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USE OF ANTICHOLINERGIC MEDICATIONS

PREDICTS

SYMPTOM SEVERITY OF DELIRIUM IN OLDER MEDICAL INPATIENTS

----- A Prospective Cohort Study with Repeated Measurements

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ABSTRACT

Background: Anticholinergic (ACH) medications are among biologically plausible and potentially modifiable risk factors of delirium. But the epidemiological findings on its role in hospitalized elderly patients are conflicting. **Objectives:** To evaluate the association between use of ACH medications and delirium severity and the potential effect-modification on this association by dementia. **Methods:** A cohort of 278 medical inpatients aged 65 years and over with diagnosed delirium was prospectively followed up with the Delirium Index (DI) every 2-7 days up to 3 weeks in a primary acute care hospital. Their DI scores were associated with measures of ACH medication exposure in the previous day using the mixed linear regression model adjusting for potential confounders or effect modifiers. **Results:** A total of 47 potential ACH medications were used in the cohort (mean: 1.4 per patient per day). An increase in daily ACH medication exposure of one such medication was on average associated with a subsequent increase in delirium severity of 0.52 DI points (95% CI: 0.3-0.8) after adjusting for dementia, baseline DI score, length of follow-up and concurrent use of non-ACH medications. Dementia did not modify the association. Sensitivity analyses using alternative definitions of ACH medications or excluding antipsychotics did not change the results. **Conclusions:** Exposure to ACH medications is independently and specifically associated with a subsequent increase in symptom severity of delirium among elderly medical inpatients.

RÉSUMÉ

Contexte : Les médicaments anticholinergiques (ACH) sont parmi les facteurs de risque biologiquement plausibles et potentiellement modifiables de delirium. Cependant les résultats épidémiologiques sur leur rôle chez les patients âgés hospitalisés sont en controversés. **Objectif :** Évaluer l'association entre l'usage des médicaments ACH et la sévérité du délirium et de l'effet-modificateur de la démence sur cette association. **Méthodologie :** Une cohorte de 278 patients âgés de 65 ans et plus, hospitalisés sur une unité médicale dans un hôpital de soins primaires avec un diagnostic de delirium a été suivi prospectivement à tous les 2 à 7 jours avec l'Index de Délirium (ID) et ce, jusqu' à concurrence de 3 semaines. Leurs scores de ID a été associé à la mesure d'exposition de médications ACH en utilisant un mode de régression linéaire mixte en ajustant Pour des éléments confondants potentiels ou des effets modificateurs. **Résultats :** 47 médicaments ACH furent utilisés par les membres de le cohorte (moyenne: 1.4 par patient par jour). Une augmentation significative du score de l'ID fut associée à l'exposition aux médications ACH en ajustant pour la présence de démence, du score initial de l'ID et du nombre de médications non-ACH. La présence de démence n'a pas modifié cette association. Une analyse de sensibilité en utilisant les autres définitions de médicaments ACH ou en excluant les antipsychotiques n'a pas changé les résultats. **Conclusion :** L'exposition aux médicaments ACH est indépendamment et spécifiquement associée à une augmentation subséquente de la sévérité de symptômes de délirium chez les patients âgés hospitalisés.

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PREFACE

All the work presented in this thesis is my original contribution, unless otherwise stated. The study or any part has not been published and is not in press. The data used in this thesis are from the two ongoing studies led by Dr Cole and Dr McCusker at St. Mary's Hospital, as indicated in the thesis. The rating of the anticholinergic effect of study medications on which the clinician-rated ACH score was based was conducted by Dr Martin Cole, Dr Francois Primeau and Dr Michel Elie. The weighting system for measuring the change of medication exposure over time was derived from Dr McCusker's idea. The use of the mixed linear regression model was Dr Abrahamowicz's idea and implemented under his supervision.

I want to dedicate this thesis to my loving family: my wife, daughter and parents.

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LIST OF ABBREVIATIONS

ACH	Anticholinergic
ACHM-CR	Clinicians' Rating Based ACH Medications
ACHM-TC	Therapeutic Classes Based ACH Medications
AD	Antidepressants.
AIC	Akaike's Information Criterion
ANOVA	Analyses of variance
BUN	Blood Urea Nitrogen
BZD	Benzodiazepines.
CI	Confidence Interval
CAM	Confusion Assessment Method
CCI	Charlson Comorbidity Index
COD	(Summers') Class of Drug
DED	Daily Effective Dosage
DI	Delirium Index
DRN	(Summers') Drug Risk Number
DRS	The Delirium Rating Scale
DSM-III (IIIR. or IV)	Diagnostic and Statistical Manual of Mental Disorders. the third (third revised. or fourth) edition.
IADL	Instrumental Activities of Daily Living
ICD-9 (or -10)	International Classification of Disease. 9th (10th) edition
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MLR	Multiple Linear Regression
MMSE	Mini-Mental State Examination
NACHD-CR	Clinicians' Rating Based Non-ACH Deliriogenics
NACHD-TC	Therapeutic Classes Based Non-ACH Deliriogenics
NACHM-CR	Clinicians' Rating Based Non-ACH Medications
NS	Not statistically significant ($p>0.05$).
NSAID	Non-Steroid Antiinflamentory Drugs
OM-CR	Clinicians' Rating Based Other Medications
OM-TC	Therapeutic Classes Based Other Medications
RCT	Randomized Clinical Trial
REML	Restricted Maximum Likelihood Estimation
SAS	Statistical Analysis System
SPMSQ	Short Portable Mental Status Questionnaire
SSRI	Selective Serotonin Receptor Inhibitors

1. INTRODUCTION

Delirium may be the most common cognitive disorder in hospitalized elderly, and has been associated with prolonged hospital stay, increased functional decline, morbidity, mortality and nursing home placement (1-4). However, delirium is often under-recognized clinically (5,6) and, to date, evidence of treatment intervention benefits is limited (7). 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 factors that may predispose to, precipitate, or perpetuate delirium (9-18). Among the risk factors studied, medication use in general, and anticholinergic (ACH) medication in particular, has been suspected to be a common precipitating risk factor (9-15,19-21).

The ACH medication-delirium association may be particularly important given its high biological plausibility, as suggested by a central cholinergic deficit mechanism for delirium (19,22-24) and the clinical correlation between serum ACH activity and delirium (18, 25-28). However, the research findings to date are controversial. Some studies have found a significant association between use of ACH medications and delirium (23,27-30), while others have not (12-14). The methodological differences between these studies, particularly on measures of ACH exposure, have impeded a consistent interpretation of the ACH-delirium association. Most published studies consider medication use as a precipitating factor only, with exposure typically measured prior to the onset of delirium, either at a single point or accumulated over a period of time up to the onset of delirium (11,12-14, 17,18). The role of ACH medication as a perpetuating factor that predicts the longitudinal variation of delirium symptoms following the onset of delirium has not yet

been investigated. Since the type, dose and timing of prescribed medications may change frequently, especially in hospitalized patients, and the presentation and severity of delirium symptoms typically fluctuate over time, studies ignoring the dynamic features of medication exposure and/or delirium symptomatology may be biased by a false temporal sequence or confounding by indication. Therefore, this thesis was conducted to explore the dynamic relationship between exposure to ACH medications and the severity of delirium symptoms among hospitalized elderly patients with diagnosed delirium.

2. REVIEW OF LITERATURE

2.1. Evolution of Delirium Concept

2.1.1. Historical background

Delirium, or a cluster of mental and behavioral symptoms described under the name of delirium, may be one of the oldest recognized medical phenomena (19,31). The term delirium can be found in the medical literature as early as in the era of Galen when it presented as *mentis alienatio* (alienation of mind) frequently following fever or other serious physical illness (31). However, during different periods the term delirium has encompassed many different forms of disturbances of thought, mood or action, and has included such diverse clinical entities as phrenitis, functional insanity and psychoses (19,31-33). A recent review noted that more than 30 synonyms have been used to describe the same condition (32). This terminological muddle has impeded effective clinical communication, education and research on this important condition.

2.1.2. Current Delirium Concept in DSM-III

It was not until 1980 that for the first time delirium was included as an independent diagnostic category into formal medical nomenclature, the American Psychiatric Association's Diagnostic and Statistical Manual, third Edition (DSM-III) (34). Using consistent terminology and explicit diagnostic criteria, DSM-III defined delirium as an organic mental disorder (with a recognized synonym of acute confusional state), characterized by clouding of consciousness with reduced capacity to shift, focus or sustain attention, accompanied by disturbances in orientation, memory, perception, speech, sleep-wake cycle, and psychomotor activity. DSM-III also distinguished other types of organic mental disorders from delirium. On the other hand, the notion that

delirium is a reversible disorder was not kept as an explicit criterion. The DSM-III's descriptive definition and diagnostic criteria provide a conceptual framework for our current understanding of a delirium syndrome along the following three dimensions:

1) Global cognitive impairment: the main domains of cognition — perception, memory, attention and thinking are all affected to some degree, with most obvious clinical picture of reduced ability to appropriately maintain and shift attention to external stimuli.

2) Transient course, acute or abrupt onset, and diurnal fluctuation in severity of the symptoms with typical worsening at night.

3) Putative organic etiologies that may affect the integrative functioning of the brain via direct or indirect derangement of central neurotransmission and alteration of cerebral metabolism.

These three aspects constitute both critical components of our current delirium concept and key clues for diagnosis and differential diagnoses. For example, delirium can be distinguished from another common global cognitive disorder in the elderly, dementia, by its transient course, acute onset and fluctuating severity of the cognition impairment. These core clinical features have been retained in the subsequent revisions of the DSM, i.e., DSM-IIIR (35) and DSM-IV (36), with some obvious conceptual shiftings and redefinitions.

2.1.3. Modification in DSM-IIIR and DSM-IV

One major modification made in DSM-IIIR (35) was that it shifted emphasis from clouding of consciousness to reduced attentiveness and disorganized thinking. Accordingly, the diagnostic criteria were further operationalized as follows:

A). Reduced ability to maintain attention to external stimuli and to appropriately shift attention to new external stimuli.

B). Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech.

C). At least two of the following:

(1) reduced level of consciousness, e.g., difficulty keeping awake during examination

(2) perceptual disturbances: misinterpretations, illusions, or hallucinations

(3) disturbance of sleep-wake cycle with insomnia or daytime sleepiness

(4) increased or decreased psychomotor activity

(5) disorientation to time, place, or person

(6) memory impairment, e.g., inability to learn new material, such as the names of several unrelated objects after five minutes, or to remember past events, such as history of current episode of illness

D). Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.

E). Either (1) or (2):

(1) evidence from the history, physical examination, or laboratory tests of a specific organic factor(s) judged to be etiologically related to the disturbance

(2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., manic episode accounting for agitation and sleep disturbance.

The operationalization of diagnostic criteria in DSM-IIIR has facilitated clinical detection of and research on delirium (9,19-21,37-40) and makes DSM-IIIR become the

de facto "gold standard" in North America (40,41). On the other hand, however, some authors still believe that DSM-III criteria correspond more closely than the DSM-IIIR to the clinical features of delirium (37-39). In an attempt to overcome the drawbacks of DSM-IIIR and to increase agreement with the International Classification of Disease, 10th edition (ICD-10), DSM-IV (36) redefined delirium as a disturbance of consciousness and further specified five separate etiologic subcategories by general medical conditions, substance intoxication or withdrawal, multiple etiologies and not otherwise specified (36,37). It can be expected that the current concept of delirium will continue to evolve as evidence accumulates from the applications of these criteria to both clinical work and research.

2.2. Clinical Assessment Instruments

Publication of DSM-III and DSM-IIIR criteria has also inspired efforts to develop more explicit operationalizated instruments for detecting and measuring delirium (41,42). Most instruments are devised for use by clinicians to detect delirium cases in high-risk populations. Some can also assess severity of delirium symptoms and thus can be used to monitor the clinical course of delirium patient. Some of the most widely used instruments in delirium clinics and research settings are briefly described below.

2.2.1. Brief cognitive tests:

1). The Mini-Mental State Examination (MMSE) (43): MMSE was originally devised to grade the global cognitive status of patients. It includes eleven questions, takes about 15 to 20 minutes to administer and is suitable for clinical assessment of elderly patients. Scores range from 30 (no impairment) to 0 (maximum impairment), with 24 or less indicating possible cognitive impairment. The MMSE is widely used in dementia clinics

and has established validity and reliability in detecting cognitive impairments in a variety of clinical and research settings (44). In general medical inpatients, a sensitivity of 87% and specificity of 82% in detection of either dementia or delirium using clinical diagnosis of a psychiatrist as gold standard has been reported (45).

2). The Short Portable Mental Status Questionnaire (SPMSQ) (46,47). The SPMSQ is a widely used, observer-rated brief cognitive rating scale, with 10 items evaluating orientation, memory, and concentration. A score of 10 indicates severe impairment. Given its brevity and simplicity, the SPMSQ is often used as a screening test for delirium and is particularly acceptable for elderly patients. Using a cutoff point of 3 or more errors to detect organic brain syndromes in a medical inpatient population, the sensitivity was found to be 84% and the specificity 89% (48).

Since MMSE and SPMSQ do not include all the defining features of delirium (e.g., acute onset and disturbance of consciousness) and rely on patient's verbal response, they can not be used as an independent diagnostic instrument or to assess non-communicative patients. Instead they were often included as screening tools in a more comprehensive delirium detection procedure (41).

2.2.2. The Confusion Assessment Method (CAM) (49)

The CAM is a structured interview that assesses the nine symptom domains of delirium specified in DSM-IIIR: acute onset and fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor activity and sleep-wake disturbance. Since each symptom is operationalized in explicit terms and information obtained through both direct interview and observation, the CAM can also be used by a trained

lay-interviewer and to assess non-communicative patients. Against clinical judgment of a psychiatrist in identifying patients with delirium, the sensitivity of CAM was found to be 97% and specificity 92% (49). The interrater reliability (Kappa coefficient) with trained personnel was 1.0 in a randomized clinical trial of systematic intervention among elderly inpatients with delirium (7).

2.2.3. The Delirium Rating Scale (DRS) (50)

DRS includes 10 items assessing different domains of delirium. Each item was rated on a 4-point scale using all available information over a 24-hour period from patient and family interview, mental state exam, medical history, laboratory tests, and nursing observation. DRS has been reported to be able to differentiate delirium patients from dementia, schizophrenia and normal controls (50). Although its summary score ranging from 0 (least severe) to 32 (most severe) looks like a severity scale, DRS includes three items (acuteness of onset, fluctuation in symptoms and putative cause) that reflect the course or etiology rather than the severity of delirium (51). In addition, its unstructured methods to elicit information may restrict comparability with other standardized assessments (41).

2.2.4. The Delirium Symptom Interview (DSI) (52)

DSI is a structured symptom checklist covering seven domains of the DSM-III criteria for delirium except temporal course and organic cause. Each domain is rated as being present or absent based on information obtained via interview or observation. Although a detailed symptom profiles can be constructed on DIS, the checklist per se does not seem to be a functional severity scale or independent diagnostic instrument due to lack of severity grading of the symptoms and some defining criteria. In addition, its

lengthy format and complex administration makes it unfeasible for frequent assessments of delirium symptoms.

2.2.5. The Delirium Index (DI) (53)

The DI was developed by McCusker and colleagues in the ongoing randomized clinical trial as a tool for longitudinal assessment of symptom severity of delirium (53). It includes seven items that cover all the major domains of delirium symptoms specified in DSM-IIIR including inattention, disorganized thinking, altered consciousness, disorientation, memory and perceptual disturbance and motor activity (see Appendix 1 for details). Each item was rated on a 4-point scale based solely on observation and interview of the patient without additional information from family members, nursing staff or the patient's medical chart; the total score ranges from 0 to 21, with a higher score indicating greater severity. The DI was designed to be used in conjunction with several questions in the MMSE, which reduces the time of assessment and enhances patients' cooperation when both cognitive function and delirium severity need to be assessed, as often is the cases in dementia clinic. Preliminary study showed that its concurrent criterion validity with the DRS was 0.84 (Spearman's correlation coefficient), and the interrater reliability between research assistants and geriatric psychiatrists was 0.88 (53). In addition, the DI was sensitive to change in delirium severity over time, as evidenced by a summary Spearman's r of 0.71 (95% CI: 0.53, 0.82) between change scores of the DI and of the adjusted DRS using serial ratings of two geriatric psychiatrists (53).

Efforts have also been made to develop instruments that serve both diagnostic and severity rating purpose, such as the Delirium Assessment Scale, the Memorial Delirium Assessment Scale and the Confusional State Evaluation, or specifically devised

instruments for use by nurses, such as the NEECHAM Confusion Scale and the Nursing Delirium Rating Scale (41,42). The continuing effort to develop new instruments reflects both conceptual discrepancies in defining delirium and practical difficulty in evaluating delirium patients clinically, and will eventually lead to better understanding of delirium symptomatology.

2.3. Epidemiology of Delirium

2.3.1. Prevalence and Incidence

Almost all the incidence and prevalence estimates of delirium were derived from hospitalized populations. The only study in non-hospital population, to our knowledge, is the Eastern Baltimore Mental Health Survey that reported a prevalence of 1.1% among a community-dwelling population aged 55 years and over (54).

