Published in final edited form as:

J Clin Psychopharmacol. 2016 October ; 36(5): 445–452. doi:10.1097/JCP.0000000000000545.

Antidepressant Medication Treatment and Risk of Death

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Abstract

Objective—Although prior studies have assessed whether depression is a mortality risk factor, few have examined whether antidepressant medications (ADMs) influence mortality risk.

Methods—We estimated hazards of one-year all-cause mortality associated with ADMs, with use occurring within 90 days of depression diagnosis among 720,821 patients who received treatment in a Veterans Health Administration facility during fiscal year 2006. We addressed treatment selection biases using conventional Cox regression, propensity-stratified Cox regression (PS), and two forms of marginal structural models (MSM). Models accounted for multiple potential clinical and demographic confounders, and sensitivity analyses compared findings by antidepressant class.

Results—ADM use compared to no use was associated with significantly lower hazards of one-year mortality risk in Cox (HR = 0.93, 95% CI = 0.90, 0.97) and PS estimates (HR = 0.94, 95% CI = 0.91, 0.98), while MSM-based estimates showed no difference in mortality risk when the exposure was specified as ‘as-treated’ in every 90-day intervals of the one-year follow-up (HR = 0.91, 95% CI = 0.66, 1.26), but showed increased risk when specified as ‘intent-to-treat’ (HR = 1.07, 95% CI = 1.02, 1.13).

Conclusions—Among patients treated with ADMs belonging to a single class in the first 90 days, there were no significant differences in one-year all-cause mortality risks. When accounting

for clinical and demographic characteristics and treatment selection bias, ADM use was associated with no excess harm.

Keywords

antidepressants; mortality; propensity scores; marginal structural models

INTRODUCTION

Comprehensive assessments of potential mortality risks associated with antidepressant medication (ADM) use are relatively rare, and to the extent that they exist, they typically focus on suicide or self-harm,¹ or single causes of mortality, such as cardiac death. Most research on the efficacy of depression treatment employs randomized controlled trials (RCTs), which often include highly selected populations (typically excluding sick and older adults) receiving state-of-the-art care with close clinical follow-up over short time horizons. Although RCTs may be the gold standard of depression treatment trials, they do not inform policy or practice on how real world treatment influences depression or mortality outcomes at the population level. Large longitudinal studies that carefully address treatment selection biases can complement RCTs by providing useful and rarely available information on how depression treatment may or may not affect longer-term outcomes such as mortality.

Among the existing studies on the relationship between depression treatment and mortality, results have been somewhat inconsistent, perhaps in part based on different research designs and study questions. One study demonstrated that a depression care management intervention for older adults decreased mortality; however the specific impact of ADMs on mortality in this study is unclear.² An observational study in the Veterans Health Administration (VHA) found that depressed patients who received adequate follow-up visits during ADM treatment had reduced mortality rates twelve months later; however, this study did not isolate the impact of ADMs on mortality.³ Other studies have examined the impact of ADMs on mortality, but these studies have not limited study cohorts to patients with diagnosed depression.^{4, 5} One such study found gender differences in the relationship between ADMs and mortality, with higher mortality risks present among men treated with ADMs and women not treated with ADMs.⁶ We identified one research group that sought to comprehensively assess the relationship between ADMs and mortality outcomes among individuals with depression treated in primary care in the United Kingdom.^{7, 8} This study found substantial risks of mortality associated with ADM treatment in older adults, with a follow-up study of ADM use and mortality among younger adults forthcoming.⁹ Therefore, it remains unclear whether ADM treatment for depression confers a greater or lower risk of mortality compared to untreated depression.

The present study extends upon prior work on depression and mortality^{10, 11} to assess the association between ADM use among patients with depression and risk of all-cause mortality compared to closely comparable patients not receiving ADMs in a large health system, employing several methods to address potential treatment selection biases as well as controlling for multiple clinical and demographic factors. We hypothesized that in analyses that did not fully address potential treatment selection biases, it may appear that ADMs are

associated with an increased risk of mortality (e.g., sicker patients take ADMs and are also more likely to die). However, we also hypothesized that in analyses that addressed potential selection biases, ADMs may be associated with a decreased risk of mortality, or no increased risk of mortality. Finally, although older ADMs are known to have more side effects than newer ADMs or selective serotonin reuptake inhibitors (SSRIs), based on prior research^{7, 8}, we hypothesized that older ADMs would be associated with lower mortality risks than newer ADMs or SSRIs.

MATERIALS AND METHODS

Patient cohort

All Veterans older than 18 years with a depression diagnosis (International Classification of Diseases Ninth Revision codes: 293.83, 296.2, 296.3, 296.90, 296.99, 298.0, 300.4, 301.12, 309.0, 309.1, 311) recorded during fiscal year (FY) 2006 who received treatment in a VHA facility at least once in that same year were included in this study. After identifying the earliest VA facility visit in FY2006 with a depression diagnosis (index date), patient clinical administrative data (including inpatient and outpatient diagnoses and health services utilization) were obtained for one year preceding and one year following the index date.

The study protocol was approved by the VA Ann Arbor Institutional Review Board.

Dependent variable

The primary outcome, all-cause mortality, was assessed using National Death Index (NDI) data up to one year post-index date.

