DEPRESSION, MEDICATION USE, AND COGNITIVE FUNCTIONING IN OLDER MEDICAL PATIENTS

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MONTREAL QUEBEC, CANADA

August 28, 2006

A Thesis

Submitted to the Faculty of Graduate and Postdoctoral Studies

In Partial Fulfillment of the Requirements

for

The Degree of Doctor of Philosophy in Epidemiology and Biostatistics

Your file Votre référence
ISBN: 978-0-494-32356-4
Our file Notre référence
ISBN: 978-0-494-32356-4

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ABSTRACT

The inter-relationship between depression, medication use and cognitive decline in older persons has potentially important clinical and public health implications, yet research findings on the nature of this relationship remain inconclusive. This thesis presents a systematic investigation into this topic in a sample of 281 medical inpatients aged 65 and over, who were followed for up to 12 months after admission.

In the first three chapters, the concept, population burden and measurement of depression and cognitive function in the elderly population are described. The relevant literature is reviewed, and the rationale and approaches of this thesis are presented.

In the fourth chapter (1st manuscript), the short-term temporal relationship between depression and cognitive functioning was explored using an interviewer-rated depression severity scale. Based on competing mixed effects models under alternative temporal assumptions, the severity of depression symptoms appeared to have a concurrent rather than prospective relationship with cognitive functioning.

In the fifth chapter (2nd manuscript), diagnostic criteria were used to define depression. After adjusting for covariates, both major and minor depression were significantly predictive of subsequent cognitive decline, and the strength of the association appeared to increase with the duration of "exposure".

In the sixth chapter (3rd manuscript), using a provincial prescription database, the effects of medication exposure on cognitive function were evaluated. Antidepressant use was not associated with cognitive decline in general, but interacted with depression diagnoses. In exploratory analyses, antidepressant use appeared to be associated with improved cognitive function over time in the minor depression group, independent of comorbid diseases, current depression symptoms and concomitant medications. Both major and minor depression were independently predictive of subsequent cognitive decline, especially in those not prescribed antidepressants.

In summary, this thesis demonstrates that, in this sample of older medical inpatients, both major and minor depression are independent risk factors for 12-month cognitive decline. The potentially beneficial effects of antidepressants for patients with minor depression should be investigated.

RÉSUMÉ

La corrélation entre la dépression, l'utilisation de médicaments et le déclin cognitif chez les personnes âgées porte des implications de santé publiques et cliniques importantes, pourtant les résultats des recherches demeurent non-conclusifs. Cette thèse présente une recherche systématique de ce sujet avec un échantillon de 281 patients hospitalisés, âgés de 65 ans et plus, qui ont été suivis jusqu'à 12 mois après leur hospitalisation.

Dans les trois premiers chapitres, le concept, l'effet sur la population, la mesure de la dépression et de la fonction cognitive chez les personnes âgées sont traités; un examen des études appropriées est présenté, ainsi que le raisonnement et la méthodologie pour cette thèse.

Dans le quatrième chapitre (premier manuscrit), le rapport temporel à court terme a été exploré en utilisant un système d'évaluation déterminé par les résultats d'entrevues. Basé sur des modèles d'effets mélangés en concurrence, sous de diverses prétentions temporelles, les symptômes de dépression ont semblé avoir un rapport plus concourant que prospectif avec le déclin cognitif.

Dans le cinquième chapitre (2ème manuscrit), des critères diagnostiques ont été employés pour définir la dépression. Après avoir ajusté aux covariantes, la dépression majeure et mineure étaient toutes deux prédictives du déclin cognitif qui suivait, et la force de l'association a semblé augmenter avec la durée de "l'exposition" aux diagnostiqués.

Dans le sixième chapitre (3ème manuscrit), en utilisant une base de données provinciale sur les ordonnances, les effets de l'exposition de médicaments sur la fonction cognitive ont été évalués. L'utilisation d'antidépresseurs n'a pas été associée au déclin cognitif en général, mais a eu une interaction avec les diagnostiqués de dépression. Des analyses exploratoires ont montré que cette utilisation semble être associée à une amélioration de la fonction cognitive à long terme chez le groupe atteint de dépression mineure, indépendamment des maladies comorbides, aux symptômes courants de dépression et aux médicaments concomitants. La dépression majeure et mineure étaient toutes deux indépendamment prédictives du déclin cognitif qui suivait; particulièrement chez ceux pour qui les antidépresseurs n'étaient pas prescrits.

En bref, cette thèse démontre que, dans cet échantillon de patients âgés hospitalisés, la dépression majeure et mineure sont toutes deux des facteurs de risque indépendants du déclin cognitif sur une période de 12 mois. Il faut faire des études sur les effets bénéfiques que peuvent avoir les antidépresseurs chez les patients atteints de dépression mineure.

CONTRIBUTION OF MANUSCRIPT AUTHORS

All the authors listed in the three manuscripts have participated sufficiently in the work to take public responsibility for the whole content of the work. All the authors have made substantial contributions to the conception and design of the study, interpretation of the findings, and critical revisions of the manuscripts, and given final approval of the submitted manuscripts. In addition, LH formulated the initial hypothesis, designed the study, conducted statistical analysis, interpreted the findings, drafted and revised the manuscripts. JM obtained the funding, provided the data, and oversaw and directed the entire thesis work. MC contributed to the obtaining of the funding, acquisition of the data, and development of the clinician-rated anticholinergic score. MA directed and supervised the statistical analyses. RC contributed to the rating of the clinician-rated anticholinergic score for additional medications.

STATEMENT OF ORIGINALITY

All the work presented in this thesis is my original contribution, unless otherwise stated. The first manuscript (included as Chapter 4) has been accepted for publication in the Journal of Gerontology: Medical Sciences, volume 61A, pages 1319-1323, December, 2006. (Copyright © The Gerontological Society of America. Reproduced by permission of the publisher.) No other part of the thesis has been published or is in press elsewhere. The design of the alternative exposure time-windows and the total exposed drug-days was my idea and has incorporated valuable inputs from my thesis committee. The method of the clinician-rated ACH scores was originally developed in my MSc thesis and extended in this PhD dissertation by a consensus rating of additional medications by Dr. Cole and Dr. Capek. The use of the mixed effects models and transformed HDRS scores were suggested by Dr. Abrahamowicz and implemented under his guidance.

ACKNOWLEDGMENTS

I would like to thank my thesis supervisor, Dr. Jane McCusker, for her constant and rigorous guidance, insightful and precise advice, and remarkable promptness and patience in supervising this thesis study. I extend sincere gratitude to my thesis committee members, Dr. Martin Cole, Dr. Michal Abrahamowicz, and Dr. Radan Capek. Dr. Cole has provided invaluable clinical insights during the development of the study protocol and formulation of the conceptual models for the thesis, whereas Dr. Abrahamowicz and Dr. Capek have provided important guidance and inputs with their respective expertise in biostatistics or clinical pharmacology.

I am deeply indebted to Eric Belzile, MSc. for his continuous assistance in providing the source datasets, study variables and instruments, and to Christine Gagné for her administrative assistance. I gratefully acknowledge Dr. Eric Latimer's assistance in acquisition of the RAMQ data, and all the research assistants and nurses' work in data collection and patient interviews. I also want to thank Dr Heather Allore from Yale University Internal Medicine for insightful statistical advice and other help.

The study was funded by Canadian Institutes for Health Research grants # MOP82494 and MCT–15476 to Dr. Jane McCusker and Dr Martin Cole. A poster from the thesis was presented at the Second North America Congress of Epidemiology, Seattle, Washington, USA, June 21-24, 2006, with partial support from the Yale Claude D. Pepper Older Americans Independence Center grant # P30AG021342 by National Institute on Aging.

I dedicate this thesis to my loving family: my wife, daughter and parents. Without their understanding and support, this accomplishment could never be achieved.

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LIST OF ABBREVIATIONS

ACH	Anticholinergic
ADL	Activities of Daily Living
AIC	Akaike's Information Criterion
ANOVA	Analyses of variance
ARC	Annual rate of change
CAGE	Cut down, Annoyed, Guilty, Eye-opener
CCI	Charlson Comorbidity Index
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CIND	Cognitive Impairment-No Dementia
CVD	Cardiovascular disease
DIS-D	Diagnostic Interview Schedule, Depression Section
DSM-IV (IIIR, III)	Diagnostic and Statistical Manual of Mental Disorders, the fourth (third revised, third) edition.
EDD	Exposed Drug Days
GDS	Geriatric Depression Scale
HDRS/HAMD	Hamilton Depression Rating Scale
IADL	Instrumental Activities of Daily Living
ICD-9 (or -10)	International Classification of Disease, 9^{th} (10^{th}) edition
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LRT	Likelihood Ratio Chi-square Test
MAOI	Monoamine Oxidase Inhibitors
MLR	Multiple Linear Regression
MMSE	Mini-Mental State Examination
3MS	Modified Mini-Mental State Examination
OR	Odds Ratio
RCT	Randomized Clinical Trial
REML	Restricted Maximum Likelihood Estimation
RR	Risk Ratio
SAS	Statistical Analysis System
SPMSQ	Short Portable Mental Status Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic antidepressants
WHO	World Health Organization

CHAPTER 1 — INTRODUCTION

1.1 BURDEN OF DEPRESSION AND COGNITIVE IMPAIRMENT IN OLDER POPULATIONS

Among elderly people depression and cognitive impairment (including dementia) represent two major public health problems. Together, they affect more than one quarter of those aged 65 years and older [1-4], and both have been associated with higher mortality [5-7], faster functional decline [8, 9] and increased utilization of health care services [10, 11]. The net economic cost for caring of patients with major depression [12] and dementia [13] is tremendous. With the rapid expansion of the aged population in modern societies, prevention and treatment of depression and cognitive impairment have become a major challenge to the health care system.

Depression and cognitive impairment often coexist clinically: as many as 30% of elderly patients with dementia manifest some depressive syndromes or meet the diagnostic criteria for major or minor depressive disorders [14-17]. More than 50% of major depression patients with normal cognition may eventually develop dementia several years later [18]. However, epidemiological evidence to date remains inconclusive as to whether the correlation between the two conditions reflects a causal relationship, a psychological reaction, or a clinical concomitant due to the effect of a third factor that is associated with both depression and cognitive impairment–such as cardiovascular disease [19, 20] or use of antidepressant or other psychotropic medications [21, 22]. In addition, older persons with depression in the community are often left untreated [23-26], partially due to insufficient evidence regarding the benefits and harms of rigorous antidepressant treatments in late-life depression, especially in those with mild or minor depression or

with complex medical conditions [27-31]. Therefore, a clarification of the interrelationship between depression, antidepressant and other psychotropic use, and cognitive impairment in the elderly population may bear important public health, clinical as well as etiological implications [32-34].

1.2 OBJECTIVES OF THE THESIS

The main objectives of this thesis are two fold:

1) To examine the temporal relationship between depression (symptoms and diagnoses) and cognitive decline in older medical patients and to determine whether depression is an independent risk factor or a clinical concomitant of cognitive decline; and

2) To explore the role of antidepressant and other medication use in the relationship and to determine whether it is an independent risk factor for cognitive decline, an effect modifier, or a mediating factor.

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CHAPTER 2 — REVIEW OF LITERATURE

2.1 DEPRESSION

2.1.1 Definition and Measurement

There are two general approaches to the definition of depression: categorical and dimensional [1-3]. The categorical approach considers depression as a group of distinct entities or independent latent classes, each with its own clinical and biological profile [4, 5]. For instance, the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [6] has defined two major diagnostic entities of depression: major depression and dysthymic disorder. Major depression requires the core symptoms of depressed mood or loss of interest or pleasure for two weeks or longer, plus four other symptoms. Dysthymic disorder requires a predominantly depressed mood to exist for at least two years plus two or more other symptoms. In addition, a minor depression category has also been proposed as a research diagnosis for sub-syndromal, sub-threshold, or sub-clinical depression and requires the same core symptoms as major depression but only one to three other symptoms. However, in clinical and research practice, a minor depression diagnosis is often defined loosely, encompassing all the mild types of depression including dysthymia [7]. A categorical or diagnostic definition is most useful in clinical settings, where the main objective of depression detection is to capture depressed patients or "cases" that require clinical, especially pharmacological interventions.

Depression can also be conceptualized as a unitary phenomenon or a continuous spectrum in terms of the population distribution of the depressive symptoms [4, 5, 8], which includes most often depressed mood or affect, tearfulness, irritability, suicidal ideas, and somatic complaints (e.g., poor appetite, energy, and libido etc.) [9]. Almost

every human being will experience one or more such symptoms during their life time. Although the manifestations and consequences of such symptoms may vary dramatically from person to person, ranging from little impact on social and psychological functioning to extreme disability, there are no clear-cut boundaries between different levels or different domains of depressive symptomatology. Therefore, depression may better be understood as a constellation of interrelated component symptoms rather than several distinct entities. Such a dimensional definition provides an alternative tool to describe depressive symptomatology and to depict its natural history. It has found wide use in non-clinical settings, where the main goal is to assess total population burden of depression at all levels of severity for public health policy making and prevention planning, rather than to offer treatment or intervention options to the individuals.

Although conceptually distinctive, in practice the two approaches often interact in many aspects. For instance, both categorically and dimensionally oriented researchers tend to define depression using standard depression scales, being either self-report, such as the Geriatric Depression Scale (GDS) [10] and the Center for Epidemiological Studies Depression Scale (CES-D) [11], or observer-rated, such as the Hamilton Depression Rating Scale (HDRS or HAMD) [12]. Moreover, in the recent decade there has been an increasing trend of integration of the two approaches, especially in the research setting. On one hand, population surveys of depression have often used cut-off points on rating scales to identify potential "cases"; on the other, emerging criteria for "recurrent brief depression" [13], "mixed anxiety-depression" [14] and "minor depression" [3, 6, 9, 15] in diagnosis-oriented medical nomenclature reflect an adoption of a dimensional alternative to approach those otherwise unclassifiable, sub-clinical depressions. Recent studies have

also suggested that the presence of depressive symptoms or sub-threshold depression (i.e., not meeting full diagnostic criteria) were predictive of both a subsequent diagnosis of major depression and several adverse outcomes including functional disabilities [10, 16, 17]. From both public health and etiological perspectives, it seems apparent that epidemiological studies would benefit most from such integration [3, 18, 19].

2.1.2 Occurrence

Major depression has been reported in at least 1 to 3% of the population aged 65 and over and an additional 8 to 16% have clinically significant depressive symptoms [20]. In primary care settings, the prevalence of depressive disorders is about 5 to 17%, and that of depressive symptoms about 11 to 29% [21]. Studies reporting the incidence of new-onset depressive disorders in community-living seniors were sparse, and the estimates varied from 5.4% in 6 months [22] to 11.7% in 9 months [23]. However, such figures probably reflected an underestimation. According to a questionnaire survey of 1000 primary care physicians, up to 80% of depressed patients might have failed to be recognised [21] and less than 50% of those with major or minor depressive disorder obtained an accurate diagnosis [24, 25].

Depression prevalence appears to decrease with increasing age in the general population [26, 27], although opposite observations exist [9, 28]. This discrepancy may be partially attributable to the difference in the definition of depression across studies. In general, studies employing self-rating scales as the sole definition of depression tend to report a higher prevalence, whereas those following strict diagnostic criteria often found lower estimates [29]. Thus, although older adults may experience depressive symptoms more frequently than younger ones [16, 30], the proportion with "full blown" major

depressive disorder among elderly populations tends to be lower [27, 31]. Another possible explanation is the selective attrition of the depressed elderly from community-based samples due to age-related increases in dementia and other morbidities, mortality and institutionalization, but this speculation has yet to be confirmed [29].

2.1.3 Risk Factors

Many factors associated with an increased risk of depression in the general population apply also to late-life depression, including a family history of depression [20, 32], a history of other psychiatric disorders, depressive symptoms or anxious-pessimistic personalities [33-35], stressful life events such as recent family loss [20, 32, 36], poor physical health or functional status [20, 36, 37] , socio-cultural isolation or lack of social support [37-39] , and demographic factors such as lower education or economic status [34, 38, 39] and female gender [32, 40].

Medical illness and related physical disability increase in frequency among seniors and are major risk factors for a depressive episode [41, 42]. Illness severity and disability are almost always associated with major depression in studies that measured them [33, 39, 43]. Older patients with certain medical conditions were reported to be particularly vulnerable to major depression, which included especially neurological disorders [40, 44], endocrine disorders [45], myocardial infarction and other cardiovascular diseases [46], cancer [34, 47], and chronic obstructive lung disease [34, 43].

The relationship between cardiovascular diseases (CVD) and depression seems complex. Vascular diseases have been suspected to be a putative cause of late-life depression (so-called: vascular depression) [48, 49]; low blood pressure has been

associated with an increased risk of depression in a prospective community-based follow-up study of 1112 initially non-depressed elderly [50]. On the other hand, depression has also been associated with the subsequent incidence of several CVD events, including hypertension in young adults [51] and myocardial infarction or stroke in older people [52, 53]. Thus, the causal pathway of CVD and late-life depression remains to be understood.

2.1.4 Prognosis and Outcome

A meta-analysis of outcomes of major depression in community-based seniors found that at 24 months from study enrollment, 33% of patients were well, 33% were depressed, and 21% were dead [54], despite the appreciable methodological heterogeneity across the studies in outcome measures, length of follow-up, age and gender distribution and the diagnostic criteria and antidepressant treatment histories. Although less well studied, minor depression is associated with persistence of symptoms for up to a year [46, 55, 56]. Two other studies suggested that adults with even a few depressive symptoms appeared to be at an increased risk for developing major depression [16, 17]. A recent longitudinal study of 3434 community-dwelling older adults aged 65 and over reported that mild depressive symptoms are predictive of becoming and remaining disabled several years later [57]. In addition, depression has also been associated with greater use of health services, including both specialized psychiatric care and other services [58-60] and correspondingly higher health care costs [59, 61]. For studies of the cognitive outcomes of late-life depression, a detailed review will be presented in section 2.3. Relationship between Depression and Cognitive Decline.

2.1.5 Treatment and Intervention

The most common treatment or intervention modalities for late-life depression are antidepressant medications and psychotherapy [62-64]. Antidepressant medications include tricyclics (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other newer agents. Traditionally, antidepressant medications are often reserved to treat major depressions, while cognitive and interpersonal psychotherapies are often used in the treatment of the mildly depressed patients [62].

During the recent decades, SSRIs and other new antidepressants gained increased popularity and have become the first line antidepressant modality in depressed elderly, due mainly to their low side-effect profiles and better tolerability [63]. In a meta-analysis of randomized, controlled clinical trials of antidepressant treatment in older persons diagnosed with major or unipolar depression, Mittmann and colleagues compared four major classes of antidepressants and concluded that the efficacy, safety and tolerability of the different classes are comparable [65]. However, in older persons with major depression who did tolerate the side-effects of the drugs, the overall response rates to TCAs appeared to be higher than that to SSRIs or atypical antidepressant [65, 66]. According to the consensus statement update from a NIH expert panel, there was good evidence to support the antidepressant efficacy of both TCAs and SSRIs in major depression and to justify a recommendation of aggressive approaches to detect and treat late-life depression [63]. Research evidence for the antidepressant efficacy and benefits in the elderly with mild depression or with complex medical conditions is sparse [7, 65-67]. A few randomized clinical trials, including one conducted in a primary care

population [67] and several from ambulatory populations, synthesized in a meta-analysis [66], reported modest to moderate benefits of SSRIs or heterocyclics in treating dysthymia or mild depression.

Although potentially efficacious and safer treatment modalities are available, a number of epidemiological studies have suggested that depressed elderly living in the community, either diagnosed [68] or suspected [69], were often left untreated. Newman and colleagues collected information on current drug use in 2914 elderly Canadians and found that only 9.4% (4.2% for community and 36% for institutionalized populations) of those depressed were receiving antidepressants [70]. A population survey by Ganguli and colleagues [71] found that only 10% of the community-dwelling elderly with five or more depressive symptoms had ever used antidepressants. A similar trend of undertreatment exists in studies from primary care populations [39, 54].

One ready explanation of the "undertreatment" phenomenon is the lack of sufficient evidence for an antidepressant benefit, especially in those with mild or sub-syndromal depressions or with complex medical conditions [7, 64-67, 72]. Randomized clinical trials for potential antidepressant benefits in late-life depression have largely excluded such patients [63-67]. Another reason is the concern of the potentiql cognitive and other side-effects of antidepressants by patients, their families and physicians, especially TCAs, which will be discussed under section 2.3 Medications As a Potential Risk Factor For Cognitive Decline.

2.1.6 Summary

Depression is common in the elderly population, and has been associated with multiple adverse outcomes, increased health care utilization and costs. Conceptually

depression can be defined as a dimensional continuum (by severity of symptoms) or as distinct entities (by diagnostic criteria), with each serving a different perspective; but in practice the two approaches often converge. Great variations across studies exist in the prevalence and incidence estimates and the identified risk factors, which may be attributed to the differences in study populations (clinical versus community), definitions of depression (symptoms versus diagnoses), and study designs (cross-sectional versus prospective). Many socio-demographic and clinical factors may increase the risk of developing depression in older people, of which CVD may deserve specific attention for this thesis, because it might confound the relationship between depression and cognitive decline. The lack of sufficient evidence for the benefits of antidepressant treatment for late-life depression, especially for older persons with mild depression or with complex medical conditions, may have contributed to the under-treatment phenomenon, and calls for rigorous epidemiological investigation and randomized clinical trials.

2.2 COGNITIVE IMPAIRMENT AND COGNITIVE DECLINE

2.2.1 Definition and Measurement

Cognitive function can be conceptualized as a constellation of the brain's power to acquire, process, integrate, store and retrieve information. It is generally believed that human cognitive function reaches its peak in early adulthood and appears to decline later in life [73], although the limits of normal aging of the human brain and its impact on cognitive function has not yet been established [73-75]. Quantitatively, cognitive function can be measured by performance on memory, language, praxis, abstraction, and execution tasks. Examples included conventional intellectual tests, such as the Wechsler Adult Intellectual Scale and its revised versions (WAIS, WAIS-R) and the Nation Adult

Reading Test (NART) [76]. A score within two standard deviations of the population norm at the same age can be viewed as a rough guide for normal cognition. However, such conventional intelligence tests are not suitable for clinical or epidemiological purposes due to their insensitivity to low cognition, lengthy format and complex administrative procedure. In the latter settings, most frequently employed cognitive tests are brief ones, such as the Short Portable Mental Status Questionnaire (SPMSQ) [77], the Mini Mental State Examination (MMSE) [78] and its modified versions (e.g., 3MS) [79]. A score below some clinically validated cut-point, such as 24 points (out of 30) on the MMSE, is usually considered as indicative of cognitive impairment [78, 80]. A major advantage of such brief cognitive tests is their ease of use: they involve no complicated tasks, can be administered in less than 10 minutes, and thus, are suitable for frail or physically handicapped elderly.

From a longitudinal perspective, cognitive impairment can be approached in terms of deterioration in cognitive performance, or cognitive decline from the previous level. A common measure for cognitive decline is the so-called annual rate of change (ARC), i.e., the change score on a given test over a one year period [81]. An advantage of the ARC is that it may reveal a downward trend when the overall level of the individual's cognition may still be within the normal population range [82]. However, difficulties often arise in comparing change scores across studies due to variations in study methodology and the lack of consensus with regard how to distinguish normal, age-related decrements from pathological declines [75, 83]. In addition, appropriate statistical methods to simultaneously deal with both between- and within-subject

variation have fallen behind the advances in the research setting with longitudinal, repeated measure cohort design until very recently [84].

In clinical settings, specific diagnostic entities have been developed to capture patients who manifest predominantly cognitive impairments and whose cognitive impairments are severe enough to interfere with his or her physical or social functioning. For instance, DSM-IV [6] defines three main categories of cognitive disorders: delirium, dementia and amnesic disorders. Dementia is defined as a presentation of multiple chronic cognitive deficits that include memory impairment, with Alzheimer's disease being the most predominant and common type. Delirium typically presents with acute and transient cognitive changes coupled with a reduced level of consciousness, often with identifiable extraneous cause; whereas amnesic disorder involves only memory impairment without other significant cognitive impairments.

The definition and classification of non-dementing cognitive impairments, other than those described above, have posed major challenges to both researchers and clinicians. DSM-IV [6] proposed an "age-related cognitive decline" to denote low measurable cognitive performance within normal limits of a person's age, to replace its non-specific precursor–"mild cognitive impairment" in DSM-III-R [86], and the International Classification of Disease 10^{th} Edition (ICD-10) [87]. Another collective term, "cognitive impairment, no dementia", was subsequently proposed by the working committee of the Lancet conference on dementias (1996) to encompass not only delirium and mental retardation, but also other cognitive impairments due to depression and chronic alcohol and drug use, etc [88]. Similarly, both "circumscribed memory impairment" [88] and "age-related memory impairment" [89, 90] refer to isolated

amnesic impairments but attribute them to different causes. Despite the terminological confusion, the importance of such non-dementing cognitive impairments is that they may signal an early phase of an underlying progressive neurodegenerative disease, during which the intervention modalities may prevent or halt disease progression [91]. Towards this end, it has been proposed that the currently predominant "dementia epidemiology" should be complemented by an "epidemiology of cognitive impairment" [92, 93].

2.2.2 Occurrence

The prevalence estimates of cognitive impairment in community-dwelling elderly vary greatly depending on the measurement, definition, and detection methods as well as the age composition of study populations. For dementia and moderate to severe cognitive impairment, a few review articles [94-96] provided prevalence estimates. The overall prevalence of dementia, variously defined, ranged from 2% [97] to 7.8% [98]. Of all the dementing disorders, Alzheimer's disease had the highest prevalence rates ranging from 1.4% [99] to 11.2% [100]. In the Canadian population aged 65 and over, the prevalence of Alzheimer's disease was estimated to be 5.1%, followed by vascular dementia (1.5%) [101]. The prevalence of Alzheimer's disease seems to increase with age, at approximately two to five fold every five years after 60, reaching over 20% in those aged 85 and over [95, 101]. The incidence of Alzheimer's disease and dementia parallels this age-trend but at lower magnitudes [96, 102].

Delirium, given its acuteness in onset and relation to extraneous pathologies, is often detected in hospital rather than the community setting. Its prevalence at hospital admission ranged from 5% to 22% and incidence during hospitalization from 17% to 52% [103, 104].

Prevalence estimates for mild cognitive impairment, variably defined, ranged from 12.9 to 17.0 % [105, 106]. Epidemiologic studies of specific conditions, such as "cognitive impairment, no dementia" etc, are sparse. A recent study that employed improved diagnostic criteria reported prevalence estimates of 16.8% for "cognitive impairment, no dementia" and 5.3% for "circumscribed memory impairment" (or "age-related memory impairment") [88].

Longitudinal studies measuring cognitive decline in community-dwelling elderly varied greatly in the instruments used and the length of follow-up, which makes resulting estimates difficult to compare. A few of these using the MMSE may be worth noting given the popularity of the MMSE in both clinical and research settings and its relevance to this thesis. Jacqmin-Gadda and colleagues [107] followed 2537 elderly people aged 65 years and older with annual MMSE assessments for five years and observed a small but statistically significant mean ARC of 0.02 to 0.57 declining points. In another longitudinal study of community-dwelling population, the change scores over a mean interval of 11.5 years for those aged 60 years and above (n=260) were 2.6 and 3.2, respectively [108], corresponding to an ARC of 0.22-0.28. For the most common type of primary dementia–Alzheimer's disease, our group conducted a meta-analysis of 37 longitudinal studies and obtained a pooled ARC estimate of 3.3 (95% CI: 2.9-3.7) during the first one or two years following the disease diagnosis [109].

2.2.3 Risk Factors

Studies of cognitive impairment, cognitive decline and dementia have generated an extended list of potential risk factors. In the case of Alzheimer's disease and other dementias, these have included genetic factors (e.g., ApoE 4 genotype [110], loci on

chromosomes 14, 19 and 21) [111], environmental factors (e.g., drinking water aluminum) [112], and demographic factors (e.g., male gender, older age, and less education) [102, 107, 108].

Medical conditions constitute a major group of such factors, which have included depression [113, 114, 115], other psychiatric disorders (e.g., alcohol abuse) [102], neurological conditions (e.g., epilepsy, head trauma, etc) [102], diabetes [116], and cardiovascular diseases (CVD) [117, 118]. Among physical diseases, CVD seems particularly important, because it has been implicated directly or indirectly in etiologies of different types of dementia [117, 118]. Evidence for the role of depression as a potentially important risk factor is the topic of this thesis and will be reviewed separately in section 2.4.

Another potentially important risk factor is the medications used to treat depression or alleviate its accompanying symptoms, such as insomnia and restlessness, etc. Given its specific relevance to this thesis, the clinical pharmacological and epidemiological evidence for drug-induced cognitive impairment in the elderly population will be reviewed separately in the next section.

2.2.4 Summary

The concept of cognitive impairment can be approached dimensionally or categorically. While the categorical approach considers various forms of "cognitive impairment" having distinct characteristics, the dimensional definition perceives them as coming from a single population continuum. In practice, the categorical approach finds wide use in clinical setting, where standardized diagnostic criteria are employed to identify significant cases of cognitive impairments or cognitive disorders that may

require pharmacological or other therapeutic interventions. The dimensional approach is often adopted to measure the severity of cognitive impairments and to assess the total population burden due to such cognitive impairments in community-based epidemiological studies. No matter which definition one follows, cognitive impairment in older persons represents a common, devastating and costly public health problem, to which amenable intervention modalities have yet to be discovered. A possible alternative to intervention, though, is to identify potential risk factors for cognitive impairment well before it develops into the full blown, non-reversible phase, upon which effective treatment modalities may be devised to prevent or halt the progression of the underlying disease process. Depression and psychotropic medications are among such potentially important and modifiable risk factors that require further investigation.

2.3 MEDICATIONS AS A POTENTIAL RISK FACTOR FOR COGNITIVE DECLINE

2.3.1 Drug-induced Cognitive Impairment in Older Populations

Drug-induced cognitive impairment has long been recognized as an important and challenging problem in the elderly [119, 120], and seems to be increasing during the past decades with the increased consumption of drugs in that population [119, 121]. Such impairment can manifest as limited deficits in cognitive performance or apparent clinical syndromes, such as acute confusional state or delirium. Many authors believe that drug intoxication is a leading or common cause of acute cognitive impairment [103, 122]. The depressed elderly have been reported to have a significantly higher risk of developing adverse drug events than non-depressed older persons [123].