According to our literature review, in hospitalized elderly populations admitted to medical or geriatric wards, the estimated prevalence at hospital admission ranges from 5% to 22% (2,11,13,55, 56,57) and the incidence during hospitalization from 5% to 28% (2,11,13,39,55,56,58,59). For elderly surgical patients undergoing hip fracture or orthopedic operations, the incidence estimates range from 17% to 52% (60-66); whereas patients who underwent elective noncardiac surgery had rates ranging from 9% to 18% (67-69). Prevalence and incidence estimates from other clinical populations fell within these ranges (20,70).

Table 1 presents information from a selected 19 studies (2,11,13,39,55-59,60-64,66,68) that used DSM-III or DSM-IIIR criteria and prospective case-detection procedure and thus were judged to be methodologically more reliable and diagnostically comparable. Although there still was considerable variation, patient population and

clinical setting appear to influence frequency estimates. The hip-fracture surgery population tends to have the highest incidence (17% to 52%) (60-66) whereas the medical population has the lowest rates (5%-30%) (2,11,13,39,55,56-59), with the mixed population coming in between (10%-31%) (14,71-75). Also studies in surgical populations tended to have a higher incidence than prevalence, whereas in medical populations the opposite was usually the case (except for study 11). Although the higher incidence rates alone may be explained by a higher baseline risk of surgical patients due to their more severe and emergent admission conditions (76), the higher incidence to prevalence ratios in surgical populations than in medical populations can be attributed only to an increased in-hospital risk related to surgery, such as anesthesia medications or the trauma incurred through operation, since the incidence and prevalence estimated within each study population would conceptually reflect only the force of hospitalization not the population.

2.3.2. Clinical Course and Natural History

By definition, delirium is an acute disease that usually develops over a short period of time, within hours or days in patients with systemic illness or abruptly following head trauma or seizure. An episode of delirium typically lasts about one week and seldom persists for more than one month (35). The research findings from clinical epidemiological studies in general agreed with such description. Roughly 70% to 90% of incident delirium occurred during the first two weeks following hospital admission or initial evaluation (11,14), although a few patients might have their first delirium episode as late as more than one month after admission (56,74). In 60% to 100% of incident cases the duration of an episode of delirium lasted no more than one week (64,72, 74).

but individual symptoms might persist for weeks or even months (2, 71). Average duration of hospital stay for delirium patients was frequently reported to be in the order of 8 to 25 days and usually significantly longer than patients without delirium (11, 13, 14, 58,60,61,63,67,71,72).

The variability of duration estimates of delirium may, again, be partially attributable to the methodological differences across studies, particularly the clinical setting, population characteristics, and procedure and length of case-detection. Alternatively, it may reflect a true heterogeneity of delirium with clinically significant subtypes or symptomatic variants related, perhaps, to different etiologies (71,75). As observed by Levkoff et al, 34% of 325 elderly hospitalized patients experienced individual symptoms of delirium without meeting full DSM-III criteria, outnumbering the diagnosed cases of incident delirium (31%), and the clinical outcomes of the "partial" delirium and diagnosed delirium cases were quite similar (71). In addition, the proportions of patients whose delirium symptoms completely resolved were only 4% at hospital discharge, and 21% and 18% at 3 and 6 months after discharge, respectively. Another study closely monitored 64 delirium cases out of 432 elderly medical or surgical inpatients during the entire hospitalization period, and found that about one third of the cases experienced more than 1 episode and that the initial DRS scores for those with multiple episodes were significantly higher than those of patients with a single episode (74). Although it is unclear whether the partial syndrome is merely a prodromal phase or an intermediate stage between full-blown episodes of delirium syndrome, these data highlighted the importance of longitudinal monitoring of delirium symptoms after the initial diagnosis.

The prognosis of delirium in the elderly has been well documented in the past decade. Patients with delirium tend to have a higher short-term mortality, especially during hospitalization, than other diagnostic groups of patients including dementia, depression or medical illnesses (13, 56, 63, 69, 71). However, the higher hospital mortality may be largely attributable to the underlying serious illnesses or comorbidity rather than delirium per se (13, 20, 71). Other adverse outcomes potentially associated with delirium include longer hospital stay, high rates of institutional placement, functional decline, increased dependence of activities for daily living (ADL) and high post-discharge mortality. A recent systematic review and meta-analysis of 8 prospective studies of delirium prognosis reported that delirium patients had a mean length of hospital stay of 20.7 days, mortality of 14.2% one month after admission, and institutional placement of 46.5% 6 months after admission. All these outcomes were significantly worse than among unmatched non-delirious control subjects (4). The obvious contrast between the observed poor outcomes and conceptual reversibility of delirium has inspired efforts to identify factors that may contribute to the development or progression of delirium.

2.3.3. Risk Factors

In traditional epidemiologic terminology, risk factors refer to factors that cause or predict development of diseases. Factors influencing the severity or manifestation of disease symptomatology after disease onset are usually termed prognostic factors (77-80). In regard to delirium, however, risk factors have been defined to include factors existing prior to onset of delirium (so called predisposing or precipitating factors), and factors that sustain or aggravate its clinical symptoms during the active phase of the clinical course

(perpetuating factors) (19). In accordance with this convention, this thesis will use the term "risk factor" in its broad sense, while leaving the term "prognostic factor" for those factors predicting longer term consequences or prognosis of delirium.

In recent decades, risk factor studies of delirium have proliferated, many of which have employed standardized diagnostic criteria, prospective detection procedures, and multivariate methods to control for confounding. Although methodological diversity remains, several risk factors have been consistently identified as being independently associated with delirium, which will be briefly described below.

1). Predisposing Risk Factors

Predisposing risk factors usually refer to the factors that occur some time before the onset of delirium. All such factors may in fact exist prior to the index hospitalization but some may not be detected or ascertained until the time of admission. Predisposing factors identified by recent prospective studies have included preexisting cognitive impairment or dementia (10, 13, 14, 56,57,64,68,72), old age (14, 56-59,62,64,66,67), male sex (14, 60,62), severe illness (13,56,68,72), medications (10, 12-14,61,64), alcohol abuse (62,68,72), hypoalbuminemia (71,75,81), increased blood urea nitrogen (10, 13, 39), history of depression (63,64,72) and physical function (13, 56). Other less consistently or less frequently identified predisposing factors included admission diagnosis or procedure (e.g., fever or infection, type of surgery) (12,14), laboratory abnormality (e.g., low sodium or potassium) (12,13) and visual impairment (10).

Among all the identified predisposing factors, cognitive impairment or dementia appears to be the most important and consistent; about 40 to 70% of delirium patients across studies had preexisting dementia or cognitive impairment (13, 14, 20, 56). The

presence of dementia was estimated to increase the risk of developing delirium more than 4-fold in a recent meta-analysis (9). The incidence rates from dementia-free populations at study entry tended to be lower than those from similar clinical settings but without screening out dementia patients (See Table 1). In addition, dementia, probably via its underlying physiological mechanism, may also modify the effect of other risk factors such as medications. It has been shown that patients with Alzheimer's dementia can be experimentally confused by anticholinergic drugs at doses that did not impair the cognitive performance of age-matched normal controls (16). However, ascertaining preexisting dementia in a delirious patient sometimes raises difficulty due to the patient's disturbed consciousness and behavior. Retrospective review of the patient's history of cognitive functioning before onset of delirium and follow-up after resolution of the delirium are usually required to establish the diagnosis.

Another common predisposing factor is old age. The incidence of delirium has been found to be positively associated with increasing age (14, 56-59,62,64,66,67). However, increase in age may be correlated with a variety of other predisposing or precipitating risk factors, such as medications, sensory impairments and multiple medical conditions (9,19,33,40). It remains unanswered as to whether the relation between age and delirium is accounted for by the aging process per se or through an independent pathology. An effort to clarify this relationship would help expand our understanding of the etiology of both delirium and dementia, as well as the normal aging process.

2). Precipitating Factors

Precipitating factors usually refer to those factors immediately preceding the onset of delirium and thus considered as putative causes or triggers of the disorder. Common

precipitating factors in the elderly may include substance abuse or withdrawal, sleep deprivation, infection and special medical procedures such as major surgery and use of restraints (10, 13, 20). Environmental factors may also provoke delirium, including lack of light in the room, frequent changes of nursing staff or room, noise from surrounding areas or a roommate with agitation or psychomotor excitement (19,20,32,33).

Medication use is another common risk factor for delirium. Though sometimes referred to as predisposing, it may better be classified as precipitating, since intoxication delirium due to medication or other chemical substance usually occurs very shortly following intake of the substance (23). As has been claimed (82), almost every class of medication can induce delirium in susceptible persons, especially the elderly who are at high risk due to age-related changes in pharmacokinetics and pharmacodynamics, comorbidity and polypharmacy. Several classes of medications have been found to be most potent in inducing delirium. These medications included anticholinergics (ACH), antipsychotics, tricyclic antidepressants, narcotics, like benzodiazepines, and histamine receptor antagonists (H2-blocker) and others (19,20,22-24,82). However, most of the observed medication-delirium associations were from case reports or case series. Large scale epidemiological studies are limited and often used different criteria to define medication exposure, or studied different agents or doses under the same class of medications, making it difficult to draw consistent conclusion for any particular medication or medication class. This may be especially true with ACH medications. A systematic literature review with particular focus on ACH medications will be presented separately below.

3). Perpetuating Factors

Perpetuating factors refer to those that sustain or aggravate clinical symptoms of delirium after their onset. Compared to predisposing or precipitating factors, studies of perpetuating risk factors are lacking. A few studies have suggested that unfamiliar environment and people, sensory deprivation, decreased comprehension, decreased mobility, sleep disorder, fear and anxiety might play a perpetuating role (19,20, 21,32,33). One methodological difficulty in addressing perpetuating factors is that some such factors (e.g., anxiety or sleep disorder) may not be true risk factors, but may contribute part of delirium symptomatology or result from its progression.

Similar to precipitating factors, many perpetuating factors in hospital settings are iatrogenic in origin and thus are potentially modifiable (19). In fact, some iatrogenic precipitating factors (e.g., ACH medications) would certainly continue to play a perpetuating role if their hazard were not recognized. Unfortunately, the potential perpetuating effect of medication use, though clinically appreciable, has seldom attracted research attention.

4). Interrelationship between Different Risk Factors

Although conceptually predisposing, precipitating and perpetuating factors play their respective roles at different stages of delirium pathogenesis, in the real world their effects may be highly interdependent and integrated. As suggested by Inouye et al, patients with high baseline susceptibility can develop delirium with a minimal amount of in-hospital insults, while those without obvious predisposing vulnerability may become delirious only when they encounter serious in-hospital insults (11). In this regard, little is known about the relationship between predisposing and perpetuating factors.

On the other hand, iatrogenic risk factors that possess both precipitating and perpetuating properties may have particular importance for intervention. The identification of potentially deliriogenic medications and avoidance of their use whenever possible have the potential to significantly reduce both the incidence and prevalence of delirium in elderly inpatients during hospitalization (7, 8).

2.4. ACH Medications and Delirium

2.4.1. Neurotransmitting Mechanism of Delirium

Although delirium has many putative causes, it is generally believed that there might exist a final neuropathogenic pathway through which such putative causes alter the brain function, leading to clinical manifestation of delirium syndrome (23, 24, 40, 83,84). One such postulated pathway is dysfunction of the central cholinergic neurotransmitting system (23, 24, 40, 83-87).

Acetylcholine is an important central neurotransmitter in regulating arousal, consciousness, attention and cognitive functions, either via direct stimulation of muscarinic receptors at the brainstem, basal forebrain and neocortex, or by indirect mediation of the effects of other transmitters (e.g., dopamine). Considerable evidence suggests that failure of cholinergic transmission plays a key role in several memory disorders including Alzheimer's disease (85). A decreased synthesis of cerebral acetylcholine and epinephrine has been postulated to account for the impaired cognitive and attentional function and slowing of the electroencephalographic background activity commonly seen in delirium (19,23,24,83-87). Induction of experimental delirium by administration of anticholinergic drugs has been observed in both human (23, 24, 87) and animal subjects (23,84) and could be reversed by a cholinergic agonist (87). In addition,

serum anticholinergic activity has been associated with delirium in medical (18), postoperative (25,27-28) and post-electro-convulsive patients (88). On the other hand, cholinergic mechanism may be particularly important in delirium of elderly patients in that elderly become more susceptible to anticholinergic intoxication due to an aging-related reduction in cholinergic brain receptors and altered pharmacokinetics (20,23,27,83-86, 89-93).

Another potentially important neurotransmitter that may play a role in the pathogenesis of delirium is dopamine (19,24,40,83). In fact, an excess dopaminergic hypothesis is a counterpart of cholinergic deficit mechanism. Based on the reciprocal activity between dopamine and acetylcholine, delirium following administration of dopaminergic medications (e.g., L-dopa) has been interpreted in the light of acetylcholine-dopamine imbalance, whereas the reversal of delirium symptoms due to anticholinergic intoxication by neuroleptics may be through the known antidopaminergic properties of such drugs (24,40). However, research evidence to link dopamine and delirium from either animal experiments or clinical studies is relatively limited in comparison with that for the acetylcholine deficit hypothesis. The same is true for other candidate neurotransmitters including serotonin, γ-aminobutyric acid (GABA), nor-adrenaline, and histamine (19,23,24,40).

2.4.2. Clinical Epidemiologic Studies of ACH Medication-Delirium Association

In reviewing clinical epidemiological studies of delirium, one has to face two particular difficulties. First, although ACH medications delirium association has been a clinical research topic long before the appearance of DSM-III in 1980's, most of these

early studies were case reports or case series and the delirium cases may not be fully comparable to the currently defined cases. Second, until now clinical epidemiologic studies that specifically focused on ACH medications are scarce, and definition or measurement of exposure to ACH medications varies greatly across studies. In order to reduce diagnostic uncertainty while avoiding missing important papers, we, on one hand, have used multiple sources to locate relevant studies that may have addressed association between delirium and ACH medications, and on the other, tried to set strict inclusion criteria to ensure methodological quality and diagnostic comparability of studies.

Three different approaches were used to identify potentially relevant studies: A). electronic search of MEDLINE database for studies in hospitalized elderly populations aged 45 years or older, published in English between year 1966 and 1999, using keywords: delirium, confusion or acute confusional state, and medications or drugs; B).manual search of the bibliographies of review articles and identified papers; and C). contact with influential researchers in this area for additional relevant studies (and for advice on measuring ACH exposure). Then, the following 7 criteria were used to screen identified citations or papers: 1. Original study; 2. Addressed relationship between delirium and medication(s), either as a primary or secondary focus; 3. Study population included at least one group of elderly delirium patients with ascertainable number of not less than 10; 4. Used DSM-III, IIIR or IV criteria or their analogue to define delirium cases; 5. Delirium cases were identified following a prospective detection procedure; 6. Outcome measures included indices that represented occurrence or severity of delirium during hospitalization; and 7. Risk factors included use of medications with potential

ACH effect, either explicitly specified or not (see below for details). Through this strategy, 140 potentially relevant studies were identified.

Of the 140 studies, 11 were judged to have met all the 7 criteria (11,12, 13, 14, 39, 58, 61-64,66). For both logistic and feasibility reasons, a study would be excluded if evidence for inclusion was not adequate; similarly, no effort was made to retrieve all the articles that were not locally available. However, compared with two recent systematic reviews that used more thorough search strategy for risk factor studies of delirium, the 11 studies we selected included all the 10 that involved medication use cited in the two review articles (9,21). This overlap gives indirect evidence that the chance for our search to have missed important studies of ACH medication-delirium association would be low. Thus, though not an exhaustive coverage for all the relevant studies, these 11 papers would provide available clinical/epidemiologic evidence for an ACH medication-delirium association in hospitalized elderly populations.

2.4.2.1.Overview of Study Design

Table 2 summarizes information about medication exposure and risk of delirium in the 11 reviewed studies, which are abstracted directly or estimated by us (see the footnotes for details) from the data relevant to our study purposes. When multiple medications were evaluated in a study, we abstracted only the data regarding (potential) ACH medications; when multiple methods were used to evaluate the same medication(s) in a study, we abstracted only the data that were judged to be most scientifically reasonable.

There are 9 observational cohort (11,39,58,61,64,66) or case-control (12,13,14) studies and two randomized clinical trials (62,63) from which we abstracted the data

pertaining to medication exposure-delirium association without regard to random allocation. The study populations consisted of patients from medical, hip fracture or orthopedic or other non-cardiac surgery, or mixed clinical settings, with a sample size ranging from 46 to 418 and an average age between 64 and 82.7 years.

In all the studies one of main outcomes was the occurrence of delirium cases during either a specified post-admission or post-operation period (11, 12, 14, 58, 61-63, 66) or entire hospitalization (13,39,66). The effect estimates for a risk factor included incidence odds ratios or cumulative incidence ratio. But in 2 studies the occurrence of delirium included both new incident and prevalent cases (13,64). The time-window for assessing the medication exposure-delirium association was defined as a period prior to onset of delirium (11,12,14) or hospital admission (13,58,63,64), or the same as the at-risk period for detecting delirium cases (61,62,66). In one study the time-window was not explicitly defined (39). The length of time-window was 1 day in 3 studies (11,12,66), 2-7 days in 2 (58, 62), one month in 1 (58) and unspecified in the others (13,14,63,64).