Key independent variable

The analyses considered exposure in two ways: as time-fixed and binary (any ADM used versus not) or as time-varying exposure over the follow-up time. The primary exposure variable was exposure to any ADM in the first 90 days following the index date in FY2006. To determine exposure in this 90-day period, each day was considered as either exposed to an ADM or not based on days of supply and date of fill. ADM fills that occurred during the 90 days prior to the index date were also included when assessing medication exposure during this period; for example, if a patient received a 30-day fill two weeks before the index date, then the 16 days following the index date (i.e., 30 days dispensed minus 14 pre-index days) were considered as exposed. Thus a patient can be considered as exposed to ADM based on a prescription filled prior to index date if the supply remained beyond the index date. When accounting for exposure days as time-varying, we considered seven days or less of a gap between two consecutive fills as a continuous exposure, which is smaller gap than the 14-day gap previous researchers have used to predict discontinuation.¹²

For secondary analyses, we also constructed exposure variables for three classes of ADMs: 1) selective serotonin reuptake inhibitors (SSRIs); citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), 2) older agents: amitriptyline, amoxapine, clomipramine, desipramine, dothepin, doxepin, imipramine, lofepramine, iprindole, mianserin, isocarboxazid, moclobemide, maprotiline, nortriptyline, protriptyline,

trimipramine, phenelzine, tranylcypromine, trazodone (300 mg only), selegiline, and 3) newer agents: bupropion, desvenlafaxine, duloxetine, mirtazapine, nefazodone, reboxetine, venlafaxine, vilazodone. Exposure status to each ADM class was determined based on exposure to each ADM class separately; for this analysis, individuals on more than one ADM were excluded.

Patient characteristics

We controlled for baseline sociodemographic, clinical, and utilization characteristics that could be associated with patient mortality. Demographic characteristics included: age at index date (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80), sex (female, male), and race (White, African American, other). Prior psychotherapy was defined based on having any psychotherapy (Current Procedural Terminology codes 90804–90815, 90845, 90847, 90853, 90857) in 90 days prior to the index date. Baseline utilization characteristics were defined based on administrative data during the 90 days prior to the index date and included: psychotherapy visits (0, 1), the numbers of outpatient visits excluding psychotherapy visits (0, 1, or 2), psychiatric hospitalizations (0, 1), non-psychiatric hospitalizations (0, 1).

For baseline clinical characteristics, all administratively available data in the year before baseline were used to capture all diagnostic codes. Clinical characteristics included comorbidity adjustment using the Charlson comorbidity index^{13, 14} as a categorical variable (0, 1, 2, 3, 4), with higher scores indicating greater comorbidity burden, and indicators of psychiatric comorbidities. Psychiatric conditions included: anxiety disorder and/or post-traumatic stress disorder (PTSD; ICD-9 codes: 300.00–300.02, 300.09–300.10, 300.20–300.23, 300.29, 309.81), serious mental illness (including bipolar disorder, schizophrenia, and other psychoses; 295, 296.0–296.1, 296.4–296.8, 297.0–297.3, 297.8–297.9, 298.0–298.4, 298.8–298.9), nicotine use (305.1), alcohol use disorder (303.0, 303.9, 305.0), and drug use disorder (292, 304, 305.2–305.9).

All included patients were diagnosed with depression on the index date, but their baseline depression severity may differ, and therefore we created a proxy of baseline depression severity based on administrative data in order to adjust for baseline differences. We categorized patients into six mutually exclusive groups based on frequency and recency of depression diagnoses in the four quarters prior to index date, which we expected to approximate varying depression severity at the time of index date. The levels were (1) depression diagnoses noted at least once in every quarter (90-day interval) prior to index date (Group A), (2) depression diagnoses noted in the quarter immediately prior to the index date, but not in all prior quarters (Group B), (3) depression diagnoses not noted in the first quarter, but in the second quarter prior to the index date (Group C), (4) depression diagnoses not noted in the first two quarters, but noted in the third quarter prior to the index date (Group D), (5) depression diagnoses noted only in the most distant quarter prior to the index date (Group E), and (6) no depression diagnosis in prior year (Group F). The groups were expected to approximate a range from most to least severe, with Group A corresponding to most severe and Group F to “newly” diagnosed.

For models requiring time-dependent covariates (e.g., MSMs), all exposure, clinical and utilization variables were updated for every 90-day interval during the year after the index

date based on data during the year prior to, and including that 90-day interval (i.e., four quarters of data).

Data analyses

The primary analytic goal was to assess the relative hazard of death associated with ADM use during a one year follow-up period after depression diagnosis (i.e., index date), and the secondary goal was to compare the mortality risks across the three different classes of ADMs. We first examined the distributions of all baseline variables and their relationships with ADM exposure, as well as with one-year mortality. As the analyses are based on observational data, ADM exposure is not independent of baseline factors. Hence, for both the primary and secondary objectives, we used three analytic approaches to address potential confounding and treatment indication biases: conventional Cox regression (Cox), propensity-based Cox regression (PS), and marginal structural models (MSM). Each approach has its own assumptions,¹ and the goal was to draw a careful conclusion across the different approaches. Cox and PS analyses were adjusted for potential clustering at the VA facility level using robust sandwich estimation.

