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Antidepressant Use and Cognitive Functioning in Older Medical Patients with Major or Minor Depression—a prospective cohort study with database linkage

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Abstract

OBJECTIVE—The long-term cognitive effect of antidepressant medications in older persons is not well understood, especially in those with minor depression and complex medical conditions. The objective of this study is to examine this relationship in older medical patients with different depression diagnoses.

METHODS—281 medical inpatients aged 65 and older from two acute care hospitals in Montreal, Canada were diagnosed as with major or minor depression or without depression according to DSM-IV criteria. They were followed up with the Mini-Mental State Examination (MMSE) for cognitive function and the Hamilton Depression Rating Scale (HDRS) for depressive symptoms at baseline and three, six and twelve months after discharge. Antidepressant medication was ascertained from a provincial prescription database and quantified as cumulative exposures over each follow-up interval.

RESULTS—During the 12-month follow-up period, 1, 027 antidepressant prescriptions were filled. The most frequently prescribed antidepressant agents were citalopram (0.81 prescriptions per person), sertraline (0.76) and paroxetine (0.66). Antidepressant use was not associated with cognitive changes among patients with major depression or without depression, but was associated with an increased MMSE score in patients with minor depression (1.4 point, 95% CI: 0.1–2.6), independent of change in the severity of depression symptoms, concomitant benzodiazepine or psychotropic drug use and other potentially important confounders.

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CONCLUSIONS—In this cohort of older medical patients, antidepressant use over 12-months did not lead to significant cognitive impairment. The small cognitive improvement among minor depression associated with antidepressant use deserves further investigation.

Keywords

Antidepressant use; minor depression; cognitive function; older persons; medical patients

INTRODUCTION

Depression in later life represents a major public health problem in modern society. It affects more than one quarter of those aged 65 years and older^{1–3} and has been associated with higher mortality, faster functional decline and increased health care costs.^{3–5} Therefore, development of effective pharmacological and other intervention strategies has potentially profound clinical and public health implications.

To date, antidepressant treatment has been recommended for major depression and, possibly, dysthymia.^{6–8} Whether or not it should be directed to elderly patients with milder depressive symptoms is controversial,^{7,9,10} due mainly to the limited and inconsistent evidence of efficacy and concern about the cognitive and other side effects, especially for the traditional tricyclic antidepressants (TCAs).^{11–13} Published randomized clinical trials (RCTs) that targeted specifically minor depression are sparse and have demonstrated only modest antidepressant benefit,^{7,10,14} mostly in subgroups of patients with more severe functional impairment¹⁰ or depression symptoms.¹⁴ Similarly, studies of the cognitive outcome of antidepressant treatment in the elderly are limited to major depression, with mixed results. Some demonstrated cognitive benefits following successful antidepressant treatment with both TCAs (e.g., nortriptyline) and selective serotonin reuptake inhibitors (SSRIs, e.g., sertraline),^{15–17} while others found no significant difference in cognitive gains between SSRIs-responders (citalopram etc) and placebo-responders or non-responders. Furthermore, the non-responders of treatment arms declined on verbal learning and psychomotor speed tests more than placebo groups.¹⁸ Given the measurable anticholinergic effects of several SSRI agents¹⁹ and increased vulnerability of elderly people to anticholinergic toxicity,^{11,13} clinicians working in geriatric or primary care settings, where non-major depression preponderates,^{2,5–7,9,10} still face a difficult decision: do the potential benefits of antidepressant treatment outweigh the potential risks of cognitive impairment and other side-effects^{3,6–9,13} if prescribed to their aged patients with milder depressive symptoms yet multiple comorbid conditions? Epidemiological studies are needed to fill the knowledge gap in this special population, in which RCTs have been sparse and methodologically inadequate due to overrepresentation of younger and healthier older persons, restriction on co-medications and short follow-up intervals.²⁰