All the studies included use of medications as exposure or covariate variable, which involved one or more ACH medications, either explicitly specified or not. The definitions of ACH medications varied greatly: some included only pure atropine preparations and antihistamines (14), others encompassed both pure ACH drugs and neuroleptics, antidepressants, and sedative-hypnotics etc (12, 62, 63). Some studies used a name other than ACH (e.g., psychoactive) to group the same classes of medications (11), or treated each therapeutic class separately such as neuroleptics, narcotics, or benzodiazepines etc (58,66). In addition to medication use, each study considered at least one other risk factor and used multivariate regression modeling, mostly logistic, to adjust

for covariates. Among these, most common were dementia, severity of illnesses or comorbidity and age at hospital admission.

2.4.2.2. Main research findings

Among the 8 studies that explicitly specified a group of ACH medications as one of potential risk factors (12, 13, 14, 39, 61-64), 3 found an independent effect of exposure to ACH medications on the occurrence of delirium (61, 63,64). Another 3 studies did not specifically evaluate the effect of ACH medications, but the study medication(s) included an "ACH" subgroup (11, content not specified), or nevertheless involved some ACH agents, e.g., neuroleptics (58) or narcotics (66). In addition, in the 3 studies that reported a positive effect for ACH medications, the Rogers study did not adjust the exposure odds ratio for ACH medication use for the 8 potential confounders since they were not included in the final logistic regression model after stepwise selection (61); whereas Berggren et al (63) and Gustafson et al (64) studies used a linear model to estimate adjusted effect of ACH medications on a dichotomous outcome (i.e., occurrence of delirium) which was conceptually inappropriate. On the other hand, in studies reporting negative results of ACH medications as a group, several subclasses or individual medications with potent ACH properties were found to be significant predictors, including neuroleptics (14), narcotics (14) and mepredine (12). Thus, although more studies seemed to suggest no significant effect of ACH medications as a group, the heterogeneity of the definition of ACH medications has prevented a meaningful overall conclusion, even a narrative one, to be drawn from the reported effect estimates. Alternatively, potential methodological flaws may also have biased the observed effect estimates in the reviewed studies. Therefore, instead of trying to synthesize the studies

into a general conclusion, it seems more reasonable and meaningful to identify underlying reasons of the discrepancies and to provide insights into their potential impact on the estimated ACH medication-delirium association. Based on this consideration, the following two sections are thus devoted to heuristic commentary on the methodology of the reviewed studies in measuring medication exposure, identification of potential sources of bias, and suggestions of alternative approaches.

2.4.2.3. Potential Methodological Flaws in Measuring ACH Medication Exposure

In the reviewed studies, several potential methodological flaws may have contributed to the lack of association between exposure to ACH medication and delirium, which can be summarized as follows:

1). Flaws Involving Time-window Designs:

Exposure time-window, a key concept of pharmacoepidemiology, refers to a period of time during which both the exposure to a medication and the risk of toxic effect of the medication are assumed to exist (77, 78, 95-97). Design of the time-window requires specification of an index date, which is usually the date of an outcome event for subjects who develop the outcome (95-98). A time-window can then be defined by the maximum days allowable prior to the index date for a relevant medication exposure to occur (95, 96, 98).

Design of the exposure time-window plays a fundamentally important role in pharmacoepidemiology, since it provides the context within which the impact of potential bias and causality of an alleged medication-disease relationship can be assessed from the temporal sequence perspective (76, 77). An appropriate time-window should be defined using biologically plausible assumptions for medication action and disease etiology, and

epidemiological/statistical justification for enhancing comparability between comparison groups and precision of effect estimates (77,78,95-98). In addition to difference in length of the time-windows between the comparison groups, an excessively long time-window has been shown to bias the risk estimate of exposure toward the null (96). Although a time-window can be assigned with great certainty in the hospital setting with the aid of detailed information on actual use of prescribed medications by patients, its validity and efficiency for assessing a medication exposure-disease outcome association will depend also on the specific characteristics of both the medication and the disease of interest.

Several major methodological flaws in this regard included:

a). Inappropriate Time-window: Several studies assessed medication exposure for a prior time period up to hospital admission whereas delirium occurrence was counted during the period of hospitalization or at hospital admission (13, 39, 58, 64), which seems biologically implausible in terms of current knowledge about drug action and delirium etiology. Toxic delirium typically starts within 24 hours following intake of a medication or chemical substance (15,23,36,40) and the clinical effect of most ACH (or other psychoactive) medications can seldom last for several days or weeks (99,100). Unless in extreme circumstances where both the times of medication exposure and of delirium onset are quite close to the time of hospital admission, or where the residual effect of a medication becomes extraordinarily long, there would be no possibility for such pre-admission medication exposure to induce incident delirium after a time lag in days or weeks; whereas for prevalent cases of delirium whose onset may have taken place at any time prior to admission, the pre-admission medication exposure may be entirely irrelevant to the delirium occurrence or may actually follow rather than precede the

delirium onset. In addition, ascertainment of pre-admission medication exposure per se is more likely to cause misclassification, both nondifferential (due to missing records or inaccurate recall of the remote medication history for both delirium and non-delirium patients) and differential (delirium patients recall less exposure due to impaired memory). Thus, defining an exposure time-window up to hospital admission, especially when coupled with extended (58) or unspecified length (13,39,64), would be biologically invalid and, in most cases, would end up with a failure of detecting the true association.

b). Time-incomparability: Time-comparability is another important principle in defining the time-window for case-control studies (97). In the Schor et al study, the time-window for cases was defined as from admission to delirium onset, whereas for controls it was from admission to discharge or death (14). Since the time-window for cases (median latency: 3 days) was apparently shorter that that for controls (mean hospital stay: 7.4 days), it would be expected that more controls than cases would become exposed merely because they had more time to do so (14). Thus, the lack of association for ACH medications may be biased by potential overcounting of exposed controls due to time-incomparability, since the length of hospitalization was not adjusted for in their stepwise logistic regression model. Other indirect evidence for this speculation is that the paper observed higher prevalence in controls than in cases in 5 out of 8 groups of medications, including ACH (31% vs. 23%), digoxin (27% vs. 21%), and benzodiazepines (56% vs. 35%) etc. Moreover, benzodiazepines and digoxin were even found to be protective against delirium after adjusting for age and sex (adjusted OR: 0.43, 0.52, respectively). These results seem quite disparate with most published studies in which delirium patients

were often found to use more, or at least, a comparable number of such medications than non-delirium patients (12,13, 18,26-29,58,61,63).

c). Concurrent time-window: Two studies defined (implicitly) time-window as the same period as the at-risk period without regard to time of delirium onset or hospital admission (61,62). This equal-length or concurrent time-window design is often employed in automated record-linkage studies in the pharmacoepidemiology field for approximating exposed person-time, due to lack of detailed data about the timing of a prescription (95,96,98). Although bearing the advantage of enhancing time-comparability, this concurrent time-window may introduce another kind of misclassification bias in that a patient who developed delirium first and then was exposed to a medication during the same day or at a later day may be erroneously counted as exposed. As a result, a differential misclassification of exposed cases would occur, which may lead to exaggeration of the observed association. However, this misclassification is not applicable to the negative findings of ACH medication-delirium association in general, but may explain some spuriously large estimate of an observed medication effect (61). In addition, the prevalence of such misclassification would be conceivably very low if the at-risk period is quite short.

2). Confounding by indication and contra-indication:

In non-randomized clinical epidemiological studies evaluating effect of medication exposure, a crucial methodological concern is confounding by indication (79, 94-98). That is, the observed association between a particular medication or therapy and the disease outcome may be attributable to the indication for its use, i.e., the underlying (pathological) condition that requires the use of the medication which itself is a risk factor

of the target disease (79). Confounding by indication may also result when a medication is restricted due to physicians' concerns of its specific side effects on patients with a particular disease, i.e., confounding by "contra-indication" (79).

3). Protopathic bias:

Related to the problems of confounding by indication and contra-indication is the so-called "protopathic bias", in that use (or non-use) of a specific medication or therapy is induced by the early manifestation of the target disease before its diagnosis or certain outcomes becomes clinically apparent (94). Due to systematic use of the medication in these patients, a fallacious relationship might be established that the medication is (or is not) the cause of the target disease, while in fact the opposite is true. Given the fluctuating feature of delirium symptoms, controlling potential protopathic or "reverse causality" bias poses a major challenge to the validity of observational epidemiological studies of the relationship between medication exposure and disease outcomes. For example, both Marcantonio and Schor et al suspected that low exposure to ACH medications in their populations might have prevented an otherwise positive association to be detected (12,14). One probable reason they cited was that physicians may have intentionally restricted use of ACH medications due to awareness of early signs of delirium when patients have not met the full diagnostic criteria, especially when the medication exposure was assessed immediately preceding the delirium onset (12). Since now their study populations were no longer representative of the reference populations in terms of the exposure distribution to ACH medications, the effect of ACH medication could not be validly evaluated, a consequence similar to that of application of restriction to patient selection (77,78). Depending on the degree of the restricted use of the

contraindicated medications, a true medication-disease association could be attenuated toward the null or utterly hidden, due to reduced prevalence and between-group variance of the medication exposure.

4). Lack of Adjustment for Potential Effect of Polypharmacy

Another potential source of bias of the reviewed studies lies in the ignorance of polypharmacy. Except for Inouye et al, all other studies measured (ACH) medication exposure by counting the number and proportion of the exposed patients only. Such a measure precludes the possibility to evaluate cumulative effect of concurrent use of multiple ACH (and non-ACH) medications, which is a common phenomenon in elderly patients (17, 18,29,91-92,101); moreover, delirium patients were often reported to use a larger number of several classes of medications than their non-delirium counterparts (11,17, 27, 86, 91, 92). Inouye et al (11) reported that the number of medications of all types was the most significant variable in predicting the development of incident delirium.

2.4.3. Approaches to the Measurement of ACH Medication Exposure

In an attempt to find an optimal method for measuring ACH exposure, we expanded our literature review to studies that involved measures of ACH medications but did not meet the other inclusion criteria specified above. We also referred to textbooks of pharmacology and clinician's reference books for the definition and classification of ACH medications.

According to the clinical pharmacology nomenclature, ACH medications are usually defined in a narrow sense as those that function therapeutically through anticotinic and/or antimuscarinic activities (99-104). These medications are typically classified under

several major therapeutic classes including atropine and closely related agents, synthetic quaternary ammonium compounds, tertiary amines used in visceral disorders, and antiparkinsonism drugs with primary anticholinergic effects (99-104). In clinical practice and clinical epidemiological studies, ACH medications may refer to a broad array of medication classes that can induce significant clinical anticholinergic side-effects, which most commonly include tricyclic antidepressants, antipsychotics, major narcotics and sleeping medications (12,17,30,62,63,91,93,99,105,106). However, the scope of ACH medications studied often varied greatly: some authors included most benzodiazepines, antiarrhythmics and laxatives (105,106); while others focused only on the pure or typical ACH agents (14,61). In addition, defining ACH exposure according to clinical observation and/or detectable serum ACH activities of individual medication may represent another direction of evidence-based approaches that can incorporate emerging new evidences and be adapted for studying specific medications (25-30). Alternatively, Flacker et al defined ACH medications as either "definite" or "possible" groups, based on available evidence from the literature (18). Thus, it seems apparent that although the major classes of ACH medication can be agreed on by different investigators, the research definition for exposure to ACH medications seemed to depend mainly on the amount and types of the involved medications in a study.

Under such varied definitions, studies in the clinical epidemiological context used various methods to measure exposure to ACH medications. Among these some were commonly used in the studies of medication exposures in general and thus applicable to both ACH and non-ACH medications, whereas others may be particularly devised to measure ACH exposure in particular. Based on our literature review, the commonest

methods and their potential advantages and disadvantages in terms of addressing ACH medication-delirium association are summarized below, regardless of whether they were particularly used to measure ACH medication exposure.

1). Dichotomous measure of exposed persons

As indicated above, counting the number of patients exposed to a defined class of ACH medication within each comparison groups, with or without referring to a certain level of dose, has been the most frequently used method in the reviewed studies. Using this measure, each subject is assigned a dichotomous exposure status as either exposed or not exposed according to whether he or she used the medication(s) of interests during a specified time-window. The advantages of this measure include computational and interpretative simplicity in terms of the resulting summary effect estimate of odds ratio or risk ratio. However, since the unit of this measure is the person rather than the medication, the difference in exposure between two persons who used different numbers or doses of the same medication(s) cannot be appropriately accounted for, which may bias a particular medication-disease association if the multiple exposure is differential between the comparison groups. In terms of ACH medication-delirium association, an attenuation would be usually the case, because more delirious than non-delirious patients tend to use multiple ACH medications concurrently. Major research findings in this regard have been reviewed above.

2). Number of medications used by each person:

Another common measure is the number of medications used by each subject. As discussed above, this measure has an advantage in that it allows for evaluating potential cumulative effect of concurrent use of multiple ACH medications. This allowance may

bear practical importance in study of ACH medication exposure in elderly population, since as many as 10% of the nursing home residents who received ACH medications annually were exposed to three or more of such medications concurrently (17,105,106); in addition, quantifying the exposure by "number of ACH medications per patient" would be more conceptually interpretable since it depends merely on the "quantity" rather than the content of the defined ACH exposure, and thus avoids conveying such a misleading message that subjects in different groups or populations were exposed to the same agents or classes of ACH medications. However, the underlying assumption that the exposure effect depends only on the number, not the pharmacological potency or the dose of ACH medications may not necessarily be true.

Although the number of medications per patient has been found to be an important risk factor of adverse drug reactions including delirium (11,29,30,90,92,101), most of the studies did not specifically target ACH medications. In addition, research findings derived from measuring the number of exposed medications per person also varied across studies. For instance, Inouye et al reported an independent effect of "adding three medicines (no ACH specification)", but not of the total number of medications (including an ACH subgroup) (11), whereas Francis et al (13) and O'Keeffe et al (39) compared the total number of medications including ACH group used by delirium and non-delirium patients at admission but did not find significant difference. Several other studies, mostly cross-sectional or case-report or case-series in nature, also used the total number of medications, with or without ACH specification, at hospital admission or time of diagnosis as comparators, but the differences between delirium and non-delirium groups were often not statistically significant (13,18,26,27,39,66,107). The potential importance

of polypharmacy in delirium pathogenesis in general and the lack of studies addressing the cumulative effect of concurrent use of multiple ACH medications highlights the necessity of measuring ACH exposure by number of medications per person.

3). Serum ACH activity

Another important method for quantifying ACH exposure is the measurement of serum ACH activity using a radioreceptor assay that measures the total antimuscarinic receptor binding potential in human serum based on competition with [^{3}H]-QNB (quainuclidinyl benzilate) in homogenized preparations of rat striatum and forebrain. The ACH potency of a drug is indexed by reduction in the known receptor occupancy rates of [^{3}H]-QNB in atropine equivalent units of pmol/mL (27,28,29,86).

Using this *in vitro* measurement technique, exposure to ACH medications have been associated with postoperative development of delirium in a group of 39 patients aged 29 to 75 years old (25, 27). In addition, serum level of ACH drugs administered was found to significantly correlate with the reduction in MMSE score (27). Similar clinical observations have been reported in hospitalized medical or geriatric elderly (18, 26,107), though none of these studies simultaneously controlled for potential confounders. Moreover, the application of this biological assay has lead to the discovery that many medications not routinely considered as ACH medications have detectable serum ACH activity in vitro (93), strengthening the notion that anticholinergic intoxication in the elderly patients is probably seriously underestimated (18, 23).

Criticisms of this laboratory-based measure of ACH exposure are both theoretical and practical. First, investigators argue that serum ACH activity may not necessarily result from administered medications. An endogenous source of such activity may exist,

as suggested by the observation that elevated ACH activity could occur in patients taking no ACH medications (108) and that the dose of administered ACH medications is not correlated closely with level of serum ACH activity (18,27,108). Second, serum ACH activity measured at a fixed dose of a medication may not be an accurate index of the clinical ACH effect of the medication, which depends also on many other factors including permeability through blood-brain-barrier, rate of protein-binding, presence of active metabolite, and alternate mechanism of action other than postsynaptic blocking of muscarinic receptors of the administered medications (18,22,108,109). Finally, this method involves an intrusive procedure (venipuncture) that reduces its acceptability to patients and requires laboratory facilities that are not available in all clinical or research settings. Thus, although biologically appealing, serum ACH activity does not seem to be a readily applicable clinical method. On the other hand, Tune et al also tried converting serum ACH activity into a cumulative ACH score and found a significant difference between 9 delirium and 16 non-delirium surgical patients (28). A similar ACH index is under development by another group (Pollock et al, personal communication), but its validity and reliability is unknown.

4). Drug Risk Number (DRN)

To estimate the risk of drug-induced delirium, Summers developed a clinical rating method to quantify the cumulative effect of ACH medications in 84 patients (age not specified) undergoing cardiotomy, cataractomy or electroconvulsive therapy (30). He tried to establish an aggregated score, a so-called Drug Risk Number (DRN), to rate the level of anticholinergic potential of 61 drugs, in 15 classes of medications. Numerically, the DRN is expressed as the product of two ordinal scales named respectively as "class of

drug" (COD) and "daily effective dosage" (DED), with COD ranging from I to III (class I is the lowest level) of ACH effect and DED representing under- (level 1), within- (level 2) or above- (level 3) the usual therapeutic dosage for a twenty-four hour period. The total DRN for a patient was then calculated by summing up the DRN's for each individual agent used in the same twenty-four hour period. The author showed graphically the significantly higher mean daily DRNs in delirium patients than in non-delirium counterparts during both pre- and post-operative days. This method has been used in several other studies, both in delirium (25,28) and non-delirium populations (110,111). When dosage information was unavailable, DRN was calculated from COD only (111).

