dopaminergic activity and/or a deficit in brain cholinergic activity would elicit delirium.[4] Other modulatory pathways (eg, γ-aminobutyric acid [GABA] system) could also be involved in delirium pathophysiology.[5] Certain types of psychoactive medications that can interfere directly or through neuroactive metabolites with the normal functioning of these systems (eg, opioids, benzodiazepines) are thus particularly plausible risk factors for delirium. Indeed, in numerous case reports and case series, these types of medications were frequently involved in delirium etiology.[6,7]

We recently reviewed the results from observational studies of the association between drug exposure and risk for delirium, which did not provide strong support for such associations.[8] Of 22 observational studies of hospitalized patients that examined psychoactive medications as a delirium risk factor in the last three decades, few studies had positive results, and most positive results have not been replicated in independent samples. Among drug classes, benzodiazepines significantly increased the risk of delirium in one study, and corticosteroids have not been significantly associated with an increased risk of delirium in any studies. The relationship between exposure to opioid analgesics and risk of delirium is particularly controversial, because it is still unclear whether opioids increase or decrease the risk of delirium in hospitalized patients. Yet, the interpretation of these results must take into account the limitations of published studies. Prior studies often presented methodologic shortcomings such as inadequate sample sizes, inaccurate medication data source and extraction, imprecise classification of agents in drug classes, or low sensitivity of delirium detection. Our study followed the eight recommendations derived from the shortcomings noted through the critical review of previous studies: (1) samples should be large enough to detect significant associations; (2) medication data should be extracted from accurate sources by trained researchers blinded to delirium status; (3) studies should consider separately several drug classes, provide details regarding which individual agents were included in the variables, and use equivalent dosing when possible; (4) results for medication variables with nonsignificant associations should be reported; (5) delirium diagnostic criteria used should be more homogeneous; (6) patients should be under continuous monitoring of delirium symptoms by a validated and sensitive instrument; (7) besides dementia/cognitive impairment, other adequately measured, potentially important confounding variables ideally should be taken into account (eg, medical illness); and (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.

To test the hypothesis that exposure to certain psychoactive medications, including anticholinergics, benzodiazepines, corticosteroids, or opioids, increases the risk for delirium in hospitalized patients, we followed up a cohort of cancer patients for incident delirium and examined the exposure to these four categories of medications. To our knowledge, this is the first study to examine psychoactive medications as a risk factor for delirium using a design and methods that avoid the methodologic limitations of previous studies.

PATIENTS AND METHODS

Patients

The study population consisted of patients admitted to the hemato-oncology/internal medicine unit at the Hôtel-Dieu de Québec Hospital. Study inclusion criteria consisted of a histologic diagnosis of cancer in consecutive patient admissions to the unit. The study interval was from January 21, 2002, to August 4, 2003. Considering the rehabilitative focus of the unit, few patients with dementia are admitted. Therefore, and consistent with recent studies,[1,9] these patients were not excluded. Assent was obtained from the patient, and informed consent was obtained from a significant other. Because there was no perceived risk for harm to patients and delirium evaluations were fully integrated into standard clinical practice, written consent was not obtained. The hospital's research ethics committee approved this study.

Outcome Measure

During hospitalization, all cohort members were followed up by using the Nursing Delirium Screening Scale (Nu-DESC),[10] which was performed by bedside nurses blinded to patients' medication use and study hypothesis. The Nu-DESC is a short (five-item), stand-alone, observational delirium diagnostic instrument that has been performed on a continuous basis as part of routine nursing clinical practice in the Hôtel-Dieu de Québec hemato-oncology/internal medicine unit since November, 2001. The Nu-DESC was developed by our group. It rates the presence and severity of five clusters of symptoms based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, delirium diagnostic criteria: disorientation, inappropriate behavior, inappropriate communication, illusions or hallucinations, and unusual physical/mental retardation, taking into account medical condition. All items are operationalized and scored as 0 (absent), 1 (present but mild), or 2 (present and severe), with total scores ranging from 0 (no symptoms) to 10 (severe) only on the basis of observation of individual patients. The Nu-DESC delirium positivity threshold is a total score of 2 or more. Test performance of the Nu-DESC was established previously by using the Confusion Assessment Method[11] as the reference standard. Nu-DESC sensitivity, specificity, and efficiency were 85.7%, 86.8%, and 86.4%, respectively.