Mortality associated with ADM treatment—ADM exposure status was defined as a baseline variable, determined by whether the patient was exposed to an ADM during the first 90-day period after the index date. This assumes that a patient was exposed to ADMs continuously if once exposed during the first 90 days. Cox regression was used to model death occurring from the index date to one year or to time of death, whichever occurred earlier, adjusting for baseline covariates, including the proxy measures of depression severity categories and ADM use in the preceding 90 days. We also fit a parallel Cox model, with ADM exposure as time-varying reflecting the actual daily exposure. We note that ADM effect estimated based on either definition of exposure is potentially biased: ADM exposure as time-fixed is likely biased as the exposure is subjected to bias from misclassification, and the ADM effect estimate based on the actual daily ADM exposure (i.e., as time-varying), is likely biased due to potential confounding in the presence of time-dependent confounders that are also affected by previous exposures.

The PS model controlled for treatment indication bias by accounting for the likelihood that a given patient will receive an ADM.¹⁵ We first estimated propensity scores for ADM use during the first 90 days after the index date using logistic regression based on a priori specified baseline variables and relevant interactions (noted below in Table 2) including demographic variables, medical and psychiatric diagnoses, proxy measures of depression severity, and health system utilization. The PS model was fitted without consideration for parsimony, with most continuous variables included without categorization, with quadratic and interaction terms. Hazard ratio (HR) estimates for one-year mortality associated with ADM use were obtained within each propensity quintile (strata), after truncating the cohort to those in the area of overlapping propensities between those treated versus not to remove residual confounding. The HR estimates were examined across the propensity strata to assess for notable non-uniform HRs, and the pooled HR estimate was obtained as the HR associated with any ADM exposure.

Lastly, the MSM model was used to appropriately account for time-varying exposures affected by earlier time-dependent confounders, other treatments, and exposures using weights, assuming no unmeasured confounders and a correctly specified mortality model.¹⁶ For the MSM model, the data were discretized to one observation per 90-day period with follow-up to one year, resulting in up to four observations per patient, and the model estimated the causal effect of the ADM use, estimating the hazard ratio at any 90-day interval if patients were continuously treated compared to if they were never treated.¹⁶ All time-varying exposures and covariates were updated every 90 days, and a pooled logistic regression model, which is equivalent to the Cox model,¹⁷ was used to model the mortality and estimate hazard ratio. The contribution of each patient to the calculation at each follow-up quarter until death or the fourth quarter (i.e., end of one year) was weighted by the stabilized inverse probability-of-ADM treatment weight, with each weight estimated from the observed data. The probability of the patient receiving ADM treatment was estimated for each quarter, given his/her own treatment history up to the current quarter including exposures to other ADMs and to other psychotropic medications, past time-varying treatment, covariates, and utilization history, using logistic regression.

Two different model specifications were done for the MSMs. Our primary MSM estimate was obtained assuming that patients initiate treatment and remained treated once they are exposed to an ADM at the first quarter after the index date, similar to *intention-to-treat*. A second MSM estimate was obtained based on observed ADM exposure status that varied *as-treated* for each 90-day interval.

Mortality comparison across three ADM classes—We first fit a Cox model using the full cohort data and indicators for exposure to each of the three ADM classes during the first 90 days, using no ADM use as the reference group, where a person can be exposed to more than one class of ADMs. We also examined the distribution of patterns of exposure to different classes of ADMs during the first 90 days, and based on these examinations, repeated the Cox model restricting the data to those patients exposed to a single ADM class during the first 90 days. In the analysis of ADM class comparison based on single class exposed patients, the primary exposure variables were two indicators, one for newer non-SSRI agents and one for older non-SSRI agents, with exposure to SSRIs as the reference group. For the comparison of three ADM classes in a PS model, a multinomial model for exposure in the first 90 days to three classes of ADMs was fit without consideration for parsimony. We then used a Cox regression model, inversely weighted by the estimated propensities, to estimate one-year hazard ratios associated with older and with newer ADMs using SSRIs as the reference group. In addition to propensity weighing, the Cox model was adjusted for a limited set of baseline covariates to adjust for their effects on mortality risk.

For the MSM, the contribution of each patient to the calculation at each follow-up quarter was weighted by the stabilized inverse probability-of-treatment weight. The probability of the patient receiving a particular ADM class or combination treatment was estimated for each quarter, given his/her own treatment history up to the current quarter, including receipt of different psychotropic medication, and covariate and utilization history, using multinomial logistic regression. We specified the MSM in two ways. One specification assumed that the person was treated with the same ADM class as the initial ADM for the remaining quarters,

equivalent to intent-to-treat. The second specification modeled exposures to different ADM classes at subsequent quarters, resulting in eight treatment combinations including no ADM or a combination of all three ADM classes at any given follow-up quarter.

RESULTS

A total of 720,821 patients were included in the study. Of them, 74.1% (N=533,836) were exposed to an ADM during the first 90 days after the index date. Distributions of baseline patient characteristics showed significant differences in all characteristics between those exposed to any ADM during the 90 days versus not. Most notably, psychotherapy use in prior 90 days, and the distribution of proxy depression severity measures, all indicated greater baseline severity in those exposed to ADMs. In addition, the two groups differed with respect to race, number of outpatient visits, comorbid anxiety disorders and PTSD, and overall psychotropic use (Table 1).

