

# Use of Medications With Anticholinergic Effect Predicts Clinical Severity of Delirium Symptoms in Older Medical Inpatients

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**Background:** Use of anticholinergic (ACH) medications is a biologically plausible and potentially modifiable risk factor of delirium, but research findings are conflicting regarding its association with delirium.

**Objectives:** To evaluate the longitudinal association between use of ACH medications and severity of delirium symptoms and to determine whether this association is modified by the presence of dementia.

**Patients and Methods:** A total of 278 medical inpatients 65 years and older with diagnosed incident or prevalent delirium were followed up with repeated assessments using the Delirium Index for up to 3 weeks. Exposure to ACH and other medications was measured daily. The association between change in medication exposure in the 24 hours preceding a Delirium Index assessment was assessed using a mixed linear regression model.

**Results:** During follow-up (mean  $\pm$  SD, 12.3  $\pm$  7.0 days), 47 medications with potential ACH effect were used in the population (mean, 1.4 medications per patient per day). Increase in delirium severity was significantly associated with several measures of ACH medication exposure on the previous day, adjusting for dementia, baseline delirium severity, length of follow-up, and number of non-ACH medications taken. Dementia did not modify the association between ACH medication use and delirium severity.

**Conclusion:** Exposure to ACH medications is independently and specifically associated with a subsequent increase in delirium symptom severity in elderly medical inpatients with diagnosed delirium.

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**D**ELIRIUM may be the most common acute cognitive dysfunction in hospitalized elderly patients, occurring in 11% to 26% of elderly medical or geriatric inpatients.<sup>1-3</sup> Delirium has been associated with prolonged hospital stay, increased functional decline, morbidity, mortality, and nursing home placement.<sup>3,4</sup> However, delirium is often underrecognized clinically,<sup>5,6</sup> and, to date, evidence of intervention benefits is limited.<sup>7,8</sup> Thus, identifying risk factors for delirium, especially modifiable risk factors, is of great importance for effective prevention of this condition.

In recent decades, an increasing number of studies have examined risk factors that might predispose, precipitate, or perpetuate development and progression of delirium.<sup>9-18</sup> Despite considerable methodological differences, most studies have found that medication use in general, and anticholinergic (ACH) medication use in particular, is a common precipitating

risk factor.<sup>9-15,19-21</sup> The ACH medication-delirium association may be potentially important given its high biological plausibility, as suggested by a central cholinergic deficit mechanism for delirium<sup>19,22-24</sup> and clinical correlation between serum ACH activity and delirium.<sup>18,25-28</sup>

However, research findings to date are still controversial. Some studies have found a significant association between use of ACH medications and delirium,<sup>23,27-30</sup> whereas others have not.<sup>12-14</sup> Several reasons may underlie this discrepancy. First, studies used different measures of ACH medication exposure, including serum ACH level,<sup>26-29</sup> aggregate risk scores of ACH potency,<sup>27,28,30-33</sup> or number and dose of ACH medications using different classifications.<sup>12-14,17,18</sup> Second, the effect of ACH medications on delirium may be confounded by other risk factors, such as dementia, age, or comorbid conditions. Third, patients with dementia showed cognitive decline with doses of ACH medications at which nondemented controls did

## PATIENTS AND METHODS

### PATIENTS AND PROCEDURES

Study patients were inpatients diagnosed as having delirium who were enrolled in a prospective, randomized controlled trial of a delirium geriatric service or in an observational cohort study of outcomes of delirium (prognosis study) at a 400-bed, university-affiliated primary acute care hospital. Consecutive patients 65 years and older admitted from the emergency department to the medical or geriatric services between March 1, 1996, and January 31, 1999, were screened by a study nurse for study eligibility within 24 hours of admission. Patients were excluded if they were (1) admitted to the hospital on a Friday or Saturday, (2) diagnosed as having stroke or terminal illness, (3) under intensive care or cardiac monitoring for more than 48 hours, or (4) unable to speak or understand English or French. Eligible patients were screened by a study nurse using the Short Portable Mental Status Questionnaire<sup>34,35</sup> and review of nursing notes for symptoms of delirium. Those with a questionnaire score of 3 or more or symptoms of delirium were assessed using the Confusion Assessment Method (CAM),<sup>36</sup> a structured interview of delirium symptoms according to *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, criteria.<sup>37</sup> Prevalent cases were defined as those that met CAM criteria for definite or probable delirium at hospital admission. Patients without delirium at hospital admission were re-screened daily for the following week; those scoring at least 1 point higher on the Short Portable Mental Status Questionnaire on any subsequent assessment than on the initial assessment, or reported in the nursing notes to have symptoms of delirium, were assessed using the CAM. Patients who met the CAM criteria more than 24 hours after hospital admission were diagnosed as having incident delirium. Both prevalent and incident delirium cases were asked to participate in the study. Assent was obtained from the patient and informed consent from a significant other. Both studies were approved by the hospital's research ethics committee.