In comparison with other measures of ACH exposure, the obvious advantages of the DRN method lies in its consideration of the level of ACH effect of individual medications and of cumulative ACH effect of polypharmacy. In addition, the approaches to establish COD and DED were clinical-evidence based, convenient for clinical application and readily updatible with emerging new evidence from both pharmacological and clinical research. Thus, although Summers' DRN list has the limitation that did not include many new drugs used today, it can be adapted to suit the current research purpose. Another limitation of DRN lies in the author's assumption that the deliriogenic potency of a medication depends entirely on its ACH effect; thus, several medications, such as benzodiazepines, were classified in a high ACH potential group (i.e., COD III), which seems to contradict current beliefs (29,91). Thus, the development of a valid and accurate standard against which the effect of ACH exposure can be objectively assessed remains a major challenge for clinical epidemiological studies.

2.5. Summary

In summary, clinical epidemiologic studies in recent decades have expanded our understanding of the postulated ACH medication-delirium association, but the research findings are far from being conclusive. Common methodological limitations underlying current studies include: poorly defined time-windows for ACH medication exposure, lack of adjustment for polypharmacy, potential confounding by indication or contraindication and protopathic bias. In addition, considerable heterogeneity in the definition and measurement of ACH medication exposure makes inter-study comparisons difficult. On the other hand, studies of the perpetuating effect of ACH medication exposure, though biologically plausible and clinically amendable, are still lacking, especially in the longitudinal context and in medical inpatient population. Therefore, further studies using improved measures of ACH exposure, appropriate time-window, longitudinal follow-up and adequate control for confounding by indication and protopathic bias are warranted.

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Table 1. Incidence and prevalence of delirium in hospitalized elderly patients from 20 prospective studies

Author/ year	Study Population		Delirium Criteria	Prevalence[b]	Detection of Incident Delirium		Incidence[d]	Comments
	N_0[a]	Age (Mean)		n (%)	at-risk period	methods/ frequency	n (%)	
Medical or Geriatric Patients								
Rockwood '93[2]	168	(79)	DSM-III & IIIR	31 (19)	adm-disch	DRS/ daily?	12 (8.8)	Overall rate:7% (12/168).
Inouye '96[11]	206	≥70 (78.5)	DSM-IIIR	10 (5)	adm-day 9	CAM/ every other day	35 (18)	development cohort
	319	≥70 (78.5)		9 (2)			47 (15)	validation cohort
Francis '90[13]	229	(78)	DSM IIIR	36 (15.7)	adm-disch	chart review, MMSE/ every 2 days	14 (7.3)	Overall rate: 22%.
O'Keeffe	100	(82.7)	DSM-III	na	adm-disch	DAS & MMSE/ every 2	28 (28)	derivation group
96[39]	84	(81.2)		na	or death	days	25 (30)	validation group
Johnson '90[55]	235	≥70	DSM-III	38 (16.2)	adm-disch	clinical exam, MMSE & BPRS / daily for 2 weeks then every other day	10 (5.1)	
Rockwood '89[56]	80	65-91	DSM-III	13 (16)	adm-disch	clinical interview/ daily	7 (10.4)	Overall rate: 25% (20/80).
Jintapunkul '92[57]	184	60~97	DSM-IIIR	40 (22)[c]	adm-disch	brief mental test /at adm, week 1 and discharge	na	
Foy '95[58]	418	55-88 (70.2)	DSM-IIIR	0 (na)	adm-day 10 or disch	clinical review & MMSE/ every 2-3 days	21 (5)	All subjects' MMSE>24 at baseline
Kolbeinsson '93[59]	272	≥70	DSM-IIIR	37 (14)	na	MSQ & MMSE/ once at adm	na	
Medical and Surgical Patients								
Levkoff '92[71]	325	≥65 (80.5)	DSM-III	34 (10.5)	adm-day 14 or disch	DSI / daily	91 (31.3)	
Pompei '94[72]	263	≥ 65	DSM-IIIR	21 (8)	adm-disch	CAM / ns	43 (17.8)[e]	derivation cohort
	323	≥70		48 (14.9)			38 (13.8)[e]	test cohort
Kishi '95[73]	60	≥ 65	DSM-IIIR	11 (18.3)[c]	adm-disch	psychiatric interview, chart review/daily	na	Total N=238, P=4.2%, I=11.4%
Rudberg '97[74]	432	≥65 (75.2)	DSM-IIIR	22 (5.0)	adm-disch	CAM, CSC, chart review etc / daily	42 (10.2)	DRS used daily for cases. # of drugs:6.9±2.6

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Fisher '95[60]	80	≥60 (71.2)	CAM	na	PO day 1-4	CAM/ twice daily	14 (17.5)	
Rogers '89[61]	46	≥60 (69.3)	DSM-III	0 (na)	adm-PO day 4	DSM-III/ once at day 4	28 (13)	All patients cognitively normal at baseline.
Williams-Russo '92[62]	51	48-80 (68)	DSM-III	na	PO day 1-7	DRS, clinical interview/ daily	21 (41)	Incidence for 2 groups: 44% vs 38%.
Berggren '87[63]	57	≥ 64	DSM-III	5 (8.8)	adm-PO day 7	OBS / at adm, day 1 and day 7	20 (38.5)	Overall incidence:44% (25/57).
Gustafson '88[64]	111	65-96 (79.3)	DSM-III	37 (33)	adm-PO day 14	OBS / daily	31 (41.9)	
Williams '85[66]	170	60-96 (78.8)	SPMSQ	(11.8)	PO day 1-5	SPMSQ / daily	na (51.5)	# of incident cases not cited.
Marcantonio '94[68]	562	≥50 (68)	DSM-IIIR	na	PO day 2-5 or disch	CAM or chart review/ daily	na (9)	total N=1341, I=9%, for various noncardiac surgery.

Notes:

a. N_0: Number of patients at baseline, including prevalent delirium cases.

b. Prevalence proportion at hospital admission, except otherwise specified.

c. Period prevalence proportion during hospitalization period.

d. Cumulative incidence during the defined at-risk period in study population free of delirium at admission.

e. Values indicated by a ** are estimated by us according to the data provided in the paper.

Abbreviations used in the table:

Adm: admission; Disch: discharge. PO: post-operative; na: not applicable or not available.

BPRS. Brief Psychiatric Rating Scale, Overall 1962; CAM: Confusion Assessment Methods, Inouye et al. 1990;

DAS: Delirium Assessment Scale, O'Keeffe et al, 1996. DSI: Delirium Symptom Interview, Albert et al, 1992. CSC.

DRS: Delirium Rating Scale, Trzepacz 1988. MMSE. Mini-Mental Status Exam. Folstein 1975.

DSM-III (R): The Diagnostic and Statistical Manual of Mental Disorders, 3rd Edi (revised), APA;

MSQ: Mental Status Questionnaire, Kahn 1960, Robertson 1982.

OBS: Organic Brain Syndrome scale, Gustafsson 1995. SPMSQ: Short Portable Mental Status Questionnaire, Pfeiffer 1975.

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Table 2. Summary of 11 studies of medication-delirium association in hospitalized elderly patients

Author/year (design)	Population (n & Age)[a]	Medication Exposure: time-window	Medication Exposure: Major Class/Brand	Medication Exposure: Exposed (%)[b]	Adjusted Medication Effect: OR or RR[c]	Adjusted Medication Effect: Covariates/ methods	Comments
Medical or Geriatric Patients							
Inouye '96[11] (cohort)	n: 35/161; Age: 78.5	48 to 24 hr pre onset	1. ≥ 3 types of medication added; 2. > 2 psychoactive drugs (sedative-hypnotics, narcotics, ACH, and H2-blockers)	56/14; 71/16	2.9 (1.6, 5.4); 4.5* (NS)	physical restrains, malnutrition, and bladder catheter use etc/stepwise binomial model	
Francis '90[13] (case-control)	n: 50/176; Age: 78	pre-adm	1. Psychoactive: narcotics, sedative-hyponotics & minor tranquilizers	26/10	3.9 (1.4, 10.8);	sodium level, illness severity, chronic CI, etc/ stepwise	At adm, total number of medications did not
			2. ACH (not specified)	25/15	1.9* (NS)	logistic regression	differ between groups
O'Keeffe '96[39] (cohort)	n: 28/72; Age: 82.7	na	1. Neuroleptics	18/10	1.8* (NS)	dementia, severe illness,	Narcotics, BZD, digoxin
			2. ACH (not specified)	14/10	1.4*	serum urea, etc/ multiple logistic regression	etc and number of medications at adm NS
Foy '95[58] (cohort)	n: 21/397; Age: 70.2	30 days pre-adm	1. BZD (diazepam, oxazepam, temazepam, and other 4 brands).	23.4	1.0 (0.3, 3.0)	age, baseline MMSE, dehydration etc, by logistic	OR for positive urine test of BZD at adm: 1.5
			2. Neuroleptics or tricyclic ADs	8.6	na (NS)	regression	(0.4, 5.1), with 2/3 of patients being positive.
Medical and Surgical Patients							
Schor '92[14] (case-control)	n: 91/200; Age: 80.5	adm-onset for cases;	1. Neuroleptics.	20.9/9.5;	4.5 (1.8, 10.5);	prior CI, fracture on adm,	number of standard dose
			2. Narcotics.	45.1/3.6;	2.5 (1.2, 5.2).	age, infection, male sex	for each class of
		adm-disch	3. BZD	35.2/56.0;	0.4[d] (NS)	/stepwise logistic	medications counted
		or death for controls.	4. ACH (diphenhydramine, meclizine, promethazine, hydroxyzine, atropine, propantheline, benztropine,oxybutinin, ipratropium)	23.1/31	0.7[d] (NS)	regression	but no data given.

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Marcantonio '94[12] (nested case-control)	n: 91/154; Age: 73	24 hrs pre-onset	1. Narcotics. 2. Meperidine. 3. BZD. 4. ACH (antihistamines, tricyclic AD, antiementics, and neuroleptics)	96/94; 65/42 21/8 11/8	1.4 (0.5, 4.3); 2.7 (1.3, 5.5) 3.0 (1.3, 6.8) 1.5 (0.6, 3.4)	Cochrane-Mantel-Haenszel analysis matched on preoperative risk, and conditional logistic regression	dose-response tested for each BZD and ACH drug with ≥3% of exposure
Rogers '89[61] (cohort)	n: 13/33; Age: 69.3	adm-day 4	1. ACH (Scoplamine, propranolol or plurazepam) 2. Morphine equivalents>80 mg (narcotics/analgesic /hypnotic / tranquilizer)	54/9 39/42	12.? (10.6, 13.8) 0.9[d] (NS)	8 covariates, none selected by stepwise logistic regression	All subjects cognitively normal at adm.
Williams-Russo '92[62] (RCT)	n: 21/30; Age: 68	peri-operative day 1-7	1. BZD 2. ACH (AD, neuroleptics, anti-incontinence, and sleeping drugs)	na na	na (NS) na (NS)	age, gender and alcohol use /multiple logistic regression	1) Rates for 2 analgesia groups: 44% vs 38%. 2) no dementia
Berggren '87[63] (RCT)	n: 25/32; Age: >64	prior to adm	ACH (AD, neuroleptics, sleeping pills and ACH for urine incontinence)	72/12.5[a]	18[d] (p<0.005)	age, preexisting disease, anesthetic technique etc/ multiple linear regression	ACH or Neuroleptic alone also has independent effect.
Gustafson '88[64] (cohort)	n: 68/43; Age: 79.3	prior to adm?	1. Regular use of ACH (not specified) 2. AD (not tested in multivariate model)	49/14 20.1/0	beta=0.18 (NS) na	age, dementia etc by multiple linear regression	BZD and antiparkinson drugs tested NS.
Williams '85[66] (cohort)	n: 88/82; Age: 78.8	PO day 1	Narcotics (by equivalence to morphine)	na	0.97 & 0.99 by severity	age, mobility etc/multiple logistic regression	number of tranquilizers or sedatives: na

Notes:

a n: The two values indicate sample sizes: delirium cases vs non-cases or controls.
Age: Except otherwise indicated, the value represent mean or median age of study population.

b The 2 values indicate proportions of exposed subjects: delirium vs non-delirium group.

c Except otherwise specified, values indicate odds ratio (OR) for case-control studies or risk ratio (RR) for cohort study, adjusted for the covariates listed in the next column, with low and upper limit of 95% confidence interval, or p value in parentheses,

d These values were crude estimates, provided in the paper or calculated by us using relevant data.

Abbreviations used in the table:

ACH: anticholinergics, AD: antidepresants. Adm: admission. BZD: Benzodiazepines. CI: Cognitive impairment. Disch: discharge.
na: not available or not applicable. NS: p>0.05 according to the paper. PO: post-operative; RCT: randomized clinical trial.

3. RATIONALE FOR THE CURRENT STUDY

3.1. Research Questions and Orientation

Based on our literature review, it is evident that the research question, "is ACH medication use an independent risk factor of delirium?" has not yet been adequately addressed; whereas the question, "does exposure to ACH medications predict symptom severity over time?" has never been addressed in a clinical epidemiological context. Another closely related and biologically plausible question is whether the effect of ACH exposure depends on other important risk factors, particularly dementia, since the latter has been postulated to share the same neuropathogenic basis of central cholinergic deficit as delirium, and thus would be expected to modify the deliriogenic effect of ACH medication. Thus, new studies aiming to answer either of these questions should help clarify current controversy regarding ACH-delirium association and expand our understanding of the pathogenesis of delirium syndrome.

However, the ability of a clinical epidemiological study to provide a valid answer to the above research questions will depend on whether it overcomes methodological limitations of previous studies, especially in representing the unique features of both medication exposure and delirium syndrome, i.e., frequent changes in the type, dose and number of prescribed medications, and transient, episodic and fluctuating symptoms of delirium. A new study would be advantageous if it could explore the relationship between ACH exposure and delirium in their real dynamic rather than static context. On the other hand, a practical and fundamental prerequisite is a longitudinal database for both ACH medication exposure, potential confounders and effect modifiers, and outcome measures of delirium severity in a large-sized elderly inpatient population. A research protocol can

only achieve its goal within the limits of the availability and quality of a suitable database. Toward this end, the two delirium studies in elderly medical inpatients in St. Mary's Hospital, Montreal, a 400 bed, university-affiliated primary acute care hospital have provided suitable data for implementation of the intended study. An overview of the data source is provided below.

3.2. Overview of Data Sources

The two studies included a randomized controlled trial (RCT) of delirium geriatric service led by Dr Cole and a prospective cohort study of outcomes of delirium (referred to as the prognostic study) led by Dr McCusker. Both studies used the same measures and follow-up protocols, and differed in eligibility only. The subjects for both studies were recruited from consecutive admissions aged 65 years and over from the emergency room to the medical or geriatric services between March 1996 and January 1999. Within 24 hours of admission, they were screened by a study nurse to determine their eligibility for the study. Patients were not eligible if they were: 1) admitted either on Friday or Saturday; 2) diagnosed with 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.

Systematic detection of delirium was conducted in all the eligible patients through a two-stage screening procedure. First, eligible patients were screened by a study nurse with the Short Portable Mental Status Questionnaire (SPMSQ) and review of nursing notes (46,47). All those who scored 3 to 9 on the SPMSQ or with symptoms of delirium in the nursing notes were assessed using the Confusion Assessment Method (CAM) (49). Prevalent cases of delirium were defined as those who met criteria at admission for

definite or probable delirium. Patients without delirium at admission were rescreened daily for the following week using the SPMSQ and a review of nursing notes. Those 000000000000000scoring at least 1 point higher on the SPMSQ on any subsequent assessment than on the initial assessment or being reported in the nursing notes to have symptoms of delirium were assessed using the CAM. Patients who met the DSM-III-R diagnostic criteria more than 24 hours after admission were diagnosed as 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 of the patient. Participants of RCT were then randomized into either intervention or control (i.e., usual care) group. The remaining participants were subjects of the prognosis study.

During hospitalization, all cohort members were followed up using Delirium Index (53) and other measures by a research assistant who was blind to the study group allocation (intervention or control arms of the trial, or prognostic study). Initially, each patient was assessed with the DI daily during the first week and weekly thereafter for 8 weeks or until death or discharge from hospital. Later on, the frequency of patient assessments during the first week was reduced to every 2-3 days, in order to reduce possible testing effects.

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 prn (use as-needed) or regular (once, twice, or multiple administrations per day). Also abstracted were the date and types of

dose/frequency changes during hospitalization by recording whether a medication was newly added or removed, and whether the dosage was increased or decreased at each day. This information was used to calculate daily medication exposure (see Section 5.4.3. for details). Patients' demographic characteristics, clinical and laboratory data were collected at hospital admission or date of enrollment into the study.