Mortality associated with ADM exposure

Crude mortality data are summarized as proportion of patients that died. Crude 90-day mortality was 0.98%, and was lower in those exposed to an ADM in the first 90 days (0.82%; 95% CI: 0.80%, 0.85%) than those not exposed (1.43%; 95% CI: 1.38%, 1.49%). One-year mortality was 3.71%, with 3.50% (95% CI: 3.45%, 3.55%) in patients exposed to any ADM in the first 90 days vs. 4.31% (95% CI: 4.21%, 4.40%) in those not exposed to an ADM in the first 90 days. The Cox regression adjusted HR for one-year mortality associated with any ADM use was 0.93 (95% CI: 0.90, 0.97; Table 2). When ADM exposure was included as time-varying reflecting the actual daily exposure, covariate adjusted HR from the Cox model was 0.61 (95% CI: 0.60, 0.63).

The PS model, stratified by propensity quintiles, yielded a pooled HR of 0.94 (95% CI: 0.91, 0.98) for one-year mortality associated ADM treatment. The estimates were 0.89 (95% CI: 0.84, 0.94), 1.06 (95% CI: 0.99, 1.13), 1.06 (95% CI: 0.98, 1.15), 0.92 (95% CI: 0.84, 1.02) and 0.79 (95% CI: 0.70, 0.90) from lowest to highest propensity quintiles. We checked the balance on covariates in propensity adjusted population. Due to the large sample size in this study, the distribution of majority of potential confounders we listed under Table 1 remain statistically different between the treated and untreated groups even after propensity application. The distributions of covariates between the treated and untreated within each propensity quintile, however, showed much greater similarity, as demonstrated by the reduction in standardized bias where the standardized bias for each covariate was calculated as the mean difference in the covariates between groups, divided by the standard deviation of treated group. The largest standardized bias before adjustment was 0.265 for antianxiety medication use in prior three months, but after propensity adjustment, the largest standardized bias observed in any quintile for all assessed covariates was 0.182.

Lastly, the MSM based estimates gave inconsistent results; higher risk with ADM treatment was estimated (HR = 1.07; 95% CI: 1.02, 1.13) based on the model assuming that the patient was treated with an ADM for the remaining quarters once an ADM was initiated, i.e., as intent-to-treat, while lower risk with ADM treatment was estimated (HR = 0.91; 95% CI = 0.66, 1.26) based on the model specified as as-treated.

Mortality associated with different classes of ADMs

Analyses examining patients by exposure to the three ADM classes showed that during the first 90-day period, 8.4% were exposed to older agents, 25.3% to newer non-SSRI agents, and 54.4% to SSRIs, each with or without agents belonging to other classes of ADM. Of the 74.1% (N=533,836) exposed to an ADM during the first 90 days, 82% (N=437,654) were exposed to a single class of ADMs during the first 90-days.

Variations in mortality were seen across the different ADM classes, but none of the ADM exposed classes showed crude mortality as high as that seen in patients not exposed to any ADMs during the same periods. In the Cox regression analysis of the full cohort (N=720,821) adjusting for baseline covariates, although HR associated with older agents and with newer agents were both in the direction of lower mortality relative to no ADM use, neither was significant; however, mortality associated with SSRIs was significantly lower than no ADM use (HR = 0.96; 95% CI: 0.94, 0.99; Table 1). No difference in mortality risks between pairs of ADM classes were seen based on contrasts of parameter estimates.

In the subset of those exposed to a single class of ADMs during the first 90 days (N=437,654), crude 90-day mortality was lowest in those exposed to newer non-SSRI agents (0.76%), followed by older agents (0.86%) and SSRIs (0.90%), and a similar pattern was seen in crude one-year mortality. However, Cox regression showed no difference in one-year mortality between newer agents versus SSRIs (HR=1.02; 95% CI: 0.98, 1.06), as well as between older agents and SSRIs (HR=0.93; 95% CI: 0.86, 1.00; Table 2). Both the PS model based estimates and the MSM-based estimates in the subset of patients exposed to single ADM classes gave similar results with minor differences in estimate precision. In short, in all three analytic approaches, no difference in one-year mortality was seen between non-SSRI newer agents and SSRIs, but we observed potentially lower one-year mortality among those exposed to older non-SSRI agents compared to SSRIs. We also note that in MSM models that assumed that the patient was treated with the same initial ADM class for the remaining quarters, the magnitudes of the association were estimated to be greater; compared with SSRIs, the HR associated with older ADM was 0.91 (95% CI: 0.83, 0.99) and the HR associated with newer non-SSRI ADM was 1.07 (95% CI: 1.03, 1.12).

DISCUSSION

This study adds to a relatively limited literature examining mortality risks associated with ADM treatment among depressed patients. In contrast to a recent study which reported an increased all-cause mortality associated with ADM use,⁸ we did not find ADM use, in comparison with no ADM treatment, to be associated with an increased mortality. ADM use was associated with a lower risk of one-year mortality after adjusting for baseline covariates using the Cox model, whether it was for any ADM treatment (Table 2) or each class of ADMs (Table 1) compared to no use. In addition to traditional Cox regression, we also utilized two additional analytic approaches, including a PS model and two MSM models. The PS model had similar findings to the Cox model. To account for time-varying exposure to ADMs while avoiding potential time-varying confounding from time-varying treatments and covariates over the follow-up period, we used an MSM to attempt to approximate the causal effect of ADM treatment. However, the MSM estimate of the ADM exposure effect

depended on the model specification. Although not significant, ADM exposure showed a somewhat lower mortality risk, when the model specified the exposure as *as-treated*, while it showed statistically significant somewhat elevated risk when the model specified the exposure as *intent-to-treat*. The latter intent-to-treat specification assumed that once a patient initiated any ADM treatment in the first 90 days, the patient is assumed to continue the treatment from that period forward.