### OUTCOME MEASURE

During hospitalization, all cohort members were followed up using the Delirium Index (DI) by a research assistant masked to patients' study group, medication use, and other patient data in medical records. Patients were assessed at least every 3 days during the first week and weekly thereafter for 8 weeks or until death or discharge from the hospital. For this study, we analyzed DI data collected during the first 21 days because DI assessments were sparse after day 21, when most patients were discharged or dead.

The DI was developed by our group, based on the CAM, to rate the severity of 7 delirium symptoms: altered attention; disorganized thinking; disorientation; and disturbances in consciousness, memory, perception, and motor activity. Each symptom is scored as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe), with total scores ranging from

0 (no symptoms) to 21 (severe), based only on observation of individual patients. Interrater reliability between psychiatrists (M.C. and F.P.) and research assistants (intra-class concordance coefficient=0.88) and concurrent validity with the Trepacz Delirium Rating Scale<sup>38</sup> ( $r=0.84$ ) are satisfactory.

### MEDICATION EXPOSURES

Data on medications were extracted from patient hospital charts by a nurse using a standard form. For medications the patient was receiving at the time of enrollment, the information abstracted included route (oral, intramuscular, intravenous, etc); dose; and frequency of administration, collapsed into either use as needed or regular use (once, twice, or multiple administrations per day). Also abstracted were the date and types of dose and frequency changes during hospitalization by recording whether a medication was newly added or removed and whether the dosage was increased or decreased each day. This information was used to calculate 5 measures of daily medication exposure:

1. Summers' Drug Risk Number (DRN): We used the Class of Drug developed by Summers<sup>30</sup> for 62 medications, a 3-level (III being the highest) ordinal scale denoting the synergistic and central nervous system ACH potency of a medication,<sup>25,28,31-33</sup> as used previously.<sup>31</sup> Medications that were not included in Summers' Class of Drug list were given a score of 0.

2. Clinician-rated ACH score: Because Summers' classification, published in 1978, did not include many newer medications, we developed an alternative measure of ACH medication exposure. First, we established a list of 340 medications that included those used in our population and those reported to have ACH effect in the literature.<sup>17,18,30,35,39-43</sup> Second, 3 geriatric psychiatrists (M.C., F.P., and M.E.) independently rated the ACH effect of each medication from 0 (none) to 3 (high) based on their clinical experience and knowledge of the properties of the medications. Then we assessed the interrater reliability of the 3 clinicians' ratings for all 340 medications and the concordance of the mean and median values of the 3 clinicians' ratings with Summers' Class of Drug<sup>30</sup> and 3 sources of laboratory data,<sup>39-41</sup> respectively. We selected the median value of the clinicians' ratings based on high correlations between the 3 clinicians' ratings for the 340 medications and strong agreement of the median ratings with Summers' Class of Drug ( $r=0.71$ ,  $n=62$ ) and with the ACH effect ratings from laboratory data ( $r=0.56-0.65$ ;  $n=14-32$ ).