We sought to examine the longitudinal relationship between antidepressant use and cognitive function using data from a cohort of older medical patients with and without meeting diagnostic criteria for major or minor depression at baseline.^{3,21,22} In light of the reported effect modification of antidepressant treatment by severity of depression symptoms,^{10–12,14–16} we hypothesized that the cognitive effects of antidepressant medications in older medical patients would differ according to depression diagnoses, a marker of the clinical severity of underlying depression pathology and the primary indication for antidepressant treatment. Accordingly, we expect that use of antidepressants may be beneficial to those with a diagnosis of major or minor depression, due presumably to the therapeutic efficacy of the drugs on resolving mood disturbance, but not to those who do not have clinically significant depressive symptoms.

MATERIALS AND METHODS

Participants

The participants of this study came from a randomized controlled trial 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 study protocol was approved by the research ethics committees of both hospitals, as described previously.^{21,22} 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);²³ 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)²⁴ and the Hamilton Depression Rating Scale (HDRS).²⁵ All patients with major or minor depression and a random sample of non-depressed patients were invited to participate in the longitudinal component of the study. 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. To enable longitudinal analyses, this study included only 281 participants with two or more MMSE assessments during the follow-up period, representing 67.9% of the baseline cohort.

Measurements

Depression—A structured psychiatric evaluation was administered by a trained research assistant at baseline and each subsequent follow-up, using the depressive disorders section of the DIS and the 21-item version of the HDRS. HDRS is the most widely used interviewer-rated scale for monitoring depressive symptoms in intervention studies, with higher scores indicating more pathology.²⁵ Patients were classified as major, minor, or no depression using an “inclusive” algorithm according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV, American Psychiatric Association, 1994), which counted current symptoms with a duration of at least two weeks towards a diagnosis regardless of their origins or aetiologies.²⁶ 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).

Cognitive function—The cognitive function was assessed using the Mini-Mental State Examination (MMSE)²⁷ by a trained research assistant initially at baseline and subsequently at three, six, and twelve months after discharge from hospitals. The MMSE is the most widely used brief cognitive instrument for screening cognitive impairment or monitoring cognitive change over time, with scores ranging from 0 to 30 (best). 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} 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).

Antidepressants and other medications—Data on medication use of study participants were obtained through linkage with the provincial prescription claims database, the Régie de l'assurance maladie du Québec (RAMQ).³⁰ RAMQ provided information on the generic name, drug identification number, total supply and date of dispensing for each drug product during the six months prior to the index hospitalization to the end of the follow-up period, as well as the therapeutic classification codes by the American Hospital Formulary Service system (AHFS).³¹

The RAMQ records of the study participants were independently reviewed by two authors (MC, LH). Antidepressant agents were identified based on drug names and specific AHFS code (28:16:04) and consisted of three subgroups: 1) SSRIs, including fluoxetine, sertraline, fluvoxamine, paroxetine and citalopram; 2) TCAs, including amitriptyline, desipramine, doxepine, imipramine, nortriptyline, trimipramine and clomipramine; and 3) other agents, including tetracyclics (maprotiline), monoamine oxidase inhibitors (tranylcypromine) and atypical antidepressants (trazodone, nefazodone, venlafaxine and bupropion). In addition, we identified other medications that are often co-prescribed to depressed elderly and may cause cognitive impairments on their own right as time-dependent covariates.^{32,33} Benzodiazepines included both long-acting (clonazepam, clobazam, chlordiazepoxide, diazepam, flurazepam and nitrazepam) and short-acting (oxazepam, lorazepam, triazolam, temazepam, bromazepam and alprazolam) agents based on a cutpoint half-life of 24 hours; psychotropics comprised all non-benzodiazepine sedatives/anxiolytics, antipsychotics, lithium, anticonvulsant and antiparkinson drugs. Anticholinergic medications were defined using a clinician-rated anticholinergic score (range: 0–3, 1 indicating anticholinergic),³⁴ given their implication in drug-induced cognitive impairments and senile dementia.

