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Benzodiazepines and adequacy of initial antidepressant treatment for depression

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Abstract

In short term efficacy studies, co-prescription of a benzodiazepine improves first-month adherence and response to antidepressant treatment. We used Veterans Health Administration (VHA) data to examine the impact of co-prescribed benzodiazepines on initial antidepressant adherence in routine clinical practice and the risks of long-term benzodiazepine use, abuse, and dependence. Our study population was 43,915 VHA patients diagnosed with depression and started on an antidepressant between October 2006 and September 2007. Using logistic regression adjusting for demographic and clinical covariates, we predicted the likelihood that patients received antidepressant treatment for an adequate duration (90 days) with our primary independent variable of interest being receipt of a benzodiazepine on the same day as the antidepressant start. We also assessed the frequency and characteristics of patients whose benzodiazepine use persisted for one year or who were diagnosed with anxiolytic abuse or dependence after receiving combined treatment. The adjusted probability of receiving antidepressant treatment of adequate duration was 42.4% for patients who received a benzodiazepine with their initial antidepressant compared to 39.3% for patients initially treated with an antidepressant alone ($p < 0.001$). Among patients who received combined treatment, 14.1% subsequently used benzodiazepines for at least one year and 0.7% were diagnosed with anxiolytic abuse or dependence. Anxiolytic abuse or dependence, but not long-term benzodiazepine use, was associated with other substance use disorders. These findings should be considered by clinicians when assessing the individual risks and benefits of combining a benzodiazepine with antidepressant treatment.

Keywords

adherence; anxiolytic; abuse; dependence; veterans

Introduction

Practice guidelines recommend initial antidepressant treatment for major depressive disorder be maintained for 6 months following remission of symptoms in order to avoid early recurrence; however, more than half of patients prescribed antidepressants discontinue treatment within 90 days (1, 2). Co-prescribing a benzodiazepine with an antidepressant reduces the likelihood of treatment dropout due to side effects and results in greater

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improvement in depression symptoms during the first 4 weeks according to meta-analyses of randomized controlled trials(3). Whether similar outcomes are obtained in routine clinical practice has not been systematically evaluated.

Benzodiazepine treatment carries risks of abuse, dependence, and withdrawal symptoms upon discontinuation, particularly with long-term use(4). Benzodiazepines also increase the risk for cognitive impairment, falls, and hip fractures in the elderly, although the impact of benzodiazepine use on these outcomes may be no worse than for many other psychotropic medications(5-8). The incidence of these outcomes when benzodiazepines are used in conjunction with antidepressants to treat depression is not well established and is important for clinicians and patients to weigh the potential risks of combined treatment with any observed benefits.

Using clinical data from the largest integrated health system in the U.S., the Veterans Health Administration (VHA), we examined whether co-prescription of a benzodiazepine with an initial antidepressant increased the likelihood of adequate antidepressant coverage in the first 90 days following treatment initiation and in the 91-180 day period following treatment initiation. We also examined the frequency of long-term benzodiazepine use, the development of anxiolytic abuse or dependence, and the incidence of hip fractures among patients who were prescribed a benzodiazepine at the time of starting an antidepressant.

Methods

Data source

Data were obtained from the VA National Registry for Depression, which contains records of demographic characteristics, clinical diagnoses, service utilization, and pharmacy use for all VA patients with a depressive disorder diagnosis. We used data from fiscal year (FY) 2007 and 2008.

Study population

We identified patients who had no antidepressant prescription in the first six months of FY 2007 (i.e., a “clean” period) followed by an antidepressant prescription in the second half of FY 2007 and a qualifying depressive disorder diagnosis during the year. We excluded patients with a benzodiazepine prescription prior to the antidepressant start. We obtained one year of follow-up data from the date of the antidepressant start, excluding patients who died during this time. We also excluded patients with a diagnosis of a psychotic disorder or bipolar disorder, those with more than 15 days in an inpatient setting during the 90 days after the antidepressant start, and patients who received prescriptions for two different antidepressants on the date of the first antidepressant fill. This study was conducted with institutional review board approval from the VA Ann Arbor Health System.

