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Antidepressant Adherence After Psychiatric Hospitalization Among VA Patients with Depression

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Abstract Depressed patients discharged from psychiatric hospitalizations face increased risks for adverse outcomes including suicide, yet antidepressant adherence rates during this high-risk period are unknown. Using Veterans Affairs (VA) data, we assessed antidepressant adherence and predictors of poor adherence among depressed veterans following psychiatric hospitalization. We identified VA patients nationwide with depressive disorders who had a psychiatric hospitalization between April 1, 1999 and September 30, 2003, received antidepressant medication, and had an outpatient appointment following discharge. We calculated medication possession ratios (MPRs), a measure of medication adherence, within 3 and 6 months following discharge. We assessed patient factors associated with having lower levels of adherence (MPRs < 0.8) after discharge. The criteria for 3- and 6-month MPRs were met by 20,931 and 23,182 patients respectively. The mean 3 month MPR was 0.79 (SD = 0.37). The mean 6 month MPR was 0.66 (SD = 0.40). Patients with poorer adherence were male, younger, non-white, and had a substance abuse disorder, but were less likely to have PTSD or other anxiety disorders. Poor antidepressant adherence is common among depressed patients after psychiatric hospitalization. Efforts to improve adherence at this time may be critical in improving the outcomes of these high-risk patients.

Keywords Antidepressant adherence · Psychiatric hospitalization discharge · Veterans

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Introduction

Antidepressant treatment is an important and effective component in the management of many patients with depressive disorders, particularly those with major depression (Geddes et al. 2003; Keller et al. 2002). Among patients who begin new antidepressant treatment in outpatient settings, incomplete adherence increases the likelihood of depression relapse or recurrence (Katon et al. 2001; Melfi et al. 1998).

Unfortunately, a broad literature demonstrates suboptimal rates of adherence to antidepressant medications following new antidepressant starts among outpatients (e.g., those with no antidepressant prescriptions for the prior 6 months) (Bull et al. 2002; Cantrell et al. 2006; Katon et al. 1992). Poor adherence may arise from side effects (Burra et al. 2007; Goethe et al. 2007) patient beliefs, and attitudes towards antidepressant use and mental disorders such as fears of addiction or habituation (Givens et al. 2006; Melartin et al. 2005; Ozmen et al. 2005) and lack of

patient education regarding the importance of continuing medication use even when symptoms improve (Maidment et al. 2002; Givens et al. 2006; Melartin et al. 2005; Ozmen et al. 2005).

However, despite a substantial literature on antidepressant adherence following treatment initiation for new depression episodes in outpatient settings (Bambauer et al. 2007; Busch et al. 2004; Olfson et al. 2006; Robinson et al. 2006; Sewitch et al. 2007) there are few studies assessing antidepressant adherence following discharge from a psychiatric hospitalization. Although the majority of patients with depression are treated in outpatient settings, patients requiring inpatient care for depression are likely to have more severe depressive disorders, higher rates of disability, poorer outcomes, and higher costs of care (Goethe et al. 2007). The Goethe et al. (2007) study was one of the few to examine differences in antidepressant adherence rates among patients with both inpatient and outpatient treatment, finding no differences in adherence by location of initial treatment, with about 25% discontinuing the antidepressant within 3 months. However, this study had a relatively small sample size and relied on self-reported antidepressant adherence.

Given that suicide rates in the first 12 weeks following inpatient stays are five times higher than the base rate of suicide for the overall VA depression population (Valenstein et al. 2009) patients emerging from inpatient stays stand to benefit more from improved antidepressant adherence than patients treated in outpatient settings—and they represent an important target population for adherence-enhancing interventions.

Therefore, our study assessed antidepressant adherence in the first 3 and 6 months following discharge of depressed VA patients from a psychiatric hospitalization. Using VA pharmacy data, we assessed adherence during these time periods using medication possession ratios (MPRs) (Cantrell et al. 2006; Finley et al. 2002; Valenstein et al. 2002) defined as the total number of days' supply received divided by the number of days' supply needed for continuous use. We also examined demographic and clinical characteristics associated with poor adherence.

The goal of the study was to inform future efforts to address adherence issues among depressed patients being discharged from the hospital. We hypothesized that: (1) there would be substantial problems with antidepressant adherence among patients with depression newly discharged from inpatient units, and (2) patients with comorbid psychiatric conditions would have lower rates of adherence than depressed patients without comorbid conditions during these time periods.