3. Number of ACH medications was a count of all the medications with a clinician-rated ACH score greater than 0.

4. Number of non-ACH medications was a count of all the medications with a clinician-rated ACH score of 0.

5. Total number of medications was a count of all the medications, ACH and non-ACH, and is a commonly used measure of medication exposure.<sup>9,11,13</sup>

not,<sup>16</sup> suggesting that dementia modifies the ACH-delirium relation. Finally, most published studies considered medication use to be a precipitating factor only. Exposure was typically measured before onset of delirium, either at a single point or accumulated over time to the onset of delirium.<sup>11-14,17,18</sup> Whether and to what de-

gree ACH medications play a role in predicting the severity of delirium symptoms after its onset has not yet been investigated, to our knowledge. Because the types, doses, and timing of prescribed medications can change frequently, especially in hospitalized patients, and presentation and severity of delirium symptoms typically fluctuate,

Because certain antipsychotic medications may be prescribed to control certain symptoms of delirium, the clinician-rated ACH score and number of ACH medications were also recomputed excluding antipsychotic medications (7 agents).

These measures of medication exposure were used as time-dependent variables, ie, measured each day during follow-up. Because drug doses were not available, except at enrollment, for computation of the Summers' DRN and clinician-rated ACH score we assigned a priori selected weights to each type of change for each medication used with respect to its previous dose and frequency. At baseline, each regularly prescribed medication, regardless of actual frequency and dose, was given a weight of 1.0, whereas that prescribed on an as-needed basis was given a weight of 0.5. For each medication used during days without dose or frequency changes, the corresponding DRN and ACH scores were assumed to be equal to those at baseline or on the last day of dose or frequency change (ie, weight=1), whichever was more recent. For any day when the dose or frequency of a medication changed, the 2 medication exposures were approximated by multiplying the exposures on the previous day by a factor of 1.5 for an increase or 0.67 for a decrease. (A list of the clinician-rated ACH scores for the 234 medications evaluated in this study and a case scenario to demonstrate the weighting strategy are available from the authors on request.)

Because toxic delirium typically starts within hours of drug or other chemical substance intake,<sup>19,24,37</sup> we defined the day before DI assessment as the exposure time window. For instance, if a patient was assessed with the DI on day 3, his or her DI score was associated with the medication exposure measured for day 2, a strategy similar to that used by Marcantonio et al.<sup>12</sup>

#### CONFOUNDING OR MODIFYING VARIABLES

Potentially important confounding or effect-modifying variables included a time-dependent variable, length of follow-up since enrollment, and the following fixed baseline variables. Dementia was assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a 16-item, clinically validated instrument based on interviewing a family member that uses a cutoff score greater than 3.5 to define dementia.<sup>44,45</sup> Because of some missing family interviews, we retained a category for missing IQCODE. The Mini-Mental State Examination<sup>45,46</sup> was used descriptively at enrollment but was not used to define dementia due to potential confounding by delirium symptoms. Comorbidity was assessed with the Charlson Comorbidity Index using data abstracted from the hospital chart by a nurse abstractor masked to study group.<sup>47</sup> Laboratory variables, including serum albumin (abnormal, <33 g/L) and serum urea nitrogen-creatinine ratio,<sup>10</sup> were also abstracted from patient hospital charts. Patients with missing data were assumed to have normal values. Visual and hearing impairment were assessed clinically

at enrollment for presence or absence. History of alcohol and/or other drug abuse (present or absent) was obtained from an informant. Sociodemographic information included sex, age, marital status, and living arrangement before hospital admission (home vs other). Other confounders included prevalent vs incident delirium and study group, denoted by 2 dummy variables: intervention vs control and trial vs prognosis.

#### STATISTICAL ANALYSES

Preliminary analyses included descriptive statistics of medication exposure and potential confounding or modifying variables. In patients with multiple DI measurements, the within-patient mean of each time-dependent variable was calculated based on all days preceding DI assessments.