Exposure time-window—We considered the last three months of each follow-up interval as clinically plausible time window to observe cognitive effect of antidepressants. Total antidepressant exposure within each time window was calculated by summing up numbers of daily doses supplied across different antidepressant agents, regardless of prescribed dosage. Because actual drug intake by patients may be delayed for several days or weeks after they fill a prescription, the antidepressant drugs dispensed immediately prior to a MMSE assessment may not be used until after the assessment and hence, can not affect patients' cognitive performance at that time. To account this possible time lag, the cumulative antidepressant exposure was derived by excluding prescriptions during the last four weeks. This exclusion also addressed a clinical scenario that apparent clinical effects of most TCA or SSRI agents typically arise after two to four weeks' continued treatment.^{6–8}

Potential confounders—Data on covariates were collected at enrolment from either patient interviews or hospital charts. The demographic factors included age, sex and education. Study design or participant selection factors included study group (RCT Intervention, RCT-Control, Not RCT), number of SPMSQ errors at screening and duration of follow-up. Severity and complexity of current illnesses were measured using the composite Charlson Comorbidity Index (CCI)³⁵ and a binary indicator for CVD risk (high vs low) 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.³ Furthermore, we collected data on previous history of depressive episodes (remote, recent, or neither), since recurrent depressive episodes may indicate poor treatment response or severe depressive pathology.^{7–9}

Statistical analysis

The characteristics of the study sample at baseline were summarized by descriptive statistics and compared among depression diagnoses using one-way ANOVA or chi-square tests, as appropriate.

A mixed effects linear regression model was used to simultaneously account for both fixed-in-time (e.g., sex) and time-varying covariates (e.g., severity of depression symptoms).³⁶ The cognitive outcome was represented by the changes in the MMSE scores from baseline to three, six and twelve months. A Spatial Power covariance structure was chosen to account for potential inter-correlation of repeated MMSE measures on the same patients.³⁶ To optimize both the capacity of the multivariable mixed model to control for confounding by indications and its efficiency, we used a “group mean” parameterization to simultaneously estimate average antidepressant effects across times, one for each depression diagnosis (major, minor or no depression).³⁴

Potential confounding was addressed in a stepwise fashion. Starting with a baseline model that included only the three diagnosis-specific antidepressant exposure variables as sole predictors, we first adjusted for age, education, number of SPMSQ errors, baseline MMSE scores, study group and duration of follow-up. Inclusion of baseline SPMSQ and MMSE allowed for drawing inference about the longitudinal cognitive change among participants with comparable initial level of cognitions; whereas adjusting for study group may help eliminate potential residual effect of the RCT intervention, despite the 6-month trial did not show statistically significant benefits during the 6-month trial.²¹ Next, we expanded the model by adding CVD risk and CCI to account for potential residual confounding by indications or contra-indications not captured by depression diagnoses. Finally, we included previous history of depressive episodes and the time-dependent HDRS change score to account for both the historical and concurrent “severity” makers of depression pathology that may predetermine the cognitive outcome of current antidepressant “treatment”.

We conducted sensitivity analyses to assess the robustness of the final model. First, to assess the validity of the cumulative exposure assumption, we redefined antidepressant use as users versus non-users within each follow-up interval, without regard to duration of use. Second, to assess the impact of assumed exposure time lag, we re-calculated the cumulative antidepressant exposure without eliminating the last four weeks from each time window. Finally, to determine whether the antidepressant effects on cognitive function may vary over time, we tested interactions between each group-specific antidepressant exposure and follow-up intervals.

To provide insight into the “specificity” of the relationship, we performed, though admittedly underpowered, exploratory analyses by further adjusting the final model for each co-medication (i.e., benzodiazepines, psychotropics and anticholinergics) and by examining specific antidepressant subclass (i.e., SSRI and TCA). Finally, to determine whether the cognitive benefit of antidepressants may result from their efficacy on resolving mood disturbance,^{15,16} we respecified the final model by regressing the HDRS change score (the dependent variable), instead of the MMSE, on remaining covariates and baseline HDRS score.