It is possible that those who are either already on or initiate an ADM treatment to discontinue ADM treatment if their medical illness burden increases. If such is the case, the intent-to-treat specification would assume that very ill patients who actually discontinued their ADM treatment are assumed to have continued the ADM treatment, and this would potentially result in estimating the ADM treatment to have null effect or higher mortality than no ADM treatment, even when the overall ADM treatment effect in fact may be protective. On the other hand, the as-treated specification would estimate the treatment to have lower mortality than no ADM treatment, if indeed ADM treatment is associated with lower mortality.

To support our speculation for the increased mortality associated with ADM use under the intent-to-treat specification, we examined the direction of the association between various baseline and time-varying covariates predicting ADM treatment during follow-up 90-day intervals using PS models. We found a rapidly decreasing rate of ADM treatment propensity with older age, as indicated by a negative association with both the age and the squared term of age of the patient in the PS model. In addition, the indicators for medical burden variables, including the time-varying history of medical hospitalization or Charlson comorbidity index of 4 or larger, were associated with lower propensity of ADM treatment. These support our speculation that the sickest and oldest patients were less likely to be exposed to ADM and less likely to continue the ADM exposure if already exposed.

Overall, our findings do not support a significant difference in mortality associated with ADM treatment. We attempted to obtain robust results and used multiple analytic methods to address potential treatment selection biases and examined mortality associated with both any ADM use and with individual ADM classes. Further, we attempted to address depression severity and account for other medical and psychiatric disorders and treatment in our analytic models. Finally, we used a very large national sample of adults of all ages, enhancing generalizability. Nonetheless as described above, MSM model estimates, which have the advantage of accounting for time-varying confounding, were sensitive to how the models were specified. In addition, although the overall one-year mortality risk associated with ADM exposure was significantly lower than no exposure in the PS model stratified by propensity quintiles (HR = 0.94), the estimates were heterogeneous with HR estimates of 0.89, 1.06, 1.06, 0.92 and 0.79 from lowest to highest propensity quintiles.

Three primary interpretations from these findings are possible: 1) that active treatment with ADMs, either through treating depression or through direct physiological effects, are potentially associated with lower all-cause mortality risk, but we did not find consistent evidence for this, 2) that residual confounding by indication exists and prescribers are selecting patients at lower mortality risk to initiate ADM treatment, or 3) that “healthy

adherer” effects are present whereby patients continuing to take ADMs are at lower mortality risk than those who discontinue the medications.

Several differences in patient cohort, study design, and analytic approaches can explain the differences between our study and the UK study, which found increased risks of mortality associated with ADM use.⁸ We included patients treated in all care settings within a health system, whereas the prior study used a primary care database. We did not exclude patients for having prior diagnoses of depression or prior ADM use, while the UK study excluded those with depression diagnosis or those with ADM prescription fill in the 12 months before recorded depression diagnosis. We did not use those exclusions in order to assess the relationship between mortality and ADM use in all patients with a depression diagnosis, and instead controlled for prior year depression diagnosis or ADM use. The UK study was also limited to older adults and excluded those with a serious mental illness diagnosis in the 12 months before the index recorded depression diagnosis. In our sensitivity analyses in the subset of patients 65 years old or older and applying the same exclusion criteria as the UK study and thus essentially including the “newly” diagnosed and “newly” treated older adults without serious mental illness diagnosis (data not shown, N=19,610), we essentially found no difference in mortality using the same Cox regression model (adjusted HR=1.08; 95% CI = 0.95, 1.23).

In this subset of older patients, yet another analytic approach giving the average treatment effect (ATE)¹⁸ based on the binary outcome of death in one year by inverse-probability weighting (estimated to correct for the missing data on the potential outcomes) also resulted in a null finding (coefficient = 0.005; 95% CI = -0.002, 0.012). The UK study followed patients for varying lengths of time up to 12 years for some patients and adjusted for baseline covariates assessed at the index depression diagnosis, while our study followed patients for one year, and that might explain their estimate of increased risk of all-cause mortality associated with ADM use. We chose to follow only for one year because it seemed unrealistic to be able to estimate the mortality risk associated with a medication use from a long and varying follow-up time while adequately adjusting for baseline differences. This factor is particularly relevant in an observational study where numerous other treatments and illnesses can affect not only the use, but the duration, discontinuation and re-initiation of medication use and long-term outcome of the patients in one way or another. In fact, in this subset of older adults, when we restricted our follow-up to death in 90 days, HR based on the same Cox regression was 0.93 (95% CI = 0.73, 1.19) and ATE for ADM based on potential-outcome means for the binary outcome of death in 90 days was estimated to be -0.001 (95% CI = -0.005, 0.002), both null results, but in the direction of decreased mortality with treatment.