An unbalanced repeated-measures analysis of variance model using the SAS 6.12 MIXED procedure<sup>48</sup> was used to account for (1) repeated measurements of the DI (dependent variable) and exposure for the same individual and (2) unbalanced design, ie, the fact that the number of available DI scores or their timing varied from patient to patient. This procedure allows for a mixture of between-patient (fixed at baseline) and within-patient (time-dependent) covariates. We assumed that the covariance structure of errors, autoregressive order 1, will account for the dependence of subsequent observations on the same patient and used the Akaike Information Criterion for comparison with alternative structures.<sup>49-51</sup> All models were estimated using restricted maximum likelihood estimation.<sup>48</sup>

Effects of the 3 ACH variables—Summers' DRN, clinician-rated ACH score, and the number of ACH medications—were each assessed in a separate model, adjusting for the number of non-ACH medications or the total number of medications, follow-up duration, dementia, age, Charlson Comorbidity Index score, visual or hearing impairment, serum albumin level, living arrangement before hospital admission, type of delirium, and study group. In addition, all models included the baseline DI score, allowing us to evaluate the exposure effect in patients with the same initial delirium severity and thereby reduced potential confounding by indication, which could occur if symptomatically severe patients are prescribed more ACH medications.

Model estimation was conducted using a 3-step strategy. First, we fitted a model with 14 a priori selected covariates. Second, we assessed the following additional covariates one at a time to test their potential confounding effects: (1) sex, (2) serum urea nitrogen-creatinine ratio, and (3) history of alcohol or other drug abuse. Finally, we tested the interactions of ACH medication exposure with dementia in the models selected via the previously stated procedure. In sensitivity analysis, the final models incorporated modified measures of ACH medications, ie, antipsychotic agents were excluded from ACH category. A significance level of  $P < .05$  was used for hypothesis testing.

tuates over time, studies that ignore the dynamic features of medication exposure and delirium symptoms might be biased by a false temporal sequence or confounding by indication. Therefore, we conducted this study to investigate the effect of ACH medication exposure on the subsequent severity of delirium symptoms

in a cohort of hospitalized elderly patients with diagnosed delirium. Our 2 a priori hypotheses were that (1) current exposure to ACH medications is independently associated with increased severity of delirium symptoms and (2) the effect of ACH medication exposure on delirium severity may depend on dementia status, with

**Table 1. Characteristics of 278 Patients With Delirium at Baseline**

Characteristic	Patients, No.	Value*
<b>Continuous Variables</b>		
Age, y	278	83.4 ± 7.3
Charlson Comorbidity Index score	278	2.9 ± 2.0
Serum urea nitrogen–creatinine ratio	278	21.1 ± 7.5
Mini-Mental State Examination score	278	15.0 ± 7.2
<b>Categorical Variables</b>		
Sex		
M	108	38.8
F	170	61.2
Marital status		
Spouse	95	34.2
No spouse	183	65.8
Dementia		
Yes	180	64.7
No	72	25.9
Missing	26	9.4
Visual or hearing impairment		
Yes	55	19.8
No	223	80.2
Serum albumin level		
Low	43	15.5
Normal	235	84.5
Living at home		
Yes	206	74.1
No	72	25.9
Alcohol or other drug abuse		
Yes	26	9.3
No	252	90.7
Delirium type		
Prevalent	234	84.2
Incident	44	15.8
Study group		
Trial, intervention	95	34.2
Trial, control	96	34.5
Prognosis	87	31.3

\*Values are mean ± SD for continuous variables and percentages for categorical variables.

demented patients being more sensitive to ACH medications than those without dementia.

## RESULTS

### CHARACTERISTICS OF THE STUDY POPULATION

Of 293 patients with delirium enrolled, we excluded 15 with only a baseline DI assessment, leaving 278 patients (191 from the trial and 87 from the prognosis study). **Table 1** presents the characteristics of this delirium cohort. **Table 2** summarizes different aspects of variation over time in time-dependent variables representing medication exposures and delirium severity. During the 21 days of follow-up, the mean ± SD number of DI assessments was 5.7 ± 2.8. The mean ± SD length of follow-up between the first and last DI assessment was 12.3 ± 7.0 days. The 278 patients used a total of 234 medications at least once, 47 (20.1%) of which were classified as ACH medications (clinician-rated ACH score >0). **Table 3** presents the prevalence of the most frequently used ACH

**Table 2. Characteristics of 278 Patients With Delirium: Time-Dependent Variables\***

Variable	Baseline Measures	Repeated Measures†
Delirium Index score	8.3 ± 3.9	7.4 ± 3.9
Summers' Drug Risk Number	2.2 ± 2.3	2.5 ± 2.3
Clinician-rated ACH score	1.7 ± 1.8	2.0 ± 1.8
ACH medications, No.	1.2 ± 1.1	1.4 ± 1.1
Non-ACH medications, No.	6.0 ± 3.5	6.3 ± 3.4
Total medications, No.	7.2 ± 3.7	7.7 ± 3.6

\*Data are given as mean ± SD. ACH indicates anticholinergic.