All the statistical analyses were conducted using SAS software version 9.1 (SAS Institute, Cary NC 2003). 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 restricted deviance ($-2 \log$ Likelihood) statistics.³⁶ The hypotheses were tested at a two-sided significance level of $\alpha = 0.05$.

RESULTS

The baseline characteristics of the study population are summarized in Table 1. In comparison with those excluded (N=133), the included patients (N=281) had more comorbid conditions ($p<0.01$), lower mean HDRS ($p=0.05$), and higher mean MMSE ($p=0.03$) scores, but comparable demographic profiles, depression diagnoses and SPMSQ scores (all p values above 0.07).

The three depression groups differed with respect to the mean HDRS scores and previous history of depression (all p values below 0.05). Patients with major or minor depression used more antidepressant drugs (overall and SSRIs alone, $p<0.05$) and benzodiazepines ($p<0.01$) than those without depression. There were no significant between-group differences in remaining baseline characteristics or with regard to psychotropic, anticholinergic or total medication use (all p values above 0.05). The MMSE scores of the three groups showed a similar trend of slight increase from baseline up to six months, then decreased at twelve months.

A total of 1,027 antidepressant prescriptions were filled during the follow-up period. Patients with major, minor or no depression, respectively, filled an average of 5.9, 2.3 and 1.8 prescriptions. The most frequent antidepressants were citalopram (229 prescriptions), paroxetine (186), sertraline (213), trazodone (73) and nortriptyline (58), with average daily doses of 20.5, 14.1, 37.2, 67.1 and 16.7 mg, respectively. The cumulative antidepressant exposures over each follow-up interval are presented in Table 2. Patients with major depression had highest exposure to total antidepressants and SSRIs at all time; while patients with minor depression had higher exposure to SSRIs than no depression only during last follow-up interval.

Table 3 summarizes a series of mixed models evaluating association between antidepressant exposure and cognitive change. There was no significant association detected in patients with major depression or without depression (all p values above 0.20). Among patients with minor depression, an eight-week cumulative antidepressant exposure was associated with 1.4 (95% CI: 0.1–2.6, $p=0.03$) point increment on the MMSE, after controlling for all preselected covariates (models # 4).

Sensitivity analyses yielded consistent results. For minor depression, on average across three follow-up intervals, antidepressant users had 1.4 (95% CI: 0.3 to 2.5, $p=0.018$) point higher MMSE scores than non-users. When counting antidepressant prescriptions during the last four weeks into the exposure, the relationship became “diluted” (0.9, 95% CI: –0.01 to 1.7, $p=0.052$), consistent with the lagged exposure assumption. There were no statistically significant relationships detected from major depression or no depression groups (all p values above 0.60), or significant exposure by time interactions (all p values above 0.15).

The relationship in minor depression patients sustained after additional adjustment for concurrent benzodiazepine (1.4, 95% CI: 0.2–2.7, $p=0.02$) or psychotropic (1.4, 95% CI: 0.1–2.6, $p=0.03$) use, but diminished after adjusting for total anticholinergic burden (1.0, 95% CI: –0.4–2.3, $p=0.15$). Neither TCAs nor SSRIs were significantly associated with cognitive changes ($p>0.09$). Antidepressant exposure was not associated with HDRS score changes over time in the “efficacy” model ($p=0.92$).

DISCUSSION

In this cohort of older medical patients, antidepressant use over twelve months was not associated with cognitive changes among those with major depression or without depression. For patients with minor depression, cumulative antidepressant exposure

appeared to be statistically significantly associated with a small improvement in cognitive performance, independent of age, baseline cognitive function, concomitant benzodiazepine or other psychotropic drug use, and concurrent change in the severity of depression symptoms. These results suggest that use of antidepressant medications over one year may not pose significant risk on comprising the cognitive function of older medical patients with different depressive pathology. This may reflect the fact that nowadays clinicians working with elderly are more vigilant of the drugs' side effects and tend to choose newer products that are largely devoid of potentially harmful anticholinergic properties (e.g., sertraline)^{13,15–17} or prescribe the regimen at lower dose, especially when treating non-depression conditions, such as chronic pain syndrome.^{12,13} These findings in general are consistent with our hypothesis that the cognitive effect of antidepressants in elderly patients varies according to the diagnoses of depression, rather than be uniformly beneficial or deleterious.