The outcome variable of the study was incident delirium that occurred within 4 weeks (28 days) of hospitalization. Incident delirium was defined as a score of 2 or more on the Nu-DESC more than 24 hours after admission to the unit. To ensure that

medication exposure preceded delirium occurrence, prevalent cases of delirium were excluded from the analyses.

Exposure to Psychoactive Medications

An experienced research nurse, blinded to outcome status and study hypothesis, reviewed the nursing medication records to extract detailed information on medication exposure by using standardized forms. Data were collected on each type of individual medication actually received by the patients, including pro re nata medications, with the precise time of administration, route, and doses used. Four mutually exclusive categories of psychoactive medications, anticholinergics, benzodiazepines, corticosteroids, and opioids, were considered in the analyses. Individual agents featured in the four categories were defined a priori. Together with equivalency tables, the information extracted was used the measures of daily medication exposure for benzodiazepines, corticosteroids, and opioids: cumulative daily dose in oral lorazepam,[12] oral dexamethasone,[13] or subcutaneous morphine,[13,14] respectively. Anticholinergics included 23 individual agents with primary (eg, atropine, benztropine) or secondary (eg, diphenhydramine, amitriptyline) antimuscarinic properties, which were chosen on the basis of available literature. Thirteen individual benzodiazepines were studied, including diazepam, oxazepam, and lorazepam. Corticosteroids included prednisone, hydrocortisone, cortisone, prednisolone, methylprednisolone, and dexamethasone. Opioid analgesics included morphine, codeine, oxycodone, hydromorphone, methadone, meperidine, fentanyl, and sufentanil. Additional information on the individual agents that were included in each category can be provided on request. To reduce potential confounding by indication, only medications used before incident delirium were considered in the analyses.

Confounding or Modifying Variables

Control variables used to study their association with delirium were chosen a priori on the basis of past work in the field and because of clinical relevance. The patients' clinical characteristics (sex, age, disease-related variables [primary cancer site, presence and sites of metastases, if applicable], diagnosis of delirium on a previous hospitalization, and dementia) were determined at admission from medical records by a trained study nurse using standardized forms. In oncology, metastatic spread is an indicator of disease severity. Thus, severity of illness as a confounding factor was taken into account indirectly through the presence of metastases. The patients' medical and nursing charts were inspected carefully for potential evidence of cognitive impairment and/or dementia. Laboratory data at admission and chemotherapy data throughout the hospital stay were collected from medical charts and computerized databases. Normal ranges for laboratory data were determined as follows: sodium, 135 to 145 mmol/L; calcium, 2.15 to 2.57 mmol/L; potassium, 3.5 to 5.1 mmol/L; AST, less than 50 U/L (males) or less than 40 U/L (females); ALT, less than 60 U/L (males) or less than 50 U/L (females); urea, 2.9 to 7.9 mmol/L (males) or 2.1 to 7.1 mmol/L (females); and creatinine, 60 to 110 μmol/L (males) or 50 to 100 μmol/L (females).