†Mean values of all available measurements for each patient taken several times during follow-up.

**Table 3. Most Frequently Used ACH Medications in Patients With Delirium\***

Medication	Patients, No. (%)†	Clinician-Rated ACH Score	Summers' COD‡
Haloperidol	120 (43.2)	2	NA
Morphine	69 (24.8)	1	III
Ranitidine	64 (23.0)	2	NA
Empracet	53 (19.1)	2	NA
Dimenhydrinate	50 (18.0)	3	NA
Metoprolol	34 (12.2)	1	NA
Atenolol	17 (6.1)	1	NA
Codeine	17 (6.1)	1	II
Risperidone	16 (5.8)	1	NA
Diazepam	14 (5.0)	1	III
Fentanyl	11 (4.0)	1	II
Fluvoxamine	10 (3.6)	1	NA
Pethidine hydrochloride	9 (3.2)	2	III
Loperamide	9 (3.2)	1	NA
Thioridazine	8 (2.9)	3	III
Paroxetine	8 (2.9)	2	NA

\*ACH indicates anticholinergic; COD, Class of Drug; and NA, not available in the study by Summers.<sup>30</sup>

†Number of patients who had taken a given medication at least once during 21-day follow-up.

‡All medications marked as NA were arbitrarily assigned a COD score of 0 in our study.

medications, ie, those used by at least 3% of the study population at any time during follow-up.

### REPEATED-MEASURES ANALYSES OF VARIANCE

There were no systematic differences in Akaike Information Criterion values between the 3 covariance structures considered (data not shown). Therefore, we decided to select autoregressive order 1 structure, based on its conceptual simplicity and stability of results. **Table 4** summarizes the results of 4 regression models, each using a different combination of medication exposure variables. The regression coefficients, their 95% confidence intervals, and the corresponding P values are shown for medication exposure and other main covariates.

In the initial models including the 14 preselected covariates, the clinician-rated ACH score was a statistically significant correlate of delirium severity on the next day, when adjusted for the number of non-ACH medications ( $P < .01$ ) (Table 4, model 1). The effect re-

**Table 4. Repeated-Measures Analyses of the Effect of ACH Medications on Severity of Delirium in 278 Patients: Mixed Linear Regression Models\***

Covariates†	Model 1		Model 2		Model 3		Model 4	
	Estimate (95% CI)	P						
Medication measure								
Summers' Drug Risk Number	...		...		...		0.07 (-0.07-0.21)	.35
Clinician-rated ACH score	0.27 (0.10-0.42)	<.01	0.20 (0.03-0.38)	.02	...		...	
No. of ACH medications	...		...		0.52 (0.26-0.78)	<.01	...	
No. of non-ACH medications	0.11 (0.01-0.20)	.02	...		0.11 (0.01-0.20)	.03	...	
Total No. of medications	...		0.13 (0.03-0.23)	.01	...		0.53 (0.43-0.62)	.01
Effect modifier								
Dementia (1 = dementia, 0 = no dementia)	1.23 (0.40-2.06)	<.01	1.25 (0.43-2.09)	<.01	1.30 (0.50-2.14)	<.01	1.23 (0.30-2.16)	<.01
Dementia missing (1 = missing, 0 = present)	1.22 (0.10-2.51)	.07	1.24 (-0.10-2.55)	.06	1.29 (-0.03-2.61)	.06	1.19 (-0.13-2.50)	.07
Baseline Delirium Index score (continuous)	0.52 (0.43-0.61)	<.01	0.52 (0.44-0.61)	<.01	0.52 (0.43-0.61)	<.01	0.53 (0.44-0.62)	<.01
Akaike Information Criterion	-2889.55		-2888.69		-2886.51		2891.07	

\*ACH indicates anticholinergic; CI, confidence interval.