Analytically, for our primary aim, we chose to consider exposure to ADM based on their ADM use in the first 90 days, although in another model, we also treated the exposure as fully time-varying. This assumption about treating the exposure as a baseline exposure is similar in spirit to intent-to-treat and considers anyone who initiated the treatment to have continued on the treatment afterwards whether they stopped or changed treatments, and likewise, those who did not initiate ADM in the first 90 days are considered not to be on an ADM during the entire follow-up time. The HR for one-year mortality associated with any

ADM use was 0.93, but when ADM exposure was included as time-varying, the HR was 0.62. It is possible that the treatment is indeed protective, but we believe this significant negative estimate based on the time-varying exposure is biased in that the time-varying treatment is likely affected by the time-varying medical or mental illnesses, when those nearing death are less likely to be treated with ADMs.

One finding that was similar across the two studies, and was perhaps surprising in both, is that older ADMs appeared safer than newer ADMs and SSRIs, although we generally did not find significant differences across the ADM classes. This is counter to prevailing evidence of the lower risk profiles associated with SSRI use.¹⁹ However, those profiles may not be focused on mortality as an outcome. It is also possible that residual confounding could explain this association, as older adults or patients with significant medical comorbidities may not be prescribed older ADMs.

Another interesting finding of note in the present study is that while ADM medications appeared to have a lower risk of mortality, other psychotropic medication use was associated with higher mortality risks. It is possible that those risks could be associated with inappropriate use of medications in a depressed patient population. Yet, many patients in this study had additional psychiatric diagnoses that could indicate need for additional psychotropic medication use, indicating that other psychotropic medication use (e.g., antipsychotic medications, benzodiazepines) could be a measure of severity.

We note some limitations to our findings. Our study focused on a very narrow time horizon, as we examined one year mortality. This is in contrast to the UK study that included multiple years of ADM treatment and follow up. It is possible that ADM use would become more problematic or lead to longer-term mortality risks, however, we believe it is difficult to carry out an observational data study looking at a long-term follow-up and outcome, unless a more sophisticated causal modeling approach is taken such as the MSM model that accounts for time-varying confounding. However, even under the best circumstances of prospective data collection, there is no guarantee that all factors that influence both the long-term treatment and outcome can be measured or collected. Our study focused on a VHA patient population that may not be generalizable to the general population. Our study was also unable to identify depression using a standardized clinical assessment tool. We did not control for dose or duration of ADM treatment, which could also have an impact on mortality risks. Finally, it is beyond the scope of this paper that uses administrative data to untangle the potential mechanism(s) that could explain the potential increased or decreased risks of mortality associated with ADM use. Such mechanisms could include the fact that depression increases the risk of mortality and not treating it adequately may be detrimental²⁰, side effects of ADMs having negative outcomes, and that depression may be an early manifestation of medical illness that becomes more apparent at a later point in time²¹, among other possible explanations. Different comorbidity profiles and combinations could also have differential effects on mortality risks.

Despite these limitations, our study found that ADM treatment could be associated with lower risks of mortality among depressed patients relative to no treatment, or at worst, ADM use did not substantially either increase or decrease mortality risk. This finding provides

additional support for ADM treatment among patients with depression in addition to the goal of appropriately managing depression outcomes and improving quality of life. Future research should follow patients for longer time periods to determine whether the effect of treatment observed here is sustained among patients treated in an overall health system population and should include patients with various medical and psychiatric illness severity profiles.

Acknowledgments

Source of Funding: Dr. Zivin reports grant funding from Department of Veterans Affairs (VA IIR 10-176-3) during the conduct of the study. Dr. Maust was supported by the Beeson Career Development Award Program (NIA K08AG048321, AFAR, The John A. Hartford Foundation, and The Atlantic Philanthropies). There are no other competing interests to report. Dr. Smith was supported by a VA HSR&D Career Development Award (CDA 09-216).

References

1. Valenstein M, Kim HM, Ganoczy D, et al. Antidepressant agents and suicide death among us department of veterans affairs patients in depression treatment. *J Clin Psychopharmacol*. 2012; 32:346–353. [PubMed: 22544011]
2. Gallo JJ, Bogner HR, Morales KH, et al. The effect of a primary care practice-based depression intervention on mortality in older adults - a randomized trial. *Ann Intern Med*. 2007; 146:689–698. [PubMed: 17502629]
3. Cully JA, Zimmer M, Khan MM, et al. Quality of depression care and its impact on health service use and mortality among veterans. *Psychiatr Serv*. 2008; 59:1399–1405. [PubMed: 19033166]
4. Smoller JW, Allison M, Cochrane BB, et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the women's health initiative study. *Archives of Internal Medicine*. 2009; 169:2128–2139. [PubMed: 20008698]
5. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch Gen Psychiatry*. 2006; 63:1358–1367. [PubMed: 17146010]
6. Ryan J, Carriere I, Ritchie K, et al. Late-life depression and mortality: Influence of gender and antidepressant use. *Br J Psychiatry*. 2008; 192:12–18. [PubMed: 18174502]
7. Coupland C, Dhiman P, Barton G, et al. A study of the safety and harms of antidepressant drugs for older people: A cohort study using a large primary care database. *Health Technol Assess*. 2011; 15:1–202. [PubMed: 21810375]
8. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. *BMJ*. 2011; 343:d4551. [PubMed: 21810886]
9. Coupland C, Morriss R, Arthur A, et al. Safety of antidepressants in adults aged under 65: Protocol for a cohort study using a large primary care database. *BMC Psychiatry*. 2013; 13:135. [PubMed: 23663769]
10. Zivin K, Ilgen MA, Pfeiffer PN, et al. Early mortality and years of potential life lost among veterans affairs patients with depression. *Psychiatr Serv*. 2012; 63:823–826. [PubMed: 22854727]
11. Zivin K, Yosef M, Miller EM, et al. Associations between depression and all-cause and cause-specific risk of death: A retrospective cohort study in the veterans health administration. *J Psychosom Res*. 2015; 78:324–331. [PubMed: 25697585]
12. Hansen RA, Dusetzina SB, Dominik RC, et al. Prescription refill records as a screening tool to identify antidepressant non-adherence. *Pharmacoepidemiol Drug Saf*. 2010; 19:33–37. [PubMed: 19998397]
13. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987; 40:373–383. [PubMed: 3558716]

14. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with icd-9-cm administrative databases. *J Clin Epidemiol*. 1992; 45:613–619. [PubMed: 1607900]
15. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983; 70:41–55.
16. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000; 11:550–560. [PubMed: 10955408]
17. Laird N, Olivier D. Covariance analysis of censored survival data using log-linear analysis techniques. *Journal of the American Statistical Association*. 1981; 76:231–240.
18. Imai K, King G, Stuart EA. Misunderstandings between experimentalists and observationalists about causal inference. *Journal of the Royal Statistical Society Series A*. 2008; 171:481–502.
19. Ferguson JM. SSRI antidepressant medications: Adverse effects and tolerability. *Prim Care Companion J Clin Psychiatry*. 2001; 3:22. [PubMed: 15014625]
20. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Arch Gen Psychiatry*. 1976; 33:1029–1037. [PubMed: 962487]
21. Cosci F, Fava GA, Sonino N. Mood and anxiety disorders as early manifestations of medical illness: A systematic review. *Psychother Psychosom*. 2015; 84:22–29. [PubMed: 25547421]

TABLE 1

Patient characteristics by any ADM exposure during first 90 days after depression diagnosis in FY2006 (unadjusted) and adjusted Cox regression estimates comparing mortality risks associated with three groups of ADMs relative to no ADMs (N=720,821)

Characteristics	Unadjusted			Adjusted	
	Non-exposed N (%)	Exposed N (%)	Total N (%)	HR	95% CI
	186,985 (25.94)	33,836 (74.06)	720,821		
ADM classes [†]					
Older agents	NA	60,567 (11.35)	60,567 (8.40)	0.96	0.92–1.01
Newer agents	NA	182,704 (34.22)	182,704 (25.35)	0.98	0.94–1.02
SSRIs	NA	392,259 (73.48)	392,259 (54.42)	0.96	0.94–0.99
Prior treatment [*]					
Any ADM treatment in the prior 90 days	17,414 (9.31)	382,342 (71.62)	399,756 (55.46)	0.90	0.87–0.93
Psychotherapy treatment in the prior 90 days	45,313 (24.23)	196,541 (36.82)	241,854 (33.55)	0.75	0.72–0.78
Depression severity (most to least severe) ^{**}					
Group A	9,963 (5.33)	68,234 (12.78)	78,197 (10.85)	0.83	0.76–0.89
Group B	125,868 (67.31)	354,013 (66.31)	479,881 (66.57)	1.00	0.93–1.08
Group C	4,136 (2.21)	18,550 (3.47)	22,686 (3.15)	0.79	0.72–0.88
Group D	5,619 (3.01)	18,046 (3.38)	23,665 (3.28)	0.81	0.74–0.89
Group E	4,261 (2.28)	10,823 (2.03)	15,084 (2.09)	0.78	0.70–0.86
Group F (“newly” diagnosed)	37,138 (19.86)	64,170 (12.02)	101,308 (14.05)	ref	ref
Demographic factors					
Age (years) – mean ± SD	58.42 ± 14.98	58.60 ± 13.82	58.55 ± 14.13	NA	NA
18 to <30	8,310 (4.44)	15,930 (2.98)	24,240 (3.36)	ref	ref
30–39	12,159 (6.50)	32,452 (6.08)	44,611 (6.19)	1.08	0.83–1.39
40–49	28,364 (15.17)	77,315 (14.48)	105,679 (14.66)	1.80	1.44–2.25
50–59	61,790 (33.05)	196,071 (36.73)	257,861 (35.77)	2.71	2.16–3.39
60–69	32,855 (17.57)	97,769 (18.31)	130,624 (18.12)	3.88	3.10–4.86
70–79	24,936 (13.34)	69,932 (13.10)	94,868 (13.16)	7.17	5.72–9.00