Statistical Analysis

Preliminary analyses included descriptive statistics of medication exposure and potential confounding or modifying variables. For the follow-up analyses, the primary outcome variable was the number of days from hospital admission to the development of delirium. For subjects who did not develop delirium, the follow-up time was censored at the last available day at which an assessment for delirium was performed. Patients were followed up for a maximum of 4 weeks (28 days). Patients without delirium on hospitalization day 28 were censored. We considered this fixed length of follow-up to prevent a potential bias toward positive associations in which severely ill patients becoming delirious at a time later than 28 days of hospitalization would have exceedingly contributed to Cox models linking psychoactive medications and delirium occurrence. This potential overcontribution would have been twofold. First, severely ill oncology patients are typically exposed to high daily doses of medications prone to induce delirium, such as benzodiazepines and opioids. Second, severely ill patients usually experience longer hospitalizations. A Kaplan-Meier curve was constructed for the time-to-delirium outcome.[15]

We examined the associations between independent variables and the time to development of delirium. Kaplan-Meier survival curves and the Cox regression method[16] were used to examine variables as single main-effect associations with survival for all control variables. Cox regression models with time-dependent covariates[17] were used to test the association between psychoactive medication variables and risk of delirium: anticholinergic medications (exposure present or absent on a given day of hospitalization), benzodiazepines (cumulative daily dose), corticosteroids (cumulative daily dose), and opioids (cumulative daily dose). Chemotherapy (exposure present or absent) was also coded as a time-dependent variable.

The continuous medication variables were categorized to ease interpretation of the hazard ratio (HR). The categorization was performed by using methods derived from available guidelines.[18,19] In a nutshell, medication variables were categorized into approximate tertiles or quartiles according to their distribution in the study population and clinical meaningfulness (eg, creating a category with a lower bound of 2.0 mg instead of 2.14 mg for lorazepam). We then examined the risk of delirium associated with each drug category and the trend of these risks (eg, linear increase) over the various categories. The lowest tertiles or quartile was used as the referent category. Although the results of the analyses did not suggest a linear trend over categories, there seemed to be thresholds of drug exposure that increased the risk of delirium. On the basis of these analyses, dichotomous cutoffs for cumulative daily doses of benzodiazepines, corticosteroids, and opioids were determined to be doses higher than 2 mg of lorazepam, 15 mg of dexamethasone, and 90 mg of morphine, respectively. The difference in the fit of models with medications as dichotomous versus continuous variables was calculated by using the likelihood-ratio χ^2 statistic.[19] This difference was not statistically significant ($P > .10$), indicating that the dichotomization of doses did not compromise the fit of the models.

The clinical characteristics and laboratory data at admission that were significantly associated to delirium in the univariate analyses were entered simultaneously into a multivariate model. $P \leq .20$ and $P > .05$ were set as limits for variable inclusion and exclusion, respectively. The subsequent analyses on medications were performed adjusting for the variables included in this multivariate model.

The proportionality of hazards was checked by testing the significance of the interactions between the variables and follow-up time; none were significant. No appreciable colinearity was observed. Potential interactions were investigated (drug-drug, drug-control variable, and control variable-control variable) for all medication and control variables that were significant in univariate analysis. We did not observe any significant interactions.

All statistical analyses were performed by using SAS 8.2 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Population

Admission characteristics of the 261 patients who met the eligibility criteria for study entry are listed in Table 1. The overall mean (± standard deviation [SD]) age of the cohort was 59.6 (± 14.3) years. The mean follow-up time (± SD) was 8.6 (± 7.7) days. No cases of dementia were recorded. A Kaplan-Meier curve summarizing time to reach the delirium end point across the entire cohort is shown in Figure 1. One hundred twenty patients were at risk at 7 days, 50 at 14 days, 33 at 21 days, and 25 at 28 days. The cumulative probability of delirium was 13.9% at 7 days of hospitalization (95% CI, 9.0 to 18.8) and 25.3% at 14 days (95% CI, 17.3 to 33.4) of hospitalization.

Effects of Control Variables on Risk of Delirium

We examined the associations between patient characteristics at admission and incident delirium in univariate analyses (Table 2). History of delirium and the presence of liver metastases were variables associated with an increased risk of delirium in univariate analysis. When these variables were fitted simultaneously into a multivariate model, both remained significant predictors of delirium.