In clinical pharmacological literature, drugs that have been reported to cause cognitive impairment include hypnotics and sedatives, especially benzodiazepines [119, 120], antidepressants, especially tricyclics [120, 124-126], antipsychotics [119, 120], and other agents with centrally active depressant effect [119, 120]. Although the pharmacological mechanisms of drug-induced cognitive impairment are probably multi-faceted, the anticholinergic effects of a medication are particularly relevant [119, 120, 122, 124-126]. Considerable evidence suggests that failure of cholinergic transmission plays a key role in several memory disorders including Alzheimer's disease [127]. 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 [127-129]. Induction of experimental delirium by administration of anticholinergic drugs has been observed in humans and could be reversed by a cholinergic agonist [129]. Elderly patients may be more vulnerable to anticholinergic intoxication due to an aging-related reduction in cholinergic brain receptors and altered pharmacokinetics [127]. Consistent with clinical observations and animal experiments, a few large-scale epidemiological studies have found independent associations between poorer cognitive performance and exposure to antidepressants [115, 132], benzodiazepines [115,132, 133, 134] and antipsychotic medications [115, 132, 127], of which many agents have potent or detectable ACH effects *in vivo* [119, 124-126, 130, 135]. In my Master Thesis, I used a clinician-rated anticholinergic score as an index for total anticholinergic burden of medication exposure and found it to be independently and specifically predictive of the severity of delirium symptoms in older medical patients [109].

2.3.2 Antidepressants and Cognitive Impairment

Traditional antidepressants, especially TCAs, are a group of medications possessing a high potential to compromise cognition [124-126, 137, 138]. In addition to the evidence from animal experiments and clinical observations, treatment of depression in older persons with TCAs has been associated with decreased cognitive functioning in some [115, 120, 124-126, 132-134], but not other studies [139-143]. A few comprehensive literature reviews covering both randomized clinical trials and observational studies that measured cognitive function have provided valuable information for the cognitive profiles of antidepressant medications in older persons [124-126,136]. In general, these reviews conclude that TCA agents, especially tertiary amine amitriptyline and doxepin and secondary amine nortriptyline, tend to have the most detrimental cognitive effects, especially on attention and concentration. Antidepressant agents with high anticholinergic properties, such as nortriptyline, maprotiline and amitriptyline, may particularly cause short-term recall memory. In addition, cognitive impairment induced by nortriptyline during treatment appears to be dose-dependent on its plasma concentrations and may last as long as treatment continues. Data regarding the effects of SSRIs or MAOI on cognitive performance in the elderly mostly indicated no detrimental effect.

A systematic review published in 1999 covering a broad range of drug-induced cognitive disorders in the elderly arrived at a similar conclusion, based on thirteen studies including eight reports of double blind, randomized clinical trials [137]. Specifically, the review concluded that there was moderate to strong evidence for an increased risk of cognitive impairment linked to TCAs (especially amitriptyline) and trazodone and for a

minimum risk linked to SSRIs and reversible MAOIs [137]. The outcome measures included global (e.g., the MMSE) or specific (e.g., short recall memory) cognitive tests. Of the three clinical trials that used the MMSE, an overall mean increase of 2.0 to 2.6 points over four weeks was observed for those treated with an SSRI . However, the studies included highly heterogeneous populations in terms of baseline cognitive function, had a short follow-up period (up to eight weeks) and did not measure the cognitive function as a primary outcome. For instance, three out of the eight clinical trials were conducted in patients with both depression and cognitive impairment or dementia, and another two did not specify the baseline cognitive function of the study population.

A more recent meta-analysis published in 2006 of 32 randomized comparative trials (selected from 163 studies) of antidepressants for depressed elderly reported that the TCAs and SSRIs had comparable efficacy, yet classical TCAs tend to have a higher profile of side effects [138]. Unfortunately, the authors grouped the side-effects by organ system (e.g., broad "neuropsychiatric" rather than specific "cognitive") and reported the results in percentage and number of persons experiencing the side-effects. Great heterogeneity across the trials was observed in terms of study quality scores, except the age of the study population and the types of studies. In addition, the duration of trials was short (up to 24 weeks) and no information on comorbidity profiles of the study populations or concomitant medication use was given [138].

A number of studies with specific measure of cognitive function showed that treatment with newer antidepressants, especially SSRIs, may even improve the cognitive function of depressed patients [141-143]. In a placebo-controlled clinical study, Siegfried and colleagues. found that the elderly depressed patients treated with antidepressant

nomifensin, in comparison to controls, showed significant improvement in both depression symptom rating and several cognitive domains [142]. Another study pooled data from two randomized clinical trials of 444 elderly persons with major depression following a double-blind treatment. After controlling for an anticholinergic severity score based on peripheral side-effects of medications (dry mouth and constipation) and number of concomitant medications and other covariates, improvement in depression symptoms was found to be significantly associated with improvement in cognitive tests in patients treated with either SSRIs (sertraline and fluoxetine) or TCAs (nortriptyline) [143]. Interestingly, although nortriptyline is highly "anticholinergic", patients with some cognitive impairment at baseline seemed to show improvement in cognitive tests after a 3-month treatment with this drug. This preliminary observation suggests that the net cognitive effect of antidepressants may depend on the relative strengths of, or a trade-off between their "antidepressant" efficacy (presumably due to serotonergic augmentation) and anticholinergic toxicity.

2.3.3 Benzodiazepines and Other Psychotropic Medications

Studies of benzodiazepines and other psychotropic medications have been inconsistent; while most found these medications to be predictive of lower cognitive functioning [115, 133, 134, 139, 144], others did not observe such a relationship [145] or conversely, found a protective effect [146]. However, given their inherent hypnotic and sedative properties in suppressing arousal, vigilance and muscular tone, it is understandable that use of benzodiazepines and other psychotropic medications with durable effect, such as long-acting benzodiazepines [115, 147], would generally depress, rather than augment, cognitive performance and other functions that requires attention

and concentration. In addition, studies also revealed that many psychotropic medications, including benzodiazepines, also have detectable anticholinergic activities *in vivo* [130], which would subject their users, especially the older ones, to an increased risk of cognitive impairment.

The implication of benzodiazepines in late-life depression lies also in their pervasive use in this population. In a study of 153 older medical inpatients with diagnosed depression, Koenig and colleagues [68] observed that 25.5% received benzodiazepines only, in comparison with 40.5% who received antidepressants at some time during their hospital stay or the follow-up period. A similar trend of overuse of benzodiazepines and underuse of antidepressant has been associated with persistence or relapse of depression in a 3-year follow-up study of 106 elderly patients with either psychiatric or neurotic depression [148].

2.3.4 Summary

Pharmacologically, both the TCAs and benzodiazepines commonly prescribed to depressed elderly are capable of causing cognitive impairment, potentially through an anticholinergic mechanism. Exposure to such medications may put older persons at increased risk for cognitive impairment due to an age-related increase in the sensitivity to anticholinergic intoxication. The new generation of antidepressants, such as SSRIs, tends to have lower anticholinergic profiles, and hence, fewer or no cognitive side-effects. Moreover, preliminary evidence from randomized clinical trials and observational studies suggest that they may even improve rather than compromise cognitive function in older persons with major depression. However, randomized clinical trials typically focused on the therapeutic efficacy rather than cognitive side-effects of the antidepressants, had short

follow-up, overrepresented healthy elderly, and did not allow for evaluating confounding by concomitant medication. In addition, potential cognitive benefits have not yet been established in older persons with minor depression or with complicated medical conditions. The underuse of antidepressants, despite the availability of safer modalities, and over-use of benzodiazepines, despite their potential to cause cognitive impairment, in depressed elderly living in the communities might reflect in part the consequence of such a knowledge gap and calls for rigorous epidemiological investigation.

2.4 RELATIONSHIP BETWEEN DEPRESSION AND COGNITIVE DECLINE

2.4.1 Background

Early studies of the depression-cognitive impairment relationship were often conducted in clinical samples with diagnosed depression or dementia. Since the onset of dementia and depression is often insidious and their clinical manifestations may significantly mimic each other, it is often difficult to ascertain their temporal sequence or establish a causal pathway. In addition, patients who seek medical attention are often prevalent cases or "survivors" of the disease who have already passed the pre- or sub-clinical stage, during which etiological agents (or causal risk factors) are most likely to be detected. Thus, the ability of the clinical studies to delineate the causal relationship of depression and cognitive impairment is limited.

The earliest epidemiological finding from community samples advocating for an association between depression and dementia may be owing to Jorm and colleagues [149]. In a pooled analysis of 6 case-control studies conducted between 1984 and 1991, the authors found a significant association between late-onset depression and diagnosis of Alzheimer's disease with either greater (relative risk (RR): 2.1 95%CI: 1.1-3.8) or less

(RR: 4.5, 95%CI: 1.2-16.0) than 10 years of previous history of depression. In addition, they also observed a non-significant effect of antidepressant use (RR=1.2, 95%CI: 0.25-2.78) from 2 studies that had such data. However, the strength of these findings was weakened by the lack of adjustment for potential confounding, the retrospective nature of depression ascertainment, and the methodological heterogeneity across the pooled studies.

2.4.2 Current State of Epidemiological Knowledge – A Critical Literature Review

To identify relevant research in the epidemiological literature addressing the relationship between depression and cognitive decline in the elderly, I searched the MEDLINE database, 1975 to February 2006, for original prospective studies of the relationship conducted in persons aged 45 years or older, using three groups of keywords: 1) depression or depressive symptoms or depressive disorders; 2) cognitive impairment or decline or dementia; and 3) epidemiological or cohort or longitudinal or prospective or follow-up studies or research methodology (e.g., confounding factors). I also reviewed the bibliographies of identified papers to locate more relevant studies. Finally, I identified 14 studies that met the following criteria: prospective design; study population consisting of elderly people age 60 year or older with ascertainable size; measured both depression and cognition, with cognition as a study outcome; and adjusted for at least one additional risk factor. In the next sections, I will provide a systematic review of these studies and try to identify potential methodological issues that may help improve the quality of my thesis.

2.4.2.1 Overview of study designs

The major study design and methodological features of the 14 reviewed studies are summarized in Table 1 (150-163). In brief, all the studies used a prospective cohort design and followed up a defined group(s) of community-dwelling elderly, with the sample sizes at baseline ranging from 500 [162] to 7511 [151]. The durations of follow-up varied from one to twelve years and the number of assessments (or follow-up waves) from two to four, with the minimum time lag of one to two years between depression and cognitive assessments. Depression was often measured using a self-rated depression scale, mostly the Geriatric Depression Scale (GDS) or Center for Epidemiological Studies Depression Scale (CES-D) or their modified versions, or further defined dichotomously by a cut-off point on these scale. The most common instruments used to measure cognitive functioning were the Mini Mental State Examination (MMSE) and Short Portable Mental Status Questionnaire (SPMSQ). The outcome measures included cognitive decline, as defined by ARC or a change score on the cognitive test between two follow-up waves [151, 153, 156-158, 160, 162, 163], or by crossing a cut-point on a cognitive test of presumed clinical significance [151-154, 156], or a diagnosis of dementia or Alzheimer's disease according to the Diagnostic and Statistical Manual of Mental Disorders, the 3rd revised (DSM-IIIR) or the 4th Edition (DSM-IV) [150, 154, 155, 157]. All the studies employed one or more multivariate modeling techniques to control for confounding from potential risk factors. Therefore, the resultant effect estimates represented the association between the depression measures and subsequent cognitive outcomes, independent of the adjusted covariates.

2.4.2.2 Main findings

Of the 14 studies reviewed, several [150-152, 154, 156-159], but not all [153, 155, 160-163] found a statistically significant association between depression and subsequent cognitive outcomes. However, in some studies the observed association seemed to vary across other risk factors. For example, it was found to be significant only in the subgroup with some cognitive impairment at baseline [152], or with greater than eight years of education [154], or in male gender only [161]. In addition, the interpretations of the association or the temporal sequence of depression and cognitive decline varied across studies. While some suggested that depression increased the risk of future cognitive decline or development of dementia [151,156-159], others interpreted it as a prodromal syndrome or early manifestation of dementia [150, 152, 154, 155, 163], still other considered it as a consequence of a third factor or common etiology [150, 152, 161], or merely a clinical concomitant of cognitive impairment [161]. Therefore, it remains inconclusive as to whether depression is an independent risk factor, a clinical concomitant, or a consequence of cognitive impairment.

Table 1. Recent prospective cohort studies of the depression-cognitive impairment association in elderly population

Author /year	Study Population*		Follow-up yrs /waves	Depression Measure† /Index	Cognitive Outcome		Main Covariates Adjusted		Adjusted Effect of Depression‡
	N, F% & Age	CI/DEM %			Measure	Main Index	Drug Use/ Treat.	Others /Method for adjustment	
Bassuk '98[152]	N: 2030/2812; F%: 62.8 Age: ≥65	12.4 (SPMSQ 0-6)	3-12 / 4	CES-D/ 1. score≥16 (15.4%); 2. Dysphoria (10.2%).	SPMSQ [category: 9-10, 7-8, 0-6].	1) Decline to a lower category; 2) Last scores.	N/A	age, functional disability, CVD profile, alcohol use/ polytomous logistic & multiple linear regression.	OR: 1.7 (1.0~2.8) for 3-y FU; 2.4 (1.3~4.3) for 6-y FU/ β=-0.44 (p=0.01)
Chen '99[155]§ (full cohort)	N: 803/954; F%: 60.0 Age: 73.7	11.5/9.6 by DEP group	1-8 / 2-3	CES-D-m/ DEP cluster (6.5%)	DSM-IIIR/ NINCDS-ADRDA (& MMSE etc)	Incident AD or DEM	N/A	age, sex, education /Cox proportional hazard model	RR: 1.3 (0.6~2.9) on DEM; 1.3 (0.5~3.2) on AlzD outcome.
(subcohort)	751 non-DEP (39 developed DEM/AD later).	N/A	2.2 / 2	(above)/ incident DEP at wave 3	same as above	same, but treated as "exposure"	N/A	(above)+ subjective memory loss / Logistic regression	OR: 5.2 (1.8~15.1) for DEM, 6.5 (2.2~19.1) for AlzD.
Cervilla '00[161]	N: 374/1083 F%: 66.1; Age: 70.2	18.5	9-12/ 2	Self-CARE-D: 1) raw score; 2) ≥6 (11.2%) vs <6.	MMSE	Log transformed (& raw) score	N/A	baseline cognition, age, sex, education, smoking etc /factorial MANOVA	β=0.004 (p=0.92);
Devanand '96[150]	N: 478/852; F%: 69.4 Age: ≥60	47.0 (≥2 deficit tests)	1-5 / > 2	HRSD/1. DEP mood (37.4%); 2. Scores.	DSM-IIIR/ NINCDS-ADRDA	Incident DEM or AlzD	N/A	age, sex, language, memory & functions/ Cox PH model	RR: 2.1 (1.2~3.6)/ β=1.1 (1.0~1.1) for total score.

Table 1 Cont'd

Dufouil '96 (cohort)[153]	N: 1600/2726 F%: 60.0; Age: 72.8	18.5	3 / 2	CES-D/ 1). ≥17 for M, ≥23 for F; (13.7%) ;2). Change score	MMSE	1) Decline > 5 points; 2) Change score.	N/A	age, sex, marital status, IADL /multiple logistic /linear regression	OR: 0.8 (0.3~2.1).
Ganguli '06[163]	N: 595/1265 F%: 60.8; Age: 74.6	0.0 (>0 on CDRS)	12/ 6	CESDm/ 1) Score>5 (10.1%); 2) Transient vs persistent DEP	MMSE/ other cognitive tests	ARC	AD use at baseline	age, sex, education incipent dementia & recruitment status/random effects model	β=0.003 (NS) in dementia-free group, & 0.02 (NS) in eventual-dementia group.
Geerlings '00[154] (cohort 1)	N1:1911/3137; F%: 62.3 Age: 73.1 (65-80)	0.0	3.2 / 2	GMSS/ DEP score 3-6 (9.7%)	DSM-IV (CAMDEX, MMSE)	Incident AlzD	N/A	age, sex, memory complaints, psychiatric history/ Logistic regression	OR: 5.3 (1.9~15.0)
(cohort 2)	N2:1894/2399; F%: 52.9 Age: 68.5 (55-84)	0.0	3.1 / 2	CES-D / 1. Score ≥16 (11.6%); 2. Total score.	MMSE	Decline ≥3 points	N/A	(from above) +baseline MMSE, - psychiatric history.	OR:1.8 (0.9~3.6) / β=1.1 (1.0~1.1) for total score.
Henderson '97[160]	N: 709/1045 F%: 51.5; Age: 76.5	N/A	3 / 2	CES-D score	MMSE (& other mental tests)	Change score	N/A	age, sex/conditional linear regression	No actual data given, only cited as NS.
Paterniti '02[156]	N: 1003/1389 F%: 57.2; Age: 65.0	0.0	4 / 3	CES-D/ DEP group by ≥17 for M and ≥23 for F	MMSE	1) Change score; 2) Decline ≥3 points; 3) Score <25	Psychotro-pic use	age, sex, education, alcohol/tabaco use, & chronic disases/ linear & logistic regression	1) β=-0.54 (p=0.002); 2) OR: 1.6 (0.95-2.55); 3) OR: 3.2 (1.2-8.4)
Saches-Ericsson '04[159]	N: 3094/4162; F%: 65.0 Age: 76.6	46.0 (SPMSQ errors >1)	3 / 2	CES-D/ scores	SPMSQ	# errors	N/A	age, gender, race, economic status, baseline cognition and physical function/ multiple regression.	β= 0.04 (p=0.01)

Table 1 Cont'd

Vinkers '04[162§]	N: 298/500 F%: 63.0; Age: 85.0	17.0 (<24 on MMSE)	4/ 4	GDS-15/ scores	MMSE/ other mental tests	ARC	N/A	sex, education/ Mixed regression model	β=-0.01 (p=0.79)
Wilson '02[157]	N: 651/821 F%: 67.5; Age: 75.4	N/A	7/ 5.5	CES-D 10-item/ scores	clinical diagnosis/ 19 cognitive tests	Incident AlzD/ ARC on a global score	N/A	age, sex, education, memory complain, apoE, comorbidities/ Cox PH & random effects models	1) HR: 1.19 (1.1-1.3); 2) β=-0.009 (p=0.004)
Wilson '04[158]	N: 2783/4392 F%: 62.1; Age: 73.9	N/A	5.3/ 3	CES-D 10-item/ scores (15% >3)	MMSE/ 4 other brief cognitive tests	ARC on a composite z score across the 4 tests	N/A	age, sex, race & education (plus chronic illnesses etc)/ random effects models	β=-0.03 unit (p=0.002)
Yaffe '99[151]	N: 5781/7511 F%: 100.0; Age: 72.8	N/A	4 / 2	GDS-s/ 1. # symptoms; 2. scores>6 (3.6%), 3-5, (vs 0-2)	MMSE-m (Trails B, Digit symbol)	1) Change score; 2) Decline ≥ 3 points	AD use in past 30 days	age, health, physical function, alcohol use etc/ ANOVA & logistic regression	OR: 2.1(1.4~3.1) for GDS-s >6; 1.6 (1.2~2.1) for GDS-s 3-5

Notes:

*. If both cross-sectional and longitudinal data were available, only the longitudinal ones were presented;

N: Denotes # subjects at the end of follow-up versus # subjects at baseline.

F%: Denotes proportion of female among the study population;

Age: Denotes mean or median (range) age in year of the study population or reference group at baseline, except otherwise indicated.

†. Refers to those used as a predictor in the multivariate analyses, which were assessed at baseline only in all the studies;

‡. Refer to effect estimates for depression associated with the Main Index for Cognitive Outcome adjusting for the selected covariates, with 95% confidence interval or p value (as specified) in parentheses.

§. The subcohort analyses on depression as an outcome in these two studies were not presented.

Table 1 Cont'd

Abbreviations:

AlzD, Alzheimer's disease; CI, Cognitive impairment; DEM, Dementia; DEP, Depression or depressed or depressive; FU, follow-up;

NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association.

M, male; F, Female; N/A, not available or not applicable; NS, $p>0.05$ or not significant according to the paper;

AD, antidepressants; PH, Proportional hazard model; CVD, Cardiovascular diseases;

CAMDEX, The Cambridge Examination for Mental Disorders of the Elderly (Roth 1988); CDRS: Clinical Dementia Rating Scale;

CES-D(-m), Center for Epidemiological Studies Depression Scale (-modified) (Radloff 1977);

DSM-III(R), The Diagnostic and Statistical Manual of Mental Disorders, 3rd Edi (Revised) (American Psychiatric Association 1987);

GMSS(-dep), GMSS(-org), Geriatric Mental State Schedule (-depression or -organic score) (Copeland 1976);

GDS(-s), Geriatric Depression Scale (-short form) (Yesavage 1983); HDRS, Hamilton Depression Rating Scale (Hamilton 1967)

MMSE(-m), Mini-Mental Status Examination (-modified) (Folstein 1975); SPMSQ, Short Portable Mental Status Questionnaire (Pfeiffer 1975);

ARC, Annual Rate of Change in the test scores; OR, Odds ratio; RR, Risk ratio or rare ratio; β, Beta coefficient;

2.4.2.3 Methodological implications

There are several common methodological issues in these studies that may have important implications for this thesis.

2.4.2.3.1 Lack of specificity of the depression measure

In all the reviewed studies with only one exception [150], the depression symptoms in the association analyses were defined using self-rated, rather than clinical assessment-based, depression scales [152, 155,156, 160, 151,162]. A cut-off score (e.g., >16 on CES-D) was often used to determine the presence or absence of depression. However, the "self-report" depression symptoms tend to have an inadequate criterion validity to identify clinically significant depression and great intra-individual variation [164, 165]. In fact, a four to ten fold overestimation of true depressive disorder (false positive) by CES-D against clinical standard diagnostic criteria for major depression has been observed [29, 166]. Therefore, studies relying solely on self-report scale to define depression symptoms may, on one hand, lead to a spurious association when clinical confounders such as physical illness or stress reaction are not adequately accounted for; on the other, their findings may be difficult to translate into clinical practice with regards to whether and to what extent these "depressed" elderly are comparable to clinically significant cases of depressive disorders, who may benefit from antidepressant intervention.

2.4.2.3.2 Ignorance of the natural course of depression symptomatology

Depression, either by symptomatic or diagnostic definition, is an episodic and recurrent condition, often with complete remission at intervals [6]. A typical major depressive episode usually lasts three to six months [6]. Without a consideration of the

biologically plausible "pathogenic" effect period of depression pathology and account for its dynamic course, a prospective study that simply associates a depression score at baseline to a distant cognitive outcome observed several years later may lead to a spurious association, which could result from an unmeasured intervening event, such as the side-effect of recent antidepressant treatment or an acute psychological stress, or fail to detect an existing causal association that may have diminished before the time when the outcome was assessed.

Almost all the reviewed studies have assessed depression and cognitive outcome at least one year, mostly two to three years apart. In addition, though some studies assessed depression on more than one occasions during the follow-up [150, 152, 155, 162, 163], no one had examined it as a dynamic, time-varying exposure when examining its prospective association with the cognitive outcome. Therefore, it is questionable that an observed cognitive decline or incident dementia could be attributed to the causal effect of the remote depression symptoms. As Dufouil suspected [153], the lack of a prospective association in some studies [153, 160-163] could simply be explained as the failure of the over-protracted follow-up intervals to capture the true depression effects, which may have diminished before the delayed outcome assessment, rather than a proof of no causality. Another drawback of such prolonged follow-up studies is that they do not allow for examining the specific short-term clinical concomitants that may confound the relationship in a close temporal context, such as an acute physical illness or a recent stressful life event.

2.4.2.3.3 Lack of consideration of potential effect of medication use

Substantive knowledge exists that both antidepressants, such as TCAs, and other psychotropic medications frequently prescribed to depressed elderly, such as benzodiazepines, may potentially compromise cognition [119, 124, 126]. In addition, the agents, dosage and frequency of antidepressant administered often varies over time in response to the variation of depression symptoms or other factors, which may affect both depression pathology and cognitive functioning of the patients. Therefore, it is important to disentangle the cognitive effects of depression pathology from those attributed to the concomitant antidepressant or other psychotropic medications.

Among the reviewed studies, only three reported an adjustment for antidepressant [151, 163] or psychotropic use [155] as a covariate. However, the medication use was merely ascertained at baseline and represented by a dichotomous indicator, exposed versus not exposed. Due to ignorance of the dose, duration and changes of medication regiment over time, the use of a single baseline measure to represent current medication exposure may introduce serious misclassification bias in observational studies [167]. Furthermore, collapsing different levels of exposure into a dichotomous exposure status may result in a significant loss of precision and efficiency in the effect estimation [168]. Both concerns may be particularly implicable in the studies of late-life depression, given the dynamic nature of the depression symptoms and the complexity of medication regimen of older persons with depression.

2.4.2.3.4 Other methodological implications:

Two other potential limitations from several studies may also be worth mentioning:

1). Omission of potentially important clinical confounders. For instance, cardiovascular diseases (CVD) have been consistently associated with both depression [48, 49] and dementia [117, 118] in literature, but was only adjusted for in one study [152]. Another study measured, but did not control for, baseline blood pressure [151].

2). Inclusion of a large proportion (10% or greater) of cognitively impaired subjects in the study population without adequate statistical adjustment [150, 152]. Elderly people with mild cognitive impairment may be more likely to report depression symptoms due to awareness of their declining cognitive function. They are also at higher risk of developing dementia subsequently than those cognitively normal elderly. Thus, these studies may be subject to great ambiguity as to whether depression was an independent or causal risk factor of cognitive decline or dementia, or merely a prodrome of or early reaction to the underlying dementia process that was already in operation.

2.4.3 Summary

While large-scale, population-based prospective epidemiological studies have added to our knowledge about the depression-cognitive impairment relationship in the elderly, the research findings remain inconclusive with regard to the nature of the relationship, i.e., whether depression is an independent risk factor, a clinical concomitant, or a consequence of cognitive decline. However, there remain several unanswered questions on this relationship. First, several methodological limitations, namely, the lack of specificity of the depression measure, lack of consideration of the dynamic course and biologically plausible short-term prospective effects of depression pathology, and omission of potential effect of antidepressant use or cardiovascular diseases, may have hampered the ability of current epidemiological studies to delineate the temporality and

causality of the relationship. New epidemiological studies attempting to solve the ongoing controversies with improved methodology are warranted.

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CHAPTER 3 — OVERVIEW OF STUDY DESIGN AND DATA SOURCE

3.1 STUDY DESIGN: APPROACHES AND RATIONALES

This thesis is concerned with the relationship between depression and changes in cognitive function. As described in section 2.2, several terms have been used in the literatures to describe levels of and changes in cognitive function in older populations. To keep terminological consistency with the literature while maintaining the conceptual clarity and unique feature of this thesis, I will use the terms "function" or "functioning" to qualitatively describe the cognitive outcome, cognitive "change" to describe the quantitative increases and decreases over time in cognitive functioning, and cognitive "decline" to refer specifically to a decrease over time in cognitive functioning. While in the literature the latter term often implies a long-term, and sometimes irreversible, cognitive deterioration, this thesis will treat it as a short-term and dynamic phenomenon, without a persistency or pathological implication.

Based on my literature review, this thesis is intended to further address the following unsolved research questions in a cohort of elderly medical inpatients who were followed for up to twelve months:

1). Is depression in older persons an independent risk factor, a clinical concomitant, or a consequence of cognitive decline?

2). Are antidepressants or other psychotropic medications associated with cognitive decline, independent of depression and other risk factors, or do they modify or mediate the relationship between depression and cognitive decline?

To avoid the methodological limitations of previous cohort studies, namely, the non-specific depression measures, long follow-up interval, lack of consideration of the

dynamic nature of depression symptoms, and omission of potentially important clinical confounders, such as medication use and cardiovascular diseases, this thesis adopted a prospective, repeated measures, cohort design, with the following innovative features:

1). Both the "exposures" (i.e., depression and medication use) and the outcome (i.e., cognitive decline) were measured at multiple time points during follow-up. A longitudinal analysis using a mixed effects linear regression model was conducted to test the hypotheses, which allowed for a simultaneous control for both baseline (or patient-specific) and time-varying risk factors and addressing the dynamics of depression symptomatology over time. In addition, the study power and efficiency were increased due to utilizing additional data from repeated measures on the same patients [1, 2].

2). The primary exposure, depression, was defined using both an interviewer-assessed symptom scale and the structured clinical diagnostic criteria, which enhanced the clinical interpretability and applicability of the study, and stimulated deeper insights into the properties of the dimensional (i.e., symptomatic) and categorical (i.e., diagnostic) approaches to the concept of depression.

3). The medication regimens of the cohort members during the follow-up period were obtained from a comprehensive administrative prescription database, linked with clinical research data, which minimized potential measurement errors in medication exposure due to sole reliance on baseline assessment, self-report or hospital records, and maximized the capacity of the study to control for confounding by indication, a major threat to the validity of pharmacoepidiological studies [3, 4].

4). The follow-up interval between repeated assessments of three to six months was shorter than any previous cohort study in the subject field and approximated the

natural course of major depressive disorder more closely. The alternative exposure time windows and measures of medication exposure were devised in light of both substantive pharmacological knowledge, and a biologically plausible cholinergic deficiency hypothesis for dementia etiology.

3.2 DATA SOURCE

This thesis used the data collected in two previous studies conducted in two university affiliated, acute care hospitals in Montreal, Canada, St. Mary's Hospital and Jewish General Hospital. The two studies included a randomized controlled trial (RCT) of the treatment of major depression and a prospective observational cohort study of 12-month outcomes of depression in older medical inpatients [5, 6]. Both studies were funded by the Canadian Institutes of Health Research. The study protocol was approved by the research ethics committees of both hospitals (see Appendices II and III for letters of approval).

The objective of the RCT was to determine the impact of systematic detection, treatment, and follow-up on the course and outcome of elderly medical inpatients with major depression. Eligible patients aged 65 years and older who were admitted from the emergency room to the medical services were screened by the study nurse using the SPMSQ; those who scored four or less (indicating at most mild cognitive impairment) were assessed using the Diagnostic Interview Schedule (DIS) [7]. Patients diagnosed with major depression (DSM-IV criteria) [8], and who consented to participate, were enrolled in the study (n=244), and randomly allocated to intervention or control groups. The intervention group received special care by a geriatric psychiatrist and study nurse. Patients in the control group received usual hospital care. All patients were assessed at

baseline, then three, six, twleve, and 24 weeks later. Primary outcomes included repeated measures of the HDRS and the Medical Outcomes Study Short Form (SF-36). Secondary outcomes included cognition, physical function, side effects of medication, and number of depressive episodes, mortality, suicide and suicide attempts and use of health services.