Qualifying antidepressants were all of the commonly available antidepressants within the U.S., excluding trazodone because this medication is frequently prescribed for insomnia and rarely administered at a dose that would adequately treat depression(9). We limited the analysis to only newer generation antidepressants (fluoxetine, citalopram, paroxetine, sertraline, bupropion, venlafaxine, mirtazapine) in a sensitivity analysis. Qualifying depression diagnoses were based on ICD-9-CM codes and included major depressive disorder, dysthymia, depression not otherwise specified, and adjustment disorder with depressed mood.

Outcome Variables

Adequate acute phase antidepressant treatment was defined as whether or not antidepressant medication was dispensed for 72 out of the 90 days following the initial prescription. We chose this definition, and focused on treatment duration rather than dose, as a similar measure was shown to predict subsequent hospitalization in a depressed VA population(10). In our primary analysis, we excluded patients initially prescribed a 90-day supply of antidepressant as they would have automatically fulfilled our criteria for adequate antidepressant treatment. Since prior studies have not reported making this exclusion, we also conducted a sensitivity analysis in which these individuals remained in the sample. We also conducted a sensitivity analysis using the Healthcare Effectiveness Data and Information Set (HEDIS) measure of adequate antidepressant treatment, which is defined as whether patients received any antidepressant for at least 84 out of the 114 days following a new antidepressant start(11). Adequate *continuation* phase antidepressant treatment was defined similarly to our acute phase measure and assessed whether medication was dispensed for 72 days out of the 90-day period following receipt of adequate acute phase treatment.

Long-term benzodiazepine use was defined as benzodiazepine use for 12 months without a 30-day gap during this period. As there is lack of consensus regarding what constitutes long-term benzodiazepine use, we also measured whether patients received a 180-day supply of benzodiazepines during the 270-day period after patients' initial benzodiazepine prescription and whether patients received more than a 30-day supply of a benzodiazepine during the follow-up year. Anxiolytic abuse or dependence was measured by receipt of a clinical diagnosis of hypnotic, sedative, or anxiolytic abuse or dependence (ICD-9-CM codes 305.4 and 304.1) during the one year follow-up period.

Hip fractures during the year after the antidepressant start were measured using ICD-9 codes 820.x and V-codes 54.13 and 54.23 among patients at least 50 years old.

Independent Variables

Co-prescription of a benzodiazepine was determined by whether any benzodiazepine was prescribed on the same day as the antidepressant start. Demographic characteristics included age (in years), sex, Hispanic ethnicity, and race (white, African-American, other, unknown), with the "other race" category including patients of Asian, Native Hawaiian, Pacific Islander, or Native American race/ethnicity and patients who were multi-racial. Region of the U.S. (West, Upper Midwest, South, Northeast) where the patient received VHA care was also determined.

Clinical characteristics which could impact the co-prescription of a benzodiazepine, adequacy of antidepressant treatment, and the likelihood of longer-term benzodiazepine use were measured during the 90 days before and after the antidepressant start and included whether patients receiving any of the following diagnoses: posttraumatic stress disorder (PTSD), any other anxiety disorder (panic disorder with or without agoraphobia, generalized anxiety disorder, anxiety disorder not otherwise specified, and all phobias), or any substance use disorder. General medical comorbidity was measured using the Charlson Comorbidity Index(12). We measured the number of non-psychotropic medications a patient was prescribed, whether the antidepressant prescribed was a newer generation agent, and whether the patient had any visit with a psychiatrist, as these factors have been shown to predict better acute phase antidepressant adherence(13). We also measured the total number of outpatient visits for any reason the patient made during the 90 days after the antidepressant start.

Analyses

Chi-square tests were used to determine whether receipt of adequate antidepressant treatment differed among patients who were or were not prescribed a benzodiazepine at the time of their antidepressant medication initiation. Frequencies were used to describe the prevalence and characteristics of patients that had long-term continuous benzodiazepine use, received an anxiolytic abuse or dependence diagnosis, or sustained a hip fracture over the one year follow-up period.