Effects of Psychoactive Medication Variables on Risk of Delirium

Univariate analyses for each of the psychoactive medication variables are listed in Table 3. Benzodiazepines, corticosteroids, and opioids were significant predictors of delirium in univariate analysis as well as in multivariate

Table 1. Summary Statistics for Control Variables Measured at Admission

Variable	All Subjects (N = 261)		Subjects Without Delirium (n = 218)		Subjects Who Developed Delirium (n = 43)	
	No.	%	No.	%	No.	%
Age, years						
Mean	59.6		59.1		62.0	
Standard deviation	14.3		14.4		13.4	
Sex						
Male	147		121		26	
Female	114		97		17	
History of delirium	15	5.7	8	3.7	7	16.3
Primary cancer diagnosis						
Hematologic	86	33.0	75	34.4	11	25.6
Gastrointestinal tract	35	13.4	27	12.4	8	18.6
Lung	21	8.0	17	7.8	4	9.3
Bones/soft tissue	24	9.2	21	9.6	3	7.0
Genital	11	4.2	9	4.1	2	4.7
Urinary	14	5.4	8	3.7	6	14.0
Breast	16	6.1	14	6.4	2	4.7
Ovary	12	4.6	11	5.0	1	2.3
Colorectal	26	10.0	24	11.0	2	4.7
Other	16	6.1	12	5.5	4	9.3
Extent of cancer disease						
Locoregional only	154	59.0	131	60.1	23	8.8
Primary site of metastases						
Brain	18	6.9	15	6.9	3	7.0
Bone	39	14.9	33	15.1	6	14.0
Liver	42	16.1	31	14.2	11	25.6
Lung	57	21.8	46	21.1	11	25.6
Metabolic abnormalities						
Low sodium	41	15.7	28	12.8	13	30.2
High sodium	2	0.8	2	0.9	0	0.0
Low potassium	42	16.1	37	17.0	5	11.6
High potassium	5	1.9	3	1.4	2	4.7
Low calcium	137	52.5	111	50.9	26	60.5
High calcium	3	1.1	2	0.9	1	2.3
High ALT	24	9.2	19	8.7	5	11.6
High AST	32	12.3	24	11.0	8	18.6
High urea	55	21.1	44	20.2	11	25.6
High creatinine	54	20.7	42	19.3	12	27.9

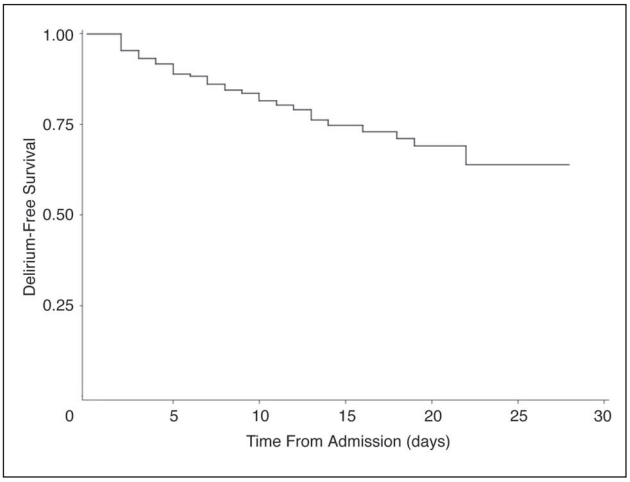

Fig 1. Kaplan-Meier plot of delirium-free survival at 28 days of hospitalization in 261 study patients.

models adjusted for history of delirium and liver metastases, which were run separately for each psychoactive medication variable (Table 3). Patients exposed to cumulative daily doses of benzodiazepines above 2 mg, of corticosteroids above 15 mg, or of opioids above 90 mg presented an increased risk of developing delirium (HR range, 2.04 to 2.67) within 28 days of hospitalization. Anticholinergic agents were not associated with delirium occurrence in our cohort (Table 3). Exposure to chemotherapy was associated with delirium neither in univariate analysis (HR, 0.94; 95% CI, 0.45 to 1.97; $P = .87$) nor when controlling for history of delirium and liver metastases (HR, 1.23; 95% CI, 0.58 to 2.62; $P = .60$).