3.3. Study Design

Based on both methodological considerations of study validity, precision and originality and data availability, I selected a prospective cohort study of all the diagnosed delirium cases with repeated follow-up measures of delirium severity (112). The basic idea of this design is to evaluate the association between measures of delirium severity and the preceding changes in exposure to ACH medications longitudinally during the hospitalization period. This design has increased power because within-individual changes are modeled. In addition, it will allow for modeling dose-response relationship between delirium severity and ACH medication exposure on their original continuous scales, thus improves the precision of the risk estimate.

3.4. Ethical Considerations

This thesis used the data already collected in the RCT and prognostic study, for which the original protocols have been approved by the Hospital's Research Ethics Committee. Assent was obtained from the patient and informed consent from a significant other of the patient. The consent forms for the two original studies are provided in Appendix 1.

4. OBJECTIVES AND HYPOTHESES

The primary objectives of the current study are:

1). To evaluate the association between the change in recent exposure to ACH medications and the change in the severity of delirium symptoms longitudinally during the clinical course of delirium in hospitalized medical elderly;

2). To test whether this association is modified by the presence or absence of dementia.

I hypothesized that:

1). The increase in current exposure to ACH medication would be independently associated with an increased severity of delirium symptoms;

2). The effect of exposure to ACH medications on delirium severity would depend on the presence or absence of dementia. with demented patients being more sensitive to deliriogenic effect of ACH medications than those not demented.

5. SUBJECTS AND METHODS

5.1. Subjects

For the purpose of this thesis, eligible subjects included all the delirium patients either diagnosed at admission (prevalent cases) or during the week after admission (incident cases) in order to achieve sufficient sample size. By January 31 1999, 293 patients who were diagnosed as with delirium and who had had at least one DI measurement were identified, accounting for 13% of the 2260 eligible patients who completed delirium screening and 6% of the 4631 consecutive admissions during the same period. Of these 293 eligible patients, 15 who had only baseline DI measure at enrollment were excluded since they provided no information for studying longitudinal variation of delirium symptoms. Thus, the final study population includes the remaining 278 patients who had both baseline and at least one follow-up DI measures.

5.2. Outcome Measures and Observation Period

Severity of delirium symptoms was defined as the study outcome, indexed by DI scores measured at multiple times during hospitalization (see Section. 3.2. for details). Since DI was not measured daily or at randomly selected dates, it would be ideal to include as many as possible DI measures for each patient in order to provide a complete profile of the natural variation of the delirium symptoms. However, in most patients DI measurements were sparse after day 21 when most patients were either discharged or dead. For this reason, I selected the first 21 days following study enrollment as the observation period of this study and analyzed DI data collected during this period only.

5.3. Development of a New Measure: Clinician-rated ACH Score

One major challenge facing this study was to define and quantify ACH exposure by deriving a sizable number of exposure variables from several hundreds of medications used in our study population. Although an aggregated ACH scores, like Summers' DRN (30), would be preferable in terms of reflecting cumulative effect of polypharmacy and increasing the power of multivariate modeling (i.e., by reducing number of parameters in the model), only 36 of our 234 study medications had a DRN number assigned in Summers' paper. In addition, neither previous study nor well-accepted gold standard is available for defining anticholinergic effects of all the medications. For the purpose of accommodating both the specific research purpose and the replicability of the study, I decided to develop a new measure of ACH medication exposure by incorporating the consensus of clinicians' judgment, conventional pharmacological classification and available evidence from previous clinical or experimental studies.

First, I established a list of 340 medications that included all 234 used in our population and additional 66 that had a grading on their potential clinical ACH effect from the pool of potential ACH medications reported in literature (17,18, 28-30, 82, 91,113-120). Second, three geriatric psychiatrists (Drs Martin Cole, Francois Primeau and Michel Élie) were invited to independently rate the ACH effect of each medication from 0 (none) to 3 (high), based on their own clinical experience and knowledge about the anticholinergic effects and other pharmacological properties of these medications. The inter-rater reliability of the three clinicians' ratings for all 340 medications and the concordance of the mean and median values of the three clinicians' ratings with Summers' COD (30) and several different sources (93, 113-116) of research data that

provided quantitative rating on ACH effects of medications were assessed. Finally, I selected the median value of the clinicians' ratings, based on high correlations between the three clinicians' ratings for the 340 medications and strong agreement of the median ratings with Summers' COD (r=0.71, rated on 62 medications) and with the ACH effect ratings from experimental data (r=0.56-0.65, rated on 14 to 32 medications, respectively). To reduce confounding of ACH exposure by other deliriogenic medications, the clinicians were also asked to rate the overall deliriogenic effect of each medication. Those that were thought of having no ACH effect but might induce delirium were identified. However, since the number of these medications was small (13 medications), they were used as a separate group in sensitivity analysis only (see also Section 5.4.2.).

The clinician-rated ACH scores for the 234 medications is listed in Appendix 3.

5.4. Defining Medication Exposures

5.4.1. Construction of Medication Variables for the Main Analysis

We constructed the following five independent variables to measure daily medication exposures:

1). Summers' Drug Risk Number (DRN): For each medication used in our study population, we tried to assign a DRN score (30). Since majority of the medications we studied were not evaluated by Summers and since we did not record detailed dose information on the medications for every day, we made two modifications on DRN assignment to each medication: i). Medications that were not evaluated by Summers were considered as having no ACH effect and were assigned a COD 0; and ii). We ignored DED and used only COD as an approximation to DRN by assuming that all the

medications were prescribed at a dose within clinical therapeutic range, a modification similar to that made by Gilley et al (110).

The main purpose of DRN is to serve as a historical reference for a quantitative measure of exposure to ACH medications, against which the validity and precision of the newly developed clinician-rated ACH score can be assessed.

2). Clinician-rated ACH score: we assigned each medication a clinician-rated ACH score based on the median ratings of the three clinicians, as defined above. This score is intended to serve as one of the main exposure measures, reflecting the variation of the ACH exposure over time due to changes in dose and frequency of the prescribed medications. It shares the same quantitative nature as Summers' DRN, but is applicable to all the study medications used in our study population.

3). Number of ACH medications based on clinicians' rating (ACHM-CR),: We calculated the number of ACH medications by counting all the medications with a clinician-rated ACH score greater than 0, as an alternative measure of ACH medication exposure. Although derived from clinician-rated ACH score and also varied over time, this measure differs from the latter in that it reflects the effect of change in actual number rather than the dose or frequency of medications.

4). Number of non-ACH medications: was calculated by summing the number of medications with a clinician-rated ACH score of 0. This quantitative measure serves as a major indicator for potential confounding by other medications, with or without deliriogenic effect. Adjustment of ACH exposure for this covariate would provide evidence for the independence and specificity of the hypothesized ACH medication-delirium association.

5). Total number of medications: was calculated by summing the numbers of ACH and non-ACH medications. This aggregated medication measure is intended to test the ACH medication-delirium association in a more strict condition. Since it has included the "number" of ACH medications, the estimate for clinician-rated ACH score would hypothetically reflect dose-response due to the "pure" change in ACH effect of the medications. Thus, adjustment of clinician-rated ACH score for this covariate would provide additional insight into the specificity of the ACH medication-delirium relationship.

5.4.2. Alternative Medication Measures for Sensitivity Analyses

To test the specificity of the observed ACH-delirium association and to assess the potential influence of the new measures of ACH exposure on its validity and precision, several alternative measures of medication exposure, which divide non-ACH medications into potentially deliriogenic and non-deliriogenic groups, were devised for purpose of sensitivity analyses using the following approaches:

1). Clinicians' Rating

According to the three clinicians' ratings, we divided the original single variable, i.e., number of non-ACH medications, into numbers of a) Non-ACH deliriogenics (NACHD-CR); and b) Other medications (OM-CR), based on the potential effect of each individual medication in inducing delirium (see Section 5.4.1. for details). The two original variables representing ACH medications, i.e., clinician-rated ACH score and number of ACHM-CR, remained unchanged.

2). Therapeutic Classes

Based on major therapeutic classes in clinical pharmacology textbooks and clinicians' references, we redefined ACH medications (ACHM-TC), Non-ACH deliriogenics (NACHD-TC) and Other medications (OM-TC) as follow.

a). ACHM-TC: Classes included in this group are atropine and belladonna alkaloids or their derivatives, used for antiemetics, antiparkinsonism, antiasthma and relaxant of smooth muscle; opioids analgesia; histamine (H_2)-receptor antagonists; antipsychotics and tricyclic antidepressants. All these classes are in general considered as major ACH agents or having well-documented clinical ACH properties (15, 17, 18, 29,30,86, 90,91, 93,99,100-106,113-120).

b). NACHD-TC: included lithium, anticonvulsants, dopaminergic antiparkinsonics, alpha- and/or beta-adrenergic blockers, central antihypertensives, corticosteroids, non-steroid antiinflamantory drug or similar analgesics, and cardiovascular agents (82,90,91,99,102). In addition, all sedative-hypnotics including benzodiazepines, selective serotonin receptor inhibitors (SSRI) and other non-tricyclic antidepressants were also included as a group, even though several individual agents under these classes may have also some ACH effect (30,91-93, 99,100, 102-107).

c). OM-TC: included all other classes of medications not categorized under the two above classes. Though some antibiotics or diuretics in this group have also been reported to be capable of inducing delirium, in general the deliriogenic potential of that class of medications appear to be low and their "deliriogenic" effect is subject to major confounding from the severe diseases for which they are often indicated (82,91).

All the three therapeutic classes-based variables were measured by counting the number of medications under each group. The inter-class correlation (Kendell's tau-b coefficient) between therapeutic classes- and clinicians' rating-based approaches for the three groups of medications is 0.43 ($n=234$, $p<0.0001$).

3). Exclusion of Antipsychotic Medications

Since some ACH medications, for instance antipsychotics, may be specifically prescribed by physicians to control delirium symptoms (19,20, 40, 83,103,119), the observed ACH medication-delirium severity association may be partially accounted for by "reverse causality" that it is the outcome (delirium severity) leads to the exposure (use of ACH medication) rather than *vice versa*. To assess the impact of such a potential bias, each measure of ACH medication exposure was also recomputed by excluding all the antipsychotic medications, under both clinicians' rating-based and therapeutic classes-based approaches.

5.4.3. Weighting of Medication Exposure According to Dose and Frequency Change

For each hospital day except the first day of starting or resuming a medication, only the date and direction of change in dose (i.e., increase, reduce, stop or add) or frequency (i.e., regular or as-needed) were abstracted rather than the actual dose. Therefore, for computation of the daily Summers' DRN and Clinician-rated ACH score, we assigned *a priori* weights selected for 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/dose, was given a weight of one, while that prescribed on an as-needed basis was given a weight of 0.5. For each medication used during days without dose/frequency changes, the corresponding DRN and ACH scores were assumed

to be equal to that at baseline or of the last day of dose/frequency change (i.e., weight=1), whichever was more recent. For any day when the dose of a medication was changed, the ACH scores and DRN for that medication in that day were approximated by multiplying the exposures on the previous day by a factor of 1.5 (for increase) or 0.67 (for decrease).

Using this weighting strategy, all the 5 medication variables were defined as time-dependent measures, i.e., their respective values were measured for each day during the entire observation period. The daily Summers' DRN and clinician-rated ACH scores were simply the sum of total quantities of each measure for all the medications used each day. Since the other medication variables count only the number of medications, they were not affected by weighting of the dose/frequency. A case scenario to demonstrate this strategy is provided in Appendix 4.

5.4.4. Definition of the 24-hour Exposure Time-window

Given the typical acuteness of delirium onset following intoxication by a medication or other substance (15,30,36), we judged that a short exposure time-window would be biologically plausible. Thus, the 24-hour period before each DI assessment was defined as time-window for medication exposure, a strategy similar to that used by Marcantonio et al (12). For example, if a patient had DI measured on day 3, this DI score would be associated with measures of medication exposure calculated for day 2.

5.5. Potential Confounders/Effect Modifiers

Based on the literature review, several most important risk factors were selected as potential confounders and/or effect modifiers of the hypothesized association between ACH medication exposure and delirium severity. These included the following time-dependent and fixed baseline variables.

Length of follow-up was defined as a time-dependent covariate, calculated as the total days from study enrollment to each day of DI assessment.

The fixed baseline variables referred to patient's demographic and clinical characteristics, which were measured either at admission to the hospital or at enrollment into the study. These variables included:

Dementia: Preexisting dementia was defined with the Informant Questionnaire on Cognitive decline in the Elderly (ICQCODE), a 16-item, clinically validated instrument for assessing dementia status by proxy interview (121). The data were collected by a study nurse from interviewing a family member at enrollment. Using different cut-off point to define dementia or delirium against DSM-IIIR criteria, the sensitivity varied between 75% and 85% and the specificity between 63%-88% in a population of 684 subjects (121). In the present study a cut-off point of 3.5 or more was used.

Two dummy variables were constructed, one for categorizing dementia (if IQCODE $\geq$ 3.5) or not dementia (if IQCODE < 3.5), and another for labeling the missing data.

Each patient was also assessed with the MMSE (43). However, it was determined that the MMSE scores were not appropriate to define dementia in our study, because delirium syndrome itself could affect patients' performance on the MMSE. Thus the MMSE scores was used only as a descriptive measure of patients' baseline cognitive function and an alternative variable for dementia in testing of ACH exposure-dementia interaction.

Sociodemographic characteristics: Data were obtained either from the informant interview or the hospital chart review, and included: age, sex, marital status (married vs. other) and living condition prior to admission (home vs. other).

Comorbidity: The Charlson Comorbidity Index (CCI) was used to measure comorbid physical diseases of patients at baseline (122). CCI is an empirically based scale that aggregates the severity and number of comorbid conditions, with a higher score indicating greater severity. Data for the CCI were obtained through reviewing patient hospital charts by a study nurse.

Laboratory variables: Measurements of serum albumin, blood urea nitrogen and creatinine were abstracted from patient hospital charts by a study nurse. To facilitate comparisons with previous studies, serum albumin was dichotomized into either within (≥33 g/L) or below (<33g/L) normal range (according to our Hospital's criterion). Blood Urea Nitrogen (BUN) and creatinine were converted to BUN/creatinine ratio in unit of mg/100ml (10). Patients without these laboratory test results were assumed to be within normal range for albumin (n=213), or were a middle value of normal range for BUN (5.3 mMol/L, n=42) or for creatinine (83.5 Mol/L, n= 41), as such laboratory tests are usually ordered when physicians suspect abnormal test results.

Visual or hearing impairments: Each patient was assessed at enrollment for presence or absence of visual and/or hearing impairment by the study nurse.

History of alcohol and/or drug abuse: A history of alcohol and or drug abuse was obtained by the research assistant using an informant questionnaire and dichotomized as either with or without such a history.

Delirium type: A binary variable was designated for the two types of delirium cases, prevalent vs. incident.

Study group: Two dummy variables denoted study group: i). Intervention allocation: intervention vs. control arms, and ii). Source of patients: RCT (trial) vs. prognosis study.

Other baseline variables

Functioning of Instrumental Activities of Daily Living (IADL) is a potentially important confounder and was assessed at enrollment using a questionnaire from Older American Resources and Services project (123). However, the IADL scores (range: 0 to 14, 0 the worst) in the study population were significantly correlated with two main covariates, dementia (Pearson's correlation coefficient: $r = -0.44$, $n=265$, $p<0.0001$) and living arrangement ($r=-0.40$; $n=278$, $p<0.0001$). To avoid potential multi-collinearity, IADL was not included in the multivariable regression analysis. Another baseline variable that served as descriptive measure only was marital status.

The definitions and coding for each covariate are presented in Table 5 (see Section 7. RESULTS for details).

6. STATISTICAL ANALYSES

6.1. Descriptive Analysis

Descriptive statistics included means, standard deviations for quantitative variables and proportions for categorical variables. Within-patient means of each quantitative time-dependent variable were calculated by averaging all the repeated DI measures during the observation period, or all the daily medication measures preceding DI assessments. Next, the distribution of these patient-specific means in the entire population was assessed.

6.2. Relationship between Baseline DI and Covariates

Pearson product-moment correlation coefficients between baseline DI score, baseline medication measures and all the fixed baseline covariates were estimated to provide background information about their interrelationship and to detect potential collinearity problem between covariates. Multivariable linear regression analyses of baseline DI score were carried out using baseline medication measures and 10 *a priori* selected baseline variables as covariates: age, CCI, visual/hearing impairment, serum albumin, living arrangement prior to admission, type of delirium and two dummy variables each for dementia and study group (see Table 5 for details).

6.3. Repeated Measure Analysis Using the MIXED Model

6.3.1. Rationale for Selection of the MIXED Model

To evaluate the effect of within-subject change in daily medication exposures on subsequent variation of DI scores over time, we used unbalanced repeated measures analysis of variance model with SAS procedure MIXED (124). This procedure allows for a mixture of between-patient (fixed at baseline) covariates, such as age and dementia status, and within-patient (time-dependent) covariates, such as daily medication exposures, or their interactions with dementia status, and thus is capable of accounting for (i) repeated measurements of DI and exposure for the same individual; and (ii) unbalanced design, i.e., the fact that the number of available DI scores and/or their timing varied from patient to patient.

Covariance structure of residuals specifies the form of dependence of the discrepancies between observed and expected values of DI scores for an individual patient (112) and thus has important implications for point estimates of the effects of

particular predictors and for the inference about these estimates (125). Due to insufficient knowledge to select *a priori* an appropriate covariance structure, we used (i) Autoregressive order 1 (AR(1)), which assumes that the correlation between repeated measures decreases with increase of time interval; (ii) Heterogeneous AR(1) and (iii) Ante-Dependence alternatively in model estimation, and then identified *a posteriori* the best-fitting one among the three according to the AIC criterion (126).