We fit a multivariable logistic regression model predicting adequacy of acute phase antidepressant treatment using receipt of a benzodiazepine as the primary predictor variable of interest and all other independent variables as additional covariates. From the resulting regression model we determined the difference in the predicted probability of receiving adequate antidepressant treatment associated with whether or not a patient received benzodiazepine treatment using the method of “recycled predictions”. This method calculates the mean predicted probability of the outcome variable based on the coefficients from the fitted regression model, fixing the independent variable of interest at a specific value (e.g., co-prescription of a benzodiazepine) while letting the others vary at their original values for every individual in the sample(14). The process is then repeated fixing the independent variable of interest at an alternate value (e.g., no benzodiazepine prescription). We used t-tests to determine whether the difference in the resulting mean probabilities was statistically significant.

We also performed separate logistic regression analyses stratified by whether patients were diagnosed with a comorbid anxiety disorder other than PTSD. In separate sensitivity analyses clustered by provider we found limited clustering (median cluster size = 2) without a change in the significance of our main findings. The results reported subsequently are for the non-clustered models. All analyses were conducted using SAS 9.2. We set our significance threshold at $\alpha = 0.05$.

Results

Patient characteristics

Of the 43,915 VHA patients diagnosed with depression and started on an antidepressant in FY 2007, 7.6% received a benzodiazepine on the same day as their initial antidepressant prescription. When compared to patients who were not prescribed a benzodiazepine, those who were prescribed a benzodiazepine at the time of their antidepressant were younger and more likely female, white, and Hispanic (Table 1). Patients prescribed a benzodiazepine were also significantly more likely to have seen a psychiatrist or be diagnosed posttraumatic stress disorder or some other anxiety disorder, but were significantly less likely to have a substance use disorder compared to patients who did not receive a benzodiazepine with their initial antidepressant.

Adequacy of antidepressant treatment

44.5% of patients prescribed a benzodiazepine on the same day as their antidepressant received adequate acute phase antidepressant treatment compared to 39.1% of patients not prescribed a benzodiazepine ($p < 0.001$). The significance of our findings did not change in sensitivity analyses including only newer generation antidepressants, using the HEDIS definition of adequate acute phase antidepressant treatment, or including patients who were initially prescribed 90 days of an antidepressant. Rates of adequate continuation phase treatment were 23.1% for benzodiazepine-treated patients and 18.8% for patients who did not receive a benzodiazepine with their initial antidepressant ($p < 0.001$).

In analyses adjusted for demographic characteristics and clinical covariates, prescription of a benzodiazepine was associated with increased likelihood of adequate acute phase antidepressant treatment when compared to no benzodiazepine treatment (Table 2). Other factors significantly associated with adequate antidepressant treatment were older age, female sex, white race, non-Hispanic ethnicity, living in the western U.S. compared to the Northeast or South, not having a comorbid substance use disorder, having an anxiety disorder other than PTSD, being prescribed a newer generation antidepressant, having a psychiatrist visit, having more non-psychotropic medications prescribed, and having more outpatient visits following the antidepressant start. In adjusted analyses stratified by comorbid anxiety disorders, benzodiazepine treatment was associated with increased likelihood of adequate antidepressant treatment among patients with (OR 1.22; 95% CI: 1.07, 1.39) and without (OR 1.11; 95% CI: 1.01, 1.22) a comorbid anxiety disorder.

Using the method of recycled predictions, the predicted probability of adequate antidepressant treatment, adjusted for clinical and demographic characteristics, was 42.4% for combined treatment compared to 39.3% for antidepressant treatment alone ($p < 0.001$), an absolute increase of 3.1% in the predicted probability of receiving adequate treatment.

Long-term benzodiazepine use, abuse, and dependence

Among patients treated with a benzodiazepine, 76.4% received more than 30 days of treatment, 28.6% received 180 days or more, and 14.1% received a benzodiazepine continuously over the one year follow-up period. Long-term users (those with continuous one year use) were more likely to have a co-morbid anxiety disorder diagnosis other than PTSD compared to those with shorter term use (45.4% vs. 33.2%). Long-term users were also older (54.6 vs. 52.0, mean age) and were more likely to be male (89.1% vs. 85.7%), white (79.0% vs. 71.8%), non-Hispanic (94.7% vs. 86.7%), to have been seen by a psychiatrist (46.9% vs. 38.6%), and to have more total outpatient visits (7.3 vs. 6.1, mean visits).