†This table lists only the main covariates of interests, ie, medication measures, effect modifiers, and baseline Delirium Index score. Each model also included the following covariates: age, length of follow-up, serum albumin level, living arrangement, Charlson Comorbidity Index, visual or hearing impairment, delirium type, and study group.

mained statistically significant even when adjusting for the total number of medications ( $P < .02$ ) (Table 4, model 2). However, the effect of Summers' DRN was not significant when adjusted for total number of medications ( $P = .35$ ) (model 4) or number of non-ACH medications ( $P = .08$ ) (data not shown). When testing the effect of the number of ACH medications, we adjusted for non-ACH medications but not for total number of medications because the latter included ACH medications. The results were consistent with model 1 in terms of the significance of the estimated regression coefficients for the ACH medication exposure (Table 4, model 3). The effect of increasing the number of non-ACH medications was also statistically significant, but the effect of ACH medications was almost 5 times stronger (0.52 vs 0.11) (Table 4, model 3).

We then included in models 1 through 3 sex, serum urea nitrogen-creatinine ratio, and alcohol and/or other drug abuse, one at a time. In all 3 models, the effect of ACH medications remained significant after adjusting for each of these additional covariates, whereas none of these additional covariates was statistically significant ( $P > .05$ ) (data not shown). In each model, we also tested the interaction between ACH medication exposures and dementia. No significant interactions were detected ( $P = .21-.89$ ) (data not shown).

Models 1 and 3 were similar in terms of goodness of fit to data and the significance of the estimate of ACH medication exposure (last row of Table 4). Translating the estimated regression coefficients (0.27 and 0.52, respectively) into practical meaning, daily exposure to ACH medications equivalent to 2 points (population mean scores) of clinician-rated ACH score, or to 1.4 ACH medications (population mean number), would be associated with an approximately 0.5- to 0.7-point increase in the subsequent DI score when the values of all other co-

variates in the model remain unchanged. Sensitivity analysis, in which antipsychotic agents were excluded, gave similar effect estimates for the clinician-rated ACH score (0.26; 95% confidence interval, 0.07-0.44) and number of ACH medications (0.47; 95% confidence interval, 0.18-0.76) (in models 1 and 3, respectively, data not shown).

Because the total number of medications in model 2 includes ACH medications, the clinician-rated ACH score hypothetically represents only the "net" ACH effect of these medications. This model provides more convincing statistical evidence of the importance of ACH effect but has limited clinical interpretability. Thus, model 2 is not selected as the final model.

#### COMMENT

In this cohort of older medical inpatients with delirium, we observed that change in exposure to ACH medications, as defined by a clinician-rated ACH score, was independently associated with change in severity of delirium symptoms. This association persisted after adjusting for the total number of medications, indicating that it is specific to the medications with suspected ACH effect and is independent of initial severity of delirium and presence of dementia or other comorbid conditions. Although previous studies have suggested use of ACH medications to be a significant risk factor precipitating onset of delirium,<sup>27-29</sup> this study is the first, to our knowledge, to investigate the dynamic nature of the relation between ACH exposures and the severity of delirium symptoms and, as such, provides additional evidence for the hypothesized ACH-delirium association. These findings may be of particular practical relevance given the fact that increased numbers of medications are prescribed for hospitalized elderly patients, many of whom

are already at increased risk of delirium by virtue of dementia and other acute and chronic medical problems.

Considerable evidence suggests that failure of cholinergic transmission plays a key role in several memory disorders, including Alzheimer disease.<sup>52</sup> Decreased synthesis of cerebral acetylcholine and epinephrine has been postulated to account for the cognitive and attentional impairment and for the slowing of the electroencephalographic background activity commonly seen in delirium.<sup>53</sup> In addition, serum ACH activity has been associated with delirium in medical<sup>18</sup> and postoperative patients<sup>25,27,28</sup> or patients who had received electroconvulsive therapy.<sup>54</sup> Elderly patients might be more susceptible to ACH intoxication because of aging-related reductions in cholinergic brain receptors<sup>20,23,27,55</sup> and metabolizing capacity of hepatic enzymes and because of concurrent use of several ACH medications.<sup>17,43</sup>