6.3.2. Model Building Strategy for the Main Analysis

Model estimation was conducted using a three-step strategy. First, we tried to fit a model with 14 *a priori* selected covariates. Effect of ACH medications was evaluated using one of the three variables, Summers' DRN, the clinician-rated ACH score, or the number of ACH medications, each in a separate model. To account for a potential deliriogenic effect that was not attributable to ACH medications, each model included one of the two measures of exposure to other medications: i.e., the number of non-ACH medications or the total number of medications. All models included also a time-dependent covariate, representing the length of follow-up, in order to account for a possible time trend for delirium severity to decrease with increasing time in the study.

Because the initial severity of delirium is expected to correlate strongly with subsequent DI scores and may be also correlated with exposure to ACH medication, we adjusted the effect of exposure for baseline DI. This adjustment allowed us to estimate the effect of ACH medication among patients with the same level of initial delirium severity and also reduced the risk of potential confounding by indication that could occur if symptomatically severe patients at study entry were prescribed more ACH medications.

Other fixed baseline covariates included the 10 variables used for multivariable linear regression analysis (see section 6.2. for details).

Second, we introduced the following additional covariates, one at a time, into the model: i) sex, ii) BUN/Creatinine ratio and iii) history of alcohol/drug abuse. These variables were excluded if they did not reach statistical significance and did not substantially affect the estimates of the main exposures.

Finally, in the optimal models selected via the above procedure, we tested the statistical significance of the interactions of ACH medication exposure with dementia. In order to provide additional insight into the relationship between ACH medication exposure and delirium severity, we also tested potential effect-modification by other baseline risk factors and the length of follow-up *post hoc*.

All models were estimated using restricted maximum likelihood estimation (REML) (124). Selection of optimal model(s) was determined according to both biological plausibility and statistical criteria.

6.3.3. Testing for Departure from Linearity

In the primary analyses, our hypothesis testing with the mixed regression model was based on the assumption that the effect of ACH medication exposure on delirium symptoms was linear. Since this *a priori* assumption may or may not be true, we tested potential departure from linearity in the final regression models by including a squared term of ACH exposure. Statistical non-significance of this quadratic term would be considered as the lack of evidence against the linearity assumption.

6.4. Sensitivity Analysis

Using both clinicians' judgment- and therapeutic classes- based approaches (described in section 5.4.2.), we reran the mixed regression model analyses with alternatively defined measures of ACH, non-ACH deliriogenics and other medications, with and without exclusion of the antipsychotic medications, adjusting for the same set of the 14 pre-selected covariates.

All the statistical analyses were conducted using the SAS 6.21 software (124). A significance level of 0.05 was used for all the hypothesis testing.

7. RESULTS

7.1. Descriptive Statistics of Study Population

Our study population consisted of 278 patients with diagnosed delirium, of which 44 were prevalent and 234 incident cases, and 191 from the trial and 87 from the prognosis study. The primary diagnoses (according to ICD-9 code) for the index hospitalization among the study subjects are listed in Table 3. Patients with pulmonary-cardiovascular disease accounted for 42% of entire study population, followed by those with mental disorders, neurological and cerebrovascular diseases.

The demographic and clinical characteristics at baseline of the study population are presented in Tables 4 and 5. The mean age of 83 years, MMSE score of 15 and IADL rating of 6.6 suggests that this is a frail elderly population with moderate cognitive and functional impairment. The main baseline characteristics of the 15 patients who were excluded due to having only one baseline DI measure, in comparison with those of the 278 included, respectively, are: mean age: 85.2 vs 83.4; daily clinician-rated ACH score: 1.7 vs 1.7; number of ACH medications: 1.3 vs 1.2; DI score: 10.5 vs 8.3; MMSE score: 11.8 vs 15.0; and length of hospital stay: 3.0 vs 20.8 days.

Table 6 provides descriptive statistics for the time-dependent variables representing medication exposures and delirium severity both at baseline and over-time. During the 21 days of follow-up, the mean number of DI assessments for this cohort was 5.7 with standard deviation of 2.8. The mean length of follow-up between the first and last DI was 12.3 days (SD: 7.0). Among the 278 patients, a total of 234 medications were used at least once. Of these, 47 (20.1%) were classified as ACH medications (the clinician-rated ACH score>0). Table 7 presents the period prevalence of most frequently used ACH

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

7.2. Relationship between Baseline DI, Exposure and Covariates

Relationship between baseline DI scores and potential confounders/effect modifiers were assessed using Pearson product-moment correlation (for continuous variables, Table 4), or Student t-test or one-way ANOVA (for DI difference between strata by categorical variables, Table 5). Older age, lower MMSE score, greater IADL dysfunction, presence of dementia, living elsewhere other than own home, having prevalent delirium and participant in the prognosis study were significantly associated with higher baseline DI scores ($p<0.05$). None of the other covariates were significantly related with baseline DI ($p>0.05$), but alcohol/drug abuse, low serum albumin, and visual/hearing impairments showed such a trend ($0.05 < p < 0.10$). In addition, of the five baseline measures of medication exposure, only total number of medications was significantly correlated with DI score ($r= -0.12$, $p=0.04$), whereas the multivariable regression models adjusting for baseline covariates revealed no significant relationship between the medication exposures and DI score (Table 8).

7.3. Repeated Measure Analyses of Variance Using the Mixed Model

7.3.1. Main Analysis of ACH Exposure

Since there were no systematic differences in AIC values between the three covariance structures considered (data not shown), we decided to select AR(1) structure for the mixed model regression analysis, based on its conceptual simplicity and stability of results.

Table 9 summarizes the results of four regression models, each using a different combination of medication exposure variables. The regression coefficients, their 95% confidence interval (CI) and the corresponding p-values are shown for the medication exposures and main covariates.

In the initial models including all 14 preselected covariates, a daily measure of clinician-rated ACH score was found to be a statistically significant correlate of delirium severity on the next day, when adjusted for the number of non-ACH medications ($p<0.01$, Table 9, Model 1). The effect remained statistically significant even when adjusted for the total number of medications ($p<0.02$, Table 9, Model 2). However, the effect of Summers' DRN was not significant when adjusted for either total number of medications ($p=0.35$, Model 4) or for the number of non-ACH medications ($p=0.08$, 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 quite consistent with Model 1 in terms of the significance of the estimated regression coefficients for the ACH medication exposure (Table 9, Model 3). It should be noted that where the effect of increasing the number of non-ACH medications was also statistically significant, the effect of ACH medications was almost 5 times stronger (0.52 vs. 0.11 in Table 9, Model 3).

7.3.2. Adjusting for Additional Covariates

We then included in Models 1 through 3, sex, BUN/Creatinine ratio, and alcohol and/or drug abuse, one at a time. In all the three models, the effect of ACH medications remained significant after adjusting for each of these additional covariates, while none of these additional covariates was statistically significant ($p>0.05$, data not shown).

7.3.3. Testing of Interactions

In Models 1 and 3, we tested the interactions between the main exposure, clinician-rated ACH score (in Model 1) or number of ACH medications (in Model 3), and the two dummy variables for dementia (dementia, dementia missing). No statistically significant interactions were detected (p=0.21~0.89, data not shown). We also used the continuous MMSE score, instead of the binary indicator of dementia, as an effect-modifier variable, there were still no significant interactions (p=0.1 and 0.2, respectively, data not shown).

The interaction between ACH medication exposure and other baseline risk factors or length of follow-up were not statistically significant (p=0.19~0.54, data not shown), except for low serum albumin (p=0.02). It was found in Model 3 that the effect of number of ACH medications depended on serum albumin, with one additional ACH medication increasing the DI score by 1.1 points for patients with low serum albumin and 0.4 for those without [formula: DI score increment = 0.38 x (number of ACHM-CR) + 0.75 x (number of ACHM-CR) x hypoalbuminia].

7.3.4. Selection of Final Models

When interaction term was not included, Models 1 and 3 were quite similar in terms of goodness of fit to the data and the significance of the estimate of ACH medication exposure (last row of Table 9). Translating the estimated regression coefficients (0.27 and 0.52, respectively) into practical meaning, an increase in daily exposure to ACH medications equivalent to 2 points (population mean score) of clinician-rated ACH score, or to one additional ACH medication (population median

number) would on average be associated with about 0.5 point increase in the subsequent DI score, when the values of all the other covariates in the model remain unchanged.

Since Model 2 divides the effect of the number of ACH medications from the "main exposure" variable and included it in the total number of medications, the clinician-rated ACH score represents only the unique ACH effect of medications over and above the number of different medications. While this model provides more convincing statistical evidence of an ACH effect, it also underestimates the total impact of ACH exposure and thus limits its clinical interpretation. On the other hand, although the interaction between ACH medications and serum albumin is biologically plausible, this interaction in Model 1 using a different exposure measure (i.e., clinician-rated ACH score) did not reach statistical significance (p=0.24, data not shown).

Taking biological plausibility, statistical criteria and clinical applicability into account, we judged that Models 1 and 3 without interaction terms might be optimal for quantifying the observed ACH exposure-delirium severity association.

7.3.5. Testing for Departure from Linearity

In Model 1 and Model 3 respectively, we tested departure from linearity by including an additional quadratic term of the ACH exposure. There was no statistically significant departure from linearity or improved model fit (p values for the quadratic term: 0.62 and 0.35; the differences in AIC values between the quadratic models from the original linear models: 3.0 and 1.2, respectively).

7.4. Sensitivity Analysis

Results from sensitivity analysis using the two different approaches to defining medication exposure are summarized in Tables 10 and 11, respectively. In brief, the main

exposure, use of ACH medications, remained statistically significant and the point estimates and 95% CIs for the exposure effect were quite similar no matter what measures were used. In addition, the estimates and significance of main covariates and the model fit showed little change. Exclusion of antipsychotics did not change these profiles (Models 1.3 and 1.4 in Table 10, and 2.3 and 2.4 in Table 11). Another consistent but unexpected result was that non-ACH deliriogenics by either definition showed no significant effect on the severity of delirium, whereas the other medications showed a significant ($p<0.05$) or marginally significant effect ($p=0.05$).

Table 3: Frequency distribution of primary diagnosis for the index hospitalization in the study population (N=278)

Diagnosis	ICD-9 Coding	n	%
Respiratory system disease	460-519	60	21.6
Cadiovascular disease including rheumatic dissease	390-429	57	20.5
Mental disorder	290-319	31	11.2
Neurological and cerebrovascular disease	320-359,430-459	29	10.4
Musculoskeletal system disorders including fracture, dislocation etc	710-739,800-849	22	7.9
Digestive system disease	530-579	12	4.3
Neoplasm	140-239	12	4.3
Endocrine, metabolic and immune system disease	240-289	10	3.6
Urinary and genital organ disease	580-629	9	3.2
Infection, poisonings and intoxication	0-139,960-989	7	2.5
Ill-defined conditions and other disorders*	all other	29	10.4

* Including one patient with missing diagnosis, one patient with skin disease.

Table 4. Baseline characteristics and relation with DI score: categorical variables.

Variable		n	%	Mean DI±SD	t or F value[1]
Gender:	*Male*	108	38.8	8.2 ± 3.7	0.44
	Female	170	61.2	8.4 ± 4.0	
Marital status:	*No spouse*	183	65.8	8.5 ± 4.1	1.43
	Having a spouse	95	34.2	7.9 ± 3.5	
Dementia	*Absent*	72	25.8	6.9 ± 3.7	9.16 **[2]
	Present	180	64.6	9.0 ± 3.9	
	Missing data	26	9.6	7.3 ± 3.8	
Visual/hearing impairment:	*Absent*	223	80.2	8.1 ± 4.0	-1.77
	Present	55	19.8	9.1 ± 3.4	
Serum albumin:	*Low*	43	15.5	8.4 ± 3.4	-0.07
	Normal	235	84.5	8.3 ± 4.0	
Living arrangement:	*Other*	72	25.9	9.4 ± 4.3	-2.63 **
	Home	206	74.1	7.9 ± 3.7	
Alcohol/drug abuse:	*Absent*	252	90.7	8.4 ± 3.9	1.87
	Present	26	9.3	7.1 ± 3.5	
Delirium type:	*Prevalent*	235	84.2	8.6 ± 3.8	-2.13 *
	Incident	44	15.8	7.0 ± 4.5	
Study group:	*Trial: Control*	96	34.4	7.4 ± 3.6	6.97 **[2]
	Trial: Intervention	95	34.2	8.1 ± 3.9	
	Prognosis	87	31.4	9.5 ± 4.0	

Notes:

1. Except for those otherwise indicated, all values represent Student t-test statistics.
   *:$p < 0.05$; **:$p < 0.01$.
2. Value represents F value for the model (general linear model, df=2).
   Subgroup comparison with Tukey test:
   Dementia: *Present* was higher than *Absent* ($p<0.05$);
   Study group: *Prognosis* was higher than *Intervention* and/or *Control* ($p<0.05$).

Table 5. Baseline characteristics and relation with DI score: continuous variables.

Variable	n	Mean±SD	Range	Correlation with DI
Age (in years)	278	83.4 ± 7.3	65-102	0.13 *
Charlson Comorbidity Index (CCI)	278	2.9 ± 2.0	0-12	0.01
BUN/Creatinine ratio	278	21.2 ± 7.5	3.6-53.6	-0.02
MMSE	278	15.0 ± 7.2	0-29	-0.79 **
IADL	265	6.6 ± 3.8	0-14	-0.30 *

Notes:

1.Values represent Pearson's product-moment correlation coefficients.

*. $p < 0.05$; **. $p < 0.01$.

Table 6. Characteristics of study population: time-dependent variables (N=278)

Variable	Baseline measures	Repeated measures*
	Mean±SD	Mean±SD
DI score	8.3 ± 3.9	7.4 ± 3.9
Summers' DRN	2.2 ± 2.3	2.5 ± 2.3
Clinician-rated ACH score	1.7 ± 1.8	2.0 ± 1.8
Number of ACHM-CR	1.2 ± 1.1	1.4 ± 1.1
Number of non-ACH medications	6.0 ± 3.5	6.3 ± 3.4
Total number of medications	7.2 ± 3.7	7.7 ± 3.6

* Refer to each patient's means of all the available repeated measures during follow-up period. The mean and SD of these 278 patient-specific means were then calculated.

Table 7. The most frequently used ACH medications in the study population (N=278)

Medication	n*	%	Clinician-rated ACH score	Summers' COD
Haloperidol	120	43.2	2	na
Morphine	69	24.8	1	III
Ranitidine	64	23.0	2	na
Acetominophen+codeine	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

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

Table 8: Multiple linear regression model on baseline DI score using baseline measures of covariates (N=278)*

Covariates*	Model 1			Model 2			Model 3			Model 4		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Summers' DRN										-0.17	-0.38~0.05	0.88
Clinician-rated ACH score	-0.07	-0.32~0.19	0.60	-0.04	-0.31~0.23	0.77						
Number of ACHM-CR							-0.12	-0.53~0.29	0.57			
Number of non-ACH medications	-0.05	-0.19~0.10	0.51				-0.05	-0.19~0.10	0.52			
Total number of medications				-0.05	-0.19~0.09	0.50				-0.05	-0.20~0.10	0.51
Dementia: 1=yes, 0=no.	1.30	0.18~2.42	0.02	1.29	0.17~2.42	0.03	1.28	0.15~2.41	0.03	1.30	0.18~2.43	0.02
Dementia missing: 1=yes, 0=no.	-0.30	-2.03~1.44	0.74	-0.30	-2.04~1.43	0.72	-0.31	-2.05~1.43	0.72	-0.30	-2.04~1.44	0.74
F (df) for the model (p value)	3.15 (12) / 0.0003			3.15 (12) / 0.0003			3.15 (12) / 0.0003			3.15 (12) / 0.0003		
Adjusted R^2	0.125			0.125			0.125			0.125		

* Listed are main covariates of interests only, i.e., medication measures and effect modifiers. Other simultaneously adjusted covariates in each of the four models include: age, serum albumin, living arrangement prior to admission, Charlson comorbidity index, visual/hearing Impairment, delirium type and study group.

Table 9: Repeated measure analysis using Mixed linear regression models (N=278)*

Covariates*	Model 1			Model 2			Model 3			Model 4		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Summers' DRN										0.07	-0.07~0.2	0.35
Clinician-rated ACH score	0.27	0.11~0.42	<0.01	0.20	0.03~0.36	0.02						
Number of ACHM-CR							0.52	0.27~0.78	<0.01			
Number of non-ACH medications	0.11	0.02~0.21	0.02				0.11	0.01~0.20	0.03			
Total number of medications				0.13	0.03~0.22	0.01				0.14	0.04~0.24	<0.01
Dementia: 1=yes, 0=no.	1.23	0.40~2.07	<0.01	1.25	0.43~2.09	<0.01	1.30	0.47~2.13	<0.01	1.24	0.40~2.07	<0.01
Dementia missing: 1=yes, 0=no.	1.22	-0.10~2.50	0.07	1.24	-0.08~2.53	0.06	1.28	-0.03~2.58	0.06	1.18	-0.13~2.4	0.08
Baseline DI score (continuous)	0.52	0.44~0.61	<0.01	0.52	0.44~0.61	<0.01	0.52	0.43~0.61	<0.01	0.53	0.44~0.61	<0.01
Akaike's Information Criterion	-2889.69			-2888.82			-2886.64			2891.20		

* Listed are main covariates of interests only, i.e., medication measures, effect modifiers and baseline DI score. Other simultaneously adjusted covariates in each of the four models include: age, length of follow-up, serum albumin, living arrangement prior to admission, Charlson comorbidity index, visual/hearing Impairment, delirium type and study group.