Only 0.7% of patients who initially received combined treatment were diagnosed with anxiolytic abuse or dependence during the subsequent year. Among these patients, 21.7% had a non-anxiolytic substance use disorder (i.e., alcohol or illicit drug abuse or dependence) noted prior to their combined treatment and 78.3% were diagnosed with a non-anxiolytic substance use disorder during the one year follow-up period. There was no significant difference in the rates of these non-anxiolytic substance use disorders between long-term and shorter-term benzodiazepine users.

Among the 2,039 patients aged 50 and older who received combined benzodiazepine and antidepressant treatment, none were diagnosed with a hip fracture in the subsequent year compared to 49 out of 26,661 (0.18%) patients aged 50 and older initially treated with an antidepressant alone.

Discussion

As an estimated 27 million U.S. Americans are treated with antidepressants annually(15), ensuring patients receive an adequate course of treatment is a common clinical concern and a major public health issue. Using clinical data from a large national health system, we found that prescription of a benzodiazepine with initiation of an antidepressant was associated with a small (3.1%) increased likelihood of adequate duration of antidepressant treatment in both the acute and continuation phase. This finding could be the result of unmeasured confounding, and because we used a large dataset, small differences in outcomes can reach statistical significance. However, despite perhaps being of limited clinical significance to an individual patient, a 3.1% improvement amounts to an estimated

837,000 more patients who might receive antidepressant treatment of adequate duration annually in the U.S. alone. Additionally, clinicians concerned that co-prescribing a benzodiazepine may result in worse antidepressant adherence (i.e. that patients will disregard the antidepressant in favor of the more immediate-acting benzodiazepine) can be reassured that this does not occur in clinical practice.

Any potential benefits of co-prescribed benzodiazepines must be weighed against the risks, including anxiolytic abuse, dependence, or, particularly in the elderly, cognitive side effects and falls. We found the vast majority of patients treated with benzodiazepines received more than a 30 day supply and about one-fourth of patients received a benzodiazepine for more than 6 months. RCTs indicate that the benefits of combined treatment are no longer significant after the first four weeks, and use beyond this period exposes patients to greater risk of withdrawal symptoms upon discontinuation (16-18). Although long-term benzodiazepine treatment may be appropriate for certain individuals with anxiety disorders or significant anxiety symptoms that fall short of disorder status, more than half of long-term (≥ 1 year) benzodiazepine users did not have an anxiety diagnosis, suggesting many may not have required long term anxiolytic treatment in addition to antidepressant treatment. Clinicians considering combining a benzodiazepine with initial antidepressant treatment for depression should be vigilant against long-term use unless specifically clinically indicated. Reassuringly, we note the overall risk of anxiolytic abuse or dependence following combined treatment appeared to be low, and most anxiolytic abuse or dependence occurred in the context of other substance use disorders, suggesting particular caution when prescribing for these patients. We also found no cases of hip fractures among patients older than 50 who were initially treated with a benzodiazepine and an antidepressant. Other potential adverse consequences of benzodiazepine treatment, such as falls and effects on cognition, were not available in administrative data but would be important to address in future studies of combined treatment.

The mechanism by which benzodiazepines might improve antidepressant adherence cannot be ascertained by this study. Others have suggested that benzodiazepines may suppress antidepressant side effects, relieve symptoms of anxiety or insomnia, or act synergistically on the core symptoms of depression(19).

Due to the observational nature of this study, the association between co-treatment with benzodiazepines and antidepressant treatment adequacy could be due to unmeasured confounding factors rather than direct effects of the medications. Patient characteristics not available from administrative data, such as illness severity or presenting symptoms, provider behaviors (e.g. attention to patient's anxiety), or remote prior experience with psychotropic medications could have contributed to both the prescription of a benzodiazepine and subsequently higher levels of antidepressant adherence. Also, as unmeasured subthreshold anxiety could contribute to poor antidepressant adherence and to benzodiazepine prescriptions, our results may also under-estimate the effect of benzodiazepine treatment (20, 21). Our measure of anxiolytic dependence or abuse may likewise be an under-estimate if providers do not actively assess for and record these conditions in clinical practice or an over-estimate if clinicians make the diagnosis based only the presence of withdrawal symptoms (i.e., "physical dependence") when other indications of maladaptive use (i.e. continued use despite negative consequences, repeated unsuccessful attempts to limit use) are not present.