The prospective observational cohort study used identical data collection methods and instruments (including follow-up at three, six, and twelve months after enrolment) among three cohorts of cognitively intact medical inpatients aged 65 and over: a major depression cohort and a minor depression cohort, in whom these diagnoses were made during the first few days of hospitalization; and a control cohort without a depressive disorder. It followed the same set of general exclusion criteria as the RCT: a) admissions to intensive care unit or to cardiac monitoring unit (unless transferred to a medical ward within 72 hours of admission); b) admissions to palliative care (unable to be followed for at least 6 weeks); c) do not speak or understand English or French (or unable to communicate), and d) do not live on the island of Montreal (who would be difficult to follow-up). However, patients with major depression who were excluded from the RCT because of severe depression or psychosis were included.

The two studies shared common methods and measures, including cognitive screening using the SPMSQ, two approaches to assessing depression (symptomatic and diagnostic), the MMSE to assess cognition, and measures of covariates (e.g., severity of illness, comorbidity, physical function, and quality of life). The research assistants conducting baseline and follow-up assessments were kept blind to study cohort. The interview instruments were limited to confine each interview to one hour, for the sake of minimizing the burden on patients and "testing effects".

Information about medication prescriptions of the study participants during the follow-up period was obtained though linkage of their hospital medical records with the provincial prescription claims databases (the Reġie de l'assurance maladie du Québec, RAMQ) [9]. RAMQ provided the product name, dose and duration of each filled prescription from the 6 months prior to the index hospitalization up to the end of the 12-month follow-up period for all the enrolled patients.

Enrollment for the two studies began in September, 1999 and concluded in October, 2002. The follow-up covered one year after enrolment. In total, 1,686 eligible patients were screened for depression, of whom 530 consented to participate and were enrolled into the study. The main reasons for exclusion included: too sick, severe cognitive impairment, admission to intensive care, already discharged, transferred to long term care, not proficient in either English or French language, and residing outside of Montreal island. Of the 530 enrollees, 22 died and 94 withdrew before the baseline interview, leaving 414 for baseline and follow-up interviews.

For this thesis, the study sample included 281 participants with at least two valid outcome measures (i.e., MMSE scores, see section 4.2 for details) during the twelve month follow-up period, including participants from the observational study and the RCT, and from both study hospitals. The main reason for this selection was to accommodate the repeated measure mixed model analysis. Patient with only one measure did not contribute data to assessing longitudinal variation, and hence, essentially irrelevant for the analyses. Similarly, participants from the RCT were included to increase study power, especially for evaluating the effect of major depression. This inclusion was also justified by the lack of any effect, clinical or statistical, of the

experimental intervention on cognitive status in the trial [5]. The 281 selected patients represented 67.9% of the baseline cohort (N0=414). The sample consisted of 185 (65.8%) women and 96 men (34.2%), with a mean age of 79.1(SD: 7.2). 121 were diagnosed as with major depression, 51 with minor depression and 109 with no depression. There were no statistically significant differences (all $p > 0.07$) between those included (N=281) and excluded (N=133) with respect to age, sex, living condition, ADL scores, study group, hospital sites, diagnosis of depression and cognitive impairment at screening. However, patients who were excluded were more severely ill ($p<0.01$), had more comorbid conditions ($p<0.01$), higher HDRS ($p=0.05$) and lower MMSE scores ($p=0.03$).

3.3 SPECIFIC AIMS AND HYPOTHESES

Three inter-related specific research aims are pursued in the three manuscripts that comprise this thesis:

1). To explore the temporal relationship between depression symptoms and cognitive functioning, independent of other risk factors, with a specific focus on testing whether depression symptoms as measured by an interviewer-assessed scale are an independent predictor of subsequent cognitive decline, versus a clinical concomitant;

2). To examine the temporal relationship between depression diagnoses and cognitive decline, independent of other risk factors as well as the severity of depression symptoms; and to determine whether the short-term trajectories of cognitive functioning of the cohort differed among persons with major, minor or no depression;

3). To examine the role of antidepressant and other psychotropic exposure in the relationship between depression and cognitive decline, and to determine whether it was an independent risk factor, an effect modifier, or a mediating factor.

My main hypotheses were as follow:

1). If depression is indeed an biologically valid risk factor for cognitive decline, then such an association would be more likely to be detected during the active clinical phase of the depression pathology than during its residual or remission period.

2). The diagnoses of depression should have better predictive power for subsequent cognitive decline than the severity of depression symptoms, since the former are more likely to identify clinically significant, and potentially more biologically homogeneous depression syndrome than latter.

3). In general, exposure to antidepressants (especially TCAs) and other psychotropic medications (in particular benzodiazepines) should be associated with a decreased cognitive function. However, since depressive pathology itself may lead to cognitive decline and such a detrimental effect may be potentially reversed or alleviated by effective antidepressant treatment, the "net" cognitive effect of the medications would depend on a trade-off between the antidepressant "efficacy" of the medications and the severity of depression pathology.

A final and exploratory hypothesis was that the detrimental effects of medication use on cognitive function would mainly be driven by the total anticholinergic burden across all the concurrent medications, consistent with the cholinergic deficit hypothesis for dementia etiology.

3.4 STUDY MEASUREMENTS

3.4.1 Measure of Depression

Severity of depressive symptoms was measured using the 21-item version of the HDRS [10] at enrolment and at each follow-up by a research assistant. The HDRS is the most widely used interviewer-rated scale for monitoring depressive symptoms and signs in intervention studies of depression patients. Items are rated from 0 to 3, with higher scores indicating more pathology. A total score of 13 or more is usually considered as indicative of clinical depression.

The depression diagnoses were made through a structured psychiatric evaluation using the depression section of DIS at baseline and then three, six and twelve months later during follow-up by a research assistant. Patients were classified as major, minor, or no depression according to DSM-IV criteria using an "inclusive" approach, which counts current symptoms with a duration of at least two weeks towards a diagnosis, regardless of their origin of physical illness or primary affective disorders [11]. This approach appears to be most reliable for assessing depression in medically ill older persons, especially from a longitudinal perspective [11].

The inter-rater reliability was checked periodically, with a kappa coefficient being 0.78 (95% CI 0.52 to 1.00) for a diagnosis of major depression vs. minor or no depression and 0.61 (95% CI: 0.35 to 0.87) for a diagnosis of either major or minor depression vs. no depression (n=28). The intra-class correlation coefficient for HDRS scores was 0.93 (95% CI: 0.86 to 0.97, n=26).

The content of HDRS and DIS, and the diagnostic criteria for depression from DSM-IV are presented in Appendices IV and V.

3.4.2 Measures of Medication Exposure

3.4.2.1 Major medication classes

Using the prescription records from RAMQ, three major classes of psychotropic medications were defined, based on their documented cognitive effects in literatures and specific relevance to depressed older persons:

1). Antidepressants included tricyclics (TCA: amitriptyline, desipramine, doxepine, imipramine, nortriptyline, trimipramine and clomipramine), selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline, fluvoxamine, paroxetine and citalopram), and other agents, which included tetracyclics (maprotiline), monoamine oxidase inhibitors (tranylcypromine) and atypical antidepressants (trazodone, nefazodone, venlafaxine and bupropion).

2). Benzodiazepines were divided into long-acting agents, which included clonazepam, clobazam, chlordiazepoxide, diazepam, flurazepam and nitrazepam, and short-acting agents, which included oxazepam, lorazepam, triazolam, temazepam, bromazepam and alprazolam, based on a half-life of above or below 24 hours [12].

3). Other psychotropics included non-benzodiazepine sedatives, anxiolytics, neuloleptics, lithium, anticonvulsant and antiparkinson drugs. These medications were collapsed together because of their potential to cause cognitive impairment [13, 14] yet low exposure frequencies in the study population.

A sample of prescription records from RAMQ is presented in Appendix IV.

3.4.2.2 The clinician-rated anticholinergic (ACH) score

To allow for causal inference in light of the cholinergic deficit hypothesis for dementia etiology, I also used a clinician-rated ACH score, originally developed in my

MSc Thesis, as a measure of total anticholinergic burden across medications without regard to their therapeutic class [15]. The ACH score is an ordinal scale, with scores ranging from 0 for no ACH effect to 3 for strongest ACH effect. It was found to be predictive of severity of delirium symptom in a cohort of hospitalized older medical patients [15]. Since its publication, the ACH score has been used in several clinical and pharmacological studies [16, 17] and was judged to have adequate criterion validity against a serum ACH activities assay and to be one of the most feasible tools for routine clinical use [17]. Although not validated against chronic cognitive decline, preliminary results from an external older community-dwelling population suggest that the cumulative ACH score of multiple medications is independently and specifically predictive of poor performance on Hopkins verbal recall over two years [18]. For this PhD thesis, the original ACH drug list was updated following the original protocol and procedure, as briefly described below.

First, a complete list of the prescription records retrieved from RAMQ database for this study population was reviewed. Medications that matched with one of the 340 generic medications evaluated in the original ACH list were assigned the available score (n=204) by myself and verified by a senior geriatric psychiatrist (MC) and a senior clinical pharmacologist (RC). For medications without an available ACH score, their pharmacological properties were judged based on the therapeutic classification by American Hospital Formulary Service (AHFS) system [19]. Medications under a class that was believed to have no anticholinergic effect as a whole were assigned a zero score (n=174), which include antibiotics, hematologic drugs, diagnostic agents, expectorants and cough preparations, ophthalmic/otic/nasal preparations, antiperspirants, dietary

supplements, and vitamins. For the remaining medications whose anticholinergic properties can not be determined (n=62), an independent rating by the two clinicians (MC and RC) was conducted and the median value of the two ratings was adopted as final ACH score, following the original protocol.

A list of psychotropic medications evaluated in this thesis, along with their therapeutic classification and assigned ACH scores is provided in Appendix VII.

3.4.2.3 Exposure time window

In traditional pharmaco-epidemiological studies, an exposure time window refers to the number of exposed days assigned to each prescription [20], during which the number of outcome events (numerators) and total exposure time (denominator) are computed. It is essential that the time window should not simply cover the duration of the drug intakes (so-called a "legend" time window), as estimated from the filled prescriptions, but should also take into consideration the potential induction and residual period of the pathogenic effects of the drugs [20, 21].

In this thesis, two alternative exposure time windows were defined based on both data availability and biologically plausible pathogenic mechanisms of the medications of interest. A long time window was defined as the 3-month period prior to each follow-up MMSE assessment, in an attempt to capture the cumulative effects of the medication exposure over time; whereas a short time window was defined as the one-day period immediately preceding each MMSE assessment, intended to capture potential acute effects of the medication exposure. Although the choice of a 3-month duration for the long time window was somehow arbitrary, constrained by the actual follow-up intervals of three or six months, it also reflects the reality that a course of successful antidepressant

treatment usually takes two to three consecutive months [22, 23], and that a maximum time window of 90 days was often tested in pharmacoepidemiological studies of adverse drug events [20]. On the other hand, the short-time window of one day represents the typical mode of acute cognitive impairment, such as delirium, and other transient adverse drug events due to intoxication of ACH and other psychotropic medications, which typically arises in minutes or hours [22, 24, 25]. A comparison of the two alternative time windows would allow for a greater insight into the biological plausibility of an observed association between chronic medication exposure and cognitive decline.

3.4.2.4 Variables to represent medication exposure

For both the long- and short- exposure time windows, the total exposure to each medication class, as defined above, was quantified by the total exposed drug-days (EDD), which was a sum of the total dispensed days across prescriptions within each class. Similarly, a total ACH burden was defined as the sum of products of the assigned ACH score and number of days dispensed for each individual medication across all the prescriptions. To account for potential residual effects of the medications after the intake of their last doses and the possibility that a patient may have skipped a few doses and then resumed beyond the prescribed duration, due to incomplete compliance or other reasons [26], a 7-day block was added to each prescription. This addition would increase the tolerance of the short-time window to the afore-mentioned potential measurement errors, thought its impact on the long time window should be trivial.

The duration-based measures described above assumed that the patients were actually taking the medication as prescribed, and that the effects of the medication exposure were proportional to the exposure duration. In case such assumptions do not

hold (e.g., a patient may not fully comply with the prescription), a simpler measure by number of medications or a sum of their ACH scores, without considering duration, was also computed. The duration-based measures also imply that the cognitive effects of the medications occur immediately following their intake, without any delay. While this assumption seems plausible for benzodiazepines or anticholinergics, it may not be so for antidepressants. The therapeutic effects of both TCAs and SSRIs usually take two to four weeks to appear after taking these drugs at recommended therapeutic dosage [22, 23]. To avoid bias on estimated cognitive effect for antidepressant use due to potential minimum induction period, the total EDDs for antidepressants were redefined by excluding all such prescriptions during the most recent two or four weeks *prior to* each follow-up assessment from the long time windows.

A case scenario demonstrating the above-strategy for definition and quantification of medication exposure is provided in Appendix VIII.

3.4.2.5 Measure of cognitive function

The study outcome, cognitive decline, was measured using the Mini-Mental State Examination (MMSE) [27] by a trained research assistant at baseline and then at 3, 6, and 12 months. The MMSE is the most widely used brief cognitive instrument for screening cognitive impairment or monitoring its progression [28, 29], with scores ranging from 30 (no impairment) to 0 (maximum impairment). It assesses global cognitive function encompassing several different domains, such as orientation, attention, short-term memory, and visual construction and execution of complex command, with great emphasis on verbal and language ability. Studies of its psychometric properties show moderate to high levels of short-term test-retest reliability, construct and criterion

validity, and adequate responsiveness to cognitive change over time [28, 29]. In practice, a score of 23 or less is usually accepted as an index for cognitive impairment.

The majority (N=214, 76.2%) of the patients completed their baseline MMSE assessments during hospital stay, while all the follow-up assessments were conducted in patients' homes after discharge from hospital. A dummy variable was used in the analysis to adjust for the place of the assessment (see next section). To reduce the burden for these elderly patients and to allow adequate time for other assessments, a time limit was set for each MMSE item. A prorated total score of 0 to 30 was generated based on the completed items, ignoring the responses beyond the set time limit. The inter-rater reliability of the MMSE was assessed in a convenience sample of patients at intervals throughout the study period, using independent simultaneous ratings by two or more raters, including the study psychiatrist (MC). The intraclass correlation coefficient was 1.00 (n=20).

3.4.2.6 Measures of covariates

Data on covariates were collected at enrolment from either patient interviews or patients' hospital charts, and included the following variables:

Sociodemographic characteristics: Variables included age, sex, education, marital status (married vs. other) and living condition prior to admission (home vs. other), and the data were obtained from interview with patients.

Baseline cognitive function: Subclinical or minimum cognitive impairment or low mental function has been associated with future development of dementia [30, 31], and may also interfere with the depression assessment of patients. Although the study protocols screened out patients with five or more errors on the 10-item SPMSQ [32], residual confounding may occur since this cutoff had only an 82% negative predictive

value for moderate to severe dementia [33]. Therefore, the SPMSQ scores obtained by a research assistant at screening were used as a covariate in the multivariate regression model.

Physical function: The pre-morbid level of ADL and IADL function was assessed at baseline by the research assistant using the OARS ADL scale [34]. Both ADL and IADL subscales consist of seven items, each on a 3-point scale, with a total score ranging from 0 (completely dependent) to 14 (completely independent). The ADL component assesses basic or physical activities of daily living, while the IADL component evaluates complex physical activities involving judgment, reasoning, decision-making, and action planning and execution. The OARS instrument has been validated in both English and French version, with the Spearman correlation coefficient with clinical assessment of disability being around 0.80 [34, 36].

History of alcohol abuse: A history of alcohol abuse was obtained by the research assistant using an informant questionnaire, CAGE (Cut down, Annoyed, Guilty, Eye-opener), and represented dichotomously as either with or without such a history. The CAGE is a 4-item questionnaire to detect people at risk of alcohol problems [37, 38], and has been validated in older adults with appreciable sensitivity (86-88%) and specificity (78-88%) [39, 40].

Physical illness and comorbidities: To maximize the ability of the thesis to control for confounding by physical illnesses and comorbid conditions, two global measures of comorbid physical conditions were defined, which included a nurse rated clinical severity of current illnesses, scored 1 (not ill) to 9 (moribund) [41], and the Charlson comorbidity index (CCI) [42] based on hospital chart— a well-validated, composite

measure of number and severity of co-morbid conditions from medical diagnoses present at or before enrollment. In addition, given the implication of cardiovascular diseases (CVD) in both dementia and depression etiologies [43, 44], we defined a binary (high vs low) indicator for risk of CVD, based on a diagnosis of stroke, diabetes, or myocardial infarction during the previous two years or a measured sitting blood pressure of at least 160/95 mm Hg from the hospital chart.

History of depression: Studies have suggested that older persons diagnosed with major depression who had a remote history of depressive episode may differ from those without such a history in terms of the clinical characteristics and prognoses [45]. To control for potential confounding due to etiological heterogeneity of the "inclusive" diagnostic criteria, we collected data on history of previous depression episode (remote, recent, versus neither) during the past two years and history of antidepressant treatment in the past year from patients' self-report and hospital records as potential markers for primary affective disorders.

Other covariates: These included a time-dependent measure for follow-up time and two baseline variables denoting the source of the study population, i.e., hospital (A versus B) and study group (RCT Intervention, RCT-Control, versus Not RCT). While the two parent studies and the two participating hospitals followed the same study protocol and used the same study measurements, adjustment for baseline heterogeneity of the study population would help reduce potential residual confounding due to unmeasured factors related to hospital sites and/or RCT.

In addition, a dummy indicator for the place of the baseline MMSE assessment, in hospital (N=124) versus at home (N=67), was used in sensitivity

analyses of the antidepressant effects. Because the RAMQ does not cover prescriptions dispensed in hospital, the medication use of the 214 participants whose baseline interviews were conducted during the index hospitalization period was approximated using the RAMQ records during the prior 3 months. As suggested by a recent study, older persons tend to have lower cognitive scores during hospitalization than at home, due to the physical and psychological impact of the hospitalization rather than real cognitive impairment [46]. An adjustment of antidepressant effects for place of baseline interview allowed for simultaneously addressing the imprecise measure of baseline medications and potential "place" effects of baseline MMSE assessment.

3.5. PRINCIPLES OF STATISTICAL ANALYSES

3.5.1 General approaches

Descriptive statistics, including means, standard deviations for quantitative variables and proportions for categorical variables, were used to describe the characteristics of the study population. Within-patient means of the quantitative time-dependent variables, including the HDRS scores, EDDs for different medication classes, total ACH burdens and corresponding measures by number of medications, were calculated by averaging all the repeated measures. Pearson product-moment and Spearman's intraclass correlation coefficients were used to examine the crude associations among exposures, covariates and outcomes, and to check for potential collinear variables. A weighted-kappa was used to evaluate the consistency of depression diagnoses between baseline and each follow up time. Graphical approaches were used to

plot the longitudinal variations in depression symptoms and cognitive functioning over time and to facilitate assessing model fit.

A general linear regression model was employed to examine the association between baseline depression measure and MMSE decline at the end of the follow-up period, following the conventional wisdom of cohort analysis. It was also employed as a mean to screen and select covariate for mixed model analyses (see Chapter 5 for details).

3.5.2 The Mixed Effects Linear Regression Model

A mixed effects linear regression model was used as the primary approach to hypotheses testing [46, 47] and to adjust for confounding, with the difference in the MMSE scores between baseline and three, six and twelve months as a time-dependent outcome. Because the follow-up intervals (or spaces) in this study were unequal (i.e., three or six months) and the number of measurements varied across subjects (ranging from 2 to 4), the only covariance structures capable of handling this level of complexity are compound symmetry (CS) and spatial power (SP(pow)) [46]. However, CS naively assumes that the between-measurement correlations remain the same regardless of their spacing or time-lag, which seems unreasonable for longitudinal data. On the contrary, SP(pow) assumes the correlations decline in a rate to the power of the time-lag between two measurements as they move far apart. Therefore, I chose SP(pow) as the default covariance structure in the mixed model analyses throughout the thesis.

Similarly, because the number of subjects (N=281) was much larger than the number of measurements per subject (4), and the main objective of this study was to estimate mean difference between depression groups, I chose a fixed-effects mixed model with the serial correlation as a main source of random variation, rather than specify extra

random effects for between-subject variations. A practical reason for this decision was that random effects model facility in current SAS environment does not enable correlations within subject to change over time (with random-intercept only) or require a much larger sample size to ensure model estimatability and valid inference due to fitting too many parameters (with both random intercept and slopes) [46, 47].

The temporal relationship between depression and cognitive decline were tested by manipulating the timing of depression measures in relative to the MMSE assessments. The precedence of medication exposure to the cognitive functioning was established by confining the medication data to the defined exposure time window preceding each MMSE assessment during the follow-up. Interactions between depression or medication exposure and follow-up time or other biologically plausible effect modifiers were tested routinely. If a statistically significant interaction were detected, different models for each level of the modifiers would be fitted to achieve more accurate effect estimates for the primary exposure.

Sensitivity analyses were performed to verify the primary analyses under alternative assumptions for exposure time windows or residual effect period, by different representations of the total medication exposure without considering duration of use, and by adjusting for an additional covariate denoting the place of baseline interview (in hospital versus at home). For details of these analytic procedures towards specific research aim, readers are referred to each manuscript under Chapters four to six.

All the statistical analyses were conducted using SAS software version 9.1 [48]. Goodness of fit was assessed using the Akaike's Information Criterion (AIC) [49] and compared among nested models using the likelihood ratio chi-square tests based on the -2

restricted Log Likelihood statistics [46]. The hypotheses were tested at a two-sided significance level of α =0.05.

3.5.3 Sample Size and Power Consideration

The sample size required for this study was estimated *a priori* on the primary outcome, MMSE scores using the approach developed for multiple linear regressions [50]. Assuming a R^2 of 10% for the covariates only and the target or minimum meaningful semipartial R^2 of 5% for the exposure (i.e., depression symptoms, diagnoses and medication use), a total of 210 subjects, or 70 in each depression group, would be required to achieve a 80% power of detecting a significant effect of the exposure at α=0.05. Then, taking into account both potential loss based on an expected overall attrition rate of 35% during the follow-up, and a potential gain due to repeated measures per patient (by a factor of one minus correlation coefficient between the repeated measures [1], the target sample size required to ensure the adequate power was estimated to be likely close to the crude estimate of 210, or 70 per group; this power prediction has been ultimately confirmed to be adequate by the significant effects for both depression and some medication exposure, as reported under each manuscript.

3.6 SUMMARY

In summary, this thesis adopted a prospective cohort design with a repeated measures analysis to achieve three specific yet closely linked research aims: the temporal relationship between depression symptoms and cognitive decline, the temporal relationship between depression diagnoses and cognitive decline, and finally, the role of antidepressant and psychotropic medication use in this relationship. The list of covariates covered a large array of potential confounders and/or effect modifiers based on their

established or postulated importance in the subject area, some of which were specifically devised to facilitate the designed hypothesis testing for the thesis, such as CVD risk and history of depression.

With the abundant data from two parent studies, this thesis was able to make several methodological innovations, namely, use of both dimensional (i.e., symptomatic) and categorical (i.e., diagnostic) approaches to defining depression, examination of depression as a dynamic and time-varying exposure, integration of clinical and administrative data to ascertain and quantify medication exposure over time and to control for confounding by indication. Finally, this thesis focused specifically on the clinically relevant, and biologically plausible short-term temporal relationship between depression and cognitive decline while taking into account potential effects from concurrent antidepressant exposure, which has rarely been examined in the epidemiological context.

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CHAPTER 4 — THE TEMPORAL RELATIONSHIP BETWEEN DEPRESSION SYMPTOMS AND COGNITIVE FUNCTIONING IN OLDER MEDICAL PATIENTS (Manuscript 1)

4.1 PREFACE TO MANUSCRIPT 1

In this manuscript, I started my systematic investigation with a specific focus on the potential temporal effects of depression symptoms on cognitive decline. As an attempt to overcome the potential methodological limitations identified from the literature review, I adopted several innovative study design and analytic approaches. First, I used a well-validated, clinical assessment-based, rather than self-report, instrument to measure depression symptoms. Second, I examined the effects of depression symptoms as a dynamic or changeable, rather than a constant or enduring, exposure, using an appropriate longitudinal analytic technique – linear mixed effects model. And finally, I targeted the investigation on disentangling two specific competing hypotheses, i.e., whether depression symptoms are a short-term predictor, or a clinical concomitant of cognitive decline due to other risk factors, while leaving the third one, i.e., cognitive decline be a consequence of or psychological reaction to cognitive decline, out of the scene by applying both "population restriction" at study entry and "statistical adjustment" in analyses on baseline cognitive function.

4.2 MANUSCRIPT 1

The Temporal Relationship between Depression Symptoms and Cognitive Functioning in Older Medical Patients --- Prospective or Concurrent?

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Total words: 3914 (w/o tables)
Text words: 2646
Abstract: 240
References: 35
Tables: 3

Running head-line: Depression and cognitive function in older persons

4.2.1 ABSTRACT

Background. Epidemiological studies remain inconclusive on whether old age depression is an independent risk factor, a prodrome, or a clinical concomitant of cognitive impairment. The objective of this study, using repeated measures over a 12-month period, was to examine the short-term temporal relationship between depressive symptoms and cognitive impairment.

Methods. 281 medical inpatients aged 65 and over were followed up with the Hamilton Depression Rating Scale (HDRS) and Mini Mental State Exam (MMSE) at enrolment and 3, 6, and 12 months later. A repeated measures mixed linear regression model was used to evaluate the association between HDRS scores and MMSE changes over time and to test competing hypothesis about their temporal sequence.

Results. After adjusting for age, cardiovascular risk, illness severity, baseline physical and cognitive function and other covariates, a one-point increase in HDRS score (baseline mean±sd: 14.4±7.4) was associated with a lower MMSE score (-0.03, 95% CI: -0.07-0.00) at the same time points, but not with the MMSE at subsequent time points (all p values above 0.40). There were no statistically significant interactions detected between follow-up time and HDRS scores measured at baseline or during follow-up. These results were confirmed in alternative models using dynamic measures of both HDRS and MMSE changes over each successive follow-up interval.

Conclusions. These findings suggest that the short-term relationship between depression symptoms and cognitive functioning may be concurrent or temporary, rather than prospective or protracted, consistent with the clinical concomitant hypothesis.

4.2.2 INTRODUCTION

While the coexistence of depression symptoms and cognitive impairment in older persons has long been recognized clinically [1], the temporal relationship between the two conditions was not examined from an epidemiological perspective until relatively recently [2]. However, early epidemiological studies [3] were often retrospective or cross-sectional in nature, and hence, inadequate to address the temporality of the relationship. In the past ten years, a number of large-scale, community-based, cohort studies have been undertaken to address the temporal relationship prospectively [4-14].

At least four hypotheses have been postulated to explain the relationship. First, late-life depression may be an independent risk factor of cognitive decline [12, 13], perhaps via the "glucocorticoid cascade" pathway [15], in which the progression of depression pathology may ultimately lead to hippocampus damage and dementia. Second, depression and cognitive decline may result from risk factors common to both disorders, such as vascular diseases [16, 17]. Third, the relationship may be confounded by short-term situational factors (e.g., acute medical illness or disability) – the clinical concomitant hypothesis [3, 4, 6, 11, 16]. Fourth, depression may be an early manifestation or prodrome of dementia (7-10,14).

Almost all the prospective studies conducted so far have assessed depression and cognitive outcomes at least one year, mostly two to three years, apart. In addition, most studies evaluated depression symptoms at baseline only as a constant or enduring predictor of cognitive decline [5, 9-13]. Studies with measures repeated at relatively frequent intervals (months rather than years) can help to elucidate the relationship by examining

whether the association is cross-sectional (consistent with the clinical concomitant hypothesis) or prospective (consistent with the prodrome hypothesis).

The objective of the current study was to examine the potential short-term temporal relationship between depression symptoms and cognitive decline, with a specific focus on depression symptoms as a dynamic, time-varying exposure. We used data from a cohort of older medical inpatients that was assessed for both depression symptoms and cognitive function at three, six and twelve months later, with no or little cognitive impairment at study entry.

4.2.3 METHODS

Participants

The participants for this study were selected from the study samples of a randomized controlled trial (RCT) of a geriatric psychiatric care service for major depression and an observational cohort study of 12-month outcomes of depression in older medical inpatients, conducted at two university-affiliated acute care hospitals in Montreal, Canada. The enrollment process of the original study has been described elsewhere [18]. In brief, 5,283 patients over age 65 admitted from the emergency room to the medical services were screened by a research clinician using the Short Portable Mental Status Questionnaire (SPMSQ) [19]. Of them 3597 were excluded due to severe cognitive impairment (n=612, 11.2%) or other reasons (too sick, entered intensive or long term care, language barriers, or residing outside of Montreal island). The remaining 1,686 patients who scored four or less (indicative of no or mild cognitive impairment) were then screened for depression using the depressive disorders section of the Diagnostic Interview Schedule (DIS) [20]. Among them 530 (31.4%) consented to participate in the

study. The study protocol was approved by the research ethics committees of both hospitals. Of the 530 enrollees, 22 died and 94 withdrew before the baseline interview, leaving 414 (78.1%) for baseline and follow-up interviews. For this longitudinal analysis, we selected 281 participants with at least 2 MMSE scores, representing 67.9% of the baseline cohort of 414. There were no statistically significant differences (all $p > 0.07$) between those included (N=281) and excluded (N=133) with respect to age, sex, living condition, ADL scores, study group, hospital sites, diagnosis of depression and cognitive impairment at screening. However, patients who were excluded were more severely ill ($p<0.01$), had more comorbid conditions ($p<0.01$), higher HDRS ($p=0.05$) and lower MMSE scores ($p=0.03$).

Measurements

Severity of depressive symptoms was measured using the 21-item version of the HDRS [21], the most widely used interviewer-rated scale for monitoring depressive symptoms and signs in intervention studies of depression. Items were rated from 0-4, with a higher score indicating more pathology. Cognitive functioning was measured using the MMSE [22] at the same 4 time points. The MMSE is the most widely used brief cognitive instrument for screening cognitive impairment or monitoring its progression [23, 24], with a score range from 30 (no impairment) to 0 (maximum impairment). Studies of its psychometric properties show moderate to high levels of short-term test-retest reliability, construct and criterion validity, and adequate responsiveness to cognitive change over time [23, 24]. The inter-rater reliabilities of the HDRS and MMSE were assessed in a convenience sample of patients at intervals throughout the study period, using independent simultaneous ratings by two or more raters, including the study psychiatrist

(MC). The intraclass correlation coefficients are 1.00 for both the HDRS (n=28) and MMSE (n=17).