Table 10: Sensitivity analysis 1.Clinicians' rating-based approach (N=278)

Covariates*	Including All 234 Medications						Excluding 7 Antipsychotics					
	Model 1.1			Model 1.2			Model 1.3			Model 1.4		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Number of ACHM-CR	0.27	0.12~0.43	<0.01				0.27	0.08~0.45	<0.01			
Number of ACHM-CR				0.53	0.28~0.79	<0.01				0.48	0.19~0.78	<0.01
Number of NACHD-CR	-0.07	-0.46~0.33	0.74	-0.07	-0.47~0.32	0.71	-0.06	-0.45~0.33	0.76	-0.05	-0.44~0.34	0.79
Number of OM-CR	0.13	0.03~0.23	0.01	0.12	0.02~0.22	0.02	0.12	0.02~0.22	0.02	0.11	0.01~0.21	0.03
Dementia: 1=yes, 0=no.	1.23	0.40~2.06	<0.01	1.30	0.47~2.13	<0.01	1.19	0.37~2.02	<0.01	1.24	0.41~2.07	<0.01
Dementia missing: 1=yes, 0=no.	1.20	-0.10~2.49	0.07	1.27	-0.03~2.57	0.07	1.20	-0.09~2.51	0.07	1.24	-0.07~2.55	0.06
Baseline DI score (continuous)	0.52	0.43~0.61	<0.01	0.52	0.43~0.60	<0.01	0.53	0.44~0.62	<0.01	0.53	0.44~0.62	<0.01
Akaike's Information Criterion	-2889.91			-2886.88			-2891.40			-2889.94		

* Listed are main covariates of interests only, i.e., medication measures, effect modifiers and baseline DI score. Other simultaneously adjusted covariates in each of the four models include: age, length of follow-up, serum albumin, living arrangement prior to admission, Charlson comorbidity index, visual/hearing Impairment, delirium type and study group.

For definition of the the medication exposures, see the text of METHODS and RESULTS.

Table 11: Sensitivity analysis 2: Therapeutic class-based approach (N=278)

Covariates*	Including All 234 Medications						Excluding 7 Antipsychotics					
	Model 2.1			Model 2.2			Model 2.3			Model 2.4		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Number of ACHM-TC	0.59	0.36~0.82	<0.01	0.60	0.37~0.83	<0.01	0.61	0.34~0.87	<0.01	0.62	0.35~0.88	<0.01
Number of NACHD-TC	-0.08	-0.28~0.11	0.39				-0.10	-0.29~0.09	0.30			
Number of OM-TC	0.15	0.00~0.30	0.05				0.15	-0.00~0.29	0.05			
Total non-ACH medications				0.05	-0.04~0.16	0.26				0.05	-0.06~0.15	0.37
Dementia: 1=yes, 0=no.	1.21	0.38~2.04	<0.01	1.26	0.43~2.09	<0.01	1.16	0.33~1.99	<0.01	1.21	0.38~2.04	<0.01
Dementia missing: 1=yes, 0=no.	1.13	-0.17~2.43	0.09	1.23	-0.07~2.52	0.07	1.11	-0.19~2.41	0.10	1.21	-0.09~2.51	0.07
Baseline DI score (continuous)	0.52	0.43~0.61	<0.01	0.52	0.43~0.61	<0.01	0.53	0.44~0.62	<0.01	0.54	0.45~0.63	<0.01
Akaike's Information Criterion	-2882.54			-2882.92			-2884.88			-2885.44		

* See the footnote to Table 10 for covariates and definition of the the medication exposures.

8. DISCUSSION

8.1. Evidence For an Association between ACH Medication and Delirium Severity

In this delirium cohort, we observed that a change in exposure to ACH medications was associated with subsequent change in severity of delirium symptoms. Specifically, adding one ACH medication per day (roughly a 2 point increase in daily ACH exposure according to the clinician-rated ACH score) would on average predict a 0.5 point increase in the subsequent DI score. This association was independent of patients' age, initial severity of delirium, presence of dementia, comorbidity, serum albumin or other baseline risk factors, and length of follow-up as well as concurrent use of other medications. It persisted even after adjusting for the total number of medications, indicating that it is specific to the group of medications with potential ACH effect. These results confirmed our hypothesis that use of ACH medications is an independent and specific predictor of symptom severity of delirium in older medical inpatients during hospitalization, and as such, provided additional epidemiological evidence in support of a positive association between exposure to ACH medications and delirium syndrome, which to date has been based only on studies of the precipitating effect of ACH exposure on occurrence of delirium (18,25, 27-29,61,63).

Although the etiology or pathogenesis of delirium seems not directly addressed given the nature of our outcome measure (i.e., symptom severity rather than incidence), the observed ACH medication-delirium severity association in this thesis shows several features of a causal relationship (77-80). First, this association can be understood in the light of the widely accepted cholinergic deficit hypothesis for the pathogenesis of

delirium. If the pathological process of delirium syndrome is indeed determined by such a biological mechanism, then the ACH medication, an extraneous pathogen impeding this mechanism, should not only induce but also worsen the syndrome. The significant effect-modification by serum albumin is similarly biologically plausible in that patients with hypoalbuminemia would be more susceptible to the deliriogenic risk of ACH medications due to reduced capability to metabolize and excrete them from the body through protein-binding with serum albumin. Second, by defining a 24-hour exposure time-window preceding each DI measure, we have tried to ensure an unambiguous temporal sequence, with changes in ACH medication preceding changes of delirium severity. We also verified this temporal sequence by excluding the possibility of protopathic or reverse causality bias (see section 8.4.3. for further discussion). Third, the linearity of the ACH effect on delirium severity, the greater effect of ACH than non-ACH medications and the specificity of ACH exposure other than number of medications suggested a unique, dose-dependent causal relationship between the exposure and outcome.

8.2. Comparison with Previous Studies

Although no previous epidemiological studies have evaluated the association between ACH medications and delirium severity in a longitudinal fashion, our findings are in agreement with the postulated cholinergic deficit hypothesis for delirium (23,24,40,83-87) and research findings that link ACH exposure to the occurrence of delirium (18,25-30, 61,63,64). However, our findings are at odds with three large-scale clinical epidemiological studies (12-14) which found no association between ACH medication and the occurrence of delirium. Potential reasons that may have biased these studies towards the null, discussed in the literature review, include: inappropriately

defined exposure time-windows, lack of adjustment for the effect of polypharmacy, and confounding by contraindication. In addition, all these studies measured ACH medication exposure by counting number of persons exposed to a specific or a group of ACH medications, which may also lead to an underestimation of the effect of exposure to ACH medications, since delirium patients are often exposed to greater number of ACH medications than non-deliriums (17,27,86,92). Nevertheless, it is necessary for our findings to be replicated using different exposure measures for ACH medications.

In comparison with previous studies, one unique feature of the present study is that the relationship of ACH medication exposures and delirium outcome (i.e., symptom severity) was examined over time among delirium patients in hospital where both symptoms of delirium and the medication regimen of patients are frequently changing. Accordingly, the exposure-outcome association was evaluated in a longitudinal and dynamic fashion while simultaneously accounting for both within-subject, over-time variation of time-dependent confounders/ modifiers and between-subject differences in fixed patient characteristics (so-called predisposing risk factors). Thus, the uncertainty around the independence and specificity of the observed association could be reduced to a minimum. On the other hand, the repeated measures design may be perceived as a time series of "repetitions" of the same hypothesis testing along a longitudinal dimension, whereby the probability for the observed association to be purely due to chance would also be minimized. Such a longitudinal and dynamic cohort design, to our knowledge, has never been used in previous delirium studies. Given such methodological advantages, our study results may be more directly clinically applicable.

8.3. Lack of Effect-Modification from Dementia

Our second research objective was to evaluate the modifying effect of dementia on association between ACH medication and delirium symptom. Since dementia is a major risk factor of delirium and has been postulated to share the same pathogenic basis of central cholinergic deficit, it would be reasonable to suspect that dementia patients would be more prone to the development and exaggeration of delirium symptoms when exposed to ACH medications. Previous reports of the sensitivity of the cognitive performance of Alzheimer's patients to ACH drugs provided some research evidence for such a speculation (16,85,89,127). The absence of a significant interaction between the two factors in our study may be due to several reasons.

First, most of our dementia patients were mild to moderate in severity of cognitive impairment (mean MMSE score: 15.1); a cerebral cholinergic deficit may not yet be present in these patients (128). Thus the hypothesized interaction may not occur due to lack of required biological foundation. However, this explanation seems unlikely given the significant main effects of ACH medications and dementia. Second, the suspected modifying effect of dementia may be most apparent during, but not after, the development of delirium. Once delirium has developed, all patients, whether previously demented or not, would probably become cholinergically impaired. Thus, the modifying effect of dementia would no longer be detectable in such a "homogeneous" population. Third, the measurement error in classifying dementia might have prevented an otherwise significant interaction to be detected. Although the IQCODE has been reported to have good validity for detecting dementia in the elderly population, it has not been validated in patients with delirium, whose symptoms may be confused with those of dementia.

Finally, statistical interaction or effect-measure modification itself is measure-specific and subject to many conditions such as unadjusted or poorly measured confounders (77,78). Thus, lack of statistical interaction in the present study does not rule out existence of biological interaction between ACH medication and dementia, which can take many forms such as synergistic, intercompetent or interdependent and may not be captured by a statistical model (77). When both exposure and modifier have significant independent effect on the outcome, as is the case in our study, absence of statistical interaction on any particular measure necessarily implies presence of statistical interaction on other measures (i.e., risk ratio or odds ratio) (77). Therefore, it will be worthwhile to further investigate the role of this interaction in different stages of delirium process, and using different study populations and alternative measures of association.

8.4. Limitations of the Study

This study is subject to several potential sources of bias, which will be addressed in the following sections.

8.4.1. Selection Bias

Selection bias refers to the distortions of exposure-outcome association that result from the procedure used to select subjects and factors that influence study participation (77,78). The key element of selection bias is that the exposure-outcome relationship observed in study participants is different from that in the base population who should be theoretically eligible for the study (77-80). Although conceptually such a bias may occur in selection of either the whole sample or study population, or one particular comparison group only, modern epidemiology tends to restrict the term to the latter situation specifically, i.e, a bias that primarily affects the "internal validity" of a study in terms of

the applicability of observed effect estimates to the source population (77). Bias arising from the selection of a study population or whole sample is considered as an issue of generalizability, i.e., the "external validity" in terms of the applicability of study results to people outside of the source population (77).

Our study used a within-subject design in which no separate non-exposed group is involved; thus, selection bias pertaining to between-group comparison seems not applicable. On the other hand, patients enrolled in our study went through several stages of selection. The majority of consecutively admitted patients were not screened for delirium due to application of eligibility/exclusion criteria (such as more severe conditions or language barrier). Thus, our hospitalized delirium cohort may not be representative of cases of delirium in the general medical settings or community population. In addition, our analysis was conducted in a closed-cohort format by excluding patients with only one DI assessment. Although the number of exclusions is small (n=15) and their exposure profile seems comparable to those included, this may restrict the generalizability of our findings in a similar manner to that from losses to follow-up, especially when coupled with pre-screening selection procedure mentioned above. However, the lack of independent effects of either the length of follow-up or the type of delirium (i.e., prevalent vs incident) in our mixed model suggests that the impact of possible selective attrition on the observed ACH medication-delirium severity association would be minimal. Our results appear to be applicable to delirium patients regardless of their illness duration or length of time under observation.

8.4.2. Information Bias

Information bias refers to distortion of exposure-outcome association due to errors in the measurement of study variables (77,78). If the measurement error in one variable (i.e., exposure or disease) is dependent on the actual value of other variable (so-called differential misclassification), the risk estimates can be biased either towards or away from the null. When the measurement errors are not dependent on others (nondifferential misclassification), information bias is usually towards the null (77,78).

Potential information bias may have occurred in the present study, particularly in the measurement of ACH medication exposure. Our clinician-rated ACH score is mainly based on clinicians' experience with observable therapeutic or side-effects that are typically attributable to blockage of muscarine receptors. Such presumed ACH effect may involve also antidopaminergic, antiadrenergic, or other effects of the medication that are clinically indistinguishable (91,99,100,102,109), whereas medications without apparent clinical ACH effect or not familiar to the clinicians may be rated as having no ACH effect (93,109). Thus, both the clinician-rated ACH score and count of ACH medications are subject to measurement errors. In addition, the use of a weighting system based on patterns of dose/frequency change instead of the actual medication dose has not been validated. Finally, it is worth noting that, although the data for this thesis were derived from two concurrent studies, both used the same measures and data collection staff.

Due to lack of a "gold standard", it is difficult to assess the magnitude of potential information bias resulting from measurement errors in ACH exposure. However, given the fact that the majority of ACH medications classified according to the clinician-rated ACH score had documented ACH effect in the literature, and ACH score

itself was in good agreement with other clinical or experimental ratings of ACH medications (30, 113-119), significant misclassification of ACH medications seems unlikely. In addition, the insensitivity of the observed association to alternate measures of ACH medications suggests that this association is not measure-specific but most likely biologically-determined. Thus, the information bias due to measurement of exposure to ACH medications seems most likely to attenuate the estimate of association, and is an unlikely explanation of our results.

Information bias may also occur in measurement of outcome and confounders (77, 78). Since delirium is a fluctuating condition whose symptom severity may vary dramatically during the course of day, a single assessment at a time of day rather than at a biologically relevant time point may not capture the most relevant change in the symptom severity due to the medication exposure. Thus, information bias may have occurred in our measures of DI scores. However, since the raters were blind to the study hypothesis and patients' medication regime, systematic overrating of DI scores for patients with ACH exposure could not have occurred. In addition, since the peak-hours of most ACH medications are typically very short, assessing patients' DI scores at a random time once a day would most likely to coincide in a period when the peak effect of the medication has past, which would lead to an underestimation of the association. Thus, such potential measurement errors with DI measure would not change the observed ACH medication-delirium severity association.

8.4.3. Confounding Bias

In addition to selection and information biases, confounding is another major threat to the internal validity of an epidemiological study, which can bias the estimate of

association either towards or away from the null or in the reverse direction (77,78). By definition, confounding refers to a distortion of risk estimates due to an extraneous factor (confounder) that correlates with both exposure and outcome but results from neither (77,78). A particular form of confounding of the effect of medication exposure on disease outcome is, as described previously, confounding by indication (77,80,98) and especially protopathic bias (94). In our study, delirium patients might have been systematically given some ACH medications, like antipsychotics, by physicians in response to their increased symptom severity prior to a DI assessment. As a result, a spurious association that use of ACH medications exaggerated delirium symptoms might be observed, while in fact a "reverse causality" is the truth. Thus, controlling protopathic bias is critically important to addressing effect of medication exposure in observational clinical epidemiological context, especially for study of disease progression in prevalent cases.

In the present study, we have made great effort to control for potential confounding by indication, especially the protopathic or reverse causality bias. First, the ACH medications we studied encompassed several different therapeutic classes and had wide indications, which makes confounding by any specific indicating disease less possible; Second, we defined the previous 24-hour period as exposure time-window to ensure an unambiguous temporal sequence that use of ACH medications indeed preceded an observed change in severity of delirium. Third, we have adjusted the effect estimate of ACH exposure for baseline DI score, a presumable strong "indication" for use of some ACH medications, especially the antipsychotics. Finally, we retested the observed association by excluding all the antipsychotics from ACH medications, in order to assess the impact of potential protopathic bias. The results did not change. Thus, although some

other ACH (and non-ACH) medications may have been selectively prescribed for some patients, it seems unlikely that this would account for a significant part of the observed ACH medication-delirium association.

Selection of other potential confounders or effect modifiers was also based on their biological plausibility as well as statistical criteria. Use of selected variables increased statistical efficiency for multivariate regression analysis within the available sample size due to reduced number of parameters. On the other hand, we might have excluded some important confounders. For instance, environmental factors in hospital, such as poorly lighted rooms or noisy surroundings, may provoke delirium but were not evaluated in this study (19,20,32,33).

In addition, medications with other psychoactive properties may need to be considered more specifically as confounders of ACH medication, but an appropriate classification method is still not available. Thus, future studies are needed to further address such unresolved issues.

8.5. Clinical and Research Implications

The present study provides additional epidemiological evidence for the postulated role of ACH medications on symptoms of delirium. The clinical implications of our findings lie in the modifiability of this risk factor and its high prevalence in hospitalized elderly, both before and after the development of delirium. Thus, reasonable prescription and prompt adjustment of medications with potential ACH effects may be of particular relevance in the care of delirium patients and in reducing the population risk of delirium in the elderly. Towards this end, our clinician-rated ACH scores may represent a useful

and feasible tool for assessing the ACH burden in elderly patients. Its clinical validity, reliability and applicability may be worth investigating further.