However, the lack of protective association with cognitive impairment in patients with major depression is not consistent with results of recent studies that demonstrated an improved or stable cognitive function following successful antidepressant treatments.^{12,13,15–17} We suspect this might reflect inadequate dose or duration of antidepressant use due to non-adherence of the patients after discharge from hospital.^{6,8,9,14} Alternatively, both the “inclusive” diagnostic algorithm and the HDRS have limitations and could misclassify some patients who may not be at full blown “major” episode or manifested only moderate symptoms. Consequently, the potential secondary benefit of antidepressant treatment on cognitive function might not have been achieved, or was overshadowed by the inherent deleterious anticholinergic effects of some drugs.^{11,13,15–17}

On the other hand, this is the first observational study that reported a potential cognitive benefit of antidepressant drugs in patients with minor depression. Due to the small magnitude of the benefit and the non-random “treatment” assignment, we can not offer definite answers as to whether the finding may reflect an artifact due to high motivation and benefit expectation of the minor depression patients who self-selected to pursue antidepressant treatment, or a true cognitive enhancing property of the drugs beside their action on mood disturbance. Several recent studies, however, have suggested that some antidepressants may have direct pharmacological action on cognition through interaction with other neurotransmitter systems,³⁷ or by stimulating neurogenesis in the hippocampus and other brain regions implicated in major depressive disorder.³⁸ In light of these new insights, the potential cognitive enhancing property of low dose antidepressants in elderly patients with clinically significant minor depression deserves further investigation.

The strengths of this study are several. First, we used a comprehensive administrative database to ascertain medication prescriptions throughout the follow-up period, reducing potential misclassification bias due to ignorance of the changes in medication exposure over time. Second, we rigorously controlled for indication bias by estimating diagnostic-specific antidepressant effects, simultaneously adjusted for both current and historical markers of depression severity and for confounding by co-medications, enhancing the validity of the observed relationship. Third, we examined our *a priori* hypotheses using a biologically plausible exposure time window for drug action, facilitating clinical application of the study findings.

Three important limitations should be noted. First, we did not take into account the actual dose or adherence to the prescriptions, or otherwise have capacity to measure the blood level of the drugs to verify actual antidepressant exposure. Second, the outcome measure, MMSE, has been criticized for insensitivity to small cognitive changes and subjectivity to practice effect over a short assessment intervals.²⁶ Finally, as this was an observational study, there

is a possibility that some unmeasured confounders (e.g., use of cognitive enhancing drugs or anxiety disorders) that affected both the propensity for antidepressant use and the cognitive performance may explain, entirely or partially, an observed relationship. Therefore, the clinical pharmacological implications of this study may lie mainly in the lack of negative association, such that for elderly medical patients who met the clinical diagnostic criteria for major or minor depression, use of antidepressants over three to twelve months, likely at low dose, may not pose significant risk of cognitive impairment. Further studies using larger and more representative samples and more precise measurements are needed to replicate and understand the possible beneficial cognitive effect of antidepressant medications in older medical patients with minor depression.