Since cardiovascular diseases (CVD) have been associated with both dementia and depression [4, 5, 25], we defined a binary indicator (high vs low) for CVD risk. Patients were classified as "high" risk for CVD if they had a diagnosis of stroke, diabetes, or myocardial infarction during the previous two years or a measured sitting blood pressure of at least 160/95 mm Hg from the hospital chart. Independence in activities of daily living (ADL) was assessed at baseline by the research assistant with the Older Americans Resources and Services (OARS) ADL scale [26], with a score range from 0 (completely dependent) to 14 (completely independent). History of alcohol abuse was obtained by the research assistant using the 4-item informant questionnaire— Cut down, Annoyed, Guilty, Eye-opener (CAGE, rated from 0 for no alcohol use to 4 for heavy alcohol use) [27]. Age, sex, education, living condition prior to the admission, Charlson comorbidity index (CCI), a composite measure by number and severity of comorbid conditions [28], and a nurse rated illness severity (scored from 0 for not ill to 9 for moribound) [29] were obtained either from interview or hospital charts abstraction.

Statistical analyses

The characteristics of the study population at baseline and the distribution of HDRS and MMSE scores over time were described using means and standard deviations or frequencies and proportions, as appropriate.

We used a mixed effects linear regression model approach to examine the temporal relationship between depression symptoms and cognitive functioning over time, in which the HDRS and MMSE scores were both updated every three or six months during follow-

up. The mixed model allows for both fixed (time-invariant) covariates, whose values do not change over time (such as sex), and time-dependent covariates, whose values can be updated during the follow-up (such as HDRS scores) [30]. We adopted the Spatial Power covariance structure of errors to account for potential inter-correlations among the repeated measures on the same patient, which assumes the correlations between any two measures to decrease as their distance increases, while allows for the unequal follow-up intervals and number of assessments across subjects [31].

We tested two sets of operational mixed models under competing hypotheses, termed as "concurrent" and "prospective", respectively, by different representations of HDRS and MMSE scores. In the "concurrent model", the HDRS was associated with the MMSE changes at the same follow-up time points, without a clear-cut temporal or causal implication. Whereas in the "prospective" model, the HDRS at each follow-up was used to predict the MMSE changes at the next follow-up after a three or six month time lag, which allowed us to evaluate the depression symptoms as a potential causal risk factor of cognitive decline without temporal ambiguity. On the other hand, the last available HDRS score of a patient had to be discarded, which reduced the statistical power to some degree. We also fit a general linear regression model with baseline HDRS score as a predictor, and the difference between baseline and last available MMSE score as an outcome.

Covariates were adjusted in a hierarchical fashion. First, decided a *priori,* we included age, education, CVD risk, ADL function, hospital sites, study group (RCT-intervention, RCT-control, Non-RCT), and follow-up time in all the models, regardless of their statistical significance, given their established importance in confounding the

relationship between depression and cognitive decline in the literature or due to the study design. Second, we tested effects of other covariates, including sex, living arrangement, illness severity, CCI, and CAGE score, individually and simultaneously, but did not retain them in the final models due to lack of statistical significance. In addition, we sequentially adjusted for the baseline MMSE score, attempting to control for potential confounding by unmeasured factors or events that might have operated on the subjects' cognition before the start of the follow-up, and the baseline HDRS score, in case the longitudinal effects of depression symptoms might be pre-determined by their initial level. Finally, we tested the interaction between baseline HDRS scores and follow-up time in the final models. If a statistically significant interaction was detected, separate models would be estimated for each following-up interval. Depression group was excluded from the multivariate regression models because of the substantial conceptual overlap between this variable and HDRS score, and the significant correlation between the two variables (Spearman's ρ=0.58, $p<0.001$).

All the statistical analyses were conducted using SAS software version 9.1 [31]. Goodness of fit of nested models was compared using the Akaike's Information Criterion (AIC) [32]. The hypotheses were tested at a two-sided significance level of α =0.05.

4.2.4 RESULTS

Characteristics of the study population

The characteristics of the study population at baseline are presented in Table 1. A total of 61% of the sample were depressed at baseline. The study sample had a mean MMSE score of 25.8 (SD=3.5) with 26.0% below 24. The mean MMSE scores (25.6 vs

26.3, p=0.12) and mean numbers of SPMSQ errors (1.6 vs 1.6, p=0.82) were similar between the depressed and non-depressed patients

The distribution the HDRS and MMSE scores across time is summarized in Table 2. There was a trend of negative (Pearson product-moment) correlations between the two measures at baseline (r=-0.10, p=0.08) and three months (r= -0.12, p=0.07).

Table 3 presents the results of a series of mixed regression models. Of the three "concurrent" models, model 2 had a minimum value of AIC, and thus, can be considered as providing best fit to the data. It suggested that for patients with comparable cognitive function at baseline, a one point increment in the HDRS score was associated with a decline of -0.03 MMSE point (95% CI: -0.07 to 0.00, p=0.05) when measured at the same follow-up time points, after adjusting for other covariates. This estimate did not change materially when the baseline MMSE was not adjusted for (-0.04, 95% CI: -0.07 to -0.02, p<0.01, model 1), or when additional covariate, the baseline HDRS was adjusted (-0.04, 95% CI: -0.08 to -0.01, p=0.02, model 3). On the contrary, none of the three "prospective" models (models 4-6) yielded a statistically significant association between depression symptoms and subsequent cognitive declines (all p values above 0.40). In either concurrent or prospective models, no statistically significant interaction between depressive symptoms and follow-up time was detected (all p values above 0.25, data not shown).

In additional mixed model analyses in which both HDRS and MMSE were represented by their score changes between two adjacent follow-ups, the associations between the two measures were statistically significantly only in concurrent models (all p values below 0.05), not in the prospective models (all p values above 0.75). Similarly,

the multiple linear regression models, in which the time lag between the measures of the depression symptoms and the MMSE changes was extended up to twelve months, failed to detect an independent association (all p values above 0.35, data not shown). To ensure that our exclusion of the secondary covariates did not introduce bias, we included sex, living arrangement, illness severity, Charlson comobidity index and CAGE score altogether in the final models and found no material changes in the effect estimates for the HDRS scores in both concurrent and prospective models (data not shown).

4.2.5 DISCUSSION

In this cohort of 281 older medical inpatients followed up to twelve months, we systematically evaluated two sets of statistical models under alternative hypotheses about the temporal sequence between depression symptoms and cognitive decline. After controlling for the effects of a number of potential confounding factors and initial level of cognitive function, we observed that depression symptoms were independently associated with worse cognitive functioning cross-sectionally, at the same follow-up time points. However, such an association disappeared when the exposure and outcome were separated temporally by a three to six month time lag, a period corresponding to a typical major depressive episode [33]. These results were confirmed in the alternative mixed effects models using *dynamic* measures of depression symptoms and cognitive functioning and in the general linear model evaluating the relationship with a maximum follow-up interval of twelve months. Taken together, our study suggests that depressive symptoms are a clinical concomitant, rather than a predictor or prodrome of cognitive decline.

Our observation of a concurrent association is consistent with several previous cohort studies in older community-dwelling populations. Dufouil and colleagues [4] followed 1600 elderly persons 65 years and older in France and found the MMSE scores at 3-year follow-up were only cross-sectionally associated with CES-D scores measured at the same time point, not at baseline. Similarly, Henderson *et al* [5], Chen *et al* [8], Cervila *et al* [11], and Vinkers *et al* [14] all failed to find an independent prospective association between depression and subsequent cognitive decline or onset of dementia. However, the follow-up intervals in these studies were much longer than this one, ranging from one to twelve years.

Several reasons may underlie a cross-sectional or concurrent relationship. First, it may be determined or mediated by a shared short-term risk factor such as acute medical illness or, functional disability [3,16,17], a recent stressful life event (e.g., bereavement), and use of antidepressant medications [34]. We plan to evaluate these factors in future analyses of this cohort. Alternatively, a cross-sectional relationship may be an artifact, due to poorer performance on cognitive tests like the MMSE among depressed people, especially on the items that demand strong attention, motivation or psychomotor speed [35].

Our study has several strengths. First, we focused specifically on the short-term effects of depression symptoms as a dynamic, time-varying exposure, using a clinically plausible effect period for depression symptoms [33] and an appropriate longitudinal modeling approach. Second, we carefully selected and rigorously controlled important confounders based on both substantive knowledge and statistical efficiency, including cardiovascular diseases, functional disability and illness severity. Third, we avoided a

"reverse causality" bias by excluding patients with moderate or severe cognitive impairment at study entry and adjusting for baseline cognitive function in the analyses. Finally, we enhanced the study validity by blind exposure and outcome assessments and adopting an objective, interviewer-rated (i.e., HDRS) depression scale.

On the other hand, several study limitations should be noted. First, the MMSE has been criticized for insensitivity to small cognitive changes and ceiling or floor effects [23,24]. Second, the HDRS has been criticized for its inclusion of somatic symptoms . These measurement issues may have biased our results towards the null. A third limitation is the relatively high rate of exclusion and cohort attrition, perhaps not surprising in medically ill older people. Given that the excluded patients tended to be more severely ill than those in the study sample, our findings may not be generalizable to the most severely ill older persons or to those outside hospital settings.

To conclude, we have documented the existence of a concurrent or temporary, rather than a prospective or protracted, association between depression symptoms and cognitive decline in this cohort of older medical patients, independent of other potentially important risk factors. These results do not support the hypothesis that depression symptoms in older people are an independent short-term risk factor for cognitive decline or a prodrome of dementia. Rather, they suggest that the two conditions occur concomitantly. Future studies should account for extraneous factors that may account for this association, such as recent life events and medication use, and improve the measurements for both depression and cognition.

Acknowledgement: This study was funded by the Canadian Institutes for Health Research, grant # MOP82494 to Dr. Jane McCusker and Dr Martin Cole. We thank Mr. Eric Belzile for his assistance in managing and organizing the computerized database, and all the research assistants for recruiting participants and collecting the data. An abstract was presented at 2006 Congress of Epidemiology June 21-24 in Seattle, USA, with partial support from the Yale Claude D. Pepper Older Americans Independence Center (NIA Grant P30AG021342) for Dr. Ling Han.

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Table 1. Characteristics* of the study population at baseline

Gender	*Female*	185	(65.84)	
	Male	96	(34.16)	
Age (n, mean ± SD)		281	79.11 ±	7.15
Education	*<6 years*	31	(11.03)	
	6-12 years	105	(37.37)	
	> 12 years	132	(46.98)	
	unknown	13	(4.63)	
Living arrangement				
	Home	236	(83.99)	
	Other	45	(16.01)	
Risk for cardiovascular disease				
	Low	254	(90.39)	
	High	27	(9.61)	
Hospital	*A*	228	(81.14)	
	B	53	(18.86)	
Study group	*RCT-control*	35	(12.46)	
	RCT-intervention	43	(15.30)	
	Not RCT	203	(72.24)	
Depression group				
	Depressed	172	(61.21)	
	Not depressed	109	(38.79)	
HDRS score (n, mean ± SD)		281	14.71 ±	7.38
SPMSQ errors (n, mean ± SD)		281	1.62 ±	1.32
MMSE score (n, mean ± SD)		281	25.84 ±	3.49
ADL score (n, mean ± SD)		281	12.02 ±	2.19
Illness severity (n, mean ± SD)		270	3.83 ±	1.01
Charlson Comorbidity Index (n, mean ± SD)		279	1.43 ±	1.52
CAGE score (n, mean ± SD)		252	0.21 ±	0.30

* Values represent N and (%), except otherwise indicated.

Abbreviations: RCT, Randomized clinical trial; HDRS, Hamilton Depression Rating Scale; SPMSQ, Short Portable Mental Status Questionnaire; MMSE, Mini-Mental State Examination; ADL, Activities of daily living; CAGE, Cut down, Annoyed, Guilty, Eye- opener.

Table 2. Distribution of repeated measures HDRS and MMSE scores during follow-up

Follow-up		HDRS score		MMSE score	
Time	N	Mean ± SD		N	Mean ± SD
3 mo	228	12.69 ± 7.24		223	26.09 ± 3.22
6 mo	245	12.00 ± 6.60		243	26.58 ± 3.34
12 mo	207	12.63 ± 6.73		211	26.07 ± 3.54

Abbreviations: HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

Table 3. Mixed linear regression models evaluating the effects of depression symptoms on MMSE changes* over time.

Covariates†	Concurrent Model						Prospective Model					
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	beta	95% CI	beta	95% CI	beta	95% CI	beta	95% CI	beta	95% CI	beta	95% CI
HDRS scores during follow-up‡	-0.04	-0.07 – -0.02	-0.03	-0.07 – 0.00	-0.04	-0.08 – -0.01	0.00	-0.01 – 0.08	0.00	-0.04 – 0.03	-0.02	-0.06 – 0.02
Baseline MMSE scores	-	- -	-0.47	-0.55 – -0.39	-0.46	-0.54 – -0.38	-	- -	-0.46	-0.54 – -0.37	-0.45	-0.54 – -0.37
Baseline HDRS scores	-	- -	-	- -	0.03	-0.01 – 0.08	-	- -	-	- -	0.03	-0.02 – 0.08
Akaike's information criterion §	3974.40		2833.60		2837.20		3016.10		2922.90		2927.10	

* Defined by the score differences between baseline and 3, 6, and 12 months, respectively, with negative values indicating decline;

† All the models also adjusted for follow-up time. In addition, models 2, 3, 5 and 6 adjusted age, education, risk for cardiovascular disease, activities of daily living, hospital site and study group.

‡ Measured at time *t* for concurrent models and at time *t- 1* for prospective models;

§ Lower value indicates better fit.

Abbreviations: HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

4.3 POSTSCRIPT TO MANUSCRIPT 1

Several salient issues arise from the exploratory investigation in the 1st manuscript, First, contrary to my expectation, the clinical assessment-based depression symptoms failed to detect a prospective association, suggesting the lack of predictive validity or power for future cognitive decline may not be a shortcoming unique to the self-report method, but possibly inherent to the dimensional approach *per se*. Second, while the sharp contrast between the concurrent and prospective models seems to have provided unambiguous evidence in favor of the former, its marginal p value of 0.05 may be thought of as no more than a chance finding by the conventional frequentist wisdom. After extensive discussion with my thesis committee, I tried to address these issues in the next manuscript with following methodological improvements:

1) Two additional covariates, history of previous depression episode during the last two years and history of antidepressant treatment during the last year, were added to the list of covariates. These two factors have been suggested in the literature to be the main clinical characteristics that may distinguish major from minor depression in older persons [Koenig 1997], and presumably, primary from secondary depressive syndromes. Adjustment for these proxy "etiological" markers would help account for heterogeneity of current depression diagnoses under the "inclusive" approach that does not distinguish the origin or etiology of the depression symptoms [Koenig 1997b].

2) A transformed HDRS score was created by subtracting the mean of each diagnostic group at baseline from the observed HDRS score at each follow-up as a time-dependent covariate. The transformation (or standardization) of the original HDRS score to the group-mean by baseline depression diagnoses would statistically remove the

potential collinearity between the two measures in the multivariable models due to their substantive overlap (Spearman's ρ=0.58, $p<0.001$). This time-dependent HDRS score serves three specific purposes. First, it directly extends the first manuscript by verifying its finding of the concurrent association. Second, it helps disentangle the potential "diagnosis" effect of depression from its symptomatic variation over time, while allowing a comparison between the two conceptual approaches to depression, i.e., dimensional (or symptomatic) versus categorical (or diagnostic). Third, it partially addresses the potential confounding by unmeasured situational factors, such as a recent life event or an acute illness, which may directly precipitate or perpetuate the depression symptoms during the follow-up and whereby affect the cognitive performance on the MMSE.

A final comment I want to make was regarding the effects of gender and education on the relationship between depression symptoms and cognitive impairment. A few previous studies observed an independent association between the two conditions only in those "highly educated" elderly [Geerlings 2000] or in older men [Cervilla 2000, Fuhrer 2003] or women [Fuhrer 1992]. A common determinant or shared etiology that underlies both depression symptoms and cognitive impairments in men, such as functional disability [Cervilla 2000, Fuhrer 1992, 2003] or cerebral vascular pathology [Cervilla 2000, Fuhrer 2003], has been postulated to explain the relationship. In this manuscript, I tested, but did not find statistically significant interactions between depression symptoms and gender (p=0.89, 0.21) or education (p=0.85, 0.96) under either concurrent or prospective models, though lower educational attainment did appear to be an independent risk factor of cognitive impairment (p=0.01). Therefore, whether the effect modification

by gender or education observed in previous studies is a generalizable or sample-specific phenomenon remains to be clarified.

CHAPTER 5 — 12-MONTH COGNITIVE OUTCOMES OF MAJOR AND MINOR DEPRESSION IN OLDER MEDICAL PATIENTS (MANUSCRIPT 2)

5.1. PREFACE TO MANUSCRIPT 2

In this second manuscript, I address the second study aim, the temporal relationship between the diagnostic entities of depression and cognitive decline. Based on the results and experience from the first manuscript, I included two additional covariates (history of depression and history of antidepressant treatment) as proxy markers for primary affective disorders to account for potential etiological heterogeneity of the "inclusive" diagnostic criteria, adopted a more thorough covariate selection and adjustment procedure to enhance scientific parsimony for hypothesis testing, and used a transformed, time-dependent measure of HDRS scores to address potential confounding due to unmeasured situational confounders and the specificity of the effect of depression diagnoses. In particular, I evaluate the operational mixed models under alternative assumptions for the temporal precedence of the depression diagnoses to cognitive decline.

5.2. MANUSCRIPT 2

12-MONTH COGNITIVE OUTCOMES OF MAJOR AND MINOR DEPRESSION IN OLDER MEDICAL PATIENTS

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Text words: 3370

References: 48

Tables: 3

Figures: 0

Running heading: Cognitive decline of major and minor depression in older persons

5.2.1 ABSTRACT

Context: Epidemiologic studies relating late-life depression to cognitive decline have focused on the role of its symptoms. Little is known about the cognitive outcome of the diagnostic groups of late-life depression, especially over a short follow-up period.

Objective: To examine the short-term temporal relationship between depression diagnoses and cognitive decline in older medical patients.

Design: Prospective cohort study with repeated assessments of depression diagnoses and cognitive functioning at baseline, three, six and twelve months, using a mixed effects linear regression model.

Setting: The medical services of two acute care hospitals in Montreal, Canada.

Participants: 281 medical patients aged 65 and over without apparent cognitive impairment at baseline.

Main outcome measure: Cognitive change scores over time on the Mini-Mental State Examination (MMSE).

Results: Depression diagnoses at baseline were associated with subsequent MMSE changes. Relative to no depression, the estimated excess decline points were -0.8 (95% Confidence Intervals: -1.5–-0.1) for major and -1.0 (-1.8–-0.3) for minor depression over a median follow-up interval of 6 months, independent of age, sex, education, comorbidities, physical function, risk for cardiovascular disease, history of depression and antidepressant treatment, baseline cognitive function, and concurrent changes in depression symptoms. A general linear model adjusting for the same set of covariates yielded an average excess decline of -0.9 (-.8–-0.03) for major and -1.5 (-2.5–-0.5) for minor depression over 12 months.

Conclusions: Both major and minor depression are independently predictive of subsequent cognitive decline in this cohort of older medical patients, and the strength of association appears to increase over time.

Keywords: Minor Depression, Major depression, Cognitive decline, Aged, Longitudinal study.

5.2.2 INTRODUCTION

Depression and dementia together affect more than one quarter of those aged 65 years and older,[1, 2] and both have been associated with higher mortality,[3, 4] faster functional decline[5] and increased health care costs.[6, 7] Therefore, research efforts devoted to delineating the relationship between the two conditions are of great clinical and public health importance.

Several large-scale, community-based epidemiological studies have been undertaken to address the temporal relationship between depression and cognitive decline,[8-20] with conflicting results. In some studies, depression appeared to be an independent risk factor of cognitive decline or dementia,[10, 16-18] while in others, it either followed the onset of dementia[11, 12, 19, 20] or the relationship was cross-sectional only.[8, 15] Still others found no independent association between the two conditions.[9, 13, 14]

The published studies conducted on this topic have three limitations. First, they have focused on self-reported depression symptoms,[8-20] rather than depressive syndromes or diagnoses. Self-report depression symptom scales often lack adequate positive predictive validity for identifying clinical significant depression,[21-23] which made the study results difficult to translate into clinical practice. Second, due to lack of clinical assessments, the community-based epidemiological studies had limited ability to control confounding by comorbid physical diseases, which often manifest depression-like symptoms and interfere with patients' cognitive performance. Third, most studies assessed depression at baseline only and attempted to link such a single measure to a cognitive outcome observed several years later. This study design does not permit an examination of the dynamic temporal relationship between the two conditions over a

short period of time, which may be clinically relevant given that a typical major depressive episode usually lasts three to six months.[24]

In this study, we aimed to examine the short-term temporal relationship between depressive diagnoses and cognitive decline in a cohort of older medically ill patients who were assessed longitudinally for both depression and cognitive function at baseline, three, six and 12 months. In initial analyses of these data, we found that the severity of depression symptoms was associated with cognitive functioning only cross-sectionally.[25] In the current study, we extend the previous finding by testing two major competing hypotheses (i.e., depression diagnoses are an independent predictor versus a clinical concomitant of cognitive decline), and determining whether the 12-month trajectories of cognitive decline differ among those with major, minor, or no depression.

5.2.3 METHODS

Participants: The participants in this study were selected from the study population of a randomized controlled trial (RCT) of a geriatric psychiatric care service for major depression and an observational cohort study of 12-month outcomes of depression in older medical inpatients, conducted at two university-affiliated acute care hospitals in Montreal, Canada. The recruitment criteria and interview procedures have been described elsewhere.[26, 27] In brief, eligible patients aged 65 years and over admitted from the emergency room to the medical services were screened by a research clinician using the Short Portable Mental Status Questionnaire (SPMSQ).[28] Those scored four or less (indicative of no or mild cognitive impairment) were assessed using the depressive disorders section of the Diagnostic Interview Schedule (DIS, DSM-IV criteria)[29] and the Hamilton Depression Rating Scale (HDRS).[30] All those with a diagnosis of current major

or minor depression and a random sample of non-depressed patients were invited to participate in the longitudinal component of the study. As soon as possible after recruitment, patients were interviewed by one of two trained research assistants (psychologists). The study protocol was approved by the research ethics committees of both hospitals.

In total, 1,686 eligible patients were screened for depression, of whom 530 consented to participate and enrolled into the study. The main reasons for exclusion included: too sick, severe cognitive impairment, admission to intensive care, already discharged, transferred to long term care, not proficient in either English or French language, and residing outside of Montreal island (who would be difficult to follow up). Of the 530 enrollees, 22 died and 94 withdrew before the baseline interview, leaving 414 for baseline and follow-up interviews. For this longitudinal analysis, we selected 281 participants with at least two MMSE scores during the follow-up period, representing 67.9% of the baseline cohort.

Measurements:

Depression diagnoses and symptoms: A structured psychiatric evaluation was administered using the depressive disorders section of the DIS by a trained research assistant at baseline and each subsequent interview. Depression symptoms were assessed using the 21-item version of the HDRS, the most widely used interviewer-rated scale for monitoring depressive symptoms in intervention studies, with a higher score indicating more pathology. Patients were classified as major, minor, or no depression according to DSM-IV criteria using an "inclusive" approach, which counted current symptoms with a duration of at least two weeks towards a diagnosis, regardless of their origin of physical

illness or primary affective disorders.[31] This approach appears to be most reliable for assessing depression in medically ill older persons, especially from a longitudinal perspective.[31] The inter-rater reliability was checked periodically, with a kappa coefficient being 0.78 (95% CI 0.52–1.00) for a diagnosis of major depression vs minor or no depression and 0.61 (95% CI: 0.35–0.87) for a diagnosis of either major or minor vs no depression (n=28). The intra-class correlation coefficient for HDRS scores was 0.93 (95% CI: 0.86–0.97, n=26).

Cognitive decline: The Mini-Mental State Examination (MMSE)[32] was administered by a trained research assistant at baseline and subsequently at thee, six and twelve months. The MMSE is the most widely used brief cognitive instrument for screening cognitive impairment or monitoring its progression,[33, 34] with scores ranging from 30 (no impairment) to 0 (maximum impairment). Studies of its psychometric properties demonstrated moderate to high levels of short-term test-retest reliability, construct and criterion validity, and adequate responsiveness to cognitive change over time.[33, 34] The inter-rater reliability of the MMSE was assessed in a convenience sample of patients at intervals throughout the study period, using independent simultaneous ratings by two or more raters, including the study psychiatrist (MC). The intraclass correlation coefficient was 1.00 (n=20).

Covariates: Data on covariates were collected at enrolment from either patient interviews or hospital charts. The demographic-behavioral factors included age, sex, education, living condition prior to admission, and history of alcohol abuse (using the 4-item CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire).[35] Premorbid physical function was assessed with the Older Americans Resources and Services (OARS) Center

Instrument[36] for basic and instrumental activities of daily living (ADL and IADL), with scores ranging from 0 (completely dependent) to 14 (complete independent).

We used two global measures of comorbid physical conditions: a nurse rated clinical severity of current illnesses, scored 1 (not ill) to 9 (moribund),[37] and the Charlson comorbidity index (CCI),[38] a well-validated, composite measure of number and severity of co-morbid conditions from medical diagnoses present at or before enrolment. In addition, given the etiological implication of cardiovascular diseases (CVD) in both dementia and depression,[39, 40] we defined a binary (high vs low) indicator for risk of CVD, based on a history of diagnosed stroke, diabetes, or myocardial infarction during the previous two years or a measured sitting blood pressure of at least 160/95 mm Hg from the hospital chart. Furthermore from interviews with patients or review of their hospital charts, we collected data on history of previous depression episode (remote, recent, versus neither) and history of antidepressant treatment in the past year as potential makers for primary affective disorders. Other covariates were related to study design or participants selection, including hospital (A versus B), study group (RCT Intervention, RCT-Control, versus Not RCT), SPMSQ errors at screening and follow-up intervals.

Statistical analysis

The baseline characteristics and longitudinal profile of cognitive functions of the study population were summarized by descriptive statistics and compared across depression diagnoses using one-way ANOVA or chi-square tests, as appropriate. The consistency of the depression diagnoses over time was evaluated using weighted Kappa.

A mixed effects linear regression model for longitudinal data was adopted as the primary approach to hypothesis testing. This allowed us to include both fixed-in-time and

time-varying covariates, and to account for potential inter-dependence of repeated measures on the same patient over time.[41, 42] The depression diagnoses were represented by two dummy indicators, major and minor depression, with no depression as a reference. The cognitive decline was defined by the difference in the MMSE scores between each follow-up (at three, six and twelve months) and baseline. Given the unequal follow-up intervals and number of MMSE assessments across subjects, we chose the Spatial Power covariance structure to account for the potential interdependence among the repeated MMSE measures on the same patients.[42]

We evaluated two sets of alternative mixed models under competing temporal hypotheses, termed "prospective" and "concurrent", respectively. In the "prospective" models, the depression diagnoses were represented in two alternative ways. First (model A), the baseline depression diagnoses were used as a fixed-in-time predictor of subsequent MMSE changes at three, six and twelve months. Second (model B), the time-dependent depression diagnoses updated at each follow-up were used to predict the MMSE change at the next follow-up. In the "concurrent" model, we examined the cross-sectional relationships between the depression diagnoses and the MMSE change during follow-up at the same time points.

We sequentially adjusted the effects of depression diagnoses for potentially important covariates in the mixed effect models. First, study design variables (age, SPMSQ errors, hospital, study group and follow-up duration) were forced into all the models. Next, we included sex, education, ADL function, living arrangement, risk for cardiovascular disease, previous history of depression and antidepressant treatment. These covariates were pre-selected from a larger array of seventeen candidates through a

forward selection procedure based on their unique contributions to the model fit,[43] in an attempt to enhance the statistical efficiency of the formal hypothesis testing using the multivariable mixed models. As a way to account for the potential impact of pre-determinants of participants' cognitive function before they entered the study, we added the baseline MMSE score into all the models. To investigate if the relationship changes over time or varies across biologically plausible effect modifiers, we tested in the final models the interactions of the baseline depression diagnoses with follow-up intervals, CVD risk, illness severity, history of depression and history of antidepressant treatment.

To assess the specificity of the potential cognitive effects of depression diagnosis beyond the severity of depression symptoms, we adjusted the final models for a transformed HDRS score as a time-varying covariate. This transformed score was created by subtracting the mean of each diagnostic group at baseline from the observed HDRS score at each follow-up, which statistically removed the inter-correlations between HDRS scores and depression diagnoses (Spearman's $\rho = 0.58$, $p < 0.001$), and hereby, allowed us to evaluate both in the same multivariable models without loss of efficiency due to their potential collinearity.

To assess the potential bias due to inappropriate (mixed effects) model specification and to facilitate comparison with other studies, we conducted a conventional multiple linear regression model analysis using the difference between the baseline and last available MMSE scores as an outcome and the baseline depression diagnoses as a predictor, adjusting for the same set of covariates. Although ignoring the longitudinal dynamic of the relationship, this general linear model extended the

prospective mixed models to a maximum follow-up interval of twelve months, and as such, allowed us to examine the potential "duration" effect of the depression diagnoses.

All the statistical analyses were conducted using SAS software version 9.1.[42] Goodness of fit was assessed using the Akaike's Information Criterion (AIC), and the nested models were further compared using likelihood ratio chi-square tests (LRT) based on the models' -2 restricted Log Likelihood statistic.[43, 44] The hypotheses were tested at a two-sided significance level of α =0.05.

5.2.4 RESULTS

The baseline characteristics of the three depression diagnostic groups are summarized in Table 1. The three depression diagnostic groups differed in HDRS, ADL and IADL scores, history of depression and history of antidepressant treatments (P<0.05-0.001). Of the seventeen candidate covariates, CAGE score, Charlson Comorbidity Index and IADL score were eliminated later on in the model selection process due to inadequate contribution to the model's R squared (data not shown). There was no significant differences (all p values above 0.07) between the 281 participants and those excluded (N=133) with respect to age, sex, living condition, ADL scores, study group, hospital sites, diagnosis of depression and cognitive impairment at screening. However, the excluded patients were more severely ill (p<0.01), had more comorbid conditions (p<0.01), higher HDRS (p=0.05) and lower MMSE scores (p=0.03).