Characteristics	Unadjusted			Adjusted	
	Non-exposed N (%)	Exposed N (%)	Total N (%)	HR	95% CI
>=80	18,571 (9.93)	44,367 (8.31)	62,938 (8.73)	13.18	10.54–16.48
Male	169,481 (90.64)	479,118 (89.75)	648,599 (89.98)	1.66	1.54–1.78
Race					
African American	31,167 (16.67)	69,086 (12.94)	100,253 (13.91)	0.81	0.76–0.86
Other	27,492 (14.70)	65,625 (12.29)	93,117 (12.92)	1.39	1.31–1.47
White	128,326 (68.63)	399,125 (74.77)	527,451 (73.17)	ref	ref
Health services utilization *					
Non-psychotherapy outpatient visits					
0	8,983 (4.80)	27,384 (5.13)	36,367 (5.05)	ref	ref
1	55,070 (29.45)	124,598 (23.34)	179,668 (24.93)	0.84	0.78–0.91
2	122,932 (65.74)	381,854 (71.53)	504,786 (70.03)	0.74	0.68–0.80
Any psychiatric hospitalization	4,789 (2.56)	13,197 (2.47)	17,986 (2.50)	0.99	0.91–1.07
Any non-psychiatric hospitalization	17,304 (9.25)	38,673 (7.24)	55,977 (7.76)	2.55	2.45–2.64
Comorbidities **					
Charlson score, mean $\pm$ SD	1.10 $\pm$ 1.70	1.15 $\pm$ 1.64	1.14 $\pm$ 1.66	NA	NA
0	95,230 (50.93)	252,481 (47.30)	347,711 (48.24)	ref	ref
1	43,636 (23.34)	134,831 (25.26)	178,467 (24.76)	1.61	1.54–1.68
2	20,850 (11.15)	63,952 (11.98)	84,802 (11.76)	2.51	2.40–2.62
3	12,079 (6.46)	38,593 (7.23)	50,672 (7.03)	3.09	2.95–3.25
4	15,190 (8.12)	43,979 (8.24)	59,169 (8.21)	5.25	5.01–5.49
Anxiety and/or PTSD	50,499 (27.01)	203,025 (38.03)	253,524 (35.17)	0.80	0.78–0.83
Serious mental illness ***	18,914 (10.12)	50,406 (9.44)	69,320 (9.62)	1.15	1.09–1.20
Nicotine use	39,038 (20.88)	118,220 (22.15)	157,258 (21.82)	1.20	1.17–1.24
Alcohol use disorder	28,304 (15.14)	78,121 (14.63)	106,425 (14.76)	1.33	1.28–1.38
Substance use disorder	21,138 (11.30)	55,080 (10.32)	76,218 (10.57)	1.12	1.06–1.18
Opioid medication use	33,604 (17.97)	139,027 (26.04)	172,631 (23.95)	1.33	1.29–1.37
Psychotropic use **					

Characteristics	Unadjusted		Adjusted	
	Non-exposed N (%)	Exposed N (%)	Total N (%)	HR 95% CI
Anticholinesterase	2,802 (1.50)	14,440 (2.70)	17,242 (2.39)	1.17 1.10–1.25
Mood stabilizers	20,205 (10.81)	101,327 (18.98)	121,532 (16.86)	0.89 0.86–0.93
Atypical antipsychotics	11,867 (6.35)	66,373 (12.43)	78,240 (10.85)	1.22 1.16–1.29
Conventional antipsychotics	1,342 (0.72)	3,649 (0.68)	4,991 (0.69)	1.28 1.12–1.47
Antianxiety medications ****	23,485 (12.56)	127,319 (23.85)	150,804 (20.92)	1.25 1.20–1.30

† patients can be taking more than one ADM class

* 90 days prior to first depression diagnosis in FY2006

** one year prior to first depression diagnosis in FY2006

*** Serious mental illness includes bipolar, schizophrenia, other psychoses

**** antianxiety medications include benzodiazepines and hypnotics

TABLE 2

Hazard ratio estimates associated with ADM treatment versus no ADM treatment based on full cohort, and HR estimates associated with older or newer ADMs versus SSRI based on the restricted cohort of those treated with single ADM class during the first 90 days

Analytic Method *	ADM use vs. none (N=720,821)		Comparison across three ADM classes (N=437,654)		
	No use	ADM use	SSRI	Older ADMs	Newer ADMs
Cox	1.00	0.93 (0.90, 0.97)	1.00	0.93 (0.86, 1.00)	1.02 (0.98, 1.06)
PS ^ψ	1.00	0.94 (0.91, 0.98)	1.00	0.96 (0.88, 1.04)	1.04 (1.00, 1.08)
MSM (ITT) ^ω	1.00	1.07 (1.02, 1.13)	1.00	0.91 (0.83, 0.99)	1.07 (1.03, 1.12)
MSM (AT) ^ω	1.00	0.91 (0.66, 1.26)	1.00	0.85 (0.72, 1.01)	1.03 (0.94, 1.13)

Abbreviation: PS is propensity score; MSM is marginal structural model; ITT is intent-to-treat, and AT is as-treated.

* All models are adjusted for covariates listed in Table 1.

^ψ Additional variables in the PS models included: interactions of baseline depression severity by gender and by race, interactions of age (linear, quadratic and cubic terms) and both depression severity and gender, number of outpatient visits (linear, quadratic, cubic terms) instead of categories of outpatient visits, psychiatric hospital days (linear, quadratic, cubic terms) instead of any psychiatric hospitalization (yes/no), non-psychiatric hospital days (linear, quadratic, cubic terms) instead of any non-psychiatric hospitalization (yes/no), interactions between individual medical comorbidities included in Charlson index, psychiatric comorbidities, and psychiatric medications with gender. All variables where quadratic and cubic terms are included are first centered at their mean values.

^ω Additional variables in the propensities of treatment model of the MSM estimate included age as continuous with linear and quadratic terms (after centering) and time-dependent values for service utilization, comorbidities and medication based on data from current 90 day periods.