The study design, using a prospective cohort with repeated measurements, has showed some advantages in evaluating a transient medication exposure-disease outcome relationship. In addition, we have tried to address many important methodological issues frequently encountered in observational clinical epidemiological studies, including definition of exposure time-window, measurement of medication exposure in a dynamic and longitudinal fashion and controlling for indications and contraindications. Continuing effort should be made to clarify potential interaction between ACH medication and dementia, serum albumin and other biologically plausible effect-modifiers. In addition, future studies using incident cases of delirium, different measures of ACH medication exposure and more frequent or alternative measures of delirium symptoms are warranted.

9. CONCLUSION

To conclude, we have documented that change in exposure to ACH medications is associated with severity of delirium symptoms during the clinical course of delirium in elderly medical inpatients. The effect of ACH medications is independent of potential confounding by dementia, low albumin, comorbidity, BUN/creatinine ratio or history of alcohol/drug abuse. It can not be explained by concurrent use of non-ACH medications or the length of follow-up. Therefore, reasonable use and timely adjustment in dose and/or frequency of such medications may have significant implications for managing delirium symptoms among elderly patients during hospitalization. Further effort is needed to test the replicability and clinical importance of these findings using alternative measures of delirium symptoms, ACH medications and other potentially deliriogenic agents.

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APPENDIX 1. CONSENT FORMS

Consent Form for RCT

Elderly patients often become confused while in hospital. This study aims to determine if a new way of detecting and managing older patients with delirium (confusion) is effective in:

- reducing length of hospital stay, and increasing discharge rate to the community;
- reducing problems with confusion and memory
- increasing patients' abilities to manage independently.

Participation in this project involves the following:

In the hospital

- Patients will be visited every day during their first week, if they are still in hospital, and asked questions about their orientation and memory; these visits will take only about 10 minutes.
- Once a week, if they are still in hospital, patients will be observed while they carry out daily activities, like walking and eating; these visits will take about 30 minutes.
- A family member will be asked about how the patient was managing before being admitted to the hospital; this interview will take about 15 minutes.

After discharge from the hospital

- 8 weeks after leaving the hospital, patients and their family members will be visited at home and asked similar questions to those asked in the hospital. This visit will take not more than 1 hour.
- 6 and 12 months after the hospital admission, patients and family members will either be contacted by telephone or visited at home, to ask similar information as at 8 weeks.

Patients with confusion will be divided equally by chance in one group which will receive usual care and one group which will receive the new care programme (descriptions below).

Usual Care: this means that patients will receive the care that they would normally receive from their doctors and nurses even if they do not participate in this study.

New care programme: this will consist of two parts: a visit by a doctor who specializes in caring for older patients and visits most days by a nurse who has been trained to care for patients who are confused.

There may be no direct benefits to patients and their family members who participate in this project, but neither are there any risks. The study will not deprive anyone of the usual care they receive from their doctors and nurses. Patients will not stay in the hospital any longer because of their participation in the study. There are no experimental drugs involved in this study. The results of this study will help doctors and nurses to improve the care of patients who become confused while in hospital.

Participation in this project is voluntary and patients who do not participate will continue to receive care as usual from their doctors and nurses. Patients and their families may withdraw from the project at any time without any effect on the patient's care.
All research staff involved in the study will maintain confidentiality of records identifying the patient. All forms will be kept in a locked file cabinet. Only the study identification number will be entered in the computerized database to identify the patients.

The following people may be contacted if there are any questions from patients or their families about this project:

Dr. Martin G. Cole, principal investigator, 345-3511, ext. 3584
Johanne Laplante, study nurse, 345-3511, ext. 3823
Monique Robitaille, patient representative, 734-2618

The patient (and/or family member) will receive a copy of the signed consent form, and a copy will be placed in the medical chart.

Assent and substituted consent

A. The patient cannot presently give an informed consent to participate in the study due to his/her medical condition. However, the patient has not refused the interventions undertaken in this study.

_____ _____
Patient's assent acknowledged by: Date

B. A legal representative as understood by law, curator or significant other, _____ has been contacted by telephone on_____ and has given substituted consent. The legal representative, curator or significant other will review and sign the consent form as soon as possible.

_____ _____
Consent acknowledged by Date

I have read the consent form for the Study of a Geriatric Delirium Service and have had the opportunity to ask questions. On behalf of _____ and myself, I agree to participate in this research project.

_____ _____
Substituted Consent Date

_____ _____
Witness Date

Consent Form for Prognosis Study

Older patients often become confused when they are admitted to the hospital. This research project aims to find out how patients who become confused in the hospital manage after they leave the hospital in comparison with patients in the same age group who do not become confused.

Participation in this project involves the following:

In the hospital

- Patients will be visited every 2-3 days during their first week, if they are still in hospital, and asked questions about their orientation and memory; these visits will take only about 10 minutes.
- Once a week, if they are still in hospital, patients will be observed while they carry out daily activities, like walking and eating; these visits will take about 30 minutes.
- A family member will be asked about how the patient was managing before being admitted to the hospital; this interview will take about 15 minutes.

Patients will not stay in the hospital any longer because of their participation in the study. Some patients who become confused during the first week of their hospital stay will be invited by the study nurse to participate in another study to compare different treatment programs.

After discharge from the hospital

- 8 weeks after leaving the hospital, patients and their family members will be visited at home and asked similar questions to those asked in the hospital. This visit will take not more than 1 hour.
- 6 and 12 months after the hospital admission, patients and family members will either be contacted by telephone or visited at home, to ask similar information as at 8 weeks.

There are no direct benefits to patients and their family members who participate in this project, but neither are there any risks. The results of this study will help doctors and nurses to improve the care of patients who become confused while in hospital.

Participation in this project is voluntary and patients who do not participate will continue to receive care as usual from their doctors and nurses. Patients and their families may withdraw from the project at any time without any effect on the patient's care.

All research staff involved in the study will maintain confidentiality of records identifying the patient. All forms will be kept in a locked file cabinet. Only the study identification number will be entered in the computerized database to identify the patients.

The following people may be contacted if there are any questions from patients or their families about this project:

Dr. Jane McCusker, principal investigator, 345-3511, ext. 5060

Johanne Laplante, study nurse, 345-3511, ext. 3823
Monique Robitaille, patient representative, 734-2618

The patient (and/or family member) will receive a copy of the signed consent form, and a copy will be placed in the medical chart.

I have read and received a copy of the consent form for the project "Prognosis of Delirium" and have had the opportunity to ask questions. I agree to participate in this research project.

Patient Signature	Date
Family /Significant Other Signature	Date
Witness	Date

Assent and substituted consent

A. The patient cannot presently give an informed consent to participate in the study due to his/her medical condition. However, the patient has not refused the interventions undertaken in this study.

Patient's assent acknowledged by: _____ Date _____

B. A legal representative as understood by law, curator or significant other, _____ has been contacted by telephone on _____ and has given substituted consent. The legal representative, curator or significant other will review and sign the consent form as soon as possible.

Consent acknowledged by _____ Date _____

I have read the consent form for the Prognosis of Delirium study and have had the opportunity to ask questions. On behalf of _____ and myself, I agree to participate in this research project.

Substituted Consent	Date
Witness	Date

Appendix 2. DELIRIUM INDEX

	NO 0	MILD 1	SEVERE 2	NK 9
1. Did the patient have difficulty focussing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?				
2. Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?				
3. Overall, how would you rate this patient's level of consciousness?				
4. Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?				
5. Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?				
6. Did the patient have any evidence of perceptual disturbances, for example, hallucinations, illusions or misinterpretations (such as thinking something was moving when it was not)?				
7. At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent sudden changes of position?				
8. At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space in one position for a long time, or moving very slowly?				

Appendix 3: Classifications of 234 medications evaluated in the study by clinicians' rating (CR) and therapeutic classes (TC)

Medication	Clinician-rated ACH Score	Classifications*	
		CR-Based	TC-Based
Acetazolamide	0	0	0
Acetominophen	0	0	0
Acetominophen /codeine/caffeine	2	1	1
Acetominophen/codeine	2	1	1
Acetominophen/oxycodone	0	2	1
Acetylsalicyclic acid	0	0	0
Acyclovir	0	0	0
Adenosine	0	0	2
Allopurinol	0	0	0
Alprazolam	1	1	2
Amantadine	0	2	2
Amiloride	0	0	0
Amiodarone	0	2	2
Amitriptyline	3	1	1
Amitriptyline /Perphenazine	3	1	1
Amlodipine besylate	0	0	0
Amoxicillin	0	0	0
Amoxicillin/clavulanate	0	0	0
Ampicillin	0	0	0
Anileridine	0	0	1
Atenolol	1	1	2
Atorvastatine calcium	0	0	0
Atropine Sulfate	3	1	1
Atropine Sulfate /Diphenoxylate	3	1	1
Azithromycin dihydrate	0	0	0
Beclomethasone	0	0	2
Benztropine	3	1	1
Bethanechol	0	0	0
Bicalutamide	0	0	0
Bromocriptine	1	1	2
Brompheniramine	0	0	0
Budesonide	0	0	2
Buspirone	0	0	2
Captopril	0	0	0
Carbamazepine	1	1	2
Carvedilol	0	0	2
Cefazolin	0	0	0
Ceftriaxone	0	0	0
Cefuroxime	0	0	0
Cephalexin	0	0	0
Chlomipramine	3	1	1
Chloral hydrate	0	2	2
Chlordiazepoxide	1	1	2

(to be continued)

Chlorpromazine	3	1	1
Chlorpropamide	0	0	0
Chlorthalidone	0	0	0
Cilastatin /Imipenem	0	0	0
Ciprofloxacin	0	0	0
Cisapride monohydrate	0	0	0
Clarithromycin	0	0	0
Clindamycin	0	0	0
Clobazam	0	0	2
Clodronate	0	0	0
Clonazepam	0	2	2
Clonidine	0	0	0
Cloxacillin	0	0	0
Codeine	1	1	1
Colchicine	0	0	0
Cortisone	0	0	2
Cyclobenzaprine	1	1	1
Cyclophosphamide	0	0	0
Cyproheptadine	0	0	0
Cyproterone	0	0	0
Danazol	0	0	0
Demeclocycline	0	0	0
Desipramine	2	1	1
Dexamethasone	0	0	2
Diazepam	1	1	2
Diclofenac	0	0	2
Diclofenac/Misprostol	0	0	2
Dicyclomine	0	0	1
Digoxin	0	0	2
Diltiazem	0	0	2
Dimenhydrinate	3	1	1
Diphenhydramine	3	1	1
Dobutamine	0	0	0
Donepezil	0	0	0
Dopamine	0	2	2
Doxepin	3	1	1
Enalapril	0	0	2
Endrophonium	0	0	0
Epoetin alfa	0	0	0
Ergocalciferol	0	0	0
Erythromycin	0	0	0
Ethambutol	0	0	0
Etidronate	0	0	0
Etidronate/Calcium Carbo	0	0	0
Etodolac	0	0	0
Famotidine	0	0	1
Felodipine	0	0	2
Fentanyl	1	1	1
Florocortisone acetate	0	0	2

(to be continued)

Fluconazol	0	0	0
Flumazenil	0	0	0
Fluoxetine	1	1	2
Flurazepam	1	1	2
Flutamine	0	0	0
Fluticasone propionate	0	0	2
fluvastatin	0	0	0
fluvoxamine	1	1	2
Fosinopril	0	0	0
Furosemide	0	0	0
Gabapentin	0	0	2
Gemfibrozil	0	0	0
Gentamicine	0	0	0
Gliclazide	0	0	0
Glyburide	0	0	0
Haloperidol	2	1	1
Heparin	0	0	0
Hydralazine	0	0	2
Hydrochlorothiazide	0	0	0
Hydrochlorothiazide /Triamterene	0	0	0
Hydrochlorothiazide/Spironolactone	0	0	0
Hydrocortisone	0	0	2
Hydromorphone	0	2	1
hydroxyurea	0	0	0
Hydroxyzine	0	0	2
Ibuprofen	0	0	2
Indapamide	0	0	2
Indomethacin	0	0	2
Insulin	0	0	0
Ipratropium	0	0	1
Ipratropium bromide/Salbutamol	0	0	1
Isoniazid	0	0	0
Isosorbid	0	0	0
Labetalol	0	0	2
leuprolide	0	0	0
levodopa	0	2	2
Levofloxacin	0	0	0
Levothyroxin	0	0	0
Lidocaine	0	0	2
Lisinopril	0	0	0
Lithium carbonate	0	2	2
Loperamide	1	1	1
Lorazepam	0	2	2
Losartan	0	0	2
Lovastatin	0	0	0
Mannitol	0	0	0
Meclizine	0	0	1
Meclizine/niacin	0	0	1
Megestrol	0	0	0

(to be continued)

Metformin	0	0	0
Methazolamide	0	0	0
Methotrimeprazine	2	1	1
Methyl prednisolone	0	0	2
Methyl prednisolone	0	0	2
methyldopa	0	0	0
Metoclopramide	0	0	0
Metolazone	0	0	0
Metoprolol	1	1	2
Metronidazole	0	0	0
Midazolam	0	2	2
Midodrin	0	0	0
Misoprostol	0	0	0
Morphine	1	1	1
Nadolol	0	0	2
Naloxone	0	0	0
Naproxen	0	0	2
Nefazodone	1	1	2
Nifedipine	0	0	2
Nitrofurantonin	0	0	0
Nitroglycerin	0	0	2
Nizatidine	0	0	1
Norepinephrine	0	0	0
Norfloxacin	0	0	0
Nortriptyline	3	1	1
Nystatin	0	0	0
Octreotide	0	0	0
Omeprazole	0	0	0
Orphenadrine	2	1	1
Oxazepam	0	2	2
Oxybutinin	0	0	1
Pamidronate	0	0	0
Pancrelipase	0	0	0
Pantoprazole	0	0	0
Paroxetine	2	1	2
Penicilin G-V	0	0	0
Pentoxifylline	0	0	0
Pergolide mesylate	0	0	0
Perindopril erbumine	0	0	0
Pethidine hydrochloride	2	1	1
Phenazopyridine	0	0	0
Phenelzine	0	2	2
Phenobarbitol	1	1	2
Phenytonin	0	0	2
Pindolol	0	0	2
Piperacillin	0	0	0
Piroxicam	0	0	2
Pivampicillin	0	0	0
Prazosin	0	0	2

(to be continued)

Prednisone	0	0	2
Procainamide	0	0	2
Prochlorperazine	2	1	1
Procyclidine	3	1	1
Promethazine	3	1	1
Propafenone	0	0	2
Propranolol	0	0	2
Pyrazinamide	0	0	0
Pyridostigmine	0	0	0
Quinapril hydrochloride	0	0	0
Quinidine Sulfate	0	0	2
Quinine phenylethylbarbiturate	0	0	0
Quinine Sulfate	0	0	0
Ranitidine	2	1	1
Rifampin	0	0	0
Risperidone	1	1	1
Salbutamol	0	0	0
Selegiline	0	0	2
Sertraline	1	1	2
Simvastatin	0	0	0
Sotalol hydro	0	0	2
Spironolactone	0	0	0
Succinyl Chloline	0	0	1
Sulcrafate	0	0	0
Sulfamethoxazole	0	0	0
Sulindac	0	0	2
Tamoxiphen	0	0	0
Temazepam	0	0	2
Terbutaline	0	0	0
Terozosin hydrochloride	0	0	2
Tetracycline	0	0	0
Theophylline	0	0	0
Thioridazine	3	1	1
Tolbutamide	0	0	0
Trazodone	1	1	2
Trihexyphenidyl	3	1	1
Trimipramine	2	1	1
Ursodiol	0	0	0
Vancomycin	0	0	0
Vecuronium	0	0	1
Verapamil	0	0	2
Warfarin	0	0	0
Zopiclone	0	0	2
Zuclopenthixol	1	1	1

* Code for class: 1=ACH medication; 2=Non-ACH deliriogenics; 0=other medications.

Appendix 4: A case scenario for calculating daily medication exposures using the weighting system (assuming a patient used three medications from baseline to day 7)

Medication	ACH score		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	...
1. Haloperidol	2	Frequency/dose change	added/ regular	no change	increased	increased	reduced	reduced	stopped		
		Assigned weight	1	1	1.5	1.5	0.67	0.67	0		
		Resulting ACH score*	2	2	3	4.5	3	2	0		
2. Diazepam	1	Frequency/dose change			added/ prn	no change	stopped		added/ regular	increased	...
		Assigned weight			0.5	1	0		1	1.5	
		Resulting ACH score*			0.5	0.5	0		1	1.5	
3. ASA	0	Frequency/dose change		used once			added, regular	no change	stopped		
		Assigned weight		1			1	1	0		
		Resulting ACH score*		0			0	0	0		
Total daily medication exposure											
Daily ACH scores*			2	2	3.5	5	3	2	1	1.5	...
Number of ACH medications used each day			1	1	2	2	1	1	1	1	...
Number of non-ACH medications used each day			0	1	0	0	0	1	0	0	...
Total number of medications used each day			1	2	2	2	1	2	1	1	...

* ACH score: The clinician-rated ACH score for a give medication.

The resulting ACH score=ACH score for a given medication or the resulting ACH score at previous day x the assigned weight.

Daily ACH score=sum of the resulting ACH scores across the 3 medications used for a given day.

The same strategy applys for calculating Summers' DRN.