The longitudinal profiles of cognitive function by baseline depression diagnosis are presented in Table 2. The three diagnostic groups differed in the MMSE scores at all the follow-up times (p<0.05 to 0.01), except at baseline (P=0.14). Patients with minor depression had lower MMSE scores than those with no depression at all the three follow-

ups ($p<0.05$ to 0.01), and than those with major depression at six and twelve months ($p<0.05$); whereas major depression only had a trend toward lower MMSE scores than no depression at 3 month ($p=0.05$).

The depression diagnoses at each follow-up had a fair to moderate agreement with the baseline (weighted Kappa: 0.27 to 0.42), though significant variations existed at three ($p=0.03$) and six ($p=0.02$) months. Based on updated diagnoses during the follow-up, the MMSE scores among the three depression groups differed at six ($p<0.05$) and twelve ($P=0.06$) months, with minor depression having lower MMSE scores than no depression at six ($p<0.05$) and twelve ($p=0.03$) months and than major depression at six month ($p<0.05$).

Table 3 summarizes the results of the mixed models. In prospective models A, both major and minor depression at baseline were associated with subsequent MMSE decline ($p<0.05$ to 0.01), after sequentially adjusting for study design variables (model A1), selected covariates (model A2), as well as the time-dependent, transformed HDRS scores (model A3). There were no significant associations (all p values above 0.30) detected from prospective models B or concurrent models. Among each set of hierarchical models (i.e., A to C), models 3 appeared to provide the best fit to the data based on both AICs and LRT χ^2 tests (all $p<0.01$), and hence, were chosen as our final models.

Of the three final models, only prospective model A3 yielded a statistically significant association, with an excess MMSE decline of -0.8 (95% CI: -1.5– -0.1) for major and -1.0 (95% CI: -1.8– -0.3) for minor depression, relative to participants with no depression and with the same baseline MMSE scores. The difference between major and

minor depression was not significant (p=0.52). The depression diagnoses did not interact (all p values above 0.07) with follow-up intervals or other potential effect modifiers, indicating their effects to remain stable over time or across subgroups with different characteristics. In all the three final models, the effects of HDRS scores were not significant (-0.01 to -0.03, p=0.07 to 0.36). Beyond our expectation, a history of antidepressant treatment was independently associated with higher MMSE scores in both prospective models A3 (0.7, p=0.03) and B3 (0.7, p=0.04), and concurrent model 3 (0.7, p=0.04).

The general linear regression model using baseline depression diagnoses as a predictor and the last available MMSE change score as an outcome, adjusting for the same set of covariates as the final mixed models, yielded an average excess decline point of -0.9 (95% CI: -1.8– -0.03, p=0.04) for major and 1.5 (95% CI: -2.5– -0.5, p<0.01) for minor depression. Across the three prospective models, i.e., this general linear model and mixed effects models A3 and B3, the strength of observed association appeared to increase with the median follow-up intervals. The predicted MMSE decline points were -0.2 over three months (p=0.38, mixed model B3), -1.0 over 6 months (p<0.01, mixed model A3) and -1.5 over 12 months (p=0.01, general linear model) for minor depression, and correspondingly, -0.1 (p=0.62), -0.8 (p=0.02) and -0.9 (p=0.06) for major depression.

5.2.5 DISCUSSION

In this cohort of 281 older medical inpatients followed-up for twelve months, we observed an independent association between depression diagnosis at hospital admission and subsequent cognitive decline, with an average excess decline of -0.8 (95% CI: -1.5 – -0.1) per 6 months for major and -1.0 (95% CI: -1.8 – -0.3) for minor depression,

respectively, relative to participants with no depression but with the same age, gender, comorbidity, risk for CVD, ADL function, histories of depression and antidepressant treatment, and MMSE score at baseline. Concurrent severity of depression symptoms neither had an independent association with cognitive decline after adjusting for depression diagnosis, nor affected their effect estimates materially. To our knowledge, this is the first prospective epidemiological study that has reported an independent short-term temporal relationship between specific diagnoses of depression and subsequent cognitive decline in the older, medically ill population.

Several plausible mechanisms have been postulated to explain the apparent relationship between depression and dementia,[45, 46] such as an early reaction or manifestation of underlying dementia, a shared etiology or a causal biochemical pathway. Since we excluded participants with more than mild cognitive impairment at study entry and adjusted for baseline cognitive function in multivariable models, the observed association would be unlikely a reflection of an underlying dementia process. Similarly, a shared etiology can not readily explain our findings, at least not the cerebral-cardiovascular diseases or functional disability, because we have explicitly adjusted for these two most common extraneous determinants of the association. While we can not entirely rule out the possibility that some situational risk factors, such as recent stressful life events or side-effects of a course of antidepressant treatment, may play a precipitating or mediating role,[45, 47] our adjustment for concurrent variation of depression symptoms, a reasonable proxy for such short-term confounders, made this explanation less likely. Alternatively, the prospective association may represent the phenotype of a true causal relationship between depression and dementia pathologies via some biological

mechanisms. According to the glucocorticoid cascade hypothesis, repeated and prolonged stress, a common risk factor for depression, may over-activate and eventually exhaust the hypothalamic-pituitary-axis and lead to permanent brain damage and cognitive impairment.[45, 46] Recent advancement in neurobiology has also suggested that the serotonergic neurotransmitting system, whose deficiency has been implicated in the etiology of major depression, may play an important role in modulating cognitive behavior through interactions with cholinergic system,[48] a target of neurodegenerative disease such as dementia. If such causal mechanisms do exist, it should not be surprising that an "exposure" to the clinically significant depression syndromes should be closely and quantitatively associated with subsequent cognitive decline well before its development into a full-blown dementia at distance.[45]

The strengths of this study are several. First, we focused specifically on the clinically significant diagnostic entities of depression, rather than the severity of depression symptoms. Second, we confined our delineation of the dynamic temporal relationship within a clinically relevant, short follow-up interval. Finally, we carefully selected and rigorously controlled for potential confounders in light of substantive knowledge and statistical efficiency.

This study has some important limitations. First, the MMSE has been criticized for insensitivity to small cognitive changes and ceiling or floor effects,[32, 33] especially over a relatively short period of follow-up. Second, the rates of excluded subjects and cohort attrition were relatively high, which may limit the generalizability of this study to more severely ill patients, Third, the results may not be generalized to elderly populations

outside of hospital settings. Finally, our measure of antidepressant treatment was crude and needs to be investigated further using comprehensive data.

The clinical implications of our findings are two fold. First, these findings may strengthen the rationale for treating clinically significant depression in older, medically ill patients, who may benefit not only from relief from disabling depression but potentially from a risk reduction for cognitive deterioration. Our preliminary finding that a history of recent antidepressant treatment was independently associated with better MMSE performance further enforces this position. Second, the gradient increase in the strength of the observed prospective association with the duration of "exposure" to depression diagnoses implies that an early antidepressant intervention may be potentially more cost-efficient than later intervention in terms of reducing risk of cognitive decline.

To conclude, we have documented that both major and minor depression are predictive of cognitive decline over a course as short as twelve months, independent of other potentially important risk factors. Future epidemiological studies and clinical trials directly examining the effectiveness and feasibility of antidepressant treatment in medically ill older patients with major or minor depression are warranted.

Acknowledgement: This study was funded by Canadian Institutes for Health Research, grant # MOP82494 and MCT–15476 to Dr. Jane McCusker and Dr Martin Cole. We thank Mr. Eric Belzile at St. Mary's Hospital for assisting in managing the computerized database and Dr. Heather Allore at Yale University Internal Medicine Program on Aging for insightful statistical advice on model selection.

5.2.6. REFERENCES

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Table 1. Characteristics of the Study Population at Baseline

Characteristics		Depression Diagnoses			P Value*
		Major (N=121)	Minor (N=51)	No (N=109)	
Demographic-behavioral factors					
Age (in year), mean ± SD		78.7 ± 7.1	78.4 ± 6.9	79.9 ± 7.3	0.333
Gender, n (%):	*Female*	75 (62.0)	33 (64.7)	77 (70.6)	0.378
	Male	46 (38.0)	18 (35.3)	32 (29.4)	
Education, n (%)†:	*<6 years*	13 (11.2)	9 (18.4)	9 (8.6)	0.446
	6-12 years	43 (37.1)	18 (36.7)	45 (42.9)	
	> 12 years	60 (51.7)	22 (44.9)	51 (48.6)	
Living arrangement, n (%):	*Home*	101 (83.5)	43 (84.3)	92 (84.4)	0.979
	Other	20 (16.5)	8 (15.7)	17 (15.6)	
CAGE score, mean ± SD		0.3 ± 0.8	0.1 ± 0.3	0.2 ± 0.8	0.373
Psychological-functional factors					
HDRS score, mean ± SD		19.9 ± 5.8	13.5 ± 5.3	9.5 ± 5.7	<0.001
SPMSQ errors, mean ± SD		1.6 ± 1.2	1.6 ± 1.4	1.6 ± 1.4	0.960
ADL score, mean ± SD		11.5 ± 12.0	12.1 ± 11.7	12.5 ± 12.5	0.003
IADL score, mean ± SD		10.0 ± 2.9	10.5 ± 3.1	11.0 ± 3.1	0.025
Clinical factors					
Charlson Comorbidity Index, mean ± SD		1.4 ± 1.6	1.3 ± 1.4	1.4 ± 1.5	0.791
Nurse-rated illness severity, mean ± SD		3.9 ± 1.0	3.9 ± 1.0	3.7 ± 1.1	0.380
Risk for cardiovascular disease (CVD), n (%):	*High*	12 (9.9)	3 (5.9)	12 (11.0)	0.584
	Low	109 (90.1)	48 (94.1)	97 (89.0)	
History of depression, n (%)†:	*Remote*	16 (13.2)	8 (15.7)	5 (4.6)	<0.001
	Recent	34 (28.1)	6 (11.8)	6 (5.5)	
	Neither	71 (58.7)	37 (72.5)	98 (89.9)	
History of antidepressant treatment, n (%)†:	*Present*	54 (45.0)	16 (31.4)	23 (21.1)	<0.001
	Absent	66 (55.0)	35 (68.6)	86 (78.9)	

Characteristics of study population at baseline (cont'd)

Source of participants					
Hospital, n (%):	*A*	91 (75.2)	43 (84.3)	94 (86.2)	0.083
	B	30 (24.8)	8 (15.7)	15 (13.8)	
Study group, n (%):					
	RCT-intervention	33 (27.3)	6 (11.8)	4 (3.7)	<0.001
	RCT-control	26 (21.5)	8 (15.7)	1 (0.9)	
	Not RCT	62 (51.2)	37 (72.5)	104 (95.4)	

* Derived from X^2 (df=2) for categorical and one-way ANOVA (df=2) for continuous variables.

† The percentages may not sum up to 100 due to exclusion of a few missing observations.

Abbreviations: CAGE, Cut down, Annoyed, Guilty, Eye-opener; SPMSQ, Short Portable Mental Status Questionnaire; ADL, Activities of Daily Living; IADL, Instrumental ADL; RCT, Randomized Clinical Trial.

Table 2. Longitudinal profiles of MMSE scores by depression diagnoses at baseline

Time	Depression Diagnoses									P value*
	Major			Minor			No			
	N	mean	SD	N	mean	SD	N	mean	SD	
Baseline	121	25.8	± 3.2	59	25.1	± 3.3	109	26.2	± 3.9	0.137
3 mo	102	25.9	± 3.1	40	25.0	± 3.3	81	26.8	± 3.2	0.008 †
6 mo	102	26.5	± 2.9	43	25.3	± 4.1	98	27.2	± 3.3	0.010 ‡
12 mo	88	26.2	± 3.5	37	24.7	± 4.1	86	26.6	± 3.2	0.022 §

* Derived from one-way ANOVA (df=2) testing overall differences among the depression diagnoses at each follow-up time point, with pairwise subgroup comparisons (df=1) when appropriate.

† Major vs no depression, p=0.053; minor vs no depression, p=0.002;

‡ Minor vs no depression, p=0.002; major vs minor depression, p=0.047;

§ Minor vs no depression: p=0.006; major vs minor depression, p=0.033.

Abbreviation: MMSE, Mini-Mental State Examination.

Table 3. Association between depression diagnoses and MMSE changes* estimated using mixed effects models

Model		Prospective Model A			Prospective Model B			Concurrent Model		
No.	Predictor†	Est.¶	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value
1‡	*Major depression*	-0.68	-1.34 – -0.02	0.044	-0.19	-0.65 – 0.28	0.427	0.16	-0.28 – 0.61	0.467
	Minor depression	-1.21	-1.96 – -0.46	0.002	-0.16	-0.67 – 0.35	0.532	-0.22	-0.72 – 0.27	0.376
2§	*Major depression*	-0.77	-1.43 – -0.11	0.023	-0.17	-0.65 – 0.30	0.468	0.19	-0.26 – 0.64	0.402
	Minor depression	-1.20	-1.94 – -0.46	0.002	-0.14	-0.65 – 0.37	0.592	-0.26	-0.76 – 0.23	0.297
3‖	*Major depression*	-0.79	-1.45 – -0.14	0.018	-0.12	-0.58 – 0.35	0.622	0.30	-0.19 – 0.79	0.225
	Minor depression	-1.04	-1.77 – -0.30	0.006	-0.22	-0.72 – 0.28	0.384	-0.19	-0.69 – 0.32	0.467

* Defined by the differences in the MMSE scores between each follow-up and baseline, with negative values indicating decline.

† Refers to the two dummy indicators for depression diagnoses, as measured at baseline (prospective model A), or the preceding (prospective model B) or the same (concurrent model) follow-up time points as the MMSE, with no depression as a reference.

‡ Adjusted for age, hospital, study group, SPMSQ errors, baseline MMSE score and follow-up interval.

§ Adjusted for all the covariates in model 1, plus: sex, education, ADL score, illness severity, living arrangement, CVD risk, history of depression and history of antidepressant treatment.

‖ Adjusted for all the covariates in model 2, plus a transformed HDRS scores during follow-up.

¶ Effect estimate, denoting expected differences in MMSE changes between major or minor depression and no depression group.

Abbreviations: MMSE, Mini-Mental State Examination; SPMSQ, Short Portable Mental Status Questionnaire; ADL, Activities of Daily Living; CVD, Cardiovascular diseases.

5.3 POSTSCRIPT TO MANUSCRIPT 2

In this section, I provide additional details for the statistical analyses and further discuss some statistically insignificant yet potentially clinically meaningful results, which were omitted in the manuscript due to the journal's word limit.

5.3.1 The Covariate Selection Procedure

The screening process followed a step-wise, forward selection procedure [Hocking RR 1976]. First, I evaluated the bivariate associations between each covariate and both depression diagnoses and MMSE scores at baseline using chi-square or t tests, and among the covariates using Spearman's rank-order correlation. Covariates with a p value above 0.3 for bivariate associations with the outcome and exposure, and a correlation coefficient above 0.5, indicative of a moderate to strong relationship [Looney 2002], were eliminated from further consideration. Next, I sequentially evaluated each covariate using a general linear regression model, with the difference between the baseline and last available MMSE scores as an outcome, adjusting for the baseline depression diagnoses and five default covariates related to study design or sampling: age, hospital, study group, number of SPMSQ errors and follow-up time. Then, one at a time, each candidate covariate was entered the baseline model and its contribution to the model fit was examined based on the adjusted R squared [Cohen 2003], without regard to the p value. The covariate whose inclusion led to the largest adjusted R squared for each model was retained to update the baseline model. This process was continued iteratively until no covariate increased the model's R squared by 5%. Finally, three out of the seventeen covariates: CAGE score, Charlson Comorbidity Index and IADL score, were eliminated.

5.3.2 Examine the Appropriateness of the Mixed Model

To assess the validity of the final mixed effects models, I performed a series of residual analyses using graphical approach [Littell 1996, Verbeke 2000]. Three population-averaged residual plots for the final prospective model A, one by predicted values and the other two by baseline depression diagnoses and transformed HDRS score, respectively, are shown in Figures A-1.1 to A-1.3. There was no systematic trend of deviation from normality, homoscedasticity and linearity assumptions or extreme outliers, suggesting the fixed effects for the model were selected properly.

5.3.3 Comments on the Difference between Major and Minor Depression

While not statistically significant, the better cognitive outcome of major than minor depression patients may be worth discussion. Consistent with previous studies [Koenig 1997, McCusker 2005, Tannock 1995], I found that more people with major depression had a previous history of depression episodes and antidepressant treatment than those with minor depression, though there was no significant difference in physical comorbidities.

However, unexpectedly, there was no statistically significant interaction between depression diagnoses and either a history of depression or physical illnesses, suggesting these two potential etiological markers for primary affective disorders could not explain the apparent difference in the slopes of the cognitive trajectories between major and minor depression. While this might reflect inadequate power of this study sample to detect such an interaction, another possibility was the imprecise nature of the two proxy measures, especially the history of previous depression episodes. The latter was limited to the prior two years and did not include early adulthood when the majority of cases of

primary major depressive disorder would have their initial onset. In addition, the information was partially based on interviews of patients who may have had poor recall of previous depression episodes. Future studies using refined measures of previous history of depression or an etiological approach to depression diagnoses may help clarify the reasons for the apparent discrepancy in the cognitive trajectories between major and minor depression observed. A further exploration of potential cognitive effects of antidepressant use will be the topic of the third manuscript.

CHAPTER 6 — USE OF ANTIDEPRESSANTS AND COGNITIVE FUNCTIONING IN OLDER MEDICAL PATIENTS WITH AND WITHOUT DEPRESSION (MANUSCRIPT 3)

6.1. PREFACE TO MANUSCRIPT 3

In this third manuscript, I address the third main study aim, the role of antidepressant and other psychotropic medications in the relationship between depression and cognitive decline. The analyses build upon the findings from the first and second manuscripts that depression symptoms are cross-sectionally associated related to cognitive function, whereas depression diagnoses predict subsequent cognitive decline longitudinally. I now examine whether use of medications independently predicts cognitive decline, or whether it modifies or mediates the effects of depression diagnoses. In particular, I examine the "net" cognitive effect of antidepressant use through the interplay of the potential benefits of antidepressant medications in reducing depression pathology, their potential cognitive side-effects, and the detrimental effects of depression pathology.

6.2 MANUSCRIPT 3.

Use of Antidepressants and Cognitive Functioning

In

Older Medical Patients with and without Depression

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Text words: 3830

References: 47

Tables: 4

Figures: 0

Running head: Antidepressant use and cognitive functioning in older persons with depression

6.2.1 ABSTRACT

Background. The cognitive effects of antidepressant and other psychotropic medications in depressed older persons have important clinical implications, yet research evidence remains controversial, especially in those with minor depression or complex medical conditions.

Methods. 281 medical patients aged 65 and older with a diagnosis of either major, minor or no depression were followed up with the Mini-Mental State Examination (MMSE) at 3, 6 and 12 months. Antidepressant exposure was ascertained using a provincial prescription database and associated with MMSE changes under alternative exposure time windows using a linear mixed effects model, while simultaneously adjusting for potential confounders, indications for prescriptions, and concomitant medication.

Results. Antidepressant use was not associated with cognitive decline in general, but interacted with depression diagnoses ($p=0.038$). It appeared to be associated with an improvement in the MMSE (2.5 to 2.2 per 100-day cumulative exposure, $p=0.014$ to 0.14) in minor depression, independent of comorbid diseases, current depression symptoms and concomitant medications. Both major and minor depression were independently predictive of subsequent MMSE decline, especially in those not prescribed antidepressants ($p<0.03$).

Conclusions. Antidepressants may modify the detrimental effects of depression on cognitive functioning over time in older medical patients towards a potential cognitive benefit in those with minor depression.

Keywords: Antidepressants, minor depression, major depression, cognitive decline, older persons, selective serotonin reuptake inhibitors.

6.2.2 BACKGROUND

The cognitive side effects of medications bear important clinical and public health implications,[1,2] especially in the elderly population with depression. First, the two types of psychotropic medications commonly prescribed to the depressed elderly, antidepressants and benzodiazepines, are among the most potent drug classes that may compromise cognitive function.[1-3] Second, the use of antidepressant and psychotropic medications has been suspected, but not yet proved, to play an independent role in linking late-life depression to cognitive impairment,[4-7] two common and disabling diseases in the elderly.[4, 6] And finally, research evidence regarding the benefits and harms of antidepressant medications is equivocal and insufficient to justify a uniform recommendation of aggressive antidepressant treatment to the depressed elderly, especially those with minor depression or with complex medical conditions.[8-10] Consistent with the cholinergic deficit hypothesis of Alzheimer's dementia,[11-14] a few large-scale epidemiological studies have found independent associations between poorer cognitive performance and exposure to antidepressant,[15,16] benzodiazepines[3, 15, 16] and antipsychotic medications,[15-17] many of which have detectable anticholinergic effects *in vivo*.[1, 2, 13]

In depressed older persons, however, research findings appear to be conflicting.[18] On one hand, some studies demonstrated that an association between antidepressant or other psychotropic drug use and cognitive impairment existed even after controlling for measures of depression;[16-19] on the other, a growing number of studies reported that successful antidepressant treatment appears to improve rather than comprise patients' cognitive functioning.[18, 21-23] Recently, a pooled study of two double-blind, randomized

12 week antidepressant (sertraline, fluoxetine and nortriptyline) trial in 444 elderly people with major depression showed a significant improvement in two cognitive tasks,[22] independent of the observed peripheral anticholinergic side effects.

The methodological limitations of randomized clinical trials included small sample sizes, short follow-up durations, and overrepresentations of healthy elderly.[24] In addition, they typically focused on a few specific antidepressant agents at fixed doses, which does not allow addressing confounding by other concomitant medications or the public health burden in the elderly due to polypharmacy or multiple medication use.[25] Community-based observational epidemiological studies often suffered from incomplete ascertainment of medication exposure over time (introducing misclassification bias),[26] and inability to control for confounding by indications and "protopathic" bias due to lack of clinical evaluation.[27]

We decided to investigate the longitudinal relationship between antidepressant and other psychotropic medication use and cognitive decline in late-life depression, to determine whether these medications are independent risk factors, or they mediate or modify the effects of depression.[5, 6] We used data from a cohort of older medical patients who were followed with repeated assessments of both depression and cognition over 12 months and whose medication prescriptions during the follow-up period were obtained through automated linkage of clinical research data with a provincial prescription database.

We hypothesized that although in general antidepressants and other psychotropic medications are capable of causing cognitive impairments (presumably via anticholinergic activity), their "net" cognitive effects in depressed elderly may reflect a

balance or trade-off between the severity of depression pathology, the strength of the anti-depressant efficacy and the cognitive side-effects of the medications. As a result, we would expect that the cognitive outcome of antidepressant exposure vary across the type or level of depression pathology, whereas exposure to non-antidepressant psychotropics would lead to cognitive decline regardless of depression.

6.2.3 METHODS

Participants: As described in our previous publications,[28, 29] the participants of this study were selected from the study populations of a randomized controlled trial (RCT) of a geriatric psychiatric care service for major depression and an observational cohort study of 12-month outcomes of depression in older medical inpatients, conducted at two university-affiliated acute care hospitals in Montreal, Canada. In brief, eligible patients aged 65 years and over admitted from the emergency room to the medical services were screened by a research clinician using the Short Portable Mental Status Questionnaire (SPMSQ);[30] those who scored four or less (indicative of no or mild cognitive impairment) were assessed using the depressive disorders section of the Diagnostic Interview Schedule (DIS)[31] and the Hamilton Depression Rating Scale (HDRS).[32] All depressed and a random sample of non-depressed patients were invited to participate in the longitudinal component of the study. As soon as possible after recruitment, patients were interviewed by a trained research assistant, blind to the results of the screening assessment. The study protocol was approved by the research ethics committees of both hospitals.

In total, 1,686 eligible patients were screened for depression, of whom 530 (31.4%) consented to participate and enrolled in the study. The main reasons for

exclusion included: too sick, severe cognitive impairment, admission to intensive care, already discharged, transferred to long term care, not proficient in either English or French language, and residing outside of Montreal island. Of the 530 enrollees, 22 died and 94 withdrew before the baseline interview, leaving 414 (78.1%) for baseline and follow-up interviews. For this longitudinal analysis, we selected 281 participants with at least 2 MMSE scores, representing 67.9% of the baseline cohort. There were no statistically significant differences (all p values above 0.07) between those included (N=281) and excluded (N=133) with respect to age, sex, living condition, ADL scores, study group, hospital sites, diagnosis of depression and cognitive impairment at screening. However, the excluded patients were more severely ill ($p<0.01$), had more comorbid conditions ($p<0.01$), higher HDRS ($p=0.05$) and lower MMSE ($p=0.03$) scores.

Measurements:

Measures of depression: A structured psychiatric evaluation was administered, using the depressive disorders section of the DIS, by the research assistant at baseline and each subsequent follow-up. Depression symptoms were assessed using the 21-item version of the HDRS, the most widely used interviewer-rated scale for monitoring depressive symptoms in intervention studies, with higher scores indicating more pathology[32]. Patients were classified as major, minor, or no depression using an "inclusive" diagnostic algorithm according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria,[33] which counted current symptoms with a duration of at least two weeks towards a diagnosis regardless of their origins or aetiologies.[34] The inter-rater reliability was checked periodically, with a kappa coefficient being 0.78 (95% CI 0.52 to 1.00) for a diagnosis of major depression vs minor or no depression, and 0.61 (95% CI:

0.35 to 0.87) for a diagnosis of either major or minor vs no depression (n=28). The intra-class correlation coefficient for HDRS scores was 0.93 (95% CI: 0.86 to 0.97, n=26).

Ascertainment and quantification of medication exposure:

Data on medications of the study participants during the follow-up period were obtained though linkage of their hospital medical records with the provincial prescription claims database, the Régie de l'assurance maladie du Québec (RAMQ).[35] For all the participants, RAMQ provided information on the generic name, identification number, dosage regimen, total supply and date dispensed for each drug product during the 6 months prior to the index hospitalization to the end of the follow-up period.

For this study, we focused on two major classes of psychotropic medications that are commonly prescribed to depressed elderly, antidepressants and benzodiazepines. Antidepressants included three subgroups: 1) tricyclics (TCAs), including amitriptyline, desipramine, doxepine, imipramine, nortriptyline, trimipramine and clomipramine; 2) Serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, fluvoxamine, paroxetine and citalopram; and 3) other antidepressants, including tetracyclics (maprotiline), monoamine oxidase inhibitors (tranylcypromine) and atypical antidepressants (trazodone, nefazodone, venlafaxine and bupropion). Benzodiazepines were divided into two subgroups based on a half-life of the parent drug and its active metabolites, if applicable, of above or below 24 hours.[36] 1) long-acting agents, including clonazepam, clobazam, chlordiazepoxide, diazepam, flurazepam and nitrazepam, and 2) short-acting agents, including oxazepam, lorazepam, triazolam, temazepam, bromazepam and alprazolam. In addition, we collectively defined a group of "other psychotropics" by including non-benzodiazepine sedatives, anxiolytics, neuroleptics, lithium, anticonvulsant

and antiparkinson drugs. These medications have the potential to cause cognitive impairment,[1,3, 15-17] but are used infrequently in this study population. Finally, we used a clinician-rated anticholinergic score as a proxy measure of total anticholinergic burden across medications without regard to therapeutic classification.[37] The anticholinergic score was an ordinal scale originally developed by our group to assess risk of delirium due to multiple medication use in older medical inpatients, with a score ranging from 0 (no anticholinergic effect) to 3 (strongest anticholinergic effect).[37] A list of medications evaluated in this study and assigned anticholinergic scores is available from the first author.

We defined two alternative exposure time windows to examine the potential cognitive effects of the study medications. A long time-window was defined as the 3-month period prior to each MMSE assessment, assuming the effects of medication exposure to be enduring and cumulative over time; whereas a short time window was confined to the one-day period immediately preceding a follow-up MMSE assessment, which approximated the usual mode of clinically significant acute drug events such as delirium.[1, 2, 5, 12] To account for potential residual effects of the medications after their last doses and to increase the tolerance of the defined time windows to the variation of actual use of the medications beyond the prescribed duration, we extended each prescription by seven days, analogous to the minimum fixed time-window used in the pharmacoepidemiologic field.[38]

Within each time–window, we quantified the total exposure by the number of exposed drug-days (EDD) across medications under each therapeutic classes, namely, antidepressants, benzodiazepines, and other psychotropics, based on the prescribed

durations. Similarly, we defined a total anticholinergic burden as the sum of products of the assigned anticholinergic score and the number of days dispended for each individual medication across all the prescriptions. Since the primary objective of this study was to assess the potential cumulative effects of medication exposure over time, the EDDs based on the long time window assumption were used for primary analyses.

Measure of cognitive decline: The Mini-Mental State Examination (MMSE)[39] was administered by a trained research assistant at baseline and subsequent follow-up interview at 3, 6, and 12 month after baseline. The MMSE is the most widely used brief cognitive instrument for screening cognitive impairment or monitoring its progression,[40, 41] with a range in scores from 30 (no impairment) to 0 (maximum impairment). Studies of its psychometric properties show moderate to high levels of short-term test-retest reliability, construct and criterion validity, and adequate responsiveness to cognitive change over time.[40, 41] The inter-rater reliability of the MMSE was assessed in a convenience sample of patients at intervals throughout the study period, using independent simultaneous ratings by two or more raters, including the study psychiatrist (MC). The intraclass correlation coefficient was 1.00 (n=20).

Measures of covariates: Data on covariates were collected at enrolment from either patient interviews or hospital charts. The demographic factors included age, sex, education, and living condition prior to admission. Premorbid physical function of activities of daily living (ADL) was assessed with the Older Americans Resources and Services (OARS) Center instrument,[42] with a score ranging from 0 (completely dependent) to 14 (completely independent). Other covariates included those involved in study design or participant selection, namely, hospital (A vs B), study group (RCT

Intervention, RCT-Control, Not RCT), number of SPMSQ errors at screening, and follow-up duration.

We used nurse-rated clinical severity of current illnesses, scored 1 (not ill) to 9 (moribund),[43] as a marker for potential "protopathic" indications for prescribing medications. Given the implications of cardiovascular diseases (CVD) in both dementia and depression etiologies,[44] we defined a binary (high vs low) indicator for risk of CVD, based on a diagnosis of stroke, diabetes, or myocardial infarction during the previous 2 years or a measured sitting blood pressure of at least 160/95 mm Hg from hospital charts. Furthermore, we collected data on histories of previous depression episodes, categorized as remote, recent, or neither, from patient interviews or chart reviews, which may be a trigger for the initial sedative or other psychotropic prescribing before study inception.