Table 2. Univariate Analyses of the Predictors of Hazard of Delirium Associated With Admission Variables

Predictor	HR	95% CI	*P*
Clinical characteristic			
Sex	0.84	0.46 to 1.55	.58
Age	1.007	0.98 to 1.03	.55
History of delirium	5.45	2.40 to 12.39	< .0001
Metastases			
Brain	1.10	0.34 to 3.57	.87
Bone	0.77	0.33 to 1.84	.56
Liver	1.91	0.96 to 3.78	.07
Lung	1.59	0.62 to 4.13	.34
Laboratory data			
Low sodium	2.19	0.62 to 7.73	.23
High sodium*	—	—	—
Low potassium	0.97	0.38 to 2.48	.94
High potassium	2.04	0.49 to 8.49	.33
Low calcium	1.45	0.76 to 2.78	.26
High calcium	1.23	0.17 to 8.99	.84
High ALT	0.98	0.37 to 2.58	.96
High AST	1.24	0.54 to 2.84	.61
High urea	1.39	0.69 to 2.79	.36
High creatinine	1.56	0.79 to 3.06	.20

Abbreviation: HR, hazard ratio.
*All patients had values below the upper limit of the normality range.

DISCUSSION

To our knowledge, this is the first study to find an increased risk of delirium in hospitalized patients resulting from exposure to benzodiazepines, corticosteroids, and opioids. It is also one of the few studies to use methods suited for drug-induced delirium research. Our findings could indicate that the negative results obtained by a large proportion of the previous studies were consequential to an inappropriate methodology.

Our data indicate a relatively high occurrence of delirium in cancer patients. Forty-three (16.5%) of the 261 patients in our cohort became delirious during the 4-week follow-up. Patients were at particularly high risk of developing delirium early during hospitalization, because the probability of presenting delirium within the first 2 weeks was 25.3% (Fig 1). These data are consistent with a recent prospective study of delirium risk factors in oncology.[1]

The clinical variables at admission that were associated with increased risk of delirium in our cohort were history of delirium and liver metastases. Patients with a history of delirium might be physiologically and/or genetically more vulnerable to noxious brain insults that occur during hospitalization than other patients. To our knowledge, however, few studies have found a positive association between previous delirium and new-onset delirium on a following hospitalization.[3,20] In oncology patients, metastatic spread is an indicator of disease severity, the latter being a recognized risk factor for delirium.[21,22] Severe illness can lead to a physiologic stress response that, in turn, can influence the metabolism and function of neurotransmitters.[23] Our results indeed indicate that the presence of liver metastases significantly increases the risk of delirium. The presence of metastases also could have directly altered hepatic function; this issue would require additional investigation. Thus, a history of delirium and the presence of liver metastases could have confounded an association between psychoactive medications and delirium and were controlled for in a multivariate analysis.

Our results, like others,[20,24] support the viability of the associations that link benzodiazepine exposure and delirium. Benzodiazepines could indeed be involved in delirium pathogenesis through overstimulation of the cortical GABA system, thereby reducing corticostriatal glutamatergic tone and ultimately hampering the filtering action of the thalamus, leading to confusion or psychosis.[5] In our cohort, patients exposed to daily doses of benzodiazepines higher than 2 mg were two times more at risk of developing delirium than patients who were exposed to smaller doses.