Methods

Study Populations

We used data on patient demographic characteristics, diagnoses, and pharmacy use from the VA National Registry for Depression (NARDEP), which was created and maintained by the Serious Mental Illness Treatment Research and Evaluation Center (SMITREC) located in Ann Arbor, Michigan (Blow et al. 2003). The NARDEP integrates outpatient pharmacy data from the VA Pharmacy Benefits Management Group (PBM) with other VA administrative data for patients with depression diagnoses (Smith and Joseph 2003).

We examined antidepressant adherence in the 3 and 6 months post-discharge from psychiatric hospitalization among VA patients with depression. Specifically, patients were included in the study if they (1) received at least two depression diagnoses or one diagnosis followed by an antidepressant fill between April 1, 1999 and September 30, 2003; (2) were hospitalized for psychiatric reasons during that time; (3) received an antidepressant fill at time of discharge (up to 3 days before to 2 days after discharge); (4) had an outpatient visit within the 3 or 6 month post-discharge follow-up period; (5) received only one type of antidepressant within the 3- or 6-month post-discharge periods; and (6) had valid MPRs by having at least 90 total days outside of the hospital following discharge.

Our rationale for requiring either two diagnoses or a diagnosis and a prescription to identify a patient with depressive disorders was to ensure adequate specificity in our identification of depressive disorder. These criteria are similar to those used in several earlier studies of depression, using administrative databases (Kerr et al. 2000; Spettell et al. 2003). Conservatively, we also included patients only if they had an outpatient appointment after VA discharge to ensure that they were receiving their follow up care within the VA and not another health system. Patients were excluded from the analyses if they did not have an antidepressant prescription post-hospitalization, regardless if they had a prescription prior to hospitalization, if they had more than one type of antidepressant prescribed during the 3 or 6 months follow up period, or if they died within 90 days of hospitalization discharge.

Patient depression diagnoses were identified from the NARDEP using the International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes, which are presented in Appendix 1. All types of antidepressant medications available from VA pharmacies were included; however amitriptyline, mirtazapine, nortriptyline, and trazodone (e.g., tricyclic or tetracyclic antidepressants) were included in analyses only if doses were $\geq$75 mg, $\geq$15 mg, $\geq$25 mg,

and ≥300 mg per day respectively, as these medications are often used for other indications, such as sleep or pain at lower doses (Richeimer et al. 1997; Wiegand 2008). (Please see Appendix 2 for full list of antidepressant medications used.) By excluding patients who received only antidepressant medications that are commonly used in low doses used for other indications, we sought to prevent false positive identifications of patients as depressed.

Of the 37,058 patients who received an antidepressant fill at time of psychiatric discharge, 26,051 had at least one outpatient visit in the 3 months post-discharge and used only one type of antidepressant, and 21,289 (82%) had at least 90 outpatient days during the 3 months following hospital discharge, allowing calculation of a stable MPR. These patients constituted the 3 month patient population. During the entire 3 month period, six patients died; four of these patients had sufficient medication data for MPRs and two did not. 24,345 patients had at least one outpatient visit in the 6 months post-discharge and used only one type of antidepressant. Of these, 23,582 (97%) had at least 90 outpatient days during the 6 month post discharge period, allowing calculation of a stable MPR. These patients constituted the 6 month population. During the entire 6 month period, 322 patients died; 275 had sufficient medication data for MPRs and 47 did not. Seventy-six percent of patients had only one type of antidepressant during the 3 months post discharge and 70% of patients had only one type of antidepressant during the 6 months post-discharge.

Study Measures

Patient Characteristics

We obtained data on patient demographic characteristics including age (18–44, 45–64, ≥65), sex, race (black, other, unknown, white), and ethnicity (Hispanic or not) from the NARDEP. Other race included patients of Asian, Native Hawaiian, Pacific Islander, or Native American race/ethnicity and patients who were multi-racial.

Patient clinical characteristics included the following diagnoses in the 12 months prior to discharge including: any substance use disorder, post traumatic stress disorder, any other anxiety disorder, any personality disorder, and bipolar disorder II. Patients with schizophrenia, schizoaffective disorder, and bipolar disorder I were excluded from the study. ICD-9 codes for all clinical diagnoses are presented in Appendix 1.

Measures of Adherence

Data on medication fills and days supply dispensed were used to calculate MPRs. MPRs were calculated by adding the total number of days' supply of antidepressant medication that patients received from the outpatient pharmacy during the 3 and 6 months post-discharge (up to 3 days before to 2 days after discharge). The total number of days' supply received was divided by the number of days' supply needed for continuous use during outpatient periods. Any days that patients spend in institutional settings (including VA hospitals or nursing homes) were subtracted from the outpatient days' supply needed for MPR calculations. In sum, MPR = number of days' supply of antidepressant received from outpatient pharmacy/number of days' supply needed for continuous outpatient antidepressant use. An MPR of 1.0 therefore indicates full adherence, whereas an MPR of 0.5 indicates that a patient received only half the medication needed to ensure continuous outpatient use.