Statistical analysis

The baseline characteristics and longitudinal profiles of the medication exposures were summarized by descriptive statistics, and compared among the baseline depression diagnoses using one-way ANOVA for continuous and chi-square tests for categorical variables, respectively.

A mixed effects linear regression model was employed as the primary approach to hypothesis testing. This allowed for simultaneous accounting for both fixed and time-varying covariates, as well as potential inter-dependence of repeated measures on the same patient over time.[45] Given the unequal follow-up intervals and numbers of MMSE assessments across subjects, we chose the Spatial Power covariance structure to account for the interdependence of repeated MMSE measures.[46]

In the primary analyses, separate multivariable mixed models, designated as A to D, were estimated using the MMSE changes at 3, 6 and 12 months as an outcome, and one of the four duration-based measures of medication exposures (i.e., EDDs under antidepressants, benzodiazepines or other psychotropics, and the total anticholinergic burden) as a predictor.

We adjusted each medication exposure for potential confounding in a hierarchical fashion. Starting with a crude models that included only the medication exposure, we first adjusted for the following *a priori* selected covariates: age, sex, living arrangement, education, number of SPMSQ errors, ADL scores, hospital site, study group, duration of follow-up, and baseline MMSE score. Next, we added the protopathic indications , which included the nurse-rated illness severity, CVD risk and history of depression. Finally, we expanded the models by including, first individually and then jointly, two context-specific indications for antidepressant and/or benzodiazepine prescriptions, i.e. the baseline depression diagnoses and concurrent depression symptoms during follow-up. The latter was represented by a transformed HDRS score, created by subtracting the mean of each depression group at baseline from the raw score at each follow-up, intended to avoid potential multivariate collinearity between depression diagnoses and HDRS score. Adjustments for both indicating diseases and their severity would enhance the validity of an observational study addressing adverse drug effects.[27]

After deriving the final models, we evaluated the specificity or uniqueness of the antidepressant effects controlling for concomitant benzodiazepines and other psychotropics, total number of medications, and total anticholinergic burden, respectively. Furthermore, we evaluated biologically plausible interactions between each

medication exposure and follow-up time, baseline depression diagnoses and transformed HDRS score, as well as the interaction between follow-up time and baseline depression diagnoses. If statistically significant interactions were detected, separate models for each level of the effect modifiers would be fitted to obtain more accurate estimates.

We conducted a series of sensitivity analyses to assess potential bias of the final mixed models. First, we refitted the models using the EDDs derived from the short time-window as a predictor. Next, under the same long time window assumption, we refitted the models by: 1) using total number of (different) medications or total anticholinergic score as an alternative measure, ignoring the duration of use; 2) removing the seven-days residual period from each prescription; and 3) eliminating the prescriptions during the most recent 2 or 4 weeks (for antidepressant only), respectively.

All the statistical analyses were conducted using SAS software version 9.1.[45] Goodness of fit was assessed using the Akaike's Information Criterion (AIC) and compared among nested models using the likelihood ratio chi-square tests based on -2 restricted Log Likelihood statistics.[45, 46] The hypotheses were tested at a two-sided significance level of $\alpha = 0.05$.

6.2.4 RESULTS

The baseline characteristics of the study population are summarized in Table 1. There were significant differences among the three depression diagnostic groups in the exposure to antidepressants ($p<0.05$ for total and for SSRIs) and benzodiazepines ($p<0.01$ for total and for long-acting agents), but not other psychotropics or total anticholinergic burden ($p > 0.05$). In addition, the three groups differed in the HDRS and ADL sores,

and the history of depression (all p values below 0.05), but were comparable in the MMSE and other characteristics ($p > 0.05$).

The longitudinal profiles of the medication exposures over time are presented in Tables 2 and 3. There were significant differences in total numbers of antidepressants, SSRIs (all $p<0.01$) and benzodiazepines ($p<0.05$-0.01) across time.

Table 4 summarizes a series of mixed models estimating the effects of the four medication exposures. After adjusting for all the covariates, total anticholinergic burden was marginally associated with MMSE improvement over time ($p=0.057$, model D4). Both major ($p=0.029$ to 0.017) and minor ($p=0.007$ to 0.005) depression were associated with greater MMSE decline over time (compare to no depression), regardless of which medications were adjusted for (models A4 –D4). Further adjustment of model A4 for concomitant benzodiazepines and other psychotropics, total medications, or total anticholinergic burden had minimum impact on the effect estimates or statistical significance of antidepressant use or depression diagnoses (data not shown).

The sensitivity analyses using alternative measures of medication exposures or exposure time window, as specified in Statistical Analyses, provided comparable results. There were no independent associations (data not shown), except the total anticholinergic burden based on the short time window was associated with higher MMSE scores over time (0.23, $p=0.004$).

A significant interaction between antidepressant use and baseline depression diagnoses was detected in model A4 ($p=0.038$, Table 4). Therefore, stratified models were fitted within each depression group. The antidepressant effect was statistically significant only in the minor depression group, with an estimated MMSE increment of

2.7 (95% CI: 0.6-4.7, p=0.014) per 100-day exposure, not in major (-0.20, p=0.70) or no depression (-0.15, p=0.84) group. The antidepressant effect in minor depression remained after further adjustment for concomitant benzodiazepine and other psychotropics (2.5, 95% CI: 0.4-4.7) or total number of medications (2.5, 95% CI: 0.3-4.6), but became non-significant (2.2, 95% CI: -0.7-5.0, p=0.14) after adjusting for total anticholinergic burden. Refitting these models using antidepressant subclasses as a predictor revealed a significant effect for SSRIs (2.4 to 3.0, p=0.03 to 0.08) only, not for TCAs (p=0.32).

Alternative stratification of model A4 by antidepressant use (users versus non-users) observed significant effects of depression diagnoses in the non-user group only, with an estimated MMSE decline of -0.80 (95% CI: -1.54– -0.06, p=0.035) for major and-1.24 (95% CI: -2.08– -0.40, p=0.004) for minor depression after adjusting for the covariates. In the user group, neither major (-0.16, p=0.85) nor minor (0.33, p=0.72) depression were significantly associated with cognitive decline over time.

6.2.5 DISCUSSION

In this cohort of 281 elderly medical inpatients, we observed no overall association between antidepressants or other psychotropic medications and cognitive decline. Furthermore, the effects of both major and minor depression on cognitive decline found in our previous work[29] remained after adjustment for risk factors and different medications, including benzodiazepines and other psychotropics for which a large body of literature indicates negative cognitive effects.[1,3,17,19] These findings support the hypothesis that depression (major or minor) may be an independent risk factor for cognitive decline,[4, 6, 7, 29] and that its negative cognitive effect seems unlikely, at least in

the short-run, to result from or be mediated by the use of antidepressants or other psychotropic medications[7].

However, the statistically significant interaction between antidepressant exposure and depression diagnoses suggests a possible effect modification.[5, 6] Antidepressant use, specifically SSRIs, appeared to be associated with improved cognitive function in those with minor depression, independent of the physical illnesses, severity of current depression symptoms, and concomitant psychotropic medications. Although this apparent protecive effect should be interpreted with caution given the small sample size, it provides preliminary evidence for potential antidepressant benefits to this less severe type of late-life depression, for which evidence from randomized clinical trials and observational studies in medically ill older persons has been insufficient.[6, 8, 10,24]

Previous studies reporting an improved or stable cognitive functioning following antidepressant treatments have been restricted to major depression.[18, 20-23] Possible mechanisms included a "side"-effect of antidepressant efficacy secondary to the improvement in depression pathology,[18,21,22] and a deprivation of the disruptive anticholinergic properties of the newer antidepressant agents (e.g., SSRIs).[18,20,22-24] In addition, some antidepressants, such as SSRIs, may have direct pharmacological action on the cognitive brain through interaction with other neurotransmitter system,[6,18, 47] though the exact nature of such mechanisms has yet to be elucidated. In our study, although the estimated cognitive decline for major depression appeared to be reduced in those prescribed antidepressants (-0.16) than those not prescribed such medications (-0.80), no significant antidepressant benefit was detected from major depression group. We suspect that this might be due to an inadequate dose and/or duration of antidepressant

regimen, or to non-adherence by these patients after discharge from hospital. Alternatively, their depression pathology may be too severe to be counteracted by the antidepressant regimens they received.

Contrary to our hypothesis, the total anticholinergic burden did not predict cognitive decline; rather, it appeared to be marginally ($p=0.06$) associated with better cognitive functioning over time. One possibility is that our clinician-rated anticholinergic score may not accurately reflect the level of anticholinergic activities of the medications *in vivo*. As a result, the observed anticholinergic effect could not be disentangled from those of medications that were rated as anticholinergic. Consistent with this surmise, the anticholinergic effect became entirely non significant ($p=0.08$ to 0.74) after adjusting for antidepressant use. Alternatively, in line with the postulated direct cognitive mechanism of antidepressants,[6,47] the anticholinergic properties of antidepressants may actually contribute to the improvement of cognitive function in depressed elderly when the serotonergic system is altered, either due to the depression pathology or the treatment with SSRIs.

The strengths of this study are several. First, we used a comprehensive administrative database to ascertain medication regimens throughout the follow-up period, reducing potential misclassification bias due to ignorance of the changes in medication exposure over time.[26] Second, we rigorously controlled for potential confounding by both indicating diseases and their severity as well as important risk factors, enhancing the validity of the study.[27] Third, we scrutinized our study hypotheses using different measures of medication exposure under biologically plausible pathogenic assumptions, facilitating causal inference in the epidemiological context. Finally, we

blinded the assessors of exposure and outcome to study hypotheses and used both "restriction" and "adjustment" techniques to control for potential reverse causality bias due to baseline heterogeneity of study population in cognitive function.

Three important limitations should be noted. First, our measure of medication exposure may be imprecise, because we did not take into account the dosage or actual use of drugs, or adherence to the prescriptions. In addition, we did not have data on non-prescription medications or medications used during hospitalization. Second, the outcome measure, the MMSE, has been criticized for insensitivity to small cognitive changes and ceiling or floor effects,[40] especially over a relatively short period of follow-up, which may have limited our power to detect a small yet potentially clinically important effect of a medication exposure. Finally, due to exclusion of the most severely ill patients and substantial cohort attrition during follow-up, the results may not be generalizable either to the most severely ill older persons or to elderly populations outside of acute care hospital settings.

The clinical implications of this study are two fold. First, both major and minor depression in older medical patients may increase risk of cognitive decline, independent of antidepressant or other psychotropic use. Therefore, intervention on these clinically significant depression syndromes (either with medications or psychosocial interventions) is justified on their own count. Second, the detrimental cognitive effect of depression may be potentially reversed or prevented by antidepressant treatment among patients with minor depression. Although this finding should be interpreted with caution, rigorous investigation of potential benefits and harms of antidepressant treatment in older persons with minor depression, including randomized clinical trials, is warranted.

Acknowledgement: This study was funded by Canadian Institutes for Health Research, grant # MOP82494 to Dr. Jane McCusker and MCT–15476 to Dr Martin Cole. We thank Mr. Eric Belzile at St. Mary's Hospital for assisting in managing the computerized database and Dr. Eric Latimer at Douglas Hospital Research Centre for help with obtaining the RAMQ data.

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Table 1. Characteristics of the Study Population at Baseline

Characteristics*		Depression Diagnoses			P Value§§
		Major (N=121)	Minor (N=51)	No (N=109)	
Age — yr		78.7 ± 7.1	78.4 ± 6.9	79.9 ± 7.3	0.333
Gender — n (%)	*Female*	75 (62.0)	33 (64.7)	77 (70.6)	0.378
	Male	46 (38.0)	18 (35.3)	32 (29.4)	
Education — n (%)					
	<6	13 (11.2)	9 (18.4)	9 (8.6)	0.446
	6-12	43 (37.1)	18 (36.7)	45 (42.9)	
	> 12	60 (51.7)	22 (44.9)	51 (48.6)	
Living arrangement prior to enrolment — n (%)					
	Home	101 (83.5)	43 (84.3)	92 (84.4)	0.979
	Other	20 (16.5)	8 (15.7)	17 (15.6)	
SPMSQ score†		1.6 ± 1.2	1.6 ± 1.4	1.6 ± 1.4	0.960
MMSE score‡		25.8 ± 3.2	25.1 ± 3.3	26.2 ± 3.9	0.137
HDRS score§		19.9 ± 5.8	13.5 ± 5.3	9.5 ± 5.7	<0.001
ADL score¶		11.5 ± 12.0	12.1 ± 11.7	12.5 ± 12.5	0.003
Nurse-rated illness severity		3.9 ± 1.0	3.9 ± 1.0	3.7 ± 1.1	0.380
Risk for cardiovascular disease — n (%)					0.584
	High	12 (9.9)	3 (5.9)	12 (11.0)	
	Low	109 (90.1)	48 (94.1)	97 (89.0)	
History of previous depression episode — n (%)					
	Remote	16 (13.2)	8 (15.7)	5 (4.6)	<0.001
	Recent	34 (28.1)	6 (11.8)	6 (5.5)	
	Neither	71 (58.7)	37 (72.5)	98 (89.9)	
Hospital — n (%)	*A*	91 (75.2)	43 (84.3)	94 (86.2)	0.083
	B	30 (24.8)	8 (15.7)	15 (13.8)	
Study group — n (%)‖					
	RCT-intervention	33 (27.3)	6 (11.8)	4 (3.7)	<0.001
	RCT-control	26 (21.5)	8 (15.7)	1 (0.9)	
	Not RCT	62 (51.2)	37 (72.5)	104 (95.4)	

Table 1 (Continued)

Number of psychotropic medications					
Antidepressant**	*TCA*	0.05 ± 0.22	0.12 ± 0.38	0.05 ± 0.21	0.204
	SSRI	0.24 ± 0.50	0.12 ± 0.33	0.07 ± 0.26	0.005
	Other	0.04 ± 0.20	0.02 ± 0.14	0.03 ± 0.16	0.720
	Total	0.33 ± 0.57	0.25 ± 0.52	0.15 ± 0.36	0.018
Benzodiazepine					
	Long-acting	0.12 ± 0.36	0.12 ± 0.33	0.02 ± 0.13	0.012
	Short-acting	0.36 ± 0.55	0.22 ± 0.46	0.22 ± 0.42	0.066
	Total	0.48 ± 0.67	0.33 ± 0.59	0.24 ± 0.45	0.007
Other psychotropic drug††		0.26 ± 0.60	0.12 ± 0.38	0.17 ± 0.44	0.191
Total number of medications		7.61 ± 6.06	8.08 ± 6.39	6.79 ± 5.50	0.372
ACH score across medications‡‡		1.47 ± 1.78	1.69 ± 2.13	1.27 ± 1.51	0.348

* Plus-minus signs are means ± SD. Because of missing data on some characteristics, the denominators that were used to determine some percentages differ from the total numbers of patients.

† The Short Portable Mental Status Questionnaire (SPMSQ) scores range from 0 to 10, with higher scores indicating more cognitive impairment.

‡ The Mini-Mental State Examination (MMSE) scores range from 0 to 30, with higher scores indicating better cognitive performance.

§ The 21-item Hamilton Depression Rating Scale (HDRS) scores range from 0 to 63, with higher scores indicating greater severity of depression symptoms.

¶ The Activities of Daily Living (ADL) scores range from 0 to 14, with higher scores indicating more independence.

‖ RCT denotes Randomized Clinical Trial.

** The antidepressant was divided into Tricyclic (TCA), Selective Serotonin Reuptake Inhibitor (SSRI), and other agents.

†† The other psychotropic drug included non-benzodiazepine sedatives, anxiolytics, barbiturates, antipsychotics, antiparkinson drugs, and anticonvulsants etc.

‡‡ The clinician-rated Anticholinergic (ACH) scores range from 0 to 3, with higher scores indicating greater antichilinergic level.

§§ Derived from X^2 (df=2) for categorical and one-way ANOVA (df=2) for continuous variables, contrasting the three diagnostic groups.

Table 2. Longitudinal profile of medication exposure over time

Medication exposure*	Follow-up time	Depression Diagnoses			P Value‡
		Major	Minor	No	
		Mean ± SD	Mean ± SD	Mean ± SD	
Antidepressant					
	3 month	25.7 ± 38.6	12.0 ± 28.7	6.2 ± 21.9	<0.001 §
	6 month	25.9 ± 41.4	16.5 ± 33.1	8.3 ± 26.0	0.001 ‖
	12 month	26.9 ± 45.3	9.1 ± 24.9	4.4 ± 17.0	<0.001 ¶
Benzodiazepine					
	3 month	27.9 ± 40.5	13.9 ± 33.6	10.5 ± 25.0	<0.001 **
	6 month	24.0 ± 37.4	17.2 ± 34.3	12.4 ± 29.5	0.035 ††
	12 month	21.5 ± 37.8	13.3 ± 31.4	11.5 ± 27.0	0.055 ‡‡
Other psyhotropic					
	3 month	13.1 ± 31.4	5.5 ± 19.4	10.7 ± 37.5	0.369
	6 month	11.3 ± 31.1	4.5 ± 16.3	12.9 ± 42.8	0.342
	12 month	12.7 ± 40.8	5.2 ± 19.0	10.7 ± 39.3	0.485
Anticholinergic burden†					
	3 month	89.3 ± 122.4	79.4 ± 122.4	55.4 ± 81.6	0.058 §§
	6 month	87.4 ± 123.4	89.1 ± 119.6	72.1 ± 103.7	0.533
	12 month	82.4 ± 114.8	64.5 ± 99.4	59.8 ± 91.8	0.231

* Values represent total numbers of exposed drug-days, except otherwise indicated, to each medication class during the 3 months prior to each follow-up outcome assessment.

† Values represent the products of assigned ACH score and number of days exposed to each medication across all prescriptions during the 3 months prior to each follow-up outcome assessment.

‡ Derived from one-way ANOVA, df=2 for overall comparison among the three diagnostic groups.

§ Pairwise comparisons: major versus no depression, $p<0.001$; major versus minor depression, $p<0.01$.

‖ Pairwise comparisons: major versus no depression, $p<0.001$.

¶ Pairwise comparisons: major versus no depression, $p<0.001$; major versus minor depression, $p<0.01$.

** Pairwise comparisons: major versus no depression, $p<0.001$; major versus minor depression, $p<0.05$.

†† Pairwise comparisons: major versus no depression, $p<0.05$.

‡‡ Pairwise comparisons: major versus no depression, $p<0.05$.

§§ Pairwise comparisons: major versus no depression, $p<0.05$.

Table 3. Longitudinal profile of exposure to major subgroups of antidepressants and benzodiazepines over time

Medication exposure*	Follow-up time	Depression Diagnoses			P Value†
		Major	Minor	No	
		Mean ± SD	Mean ± SD	Mean ± SD	
Tricyclic antidepressants					
	3 month	3.9 ± 15.2	4.1 ± 19.9	1.3 ± 9.7	0.330
	6 month	2.1 ± 11.0	3.8 ± 17.7	3.5 ± 15.7	0.676
	12 month	2.7 ± 14.6	0.7 ± 5.2	1.7 ± 9.7	0.576
Selective serotonin reuptake inhibitors					
	3 month	18.7 ± 32.0	6.1 ± 18.8	4.1 ± 16.7	<0.001 ‡
	6 month	18.3 ± 33.6	11.0 ± 27.8	3.5 ± 16.4	<0.001 §
	12 month	19.3 ± 34.3	7.5 ± 23.2	2.4 ± 11.5	<0.001 ‖
Long-acting benzodiazepines					
	3 month	6.8 ± 20.8	6.7 ± 23.2	0.1 ± 0.8	0.006 ¶
	6 month	6.0 ± 19.5	7.4 ± 23.5	1.2 ± 9.4	0.043 **
	12 month	3.7 ± 16.3	4.3 ± 18.3	0.9 ± 6.9	0.212
Short-acting benzodiazepines					
	3 month	21.2 ± 35.2	7.2 ± 26.2	10.4 ± 24.8	0.004 ††
	6 month	18.0 ± 33.0	9.9 ± 26.6	11.2 ± 27.4	0.129
	12 month	17.8 ± 33.7	8.9 ± 27.0	10.5 ± 25.4	0.089

* Values represent total numbers of exposed drug-days, except otherwise indicated, to each medication class during the 3 months prior to each follow-up outcome assessment.

† Derived from one-way ANOVA, df=2 for overall comparison among the three depression diagnostic groups.

‡ Pair-wise comparisons: major versus no depression, $p<0.001$; major versus minor depression, $p<0.05$.

§ Pair-wise comparisons: major versus no depression, $p<0.001$.

‖ Pair-wise comparisons: major versus no depression, $p<0.001$; minor versus no depression, $p<0.01$.

¶ Pair-wise comparisons: major versus no depression, $p<0.01$; minor versus no depression, $p<0.05$.

**Pair-wise comparisons: major versus no depression, $p<0.05$; major versus minor depression, $p<0.05$.

†† Pair-wise comparisons: major versus no depression, $p<0.01$; major versus minor depression, $p<0.01$.

Table 4. Association between medication use and MMSE changes* evaluated using mixed effects models

Model		A. Antidepressant			B. Benzodiazepine			C. Other psychotropic			D. ACH burden		
No.	Predictors†	Est.¶	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value
1	Medication exposure	-0.17	-0.91 – 0.57	0.648	-0.60	-1.35 – 0.15	0.119	-0.28	-1.00 – 0.43	0.437	0.08	-0.15 – 0.32	0.480
2 ‡	Medication exposure	0.25	-0.42 – 0.92	0.462	-0.24	-0.90 – 0.42	0.476	-0.15	-0.76 – 0.46	0.631	0.21	0.01 – 0.42	0.044
3 §	Medication exposure	0.23	-0.46 – 0.92	0.507	-0.26	-0.92 – 0.41	0.451	-0.14	-0.74 – 0.47	0.659	0.18	-0.02 – 0.39	0.083
4 ‖	Medication exposure	0.29	-0.39 – 0.97	0.398	-0.16	-0.81 – 0.50	0.640	-0.15	-0.75 – 0.45	0.623	0.20	-0.01 – 0.40	0.057
	Depression diagnoses at baseline												
	Major	-0.82	-1.48 – -0.15	0.017	-0.75	-1.42 – -0.08	0.029	-0.77	-1.44 – -0.11	0.023	-0.81	-1.47 – -0.15	0.017
	Minor	-1.03	-1.77 – -0.29	0.007	-1.01	-1.76 – -0.27	0.008	-1.04	-1.79 – -0.29	0.007	-1.06	-1.80 – -0.32	0.005

* Defined by the differences in the Mini-Mental State Examination (MMSE) scores between each follow-up and baseline, with negative values indicating decline;

† Medication exposure as a predictor refers to one of four medications, represented by the total exposed drug-days (models A-C) or total anticholinergic (ACH) burden (model D) during the 3 months prior to each follow-up outcome assessment.

‡ Model #2 adjusted model # 1 for age, sex, education, living arrangement, activity of daily living (ADL) score, hospital, study group, Short Portable Mental Status Questionnaire (SPMSQ) score, baseline MMSE score, and follow-up duration.

§ Model # 3 adjusted model # 2 for nurse-rated illness severity, risk for cardiovascular diseases and history of depression.

‖ Model # 4 expanded model # 3 with two additional covatiates: depression diagnoses at baseline (shown in the table) and a transformed Hamilton Depression Rating Scale (HDRS) score during follow-up.

¶ Represents expected MMSE change per 100-day exposure to the specific medication, with negative values indicating decline.

6.3 POSTSCRIPT TO MANUSCRIPT 3

In this section, I supplement the manuscript and conclude the formal hypothesis testing of the thesis with the following additional data and remarks.

6.3.1 Sensitivity Analyses of Estimated Antidepressant Effects

Table A-1 of Appendix 1 provides further details about a series of sensitivity analyses of the effects of antidepressant exposure on MMSE changes, based on the final model A4 of Table 4 in the manuscript. In brief, under the short time window assumption (model A), the estimated effect for antidepressant exposure remained non-significant, though slightly increased in magnitude, in comparison to that derived from the long time window. Similarly, eliminating the antidepressants prescribed during the most recent 14 (model B) or 30 (model C) days from the long time window, or removing the 7-day residual period from all the prescriptions (model D) did not change the effect estimates for antidepressant use meaningfully. These results suggest that the cognitive effects of antidepressant medications may act through different pharmacological mechanisms from their therapeutic effects on reducing depression symptoms [Oxman 1996]. Results were consistent using number of medications to represent total antidepressant use ($P>0.05$, data not shown) and other medication exposures without considering the duration of use.

Likewise, both major and minor depression remained independently associated with MMSE decline over time ($p<0.05$ to 0.001), and their effect estimates stayed almost the same as the primary analyses, no matter which alternative exposure time window was assumed and which medications were adjusted for (data not shown).

Finally, although the participants whose baseline interviews were completed in hospital did have a lower baseline MMSE score than those interviewed at home (25.6 vs

26.7, p=0.029), adjustment of the final mixed models for place of baseline interview did not change the effect estimates for antidepressant use ($p>0.05$) or depression diagnoses ($p<0.05$ to 0.001) meaningfully. Nor was there a statistically significant "place" effect (p=0.81) or "place" interaction with depression diagnoses (p=0.19) or antidepressant use (p=0.88).

6.3.2 The Stratified Analyses

Table A-2 provides further details for the subgroup models described in the last paragraph of section 6.2.4 Results of the manuscript, including the sequential adjustments for concomitant medications. An additional message from these subgroup models is that in both major depression and no depression groups antidepressant use seemed to be associated, though not statistically significantly, with cognitive decline over time, especially when multiple medications were taken, consistent with the general belief that polypharmacy may increase the risk of adverse drug events due to a specific medication [Colley 1993, Tune 1992].

6.3.3 Joint Effect of Major Depression and Antidepressant Use

In a few previous cohort studies, antidepressant use at baseline has been included in the definition of major or persistent depression based on self-rated symptoms alone [Devanand 1996, Fuhrer 2003]. Therefore, I refit the final mixed models by adding to the major depression group those who were using antidepressants at baseline, but diagnosed as either minor (n=8) or no (n=14) depression. The effect estimates for the redefined major depression (N=143) remained strong and statistically significant (-0.72, p=0.03), even after adjusting for concomitant benzodiazepine and other psychotropic medications

(-0.69, p=0.04), total medications (-0.76, p=0.02), or total ACH burden (-0.80, p=0.02). The same was true for the redefined minor depression (N=43, effect estimates: -1.08 to -1.13, p=0.009 to 0.007).

CHAPTER 7 — GENERAL DISCUSSION

7.1 SUMMARY OF MAIN FINDINGS

This thesis examined the relationship between depression and cognitive function in a sample of older medical inpatients with repeated measures of both over a 12-month follow-up period. The main findings can be briefly summarized as follow.

1) Depression symptoms were associated with cognitive functioning cross-sectionally but not prospectively. This cross-sectional association was independent of age, cardiovascular risk, illness severity, baseline physical and cognitive function and other potentially important risk factors of cognitive impairment, but disappeared after depression diagnoses were taken into account.

2) Both major and minor depression were predictive of subsequent cognitive decline, independent of baseline characteristics including age, cardiovascular risk, illness severity, physical and cognitive function, and previous history of depression. The strength of the association appeared to increase with the duration of follow-up interval since the assessment of depression diagnoses. In addition, it remained after adjusting for the longitudinal variations in the severity of depressive symptoms, exposure to antidepressants, other psychotropic medications, and total anticholinergic burden across medications. Furthermore, the effect stayed statistically significant in patients who were not prescribed antidepressants during the follow-up.

3) There were no overall associations between antidepressants, benzodiazepines or other psychotropic medications and cognitive decline. However, antidepressant use interacted with depression diagnoses. In the minor depression group, exposure to antidepressants in general and to SSRIs of particular appeared to be associated with an

improvement in cognitive functioning over time, independent of the severity of concurrent depression symptoms, concomitant benzodiazepines and other psychotropic medications or total concomitant medications, but diminished after adjusting for total anticholinergic burden across medications.

Taken together, these findings have addressed the two main research questions towards the three specific aims, and partially confirmed our *a priori* hypotheses, as postulated in Chapter 3. Their unique contributions to the subject field and potential scientific significance will be briefly discussed in the next section.

7.2 COMPARISON WITH THE LITERATURE

7.2.1 The Temporal Relationship between Depression and Cognitive Functioning

The concurrent association observed in the first manuscript seems to agree with previous cohort studies that reported a cross-sectional relationship between depression symptoms and cognitive decline or dementia [Dufouil 1996, Henderson 1997, Chen 1999, Cervila 2000, Vinkers 2004, Ganguli 2006]. However, several unique methodological features differentiate this study from previous ones. First, depression symptoms were measured using a clinically validated, observer-rated depression scale, rather than patients' self-reports. Second, this thesis examined depression symptoms as a dynamic exposure and "replicated" the cross-sectional relationship at multiple time points (so termed as "concurrent") using longitudinal analyses, rather than at a single baseline or intermittent time point of the follow-up. Finally, this thesis rigorously examined competing hypotheses about the temporality between depression and cognitive decline through operational statistical models, rather than relying on a lack of longitudinal relationship as sole evidence [Henderson 1997, Chen 1999, Cervila 2000, Vinkers 2004, Ganguli 2006]. As

correctly pointed out by Dufouil [Dufouil 1996], a lack of prospective association from studies with extended follow-up intervals may reflect the inability of the studies to capture such an association, which may have diminished before the outcome assessment, rather than render support to refuting its existence.

On the other hand, the longitudinal prediction of cognitive decline by both major and minor depression stands out as a potentially important new finding. The consistency of this relationship against a variety of suspected causal risk factors and the concurrent variation of depression symptoms, the pattern of dose-response in terms of the "exposure" duration to the diagnoses, and the clinically relevant short follow-up interval within which the relationship was observed all point to a potential causal mechanism. And as such, it provides a strong piece of evidence in support of the hypothesis that depression is an independent risk factor for cognitive decline in older persons [Jorm 1991, 2001, Meyers 1998, Steffens 2006]. To my knowledge, this is the first prospective epidemiological study that directly examined and empirically demonstrated a short-term temporal relationship between clinically significant depression syndromes and cognitive decline in the medically ill elderly population.