Table 3. Association Between Exposure to Psychoactive Medications and Hazard of Delirium at 28 Days of Hospitalization

Predictor	HR (unadjusted)	95% CI	*P*	HR (adjusted)*	95% CI	*P*
Benzodiazepines daily dose > 2 mg†	1.57	0.84 to 2.93	.16	2.04	1.05 to 3.97	.04
Corticosteroids daily dose > 15 mg†	2.62	1.20 to 5.73	.02	2.67	1.18 to 6.03	.02
Opioids daily dose > 90 mg of morphine†	2.35	1.22 to 4.53	.01	2.12	1.09 to 4.13	.03
Anticholinergics	1.22	0.65 to 2.30	.53	1.38	0.73 to 2.60	.32

NOTE. Medication variables were all time-dependent covariates. Exposure to benzodiazepines, corticosteroids, and opioids was computed as cumulative daily equivalent doses, whereas for anticholinergic medications, exposure was determined to be either present or absent for each day of hospitalization.
Abbreviation: HR, hazard ratio.
*The HR was adjusted for history of delirium and liver metastases.
†Relative to patients exposed to cumulative daily doses ≤ 2 mg of lorazepam, ≤ 15 mg of dexamethasone, or ≤ 90 mg of morphine.

To our knowledge, this is the first prospective study to report a positive association between corticosteroids and delirium. Patients exposed to daily doses higher than 15 mg had a 2.7-fold increase in the risk of delirium compared with patients exposed to smaller doses. Using cumulative daily dosing potentially allowed us to detect this particular association, which is biologically plausible. Psychotic symptoms could result from corticosteroids increasing dopamine release in the nucleus accumbens through overstimulation of dopamine neurons in the ventral tegmental area (VTA).[25]

Opioids could be psychotogenic by enhancing the activity of VTA dopamine neurons through μ-opioid receptors located on GABA neurons within the VTA,[26] thereby increasing dopamine release in the nucleus accumbens.[27] According to our results, patients exposed to daily doses of opioids higher than 90 mg were 2.1 times more at risk of developing delirium than patients who were exposed to smaller doses. Yet, the results of previous epidemiologic studies on the opioids-delirium association are conflicting. A recent study found an increased risk of delirium for patients exposed to doses less than 10 mg of daily morphine equivalents, compared to patients exposed to more than 30 mg,[28] whereas another study found an increased risk of delirium for patients exposed to doses ranging from 18.6 to 331.6 mg compared to nonusers.[29] The pattern of the opioids-delirium relationship obviously should be investigated further.

Our study has several methodologic characteristics that were largely absent from previous studies. These strengths include data collection by an experienced nurse blinded to delirium status and study hypothesis, delirium assessment performed by bedside nurses blinded to medication exposure and study hypothesis, detailed information on medication variables, and a statistical approach featuring survival analysis with time-dependent covariates. Our study also has limitations. It is not possible to determine the extent to which the associations we observed were a result of drug combinations, because cancer patients are frequently exposed simultaneously to more than one type of psychoactive medication. Still, we did not find biologically/biochemically meaningful interactions. Because our sample was of a relatively modest size and none of the patients in our cohort had dementia, our findings may not apply to other population groups. The multivariate models presented herein would require validation in other samples. We collected and analyzed data regarding the most plausible confounders of an association between medication exposure and risk of delirium, including history of delirium, disease-related factors of severity, laboratory data, and dementia. Yet, the possibility of confounding by subtle or unknown confounders cannot be dismissed entirely.

We conclude that benzodiazepines, corticosteroids, and opioids are independent risk factors for delirium in hospitalized patients. Additional observational research is necessary to test the reproducibility and clinical importance of these findings. Randomized controlled trials should also be conducted to test the hypothesis that exposing hospitalized patients to doses of benzodiazepines, corticosteroids, and opioids below the thresholds herein determined can prevent delirium development.