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References

1. Beekman ATF, Copeland JRM, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999; 174:307–311. [PubMed: 10533549]
2. Lavretsky H, Kumar A. Clinically significant non-major depression: old concepts, new insights. *Am J Geriatr Psychiatry*. 2002; 10:239–255. [PubMed: 11994211]
3. Steffens DC, Otey E, Alexopoulos GS, et al. Perspectives on Depression, Mild Cognitive Impairment, and Cognitive Decline. *Arch Gen Psychiatry*. 2006; 63:130–138. [PubMed: 16461855]
4. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry*. 1999; 156:1182–1189. [PubMed: 10450258]
5. Beekman ATF, Deeg DJ, Braam AW, et al. Consequence of major and minor depression in later life: a study of disability, well-being, and service utilization. *Psychol Med*. 1997; 27:1397–1409. [PubMed: 9403911]
6. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. [Review]. *JAMA*. 1997; 278:1186–1190. [PubMed: 9326481]
7. Oxman TE, Sengupta A. Treatment of Minor Depression. *Am J Geriatr Psychiatry* [Review]. 2002; 10:256–264.
8. Snow V, Lascher S, Mottur-Pilson C. Pharmacological Treatment of Acute Major Depression and Dysthymia. *Ann Intern Med*. 2000; 132:738–742. [PubMed: 10787369]
9. Ackermann RT, Williams JW. Rational treatment choices for non-major depressions in primary care. An evidence-based review. *J Gen Intern Med*. 2002; 17:293–301. [PubMed: 11972726]
10. Williams JW, Barrett, Oxman T, et al. Treatment of dysthymia and minor depression in primary care. A randomized controlled trial in older adults. *JAMA*. 2000; 284:1519–1526. [PubMed: 11000645]
11. Oxman TE. Antidepressants and cognitive impairment in the elderly. *J Clin Psychiatry*. 1996; 57:38–44. [PubMed: 8647791]
12. Amado-Boccaro I, Gougoulis N, Poirier Litte MF, et al. Effects of antidepressants on cognitive functions: a review. [Review]. *Neurosci Biobehav Reviews*. 1995; 19:479–493.
13. Lotrich F, Pollock BG. Aging and Clinical Pharmacology: Implications for Antidepressants. *J Clin Pharmacology*. 2005; 45:1106–1122.
14. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-analysis. *JAMA*. 2010; 303:47–53. [PubMed: 20051569]

15. Butters MA, Becker JT, Nebes RD, et al. Changes in cognitive functioning following treatment of late-life depression. *Am J Psychiatry*. 2000; 157:1949–1954. [PubMed: 11097959]
16. Doraiswamy PM, Krishnan RR, Oxman T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *J Geront Series A Biol Sci Med Sci*. 2003; 58A:1137–1144.
17. Nebes RD, Pollock BG, Mulsant BH, et al. Cognitive effects of paroxetine in older depressed patients. *J Clin Psychiatry*. 1999; 60(Suppl 20):26–29. [PubMed: 10513855]
18. Culang M, Sneed JR, Keilp JG, et al. Change in Cognitive Functioning After Acute Antidepressant Treatment in Late-Life Depression. *Am J Geriatr Psychiatry*. 2009; 17:881–888. [PubMed: 19916207]
19. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc*. 2008; 56:1333–1341. [PubMed: 18510583]
20. Vandenbroucke JP, Psaty BM. Benefits and Risks of Drug Treatments: How to Combine the Best Evidence on Benefits With the Best Data About Adverse Effects. *JAMA*. 2008; 300:2417–2419. [PubMed: 19033592]
21. Cole MC, McCusker J, Dendukuri N, et al. Systematic detection and multidisciplinary care of depression in older medical inpatients: a randomized trial. *CMAJ*. 2006; 174:38–44. [PubMed: 16330624]
22. Han L, McCusker J, Cole M, et al. 12-month cognitive outcome of major and minor depression in older medical patients. *Am J Geriatr Psychiatry*. 2008; 16:742–751. [PubMed: 18757768]
23. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975; 23:433–441.
24. Robins LN, Helzer JE, Croughan J, et al. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Arch Gen Psychiatry*. 1981; 38:381–389. [PubMed: 6260053]
25. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967; 6:278–296. [PubMed: 6080235]
26. Koenig HG, George LK, Peterson BL, et al. Depression in medically ill hospitalized older adults: Prevalence, characteristics, and course of symptoms according to six diagnostic schemes. *Am J Psychiatry*. 1997; 154:1376–1383. [PubMed: 9326819]
27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
28. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. [Review]. *J Am Geriatr Soc*. 1992; 40:922–935. [PubMed: 1512391]
29. Han L, Cole M, Bellavance F, et al. Tracking cognitive decline in Alzheimer's disease using the mini-mental state examination: a meta-analysis. *Int Psychogeriatrics*. 2000; 12:231–247.
30. Tamblyn B, Lovaie G, Petrella L, et al. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims databases in Quebec. *J Clin Epidemiol*. 1995; 48:999–1009. [PubMed: 7775999]
31. American Society of Hospital Pharmacists. American Hospital Formulary Service. Drug information. Bethesda, MD: 1994.
32. Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol*. 2002; 22:285–293. [PubMed: 12006899]
33. Dealberto MJ, Mcavay GJ, Seeman T, et al. Psychotropic drug use and cognitive decline among older men and women. *Int J Geriatr Psychiatry*. 1997; 12:567–574. [PubMed: 9193967]
34. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med*. 2001; 161:1099–1105. [PubMed: 11322844]
35. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987; 40:373–383. [PubMed: 3558716]
36. Verbeke, G.; Molenberghs, G. Linear mixed models for longitudinal data. New York, USA: Springer-Verlag New York, Inc.; 2000.