Several biological mechanisms have been speculated to explain a potential causal relationship between depression and cognitive impairment or dementia. According to the glucocorticoid cascade hypothesis, repeated and prolonged stress, a common risk factor for depression, may over-activate and eventually exhaust the hypothalamic-pituitary-axis and lead to permanent brain damage and cognitive impairment [O'Brien 1996, Jorm 2001]. In addition, the serotonergic neurotransmitting system, whose deficiency has been implicated in the etiology of major depression, may play an important role in modulating

cognitive behavior through interactions with the cholinergic system [Steckler 1995], a target of neurodegenerative disease such as dementia. If such causal mechanisms do exist, it should not be surprising that "exposure" to clinically significant depression syndromes be closely and quantitatively associated with cognitive decline well before it may develop into a full-blown dementia. Alternatively, the relationship may be determined by a common underlying cause or shared etiology, such as vascular diseases [Alexopoulos 1997, Lyness 1998, Paterniti 2000, Lavretsky 2004, Fuhrer 2003]. As postulated in the "vascular depression" hypothesis, both clinical and subclinical cerebrovascular diseases can cause brain damage, especially in the striatofrontal region, which in turn lead to depressed mood and cognitive disturbance, particularly in the executive domain. Several epidemiological studies observed a relationship between depression symptoms and cognitive impairment only in those with some cardiovascular pathology [Cervilla 2000] or in older men in whom cardiovascular diseases are disproportionately more prevalent than in women [Fuhrer 2003]. In this thesis, however, a measure of CVD neither had a significant main effect nor modified the effect of depression symptoms or diagnoses on cognitive function. Therefore, it seems unlikely that cardiovascular diseases could explain the observed relationship.

7.2.2 Effect Modification by Antidepressant Medications

The lack of independent associations between antidepressants or other psychotropic medications and cognitive decline, and the apparent interaction between antidepressant use and depression diagnoses suggest that the antidepressant exposure behaves mostly like an effect modifier, rather than an independent risk factor or mediating factor in the depression —cognitive decline conundrum [Meyers 1998, Oxman 1996, Jorm 2000, 1991,

Steffens 2006]. While the cognitive benefit of antidepressants in minor depression should be interpreted with caution due to its small sample size, an improved or stable cognitive function following antidepressant treatments have been reported for older persons with major depression [Amado-Boccara 1995, Butters 2000, Doraiswamy 2003, Nebes 1999]. Some authors interpreted such cognitive benefits as secondary to the alleviation of depression symptoms by successful antidepressant treatment, while others postulated possible direct effects of antidepressant, especially SSRIs and other newer generations, through a different pharmacological mechanism such as interactions between serotonergic and other neurotransmitting systems [Oxman 1996, Nebes 1999], though the exact nature of such mechanisms have yet to be determined. To my knowledge, this is the first epidemiological study that empirically demonstrated an effect-modification model in the longitudinal context to explain the interrelationship between late-life depression, medication use and cognitive decline.

7.3 LIMITATIONS

As an observational study, this thesis is subject to the following potential biases.

7.3.1 Selection Bias

Selection bias refers to the distortions of exposure-outcome association that result from the procedure used to select participants and factors that influence study participation [Rothman 1998, Collet 2000]. As a result, the exposure-outcome relationship observed in study participants does not reflect the truth in the base population. Modern epidemiology tends to distinguish the selection of one particular comparison group from the selection of the study sample. The former primarily affects the "internal validity" of a study or the applicability of its observed effect estimates to the source population, whereas the latter

mainly reduces the "external validity" or generalizability of the study results to people outside of the source population [Rothman 1998, Collet 2000].

As regard external validity, in the parent studies the majority of consecutively admitted patients did not reach the screening phase for depression due to application of eligibility/exclusion criteria. Second, the thesis study further excluded patients with only one outcome assessment. Finally, there was appreciable cohort attrition over time, as is a common phenomenon to older medical cohorts [Cole 1999, Morris 1999]. Although the excluded patients had comparable characteristics to those included in terms of major demographic characteristics, diagnosis of depression and cognitive impairment at screening, they tended to be more severely physically ill, and less emotionally and cognitively well (see Chapter 4, Manuscript 1, Methods section). Therefore, the study results may not be generalizable to severely ill old persons or elderly populations outside of acute care hospital settings.

As regard internal validity, two types of selection bias may have particular implications to this thesis: reverse causality and protopathic bias [Rothman 1998, Collet 2000]. The former may occur if a large proportion of the participants who manifested depression symptoms were preclinical cases of an underlying dementing disease, whose cognitive function would naturally deteriorate over time as the dementia progresses. As a result, a spurious association between depression and cognitive decline may be found. If depression (or other) symptoms were indeed early (or more strictly, the first) signs of dementia and antidepressant (or other) medications were prescribed to treat these symptoms, then a protopathic bias may result, whereby the antidepressant medications,

rather than the underlying dementia pathology, may be erroneously claimed as the "cause" of the observed cognitive decline.

In this thesis, the risk for both types of selection bias has been reduced by restriction of the study sample to those without apparent cognitive impairment at study entry. In addition, the follow-up period of twelve months in this thesis was much shorter than the typical time course for the development of dementia, within which it is unlikely that originally cognitively intact older participants would develop dementia. Furthermore, the three baseline groups by depression diagnoses were assembled following the same inclusion/exclusion criteria (except depression) and the factors used for selection of participants have been adjusted in the regression model. Therefore, the chance of serious selection bias on the effect estimates for depression diagnoses should be minimal. The effect estimates for medication use would be largely immune to the potential protopathic or other types of selection bias due to its nature of within-subject sampling. This is especially true for antidepressant medications, which essentially demonstrated no harm or even protective effect on cognitive function, opposite to what can be expected from a dementia pathology.

7.3.2. Information Bias

Information bias refers to the distortion of exposure-outcome association due to errors in the measurement of study variables [Rothman 1998]. If the measurement errors in one variable (exposure or disease) depend on the value of the other (so-called "differential"), the effect estimates can be biased either towards or away from the null. When the measurement errors do not depend on each other (nondifferential), information bias usually leads to an attenuation of the true effect [Rothman 1998, Collet 2000].

Information bias may have specific implications for the following measurements of the thesis.

1) Medication exposure:

Use of administrative prescription database (i.e., RAMQ) for ascertaining medication exposure may be subject to several sources of information bias. First, the medication exposure was quantified based on the dispensed prescriptions rather than actual use of the medications, which may lead to an overestimation of the total exposure. Second, RAMQ does not provide information about over-the-counter medications or prescription during hospitalization, which may bias the effect estimates towards the null (if the omitted drugs have the same cognitive effects as their prescription counterparts). Third, for feasibility reasons (e.g., lack of data), I did not use dosage information or take into account the adherence of patients, which may bias the exposure effects either towards or away from the null. However, I have confined my examination of medication exposure within biologically plausible pathogenic time windows, and conducted a series of sensitivity analyses to assess potential bias using alternative measures. The results remained essentially unchanged. Therefore, serious differential information bias seems unlikely.

A specific case of potential information bias may be to the clinician-rated ACH score. The ACH score is based on clinicians' experience with observable therapeutic or side-effects that are typically attributable to the blockage of muscarine receptors [Bartus 1982, Beatty 1986, Rudd 2005, Hardman 1996]. Therefore, the ACH score may not accurately reflect the level of the true ACH activities, at least not the actual ACH activities *in vivo*. However, a systematic reversion of the true ACH effects by clinicians' rating

seems unlikely given the reported concurrent and predictive validity of the ACH score in other studies [Carnahan 2002, Rudd 2005] and the documented ACH effect of the medications with a non-zero ACH score in the literature [Larson 1987, Bowen 1993, Hardman 1996, Oxman 1996, Tune 1992]. Therefore, the measurement errors of ACH score are not likely to be a reason for the observed beneficial (though not significant) effect of ACH burden. Future studies with refined measures of ACH properties of medications, preferably with external and objective validation, would be needed to clarify whether this is a chance finding, an artifact due to confounding by unmeasured medications or other factors, or it reveals an undiscovered biological mechanism.

2) The MMSE

The cognitive outcome was measured by a global cognitive test, the MMSE, which has been criticized for insensitivity to small cognitive changes and being subject to ceiling or floor effects [Tombough 1992, Galasko 1991]. Furthermore, "practice" effects in general and "regression to the mean" in people with lower baseline MMSE scores may tend to "improve" cognitive performance over time [Tombough 1992, Morris 1999]. The overall trend of a slight increase of the MMSE scores in the study cohort from baseline to six months may partially reflect such measurement problems, in addition to the effect of place of testing referred to above. A more specific implication of such a measurement-related artifact may be the observed antidepressant effect in the minor depression, but not in the major depression group. Because patients with minor depression tended to have lower (but non-significant) baseline MMSE scores than those with major depression, they would be more likely to "improve" over time regardless of antidepressant treatment. However, this potential psychometric bias should have been removed by adjustment for

the baseline MMSE score. Similarly, place of baseline interview did not appear to have a significant impact on the cognitive functioning of the cohort ($p=0.81$) or the effect estimates for antidepressant use ($p>0.05$), suggesting that any bias due to place of testing would be minimal [Inouye 2006].

On the other hand, the MMSE is a global measure of cognitive function [Tombaugh 1992]. Its capacity is limited in measuring the specific cognitive dysfunctions that may characterize late-life depression, such as visual-spatial ability and complex executive function [Lavretsky 2004, Steffens 2006]. Future studies using instruments that are specifically tailored to assess such cognitive domains, such as the Trail Making Test, Clock Drawing Test and neuropsychological batteries [Steffens 2006], would be needed to answer this question.

7.3.3 Confounding Bias

Confounding is another major threat to the internal validity of an epidemiological study, which can bias the effect estimate either towards or away from the null or reverse its direction [Rothman 1996]. A specific form of confounding that is particularly relevant to this thesis is confounding by indication [Rothman 1996, Collet 2000, Salas 1999], which leads to a confusion between cause and drug effects when the reason for prescribing, rather than prescribed drugs, is responsible for the observed effects. In practice, it is sometimes difficult to distinguish confounding by indication from protopathic bias [Collet 2000, Salas 1999]. Similarly, while reverse causation often results from the distortion of the population selection procedure, it can also arise from confounding factors related to inclusion/exclusion criteria at study entry.

I controlled for confounding by indication first, by adjusting medication exposure for both "generic" and "context-specific" indications, and for both indicating diseases (depression) and its symptom severity over time. Furthermore, I considered and systematically evaluated a large array of potential confounders based on both *a priori* clinical knowledge and statistical principles.

Other potential confounders, such as recent life events or incidence of acute illness during the follow-up period, were not measured in this study and therefore not controlled. Although the adjustment of the depression diagnoses for the time-dependent HDRS scores during the follow-up may have partially eliminated the potential confounding due to such unmeasured situations, this adjustment does not allow for determining whether the lack of prospective effect of depression symptoms is due to the extraneous confounders or the intrinsic limitations of the instrument (i.e., HDRS). In addition, in the context of observational studies of adverse effects of medications, a complete elimination of confounding by indication is almost impossible, and the consequence of adjustment is not always in the desired direction [Collet 2000, Miettinen 1989]. For instance, some antidepressant medications may be prescribed to treat conditions other than depression, such as chronic pain syndrome, anxiety disorder and anorexia etc. Without knowing the concrete reasons for each prescription, an adjustment for the typical indication for antidepressant use, i.e., specific depression diagnosis and the severity of depressive symptoms, can at best remove some of the confounding. Therefore, the observed protective effects of antidepressant use in minor depression group also need to be verified by examining closely the specific indications for each antidepressant prescription. Ultimately, randomized clinical trials will be needed to resolve these issues.

7.3.4 Other limitations

Several other methodological limitations that are related to the study design are also worth noting.

1) Short follow-up interval:

This thesis focused on a relatively short follow-up period of twelve months - shorter than any previous cohort studies in the subject field that ranged from one to twelve years (see 2.4.2 Current State of Epidemiological Knowledge – A Critical Literature Review for details). While this short follow-up had the advantage to address the effects of depression as a potential short-term risk factor *versus* a clinical concomitant of cognitive decline in a context close to clinical reality, it also had disadvantages. First, the insensitivity of the MMSE to mild cognitive decline might be exaggerated due to more frequent "practice" of the patients over a short time interval, as discussed in section 7.3.2. Information Bias. Second, a temporal relationship between depression and cognitive decline over a short time period is a necessary, but not a sufficient, piece of evidence for establishing a causal relationship between depression and dementia. Whether or not it persists over longer period of time or leads directly to the development of dementia needs to be confirmed in future.

2) Uncertainty around the Antidepressant Effects for Minor Depression

While the thesis had adequate statistical power to test the main hypotheses, the small sample size of minor depression (N=51) added uncertainty to interpretation of the observed beneficial effects of antidepressant use in this group. More specifically, during each follow-up interval, only a small portion of patients were actually using antidepressant medications (19.6%, 23.5%, and 13.7%, respectively). To what degree the observed

beneficial effects of antidepressant use may be attributed to some unmeasured confounders (such as use of over-the-counter cognitive enhancers or other psychological therapy, etc) needs to be investigated. In addition, evidence from randomized clinical trials for antidepressant benefits is, to my knowledge, mostly derived from older persons with major depression [Lebowitz 1997, Mittmann 1997, Mottram 2006]. Little is known about the therapeutic or side (cognitive or other) effects of antidepressant treatment in minor depression, with or without comorbid medical conditions [Williams 2000, McCusker 1998, Tannock 1995, Freudenstein 2001]. Therefore, whether or not the observed effects reflected specific characteristics of the subsets of patients, typical clinical features of minor depression, or the efficacy of the antidepressant treatment remains to be clarified.

7.4 STRENGTHS

The strengths and unique methodological contributions of the thesis to the subject field include the following aspects:

1) Use of a clinically relevant short follow-up interval and standard psychiatric assessments to define depression symptoms and diagnoses, which makes the study findings readily translatable into the clinical management of late-life depression.

2) Integration of a comprehensive prescription database and first-hand clinical information to address the effect of medication exposure, which helps reduce measurement errors of medication exposure and facilitates controlling for confounding by (clinical) indications for prescriptions;

3) Adoption of a repeated measure cohort design and an appropriate longitudinal analytic approach, which enhances the validity and efficiency of the study due to

simultaneous control for both patient-specific and time-varying confounders and optimal use of multiple observations on the same patients.

4) Definition of exposure time windows under biologically plausible pathogenic hypotheses for drug-induced cognitive impairment, which facilitates the ability of this observational study to make causal inference.

7.5 CLINICAL AND PUBLIC HEALTH IMPLICATIONS

This thesis has the following implications for clinical and public health practice:

1) As clinically significant syndromes, both major and minor depression in older medical patients are likely to be independent risk factors of cognitive decline over the short-term. Therefore, intervention on late-life depression may have the potential to reduce the risk of future cognitive decline in this highly susceptible population.

Due to lack of quantitative clinical criteria, it may be difficult to meaningfully judge the clinical significance of the observed effects for depression diagnoses. However, based on an estimated annual rate of decline of 3.3 MMSE points for Alzheimer's dementia [Han 1999] and of 0.02 to 0.57 for community-dwelling older persons without dementia [Jacqmin-Gadda 1997], the estimated 0.8 (for major depression) and 1.0 (for minor depression) declining MMSE points per six months can be roughly translated into an ARC of 1.6 and 2.0 points, respectively, which falls in-between the two extremes, but is closer to that of dementia patients.

2) Antidepressant treatment, especially with SSRIs, may modify the detrimental effects of late-life depression, and potentially preserve or improve the cognitive function in those with minor depression. Although this finding needs to be replicated in larger sample of older persons with minor depression and in randomized clinical trials, it

provides preliminary evidence of the potential antidepressant benefits to elderly persons with minor depression and complex medical conditions, in whom research evidence has been lacking.

7.6 RESEARCH IMPLICATIONS

This thesis provides the following implications for research:

1) An effect-modification model seems to better explain the temporal interrelationship between depression, antidepressant medications and cognitive decline in the elderly population, in which depression pathology independently predicts subsequent cognitive decline, while antidepressant treatment may modify this relationship towards a potential cognitive benefit. Therefore, future epidemiological studies aiming to elucidate the relationship between any two factors may need to take into account the third one in order to avoid bias.

2) The disappearance of the concurrent association after adjusting for depression diagnoses raises a salient point that the dimensional approach to depression, even by objective assessment, may be inadequate to forecast future cognitive decline or address causation. To enhance internal validity and facilitate causal inference, epidemiological studies of late-life depression may need to use clinical diagnostic criteria to define depression, consider biologically plausible pathogenic processes in designing follow-up intervals, and employ longitudinal analyses to address the natural history of depression.

7.7 AREAS OF FUTURE INVESTIGATION

Several remaining questions warrant further investigations:

1) Given the study population for this thesis was drawn from acute-care hospital settings and the sample size is modest, the research findings should be replicated in larger

samples of community-dwelling elderly, preferably with longer follow-up and more specific and sensitive measures of cognitive functioning;

2) To address potential bias due to the imprecise quantification of medication exposure and the limitations of administrative database, future studies should take into account the dosage and actual use of medication, patient adherence, and use alternative data sources from patient interview and hospital records when ascertaining and quantifying medication exposure;

3) Two unexpected results, i.e., the beneficial antidepressant effects to minor depression and the apparent protective effects of anticholinergic exposure, may indicate scientifically important new findings, or result from residual confounding or chance. They deserve further investigation using larger study samples, more specific and precise measures of depression etiologies, medication exposure, anticholinergic and other alternative biological mechanisms.

7.8 FINAL CONCLUSIONS

1) As clinically significant syndromes, both major and minor depression may be independent risk factors for short-term cognitive decline in older medical patients.

2) Antidepressant medications, especially SSRIs, may modify the detrimental effects of depression pathology towards a potential cognitive benefit in older persons with minor depression.

3) An effect-modification model may better explain the interrelationship or causal pathway between depression, antidepressant use and cognitive functioning in older persons, in which depression is an independent risk factor and the antidepressant use is an effect modifier.

CHAPTER 8 — BIBLIOGRAPHY

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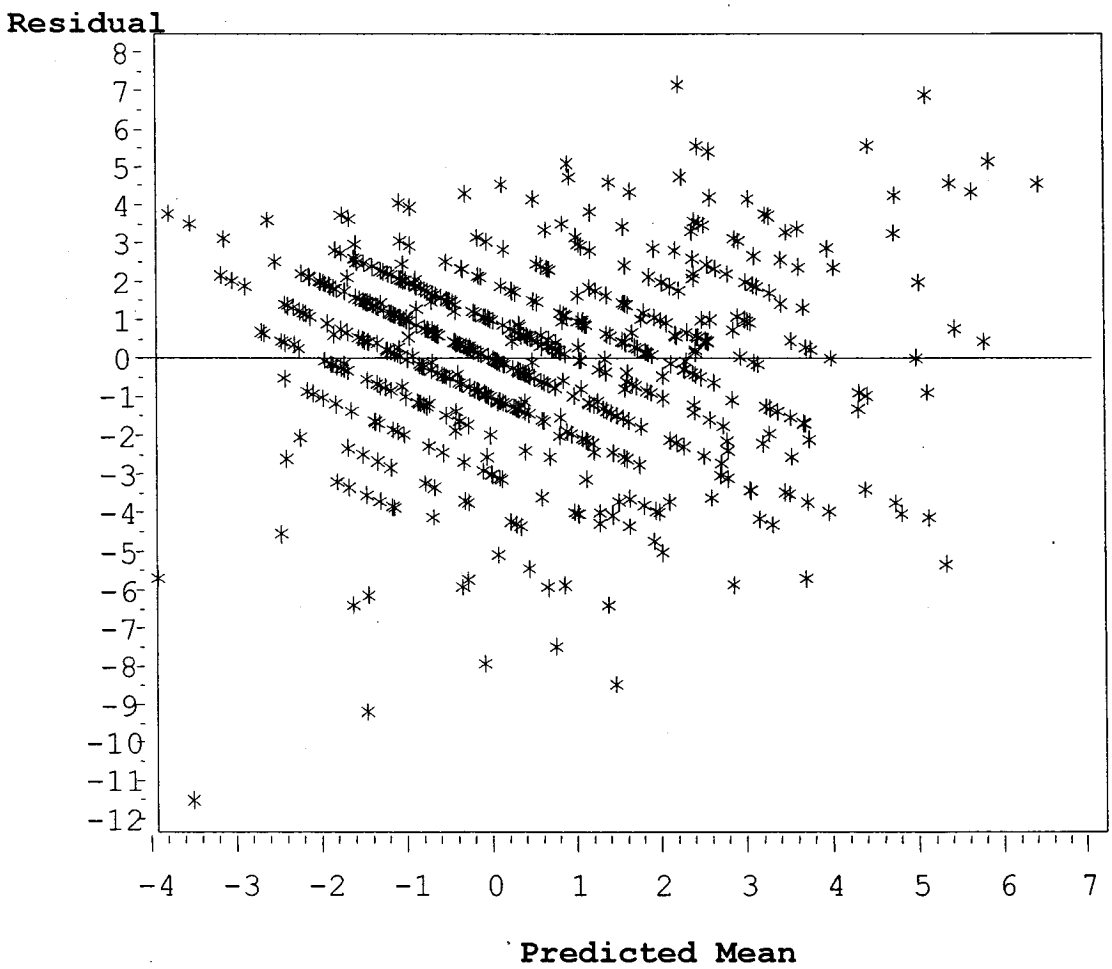
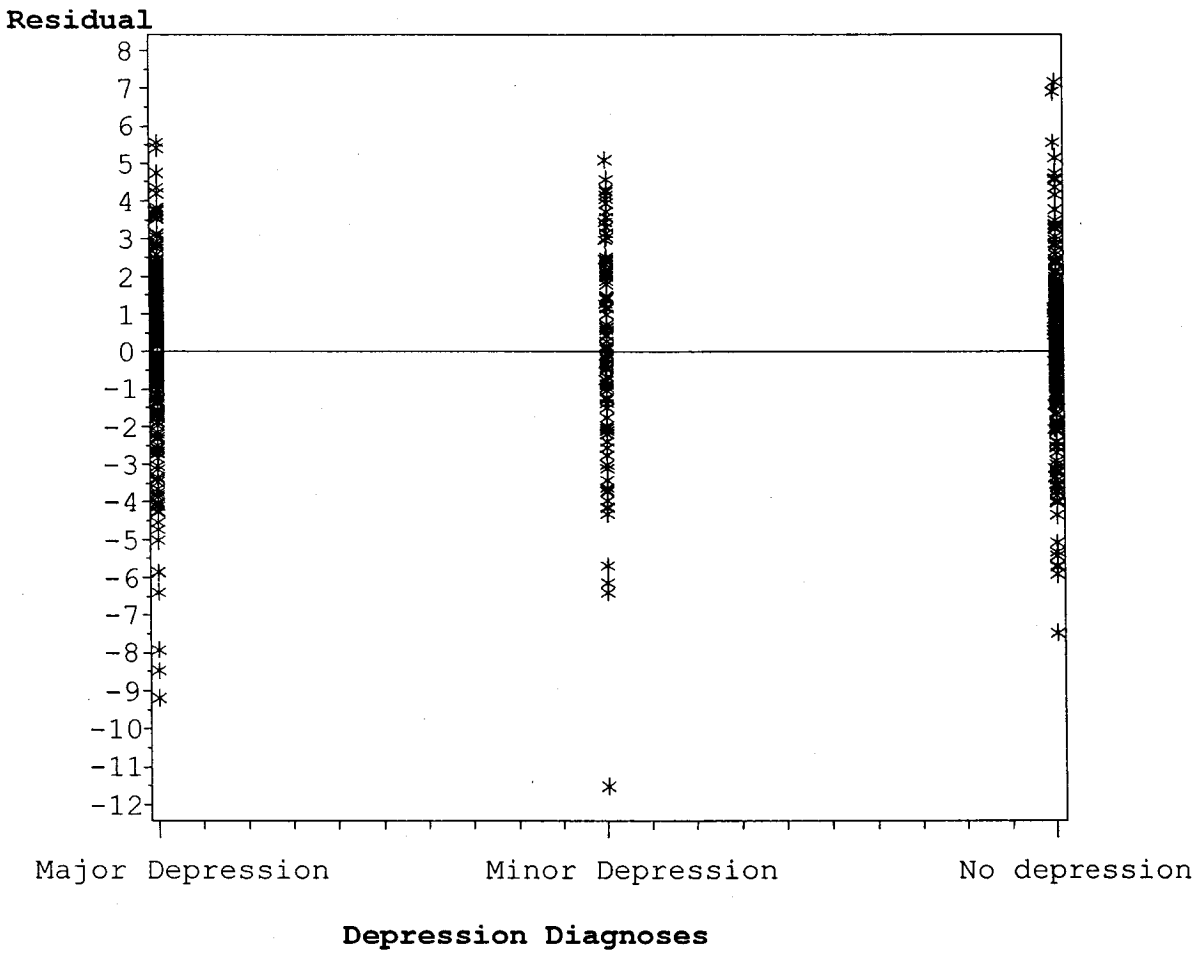
Figure A-1. Residuals Plots from the Final Mixed Model, Prospective A (supplement to Chapter 5, Manuscript 2)

(1.1). Population-averaged Residuals against Predicted Values



(1.2). Population-averaged Residuals against Depression Diagnoses at Baseline



(1.3). Population-averaged Residuals against Transformed HDRS Scores

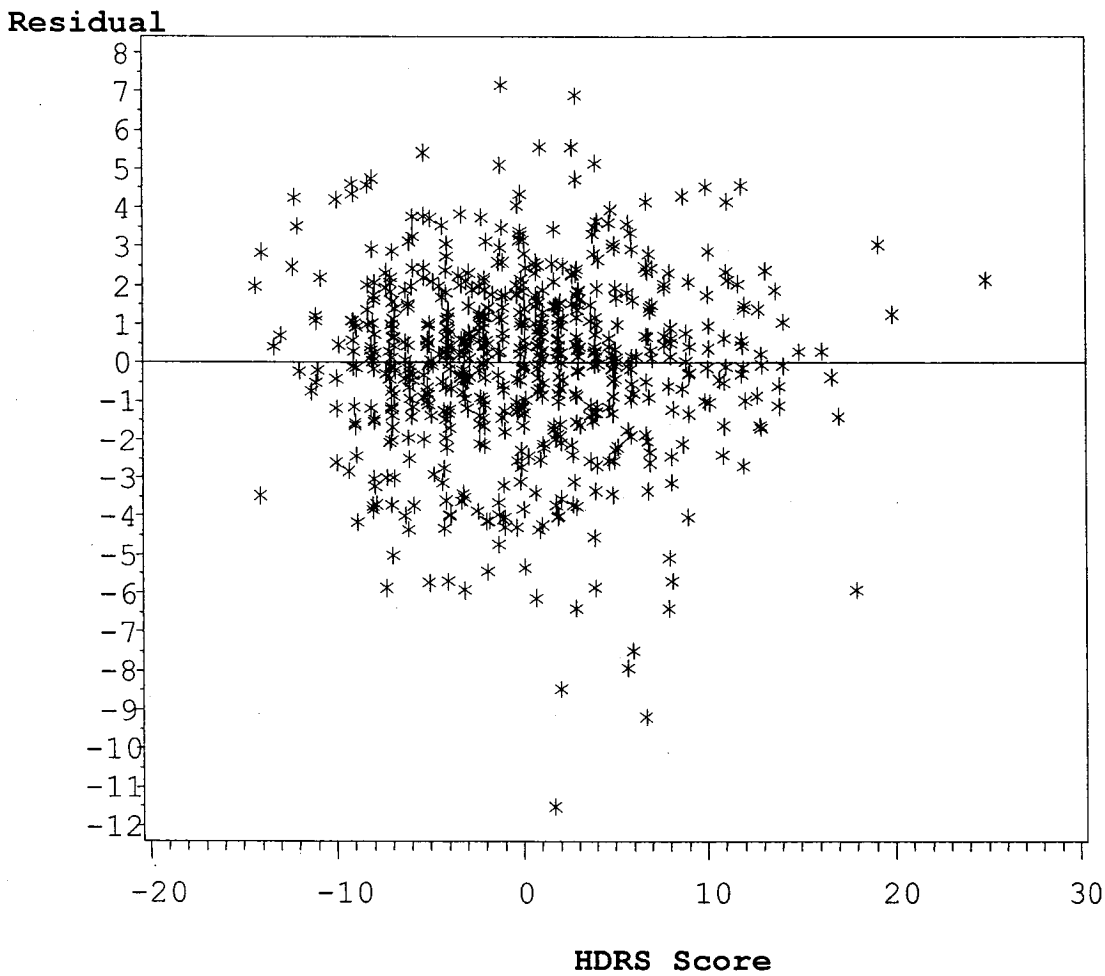


Table A-1. Sensitivity analysis: Evaluating effects of antidepressant exposure on MMSE changes* under alternative assumptioms for exposure time window (supplement to Chapter 6, Manuscript 3)

Model†	A. Under Short Time Window			B. Remove Most Recent 14 days			C. Remove Most Recent 30 days			D. Remove 7-day Residual Period		
Covariate‡	Est.‖	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value	Est.§	95% CI	P value
Antidepressant exposure§	0.33	-0.17 – 0.83	0.200	0.32	-0.50 – 1.13	0.448	0.30	-0.40 – 1.00	0.396	0.30	-0.42 – 1.02	0.412
Depression diagnoses at baseline												
Major	-0.83	-1.50 – -0.16	0.015	-0.81	-1.48 – -0.14	0.018	-0.82	-1.48 – -0.15	0.017	-0.81	-1.48 – -0.15	0.018
Minor	-1.04	-1.78 – -0.29	0.007	-1.03	-1.77 – -0.28	0.007	-1.03	-1.77 – -0.29	0.007	-1.03	-1.77 – -0.29	0.007

* Defined by the differences in the MMSE scores between each follow-up and baseline, with negative values indicating decline.

† Model A assumed a short exposure time window. Models B and C assumed a long exposure time window. Model D applied to both short- and long- time windows.

‡ Other covariates included age, sex, education, living arrangement, ADL score, hospital, study group, SPMSQ errors, baseline MMSE score, follow-up duration, a nurse-rated illness severity, risk for cardiovascular diseases, previous history of depression and a transformed HDRS score during the follow-up.

§ Represented by the total exposed drug-days during the 3 month period prior to each follow-up outcome assessment, excluding prescriptions dispensed in the assumed induction or residual period.

‖ Estimate (Est) denotes expected MMSE changes per 100-day exposure to the specific medication during the 3 month period prior to each follow-up MMSE assessment.