Acknowledgment

We are indebted to all the hemato-oncology bedside nurses and Marie-Andrée Roy, RN, for assistance in collecting and extracting the data, respectively.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Ljubisavljevic V, Kelly B: Risk factors for development of delirium among oncology patients. Gen Hosp Psychiatry 25:345-352, 2003
2. Massie MJ, Holland J, Glass E: Delirium in terminally ill cancer patients. Am J Psychiatry 140:1048-1050, 1983
3. Elie M, Cole MG, Primeau FJ, et al: Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 13:204-212, 1998
4. Trzepacz PT: Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 5:132-148, 2000
5. Gaudreau JD, Gagnon P: Psychotogenic drugs and delirium pathogenesis: The central

role of the thalamus. Med Hypotheses 64:471-475, 2005

6. Tuma R, DeAngelis LM: Altered mental status in patients with cancer. Arch Neurol 57: 1727-1731, 2000

7. Drugs that cause psychiatric symptoms. Med Lett Drugs Ther 35:65-70, 1993

8. Gaudreau JD, Gagnon P, Roy MA, et al: Association between psychoactive medications and delirium in hospitalized patients: A critical review. Psychosomatics 46:302-316, 2005

9. Lawlor PG, Gagnon B, Mancini IL, et al: Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study. Arch Intern Med 160:786-794, 2000

10. Gaudreau JD, Gagnon P, Harel F, et al: Fast, systematic, and continuous delirium assessment in hospitalized patients: The Nursing Delirium Screening Scale (Nu-DESC). J Pain Symptom Manage 29:368-375, 2005

11. Inouye SK, van Dyck CH, Alessi CA, et al: Clarifying confusion: The confusion assessment method—A new method for detection of delirium. Ann Intern Med 113:941-948, 1990

12. Rosenbaum JF, Gelenberg AJ: Anxiety, in SC Schoonover (ed): The Practitioner's Guide to Psychoactive Drugs. New York, NY, Plenum, 1991, pp 179-218

13. American Hospital Formulary Service. Drug Information 2002. Bethesda, MD, American Society of Health System Pharmacists Inc, 2002

14. Cherny NI, Portenoy RK: Cancer pain management: Current strategy. Cancer 72:3393-3415, 1993

15. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-489, 1958

16. Cox DR: Regression models and life tables (with discussion). J R Stat Soc 34:187-220, 1972

17. Allison PD: Survival Analysis Using the SAS System: A Practical Guide. Cary, NC, SAS Institute, 1995

18. Clark TG, Bradburn MJ, Love SB, et al: Survival analysis part IV: Further concepts and methods in survival analysis. Br J Cancer 89:781-786, 2003

19. Collett D: Modeling Survival Data in Medical Research. New York, NY, Chapman & Hall, 1994

20. Litaker D, Locala J, Franco K, et al: Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 23:84-89, 2001

21. Inouye SK, Viscoli CM, Horwitz RI, et al: A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 119:474-481, 1993

22. Francis J, Martin D, Kapoor WN: A prospective study of delirium in hospitalized elderly. JAMA 263:1097-1101, 1990

23. van der Mast RC, Fekkes D: Serotonin and amino acids: Partners in delirium pathophysiology? Semin Clin Neuropsychiatry 5:125-131, 2000

24. Marcantonio ER, Juarez G, Goldman L, et al: The relationship of postoperative delirium with psychoactive medications. JAMA 272: 1518-1522, 1994

25. Piazza PV, Le Moal M: Glucocorticoids as a biological substrate of reward: Physiological and pathophysiological implications. Brain Res Brain Res Rev 25:359-372, 1997

26. Tomkins DM, Sellers EM: Addiction and the brain: The role of neurotransmitters in the cause and treatment of drug dependence. CMAJ 164:817-821, 2001

27. Cowen MS, Lawrence AJ: The role of opioid-dopamine interactions in the induction and maintenance of ethanol consumption. Prog Neuropsychopharmacol Biol Psychiatry 23:1171-1212, 1999

28. Morrison RS, Magaziner J, Gilbert M, et al: Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 58:76-81, 2003

29. Dubois MJ, Bergeron N, Dumont M, et al: Delirium in an intensive care unit: A study of risk factors. Intensive Care Med 27:1297-1304, 2001