37. Steckler T, Sahgal A. The role of serotonergic-cholinergic interactions in the mediation of cognitive behavior. *Behav Brain Res.* 1995; 67:165–199. [PubMed: 7779290]
38. Perera TD, Park S, Nemirovskaya Y. Cognitive role of neurogenesis in depression and antidepressant treatment. *Neuroscientist.* 2008; 14:326–338. [PubMed: 18612087]

TABLE 1

Characteristics of Study Population by Depression Diagnosis at Baseline

Characteristics*	Major Depression	Minor Depression	No Depression	P
	(n = 121)	(n = 51)	(n = 109)	
Age, yr	78.7 ± 7.1	78.4 ± 6.9	79.9 ± 7.3	0.333
Sex, 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)	
No. SPMSQ errors [†]	1.6 ± 1.2	1.6 ± 1.4	1.6 ± 1.4	0.960
Charlson Comorbidity Index	1.4 ± 1.6	1.3 ± 1.4	1.5 ± 1.5	0.791
Risk for CVD, 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)	
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)	
HDRS score [§]	19.9 ± 5.8	13.5 ± 5.3	9.5 ± 5.7	<0.001
MMSE score [‡]	25.8 ± 3.2	25.1 ± 3.3	26.2 ± 3.9	0.137
No. prescription medications dispensed during the recent month				
Antidepressants				
TCA	0.05 ± 0.22	0.06 ± 0.31	0.04 ± 0.19	0.830
SSRI	0.21 ± 0.43	0.10 ± 0.30	0.06 ± 0.25	0.006
Other	0.03 ± 0.18	0.02 ± 0.14	0.03 ± 0.16	0.888
Total	0.29 ± 0.51	0.18 ± 0.43	0.13 ± 0.34	0.018
Benzodiazepines	0.43 ± 0.64	0.25 ± 0.48	0.21 ± 0.43	0.007
Psychotropics	0.21 ± 0.57	0.10 ± 0.30	0.16 ± 0.43	0.314
Anticholinergics	0.98 ± 1.23	1.00 ± 1.23	0.87 ± 1.08	0.737
Total no. medications	6.46 ± 5.49	6.90 ± 5.93	5.95 ± 5.11	0.561

* 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 (N).

[†] Scores range from 0 to 10, with higher scores indicating more cognitive impairment.

[‡] Scores range from 0 to 30, with higher scores indicating better cognitive performance.

[§] Scores range from 0 to 63, with higher scores indicating greater severity of depression symptoms.

^{||} Includes nonbenzodiazepine sedatives, anxiolytics, barbiturates, antipsychotics, antiparkinson drugs, and anticonvulsants.