Abbreviations: MMSE, Mini-Mental State Examination; HDRS, Hamilton Depression Rating Scale; ADL, Activities of Daily Living; SPMSQ, Short Portable Mental Status Questionnaire.

Table A-2. Stratified models by depression diagnoses: Evaluating effects of antidepressant exposure on MMSE changes* based on long time window, with and without adjusting for concomitant medications (supplement to Chapter 6, Manuscript 3)

Model	A. Major Depression			B. Minor Depression			C. No Depression		
No.	Est.¶	95% CI	P value	Est.	95% CI	P value	Est.	95% CI	P value
1 †	-0.20	-1.10 – 0.71	0.670	2.66	0.59 – 4.72	0.014	-0.15	-1.57 – 1.27	0.840
2 ‡	-0.24	-1.18 – 0.70	0.616	2.54	0.40 – 4.67	0.022	0.00	-1.46 – 1.461	0.998
3 §	-0.15	-1.11 – 0.81	0.758	2.47	0.34 – 4.60	0.026	-0.27	-1.74 – 1.193	0.715
4 ‖	-0.33	-1.50 – 0.85	0.587	2.16	0.70 – 5.02	0.142	-0.82	-2.54 – 0.90	0.351

* Defined by the differences in the MMSE scores between each follow-up and baseline, with negative values indicating decline.

† Model 1 adjusted antidepressant exposure for age, sex, education, living arrangement, ADL score, hospital, study group, SPMSQ errors, baseline MMSE score, follow-up duration, a nurse-rated illness severity, risk for cardiovascular diseases, history of depression, and a transformed HDRS score during follow-up.

‡ Model 2 adjusted model # 1 for concomitant benzodiazepines and other psychotropic medications.

§ Model 3 adjusted model 1 for total number of concomitant medications.

‖ Model 4 adjusted model 1 for total anticholinergic burden.

¶ Estimate (Est) denotes expected MMSE changes per 100-day exposure to antidepressants during the 3 month period prior to each follow-up MMSE assessment.

Abbreviations: MMSE, Mini-Mental State Examination; HDRS, Hamilton Depression Rating Scale; ADL, Activities of Daily Living; SPMSQ, Short Portable Mental Status Questionnaire.

Appendix II. (A). Patient Consent Form for RCT

St. Mary's Hospital,
Departments of Psychiatry
and Epidemiology

Principal investigator:
Dr. Martin G. Cole
Tel: (514) 734-2684

CONSENT FORM

Older patients are often depressed while in hospital. We have determined that you are depressed and invite you to participate in a study to assess if a new way of detecting and managing patients with depression is effective in:

- reducing length of hospital stay;
- reducing symptoms of depression and improving quality of life;
- increasing patients' abilities to manage independently;
- increasing survival.

Participation in this study involves the following:

You will be assigned equally by chance either to a group which will receive usual care or a group which will receive the new care programme (descriptions below).

Usual Care: this means that you will receive the care that you would normally receive from your doctors and nurses. Such care may include treatment of your depression if you and your doctor decide it is necessary.

New care programme: this means that you will be visited by a doctor who specializes in caring for older patients and by a nurse who has been trained to care for patients who are depressed. As well, care of your depression will be arranged after you are discharged from hospital.

Patients in both groups will be interviewed by a research assistant 4 times:

1. Soon after enrolling in the study
2. 3 months after enrolment
3. 6 months after enrolment
4. 12 months after enrolment

Each interview will last not more than 1 hour, and will include questions on general health, emotions, and use of medical services.

STUDY OF A GERIATRIC DEPRESSION SERVICE

St. Mary's Hospital,
Departments of Psychiatry
and Epidemiology

Principal investigator:
Dr. Martin G. Cole
Tel: (514) 734-2684

Your Medicare number will be used to obtain information on your use of physician services and medication prescriptions from the Régie de L'Assurance Maladie du Québec, during the past year and the next year. Information may also be requested from any hospitals, CLSCs, home care providers, or other organizations from which you may receive health or social services during the same two-year period.

You will be asked for the name of the family member or friend who helps you the most on a day-to-day basis. This person will also be asked to participate in the research. His or her participation will involve filling out a questionnaire about his or her health and role in your care; this will take about 20-30 minutes. S/he will be asked to fill out this questionnaire again 6 and 12 months from now.

There may be no direct benefits to you for participating in this study. There are no risks other than the potential risks associated with anti-depressant treatment. The study will not deprive you of the usual care you receive from your doctors and nurses. You will not stay in the hospital any longer because of your 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 are depressed while in hospital.

Participation in this study is voluntary and if you do not participate you will continue to receive care as usual from your doctors and nurses and you may discuss the options for treatment of your depression with your doctor. You may withdraw from the study at any time without any effect on your 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 data base to identify the patients.

If you have any questions about your rights as a participant in this research project, you may contact the patient representative, Monique Robitaille, at 734-2618

You will receive a copy of the signed consent form.

STUDY OF A GERIATRIC DEPRESSION SERVICE

St. Mary's Hospital,
Departments of Psychiatry
and Epidemiology.

Principal investigator:
Dr. Martin G. Cole
Tel: (514) 734-2684

I have read the consent form for the Study of a Geriatric Depression Service and have had the opportunity to ask questions. I agree to participate in this research project.

_____ _____

Consent Date

_____ _____

Witness Date

Medicare no _____

Appendix II. (B). Patient Consent Form for Prognosis Study

St. Mary's Hospital,
Departments of Psychiatry
and Epidemiology

Principal investigator:
Dr. Jane McCusker
Tel: (514) 345-3511 ext. 5060

CONSENT FORM

We have determined that you do not have depression that requires treatment, although you may have some symptoms of depression. We invite you to participate in a study to determine whether an older patient's mental or physical condition during a hospital admission affects their quality of life in the future.

If you participate in this study, you will be interviewed by a research assistant 4 times:

1. Soon after enrolling in the study
2. 3 months after enrolment
3. 6 months after enrolment
4. 12 months after enrolment

Each interview will last not more than 1 hour, and will include questions on general health, emotions, and use of medical services.

You will be asked for the name of the family member or friend who helps you the most on a day-to-day basis. This person will also be asked to participate in the research. His or her participation will involve filling out a questionnaire about his or her health and role in your care; this will take about 20-30 minutes. S/he will be asked to fill out this questionnaire again 6 and 12 months from now.

Your Medicare number will be used to obtain information on your use of physician services and medication prescriptions from the Régie de L'Assurance Maladie du Québec, during the past year and the next year. Information may also be requested from any hospitals, CLSCs, home care providers, or other organizations from which you may receive health or social services during the same two-year period

There may be no direct benefits to you for participating in this study. The study will not deprive you of the usual care you receive from your doctors and nurses. The results of this study will help doctors and nurses to improve the care of older patients who are hospitalized.

STUDY OF PATIENT OUTCOMES

St. Mary's Hospital,
Departments of Psychiatry
and Epidemiology

Principal investigator:
Dr. Jane McCusker
Tel: (514) 345-3511 ext 5060

Participation in this study is voluntary and if you do not participate you will continue to receive care as usual from your doctors and nurses. You may withdraw from the study at any time without any effect on your 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 data base to identify the patients.

If you have any questions about your rights as a participant in this research project, you may contact the patient representative, Monique Robitaille, at 734-2618

You will receive a copy of the signed consent form.

I have read the consent form for the Study of Patient Outcomes and have had the opportunity to ask questions. I agree to participate in this research project.

_____ _____

Consent Date

_____ _____

Witness Date

Medicare no _____

Appendix IV. An Integrated Instrument: Diagnostic Interview Schedule (Depression) (DIS-D) /Hamilton Depression Rating Scale (HDRS)

ID#: _____ **Date:** _____
D M Y

Name: _____ **Rater:** _____
Last First

A) DIS-D

Please score on the basis of subject's responses to the questions only.
*** These questions may be scored "No" based on responses to previous questions.**

1. ***Do you feel sad or blue or depressed?***

1. No → go to question # 2 2. Mild 3. Moderate 4. Severe

1a. ***How long have you felt sad or blue or depressed?***

_____ days _____ weeks _____ months _____ years

2. ***Do you have trouble falling asleep or staying asleep these days?***

1. No → go to question # 3 2. Mild 3. Moderate 4. Severe

2a. ***About how long have you had trouble falling asleep or staying asleep?***

_____ days _____ weeks _____ months _____ years

3. ***Do you wake up earlier than usual in the morning these days?***

1. No → go to question # 4 2. Mild 3. Moderate 4. Severe

3a. ***About how long have you been waking up earlier than usual in the morning?***

_____ days _____ weeks _____ months _____ years

4.* ***Do you sleep more than usual these days?*

1. No → go to question # 5 2. Mild (<1hr longer than usual)
3. Moderate (1-2 hrs longer than usual) 4. Severe (>2hrs longer than usual)

4a. ***About how long have you been sleeping more than usual?***

_____ days _____ weeks _____ months _____ years

5. ***Do you take medicine to help you sleep these days?***

1. No → go to question # 6 2. Yes

5a. ***About how long have you been taking medicine to sleep?***

_____ days _____ weeks _____ months _____ years

6. ***Is your appetite decreased?***

1. No → go to question # 2. Mild 3. Moderate 4. Severe

6a. ***About how long ago did your appetite decrease?***

_____ days _____ weeks _____ months _____ years

7. ***Are you losing weight?***

1. No → go to question # 8 2. Mild 3. Moderate 4. Severe

7a. ***About how long ago did you begin to lose weight?***

_____ days _____ weeks _____ months _____ year

8.* ***Is your appetite increased?*

1. No → go to question # 9 2. Mild 3. Moderate 4. Severe

8a. ***About how long ago did your appetite begin to increase?***

_____ days _____ weeks _____ months _____ years

9.* ***Are you gaining any weight?*

1. No → go to question # 10 2. Mild 3. Moderate 4. Severe

9a. ***About how long ago did you start to gain weight?***

_____ days _____ weeks _____ months _____ years

10. ***Do you get tired easily or do you find yourself without energy?***

1. No → go to question # 11 2. Mild 3. Moderate 4. Severe

10a. About how long have you been getting tired easily or have you been without energy?

_____ days _____ weeks _____ months _____ years

11. Do you find yourself restless? Do you have trouble sitting still? Do you pace up and down?

1. No → go to question # 12 2. Mild 3. Moderate 4. Severe

11a. About how long have you been restless or have you been unable to sit still?

_____ days _____ weeks _____ months _____ years

12. Do you talk or move more slowly than is normal for you?

1. No → go to question # 13 2. Mild 3. Moderate 4. Severe

12a. About how long have you talked or moved more slowly than is normal for you?

_____ days _____ weeks _____ months _____ years

13. How are you at making decisions? (Note: rate indecisiveness)

1. No → go to question # 14 2. Mild 3. Moderate 4. Severe

13a. About how long ago have you had trouble making decisions?

_____ days _____ weeks _____ months _____ years

14. Do you have a lot more trouble concentrating than is normal for you?

1. No → go to question # 15 2. Mild 3. Moderate 4. Severe

14a. About how long ago have you had more trouble concentrating than is usual for you?

_____ days _____ weeks _____ months _____ years

15. Have you lost your interest and pleasure in most things that you usually care about or enjoy?

1. No → go to question # 16 2. Mild 3. Moderate 4. Severe

15a. About how long have you lost interest and pleasure in things that you usually care about?

_____ days _____ weeks _____ months _____ years

16. ***Do you feel worthless or sinful or guilty?***

1. No → go to question # 17 2. Mild 3. Moderate 4. Severe

16a. ***About how long have you felt worthless (or sinful or guilty)?***

_____ days _____ weeks _____ months _____ years

17. ***Do you think about death – either your own death or death in general?***

1. No → go to question # 18 2. Mild 3. Moderate 4. Severe

17a. ***About how long have you been thinking about death?***

_____ days _____ weeks _____ months _____ years

18. ***Do you feel that life is not worth living?***

1. No → go to question # 19 2. Mild 3. Moderate 4. Severe

18a. ***About how long have you been feeling that life is not worth living?***

_____ days _____ weeks _____ months _____ years

19. ***Do you wish to die but reject the notion of taking your own life?***

1. No → go to question # 20 2. Mild 3. Moderate 4. Severe

19a. ***About how long have you wished to die but rejected the notion of taking your own life?***

_____ days _____ weeks _____ months _____ years

20.* ***Do you feel so low that you think of taking your own life?*

1. No → go to question # 21 2. Mild 3. Moderate 4. Severe

20a. ***About how long have you been thinking of taking your own life?***

_____ days _____ weeks _____ months _____ years

21.* ***Have you actually attempted to take your own life?*

1. No 2. Yes

If yes, when:

_____ days ago ___ weeks ago _____ months ago _____ years ago

B) HDRS

Please score items for the past week on the basis of all information available.

1.	**What's your mood been like this past week?** Have you been feeling down or depressed? Sad? Hopeless? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**DEPRESSED MOOD** (Sadness, hopelessness, worthlessness): 0 Absent 1 Indicated only on questioning 2 Spontaneously reported verbally 3 Communicated non-verbally, i.e. facial expression, posture, voice, tendency to weep 4 VIRTUALLY ONLY; this in spontaneous verbal and non-verbal communication
2.	**How have you been spending your time this past week (when not at work)?** Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? Have you stopped doing anything you used to do? IF YES: Why? Is there anything you look forward to? (AT FOLLOW-UP: Has your interest been back to normal?)	**WORK AND ACTIVITIES:** 0 No difficulty 1 Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies 2 Loss of interest in activity; hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities) 3 Decrease in actual time spent in activities or decrease in productivity 4 Stopped work or activities because of present illness
3.	**How has your interest in sex been this week?** (I'm not asking about performance, but about your interest in sex – how much you think about it.) Has there been any change in your interest in sex (from when you were not depressed)? Is it something you've thought much about? IF NO: Is that unusual for you?	**GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances): 0 Absent 1 Mild 2 Severe
4.	**How has your appetite been this past week?** (What about compared to your usual appetite?) Have you had to force yourself to eat? Have other people had to urge you to eat?	**SOMATIC SYMPTOMS GASTROINTESTINAL:** 0 None 1 Loss of appetite but eating without encouragement 2 Difficulty eating without urging

5.	**Have you lost any weight since this (DEPRESSION) began?** IF YES: How much? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back?	**LOSS OF WEIGHT:** A When rating by history: 0 No weight loss 1 Probable weight loss associated with present illness 2 Definite (according to patient) weight loss 3 Not assessed B When actual weight changes are measured: 0 Less than 1 lb. loss in week 1 More than 1lb. loss in one week 2 More than 2lb. loss in one week 3 Not assessed
6.	**How have you been sleeping over the last week?** Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep?	**INSOMNIA EARLY:** 0 No difficulty falling asleep 1 Complains of occasional difficulty falling asleep i.e., more than ½ hour 2 Complains of nightly difficulty falling asleep
7.	**During the past week, have you been waking up in the middle of the night?** IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? Have you felt your sleeping has been restless or disturbed some nights?	**INSOMNIA MIDDLE:** 0 No difficulty 1 Complains of being restless and disturbed during the night 2 Waking during the night – any getting out of bed (except to void)
8.	**What time have you been waking up in the morning for the last time, this past week?** IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, before you got depressed)?	**INSOMNIA LATE:** 0 No difficulty 1 Waking in early hours of morning but goes back to sleep 2 Unable to fall asleep again if he gets out of bed

9.	**How has your energy been this past week?** Have you been tired all the time? This week, have you had any backaches, headaches, or muscle aches? This week, have you felt any heaviness in your limbs, back or head?	**SOMATIC SYMPTOMS GENERAL:** 0 None 1 Heaviness in limbs, back or head. Backaches, headaches, muscles aches. Loss of energy and fatigability 2 Any clear-cut symptom
10.	**Have you been especially critical of yourself this past week, feeling you've done things wrong, or let others down?** IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? Do you feel you're being punished by being sick?	**FEELINGS OF GUILT:** 0 Absent 1 Self-reproach, feels he has let people down 2 Ideas of guilt or rumination over past errors or sinful deeds 3 Present illness is a punishment. Delusions of guilt 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
11.	**This past week, have you had any thoughts that life is not worth living, or that you'd be better off dead? What about having thoughts of hurting or even killing yourself?** IF YES: Have you actually done anything to hurt yourself?	**SUICIDE:** 0 Absent 1 Feels life is not worth living 2 Wishes he were dead or any possible death to self 3 Suicidal ideas 4 Attempts at suicide
12.	**Have you been feeling especially tense or irritable this past week?** Have you been worrying a lot about little unimportant things, things you wouldn't ordinarily worry about? IF YES: Like what, for example?	**ANXIETY PSYCHIC** 0 No difficulty 1 Subjective tension and irritability 2 Worrying about minor matters 3 Apprehensive attitude apparent in face or speech 4 Fears expressed without questioning
13.	**In this past week, have you had any of these physical symptoms? READ LIST, PAUSING AFTER EACH SX FOR REPLY.** How much have these things been bothering you this past week? (How bad have they	**ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as GI (dry mouth, gas, indigestion, diarrhea, cramps, belching); C-V (heart palpitations, headaches); Resp (hyperventilating, sighing); Having to urinate frequently; Sweating):

	gotten? How much of the time, or how often, have you had them?) NOTE: DON'T RATE IF CLEARLY DUE TO MEDICATION (E.G., DRY MOUTH AND IMIPRAMINE)	0 Absent 1 Mild 2 Moderate 3 Severe 4 Incapacitating
14.	**In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)?** Do you complain much about how you feel physically? Have you found yourself asking for help with things you could really do yourself? IF YES: Like what, for example? How often has that happened?	**HYPOCHONDRIASIS:** 0 Not present 1 Self-absorption (bodily) 2 Preoccupation with health 3 Frequent complaints, requests for help, etc. 4 Hypochondriacal delusions
15.	**RATING BASED ON OBSERVATION**	**INSIGHT:** 0 Acknowledges being depressed and ill 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc 2 Denies being ill at all
16.	**RATING BASED ON OBSERVATION DURING INTERVIEW**	**RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity): 0 Normal speech and thought 1 Slight retardation at interview 2 Obvious retardation at interview 3 Interview difficult 4 Complete stupor
17.	**RATING BASED ON OBSERVATION DURING INTERVIEW**	**AGITATION:** 0 None 1 Fidgetiness 2 Playing with hands, hair etc. 3 Moving about, can't sit still 4 Hand wringing, nail-biting, hair pulling, biting of lips

18.	**This past week have you been feeling better or worse at any particular time of day – morning or evening?** IF VARIATION: How much worse do you feel in the (MORNING OR EVENING)? IF UNSURE: A little bit worse or a lot worse?	DIURNAL VARIATION: a Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none: 0 No variation OR not currently depressed 1 Worse in the A.M. 2 Worse in the P.M. b When present, mark the severity of the variation: 0 None 1 Mild 2 Severe
19.	**In the past week, have you ever suddenly had the feeling that everything is unreal, or you're in a dream or cut of from other people in some strange way?** Any spacey feelings? IF YES: How bad has that been? How often this week has that happened?	**DEPERSONALIZATION AND DEREALIZATION** (such as feelings of unreality and nihilistic ideas): 0 Absent 1 Mild 2 Moderate 3 Severe 4 Incapacitating
20.	**This past week, have you felt that anyone was trying to give you a hard time or hurt you?** IF NO: what about talking about you behind your back? IF YES: Tell me about that.	**PARANOID SYMPTOMS:** 0 None 1 Suspicious 2 Ideas of reference 3 Delusions of reference and persecution
21.	**In the past week, have there been things you've had to do over and over again, like checking the locks on the doors several times?** IF YES: Can you give me an example? **Have you had any thoughts that don't make any sense to you but that keep running over and over in your mind?** IF YES: Can you give me an example?	**OBSESSIONAL AND COMPULSIVE SYMPTOMS:** 0 Absent 1 Mild 2 Severe

Appendix V. Diagnostic Criteria for Major and Minor Depression Episode (DSM-IV) and DIS-D based Algorithm

N.B. In order to rate a symptom as present, two criteria must be met:

1. The symptom must have been rated 2, 3, or 4.
2. The symptom must have been present for 2 weeks or longer

Criterion A. Symptom 1 is present:

0 – No
1 – Yes

Criterion B. Symptom 15 is present:

0 – No
1 – Yes

Criterion C. Among the following clusters:

1. Symptom 2, 3, 4 or 5 is present;	0 – No	1 - Yes
2. Symptom 6, 7, 8 or 9 is present;	0 – No	1 - Yes
3. Symptom 10 is present;	0 – No	1 - Yes
4. Symptom 11 or 12 is present;	0 – No	1 - Yes
5. Symptom 13 or 14 is present;	0 – No	1 - Yes
6. Symptom 16 is present;	0 – No	1 - Yes
7. Symptom 17, 18, 19, 20, or 21 is present.	0 – No	1 – Yes

Patient meets criteria for major depression (Criterion A or B plus 4-7 symptoms under Criterion C):

0 – No
1 – Yes

Patient meets criteria for minor depression (Criterion A or B plus 1-3 symptoms under Criterion C):

0 – No
1 – Yes

N.B. If symptom 20 or 21 is present or the patient has hallucinations or delusions, contact Dr. Cole before enrolling in the RCT.

Appendix VI. A Sample of Medication Records from RAMQ

Patient ID	DIN	Date of dispense	Generic code	AHFS Code	DOSE	Duration
10	2190915	10/24/1997	47146	564000	28426	30
10	2190915	11/28/1997	47146	564000	28426	30
10	2190915	12/26/1997	47146	564000	28426	30
10	2190915	1/21/1998	47146	564000	28426	30
10	2190915	2/20/1998	47146	564000	28426	30
10	2190915	3/30/1998	47146	564000	28426	30
10	2190915	4/24/1998	47146	564000	28426	30
10	2190915	5/22/1998	47146	564000	28426	30
10	2190915	6/25/1998	47146	564000	28426	30
10	2190915	7/23/1998	47146	564000	28426	30
10	2190915	8/20/1998	47146	564000	28426	30
10	2190915	9/25/1998	47146	564000	28426	30
10	2190915	10/23/1998	47146	564000	28426	30
10	2190915	11/19/1998	47146	564000	28426	30
10	2190915	12/23/1998	47146	564000	28426	30
10	2190915	1/21/1999	47146	564000	28426	28
10	2190915	2/17/1999	47146	564000	28426	28
10	836311	2/25/1999	45586	564000	21106	30
10	2190915	4/6/1999	47146	564000	28426	28
10	2190915	5/6/1999	47146	564000	28426	14
10	2190915	5/20/1999	47146	564000	28426	14
	" " "	" " "	" " "	" " "		
10	1940481	4/27/2000	47061	281604	28426	30
10	2190915	5/13/2000	47146	564000	28426	30
10	674346	5/23/2000	1664	401200	394	30
10	1940481	5/29/2000	47061	281604	28426	30
10	674346	6/22/2000	1664	401200	394	30
10	1940481	6/24/2000	47061	281604	28426	30
10	2190915	7/17/2000	47146	564000	28426	30
10	674346	7/22/2000	1664	401200	394	30
10	1940481	7/27/2000	47061	281604	28426	30
10	2230437	7/31/2000	39	280892	55924	7
10	860751	7/31/2000	3211	81224	41602	8
10	792667	8/11/2000	6591	81204	66856	7
10	2236842	8/11/2000	47258	82200	54412	1
10	2165511	8/18/2000	47140	564000	31964	30
10	2165511	9/13/2000	47140	564000	31964	30
10	2165511	10/13/2000	47140	564000	31964	30

Appendix VII. Psychotropic medications* evaluated in the study

Generic drug name	Antidepressant			Benzodiazepine		Other psychotropic	ACH Score†
	TCA	SSRI	Other	Long-HL	Short-HL		
amitriptyline (chlorhydrate d')	1	0	0	0	0	0	3
clomipramine (chlorhydrate de)	1	0	0	0	0	0	3
desipramine (chlorhydrate de)	1	0	0	0	0	0	2
doxepine (chlorhydrate de)	1	0	0	0	0	0	3
imipramine (chlorhydrate d')	1	0	0	0	0	0	3
nortriptyline (chlorhydrate de)	1	0	0	0	0	0	3
trimipramine	1	0	0	0	0	0	2
citalopram (bromhydrate de)	0	1	0	0	0	0	1
fluoxetine (chlorhydrate de)	0	1	0	0	0	0	1
fluvoxamine (maleate de)	0	1	0	0	0	0	1
paroxetine (chlorhydrate de)	0	1	0	0	0	0	2
sertraline (chlorhydrate de)	0	1	0	0	0	0	1
bupropion (chlorhydrate de)	0	0	1	0	0	0	1
maprotiline (chlorhydrate de)	0	0	1	0	0	0	2
nefazodone (chlorhydrate de)	0	0	1	0	0	0	1
tranylcypromine (sulfate de)	0	0	1	0	0	0	0
trazodone (chlorhydrate de)	0	0	1	0	0	0	1
venlafaxine (chlorhydrate de)	0	0	1	0	0	0	1
chlordiazepoxide (chlorhydrate de)	0	0	0	1	0	0	1
chlordiazepoxide (chlorhydrate de)	0	0	0	1	0	0	1
clobazam	0	0	0	1	0	0	0
clonazepam	0	0	0	1	0	0	0
diazepam	0	0	0	1	0	0	1
flurazepam (chlorhydrate de)	0	0	0	1	0	0	1
nitrazepam	0	0	0	1	0	0	0
alprazolam	0	0	0	0	1	0	1
bromazepam	0	0	0	0	1	0	1
lorazepam	0	0	0	0	1	0	0

Appendix VII. Cont'd

oxazepam	0	0	0	0	1	0	0
temazepam	0	0	0	0	1	0	0
triazolam	0	0	0	0	1	0	1
buspirone (chlorhydrate de)	0	0	0	0	0	1	0
carbamazepine	0	0	0	0	0	1	1
chloral (hydrate de)	0	0	0	0	0	1	0
chlorpromazine (chlorhydrate de)	0	0	0	0	0	1	3
divalproex sodique	0	0	0	0	0	1	0
gabapentine	0	0	0	0	0	1	0
haloperidol	0	0	0	0	0	1	2
lamotrigine	0	0	0	0	0	1	1
lithium (carbonate de)	0	0	0	0	0	1	0
l-tryptophane	0	0	0	0	0	1	0
methotrimeprazine	0	0	0	0	0	1	2
olanzapine	0	0	0	0	0	1	1
oxcarbazepine	0	0	0	0	0	1	0
phenobarbital	0	0	0	0	0	1	1
phenytoine	0	0	0	0	0	1	0
phenytoine sodique	0	0	0	0	0	1	0
phenytoine sodique	0	0	0	0	0	1	0
primidone	0	0	0	0	0	1	0
prochlorperazine	0	0	0	0	0	1	2
quetiapine (fumarate de)	0	0	0	0	0	1	1
risperidone	0	0	0	0	0	1	1
thioridazine (chlorhydrate de)	0	0	0	0	0	1	3
topiramate	0	0	0	0	0	1	0
trifluoperazine (chlorhydrate de)	0	0	0	0	0	1	1

* List only the 58 medications that were classified as psychotropics among a total of 269 generic drugs.

† Clinician-rated anticholinergic scores.

Appendix VIII. A Case-scenario demonstrating the strategy to define and quantify medication exposure*

Prescription drug		Therapeutic group	ACH score	*F/u period: day*	*1-15*	*16-30*	*31-45*	*46-60*	*61-75*	*76-91*	Summary Quantity†	
				Start and ending dates of prescriptions								
1	Chlomipramine	**Antidepressant**	3		-	20-30	-	-	-	76-91		
2	Diazepam	**Benzodiazepine**	1		1-15	16-30	31-45	-	61-75	76-82		
3	Phenobarbital	**Other psychotropic**	1		-	-	40-45	46-60	-	-		
4	Lovastatine	**(NOS)**	0		1-15	16-30	31-45	46-60	61-75	76-91		
Medication exposure (analytic variable)											**STW (D91/92)**	**LTW (D1-92)**
1	**# Drugs used**	***# Antidepressants***			0	1	0	0	0	1	1	2
		# Benzodiazepines			1	1	1	0	1	1	0	1
		#Other psychotropics			1	1	2	1	1	1	0	2
		Total # meds			2	3	3	1	2	3	2	3
2	**Exposed Drug Days (EDD)**	***EDD-Antidepressant***			0	11	0	0	0	16	1	27
		EDD-Benzodiazepine			15	15	15	0	15	7	0	67
		EDD-psychotropic			15	15	21	15	15	7	0	88
3	**ACH score**	***Cum. ACH scores***			1	4	2	1	1	4	3	5
		Total ACH burden			15	48	21	15	15	52	3	166

* Represents a hypothetical patient who used 4 meds and had his/her 3-month outcome (MMSE) assessment at day 92;

† Equal the sum of each measure across relevant time periods under short- or long- time window, respectively;

Abbreviations: ACH score, Clinician-rated anticholinergic score; STW, Short time window; LTW, Long time window.

Appendix IX. The Mini-Mental State Examination (MMSE)

1 a)	***What year is this?***	0	1	8
b)	***What season is this?***	0	1	8
c)	***What month of the year is this?***	0	1	8
d)	***What is today's date?***	0	1	8
e)	***What day of the week is this?***	0	1	8
2 a)	***What country are we in?***	0	1	8
b)	***What province are we in?***	0	1	8
c)	***What city are we in?***	0	1	8
d)	***What is the name of this place?***	0	1	8
e)	***What floor of the building are we on?***	0	1	8

Patient is competent (score of 5 or more on items 1 & 2) 1 Yes 0 No

If no, complete sections A, B, F, G, H only.

3. ***I am going to say 3 words. After I have said all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.***

   shirt, brown, honesty

   Please repeat the three words for me. 0 1 2 3 8

4. ***Spell the word "world".***
   Now spell it backwards please. _____ (30 SECONDS) 0 1 2 3 4 5 8

5. ***What were the three words I asked you to remember?*** (10 SECONDS) 0 1 2 3 8

6. Show a wrist watch. Ask, "***what is it called?***" (10 SECONDS) 0 1 8

7. Show a pencil. Ask, "***what is this called?***" (10 SECONDS) 0 1 8

8. Repeat the following phrase, "***no ifs, ands or buts***". (10 SECONDS) 0 1 8

9. ***Take this paper in your right/left hand, fold the paper in half and put it on the floor.*** (30 SECONDS) 0 1 2 3 8

10. ***Read the words on this paper and do what it says.*** (10 SECONDS) 0 1 8

11. ***Copy this design.*** (1 MINUTE) 0 1 8

12. *Write a complete sentence on this piece of paper.* 0 1 8