We note that we used a process measure, adequacy of antidepressant treatment, as our primary outcome because we could not determine the impact of combined benzodiazepine and antidepressant treatment on symptoms or functioning from the available data; however, similar process measures have been shown to predict clinical outcomes such as depression

severity and psychiatric hospitalization(10, 22). Finally, our study included only VHA patients and therefore our findings may not generalize to other depressed populations.

Benzodiazepine prescription at the time of initial antidepressant treatment for depression results in slightly greater adequacy of antidepressant treatment duration compared to use of an antidepressant alone, regardless of the presence of an anxiety disorder and after controlling for other patient factors. Combined treatment often resulted in long-term benzodiazepine use, but diagnoses of anxiolytic abuse and dependence were rare. Providers and patients should consider these potential benefits and risks when deciding upon on initial pharmacologic treatment options for depression.

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Table 1

Characteristics of depressed VA patients who did or did not receive a benzodiazepine with initial antidepressant treatment (N = 43,915)

Variable	Benzodiazepine + Antidepressant (N=3,320)	Antidepressant Only (N=40,595)	P-value *
<i>Demographic Characteristics</i>			
Age, M (SD)	52.4 (15.6)	54.1 (15.5)	<0.001
Male Sex, N (%)	2,861 (86.2)	36,080 (88.9)	<0.001
Race, N (%)			<0.001
White	2,416 (72.8)	26,574 (65.5)	
Black	414 (12.5)	7,679 (18.9)	
Other	77 (2.3)	1,017 (2.5)	
Unknown	413 (12.4)	5,325 (13.1)	
Hispanic ethnicity, N (%)	406 (12.2)	2,181 (5.4)	<0.001
U.S. region, N (%)			<0.001
Northeast	493 (14.9)	7,025 (17.3)	
Upper Midwest	777 (23.5)	8,756 (21.6)	
West	590 (17.8)	8,082 (19.9)	
South	1,454 (43.9)	16,723 (41.2)	
<i>Clinical Factors</i>			
Posttraumatic stress disorder, N (%)	1,032 (31.1)	10,281 (25.3)	<0.001
Other anxiety disorder, N (%)	1,158 (34.9)	6,123 (15.1)	<0.001
Substance use disorder, N (%)	465 (14.0)	7,730 (19.0)	<0.001
Total outpatient visits, M (SD)	6.3 (5.3)	6.2 (6.3)	<0.001
Any psychiatrist visit, N (%)	2,406 (72.5)	23,295 (57.4)	<0.001
Newer generation antidepressant, N (%)	3,250 (97.9)	38,856 (95.7)	<0.001
Non-psychotropic medications, M (SD)	4.1 (3.8)	4.3 (3.8)	0.002
General medical comorbidities, M (SD)	0.7 (1.2)	0.8 (1.4)	<0.001

* Wilcoxon tests used for means and Chi-square tests for frequencies

Table 2

Predictors of adequate acute phase antidepressant treatment among Veterans Health Administration patients with depression (N = 43,915)

Variable	OR* (95%CI)
Benzodiazepine + Antidepressant	1.15 (1.06-1.24)
Age, years	1.01 (1.01-1.01)
Male Sex	0.88 (0.83-0.94)
Race, vs. White	
Black	0.47 (0.44-0.50)
Other	0.82 (0.72-0.93)
Unknown	0.85 (0.80-0.91)
Hispanic ethnicity	0.66 (0.60-0.72)
U.S. Region, vs. West	
Northeast	0.86 (0.81-0.92)
Upper Midwest	0.95 (0.89-1.01)
South	0.80 (0.76-0.85)
Posttraumatic stress disorder	0.95 (0.90-0.99)
Other anxiety disorder	1.10 (1.04-1.16)
Substance use disorder	0.81 (0.77-0.85)
Outpatient visits	1.04 (1.04-1.04)
Any psychiatrist visit	1.40 (1.34-1.46)
Newer generation antidepressant	1.97 (1.76-2.20)
Non-psychotropic medications	1.03 (1.02-1.04)
General medical comorbidities	1.00 (0.98-1.01)

* Multivariable logistic regression including all variables simultaneously