[¶] Based on a clinician-rated anticholinergic score (range, 0–3) of 1 or higher, denoting at least mild anticholinergic effect.

[#] Two-tailed *P* value based on χ^2_2 test for categorical variables and overall *F* test (numerator *df* = 2, denominator *df* vary from 250 to 278) of unbalanced 1-way ANOVA for continuous variables.

AD indicates antidepressant.

TABLE 2
Cumulative Antidepressant Exposure* Over Time by Depression Diagnosis at Baseline

AD Class	Follow-up Period	Major Depression Mean SD	Minor Depression Mean SD	No Depression		<i>P</i> *
				Mean	SD	
TCA	Baseline to 3 mo	2.8 ± 10.9	2.7 ± 14.0	0.7 ± 5.6		0.246
	3–6 mo	1.1 ± 6.7	2.6 ± 11.8	2.1 ± 10.3		0.676
	9–12 mo	1.9 ± 10.2	0.7 ± 4.9	1.6 ± 8.9		0.576
SSRI	Baseline to 3 mo	11.3 ± 20.4	4.0 ± 13.2	2.3 ± 9.9		<0.001
	3–6 mo	12.2 ± 22.8	6.8 ± 18.3	2.4 ± 11.1		<0.001
	9–12 mo	13.3 ± 23.6	4.6 ± 14.9	1.3 ± 7.0		<0.001
Other	Baseline to 3 mo	3.1 ± 14.2	1.8 ± 12.6	0.8 ± 7.4		0.318
	3–6 mo	5.5 ± 23.1	1.7 ± 12.0	1.3 ± 10.0		0.557
	9–12 mo	4.9 ± 22.0	0.8 ± 5.6	0.3 ± 2.9		0.042
Total	Baseline to 3 mo	15.9 ± 25.1	7.8 ± 20.0	3.7 ± 13.1		<0.001
	3–6 mo	16.8 ± 27.4	10.5 ± 21.8	5.5 ± 17.4		0.001
	9–12 mo	18.3 ± 30.7	6.1 ± 16.3	2.9 ± 11.9		<0.001

Defined as cumulative number of daily doses dispensed across different antidepressant prescriptions during each specified exposure time window.

* Two-tailed *P* value based on overall *F* test (numerator *df* = 2, denominator *df* vary from 250 to 278) of unbalanced 1-way ANOVA.

AD indicates antidepressant.

Relationship Between Cumulative Antidepressant Exposure and Cognitive Function Among Older Medical Patients With Different Depression Diagnoses at Baseline

TABLE 3

Model No.	Major Depression			Minor Depression			No Depression		
	Est*	95% CI	P	Est*	95% CI	P	Est*	95% CI	P
1 [†]	-0.45	-1.15 to 0.26	0.214	0.70	-0.75 to 2.15	0.344	0.03	-1.44 to 1.50	0.968
2 [‡]	-0.14	-0.78 to 0.49	0.661	1.28	-0.01 to 2.57	0.053	0.55	-0.69 to 1.79	0.387
3	-0.10	-0.75 to 0.54	0.751	1.32	0.04 to 2.60	0.043	0.39	-0.86 to 1.64	0.540
4 [¶]	-0.21	-0.84 to 0.43	0.519	1.37	0.14 to 2.60	0.030	0.35	-0.87 to 1.56	0.576

* Values represent average decline (minus sign) or increment (otherwise) on the MMSE across the 3 follow-up assessments associated with an 8-week cumulative antidepressant exposure estimated using a mixed effects linear regression model.

[†] Included only 3 predictor variables representing each depression diagnosis.

[‡] Adjusted model 1 for age, education, study group, number of errors on the SPMSQ, baseline MMSE score, and follow-up duration.

^{||} Adjusted model 2 for risk of CVDs and Charlson Comorbidity Index.

[¶] Adjusted model 3 for previous history of depressive episodes and change in the scores of the HDRS from baseline to each follow-up assessment.

Est indicates effect estimate.