However, the results of clinical and epidemiological studies on the ACH-delirium association are conflicting. At least 3 large prospective studies have reported negative findings.<sup>12-14</sup> In a cohort of elderly institutionalized patients, Schor et al<sup>14</sup> intensively evaluated the effect of 8 pure ACH medications and a broad class of ACH medications, including neuroleptics and tricyclic antidepressants, on risk of developing delirium, finding no significant associations. Marcantonio et al,<sup>12</sup> in a nested case-control study, also did not detect a significant effect of using ACH medications, including antihistamines, tricyclic antidepressants, antiemetics, and certain neuroleptics. Low exposure of the study population to ACH medications was cited as an explanation in both studies. On the other hand, Francis et al<sup>13</sup> observed a higher, but statistically nonsignificant, frequency of ACH medication use in the delirium group than in controls (24% vs 15%). Because patients with symptoms of delirium often use more ACH medications than nondelirium patients<sup>17,18,27</sup> or patients whose delirium has resolved,<sup>26</sup> measuring ACH exposure by proportions of exposed persons between the 2 groups rather than number of ACH medications taken may lead to underestimation of the ACH-delirium association.

Our second research objective was to evaluate the interaction between ACH medication use and dementia. Previous research has reported that patients with Alzheimer disease are more sensitive to ACH drugs because of a central cholinergic deficit.<sup>16,52,53,56</sup> Sunderland et al<sup>16</sup> found that patients with Alzheimer disease showed greater impairments than controls in most cognitive tasks after receiving low doses of scopolamine hydrobromide. The absence of a significant interaction between dementia and use of ACH medications in our study may be due to 3 reasons. First, most of our patients had mild to moderate severity of dementia (Mini-Mental State Examination mean score, 15.1); a cerebral cholinergic deficit might be less evident in these patients.<sup>57</sup> Second, the measurement error in classifying dementia or quantifying ACH exposure might have prevented an otherwise significant interaction from being detected. Because the Mini-Mental State Examination score of patients with dementia might be confounded by superimposed delirium symptoms, we instead used the IQCODE to define dementia. Although this instrument has been reported to have good validity in the elderly population, it has not

been validated in demented patients with delirium. Third, dementia may modify the effect of ACH medications before but not after the development of delirium.

Our study has several limitations. First, our quantitative measures of ACH exposure may not accurately represent the ACH effect. The observable therapeutic or adverse effect of medications on which the clinicians' ratings are based may involve non-ACH effects, eg, antidopaminergic, antiadrenergic, or antihistaminic effects. On the other hand, although the ratings were in agreement with other clinical observations or experimental studies addressing ACH properties for some of the study medications,<sup>30,39-41</sup> several medications rated as having little or no ACH effect by the clinicians have been reported to have detectable serum ACH activities by radioreceptor assay.<sup>43</sup> Our clinicians' ACH ratings may not take into account medications with *in vitro* ACH activity but without observable clinical effects because of their inability to pass the blood-brain barrier or another mechanism.<sup>58</sup> However, because the medication data were abstracted from patient medical charts using standard procedures and the abstracter was masked to DI assessment, a differential misclassification or systematic overcounting or undercounting of ACH medications would be unlikely. In addition, misclassification between ACH vs non-ACH medications would most likely be nondifferential. Thus, the expected overall impact of potential misclassification of ACH medication exposure would be to attenuate rather than exaggerate the true association. Similarly, the possible loss of precision due to the use of weighted rather than exact dose change might have biased the estimates toward rather than away from the null for ACH and non-ACH medications. Finally, because delirium symptoms can vary over the course of a day and our DI assessments were made at an interval of more than a day, it is possible that some patients were given ACH medications by physicians in response to the increase in delirium on a previous day. To assess the impact of such a "reverse causality" or uncontrolled confounding by indication, we excluded all the antipsychotic medications, those most likely to have been prescribed to control delirium symptoms, with no change in the magnitude of the association.

In conclusion, reasonable use and timely adjustment in the dose and frequency of ACH medications used might have significant implications for managing delirium symptoms in older medical inpatients. Further effort is warranted to test the replicability and clinical importance of these findings using alternative measures of delirium symptoms, ACH medications, and other potentially important risk factors of delirium.

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