We calculated mean adherence (mean MPRs) for the 3 and 6 month follow-up groups. We chose 3 and 6 month follow up time periods for a course of antidepressant treatment to be in accordance with standard practice for antidepressant treatment for acute and continuation treatment (National Committee for Quality Assurance 2003; National Committee for Quality Assurance (NCQA) 2003). Patients with 6 months of follow-up would also be part of the 3 month follow-up group. We also categorized antidepressant adherence into poor and good adherence for 3 and 6 months post-discharge. Patients with MPRs < 0.8 were considered to have poor adherence, while patients with MPRs ≥ 0.8 were considered to have good antidepressant adherence. While there is no gold standard metric for calculating either adherence or good adherence (Vermeire et al. 2001) taking 80% of one's prescribed medication regimen has been considered a reasonable cut-point for good adherence in other studies using MPRs (Cantrell et al. 2006; Jones et al. 2006; Sikka et al. 2005).

Analytic Framework

First, we completed basic descriptive statistics using Wilcoxon and chi-square tests for means and frequencies. Next, we used logistic regression analysis to examine patient demographic and clinical characteristics associated with poor antidepressant adherence 3 and 6 months post-hospitalization. All predictors were included simultaneously, and the statistical significance level was set at $P < 0.05$ for all analyses. All statistical analyses were completed using SAS software version 9.1.

Results

Clinical and demographic characteristics of patients with 3 ($N = 20{,}931$) and 6 month ($N = 23{,}182$) MPRs are presented in Table 1. The patient populations for both the 3

Table 1 Characteristics of post-discharge depressed patients with 3 and 6 month antidepressant medication possession ratios (MPRs)

	3 Month MPRs				6 Month MPRs			
	All patients, *N* (%) (*N* = 20,931)	MPR < 0.80 (*N* = 10,243)	MPR ≥ 0.80 (*N* = 10,688)	*P*-value	All patients, *N* (%) (*N* = 23,182)	MPR < 0.80 (*N* = 13,835)	MPR ≥ 0.80 (*N* = 9347)	*P*-value
Sex								
Male	19,744 (94.3)	9722 (94.9)	10,022 (93.8)	<0.001	21,946 (94.7)	13,132 (94.9)	8814 (94.3)	<0.05
Female	1187 (5.7)	521 (5.1)	666 (6.2)		1236 (5.3)	703 (5.1)	533 (5.7)	
Age								
Mean	52.0 (12.4)	50.4 (11.9)	53.5 (12.7)	<0.001	52.1 (12.5)	50.4 (12.1)	54.6 (12.7)	<0.001
18–44	5532 (26.4)	3135 (30.6)	2397 (22.4)	<0.001	6138 (26.5)	4327 (31.3)	1811 (19.4)	<0.001
45–64	12,314 (58.8)	5921 (57.8)	6393 (59.8)		13,530 (58.4)	7875 (56.9)	5655 (60.5)	
65+	3085 (14.7)	1187 (11.6)	1898 (17.8)		3514 (15.2)	1633 (11.8)	1881 (20.1)	
Race								
White	15,169 (72.5)	6636 (64.8)	8533 (79.8)	<0.001	16,644 (71.8)	9027 (65.3)	7617 (81.5)	<0.001
Black	4921 (23.5)	3168 (30.9)	1753 (16.4)		5623 (24.3)	4230 (30.6)	1393 (14.9)	
Other	482 (2.3)	238 (2.3)	244 (2.3)		547 (2.4)	315 (2.3)	232 (2.5)	
Unknown	359 (1.7)	201 (2.0)	158 (1.5)		368 (1.6)	263 (1.9)	105 (1.1)	
Hispanic	1179 (5.6)	571 (5.6)	608 (5.7)	NS	1299 (5.6)	782 (5.7)	517 (5.5)	NS
Substance abuse	12,284 (58.7)	6984 (68.2)	5300 (49.6)	<0.001	14,078 (60.7)	9542 (69.0)	4536 (48.5)	<0.001
PTSD	6967 (33.3)	3129 (30.6)	3838 (35.9)	<0.001	7457 (32.2)	3978 (28.8)	3479 (37.2)	<0.001
Personality disorder	2813 (13.4)	1482 (14.5)	1331 (12.5)	<0.001	3114 (13.4)	1946 (14.1)	1168 (12.5)	<0.001
Other anxiety disorder	4431 (21.2)	1830 (17.9)	2601 (24.3)	<0.001	4771 (20.6)	2445 (17.7)	2326 (24.9)	<0.001

All values presented as *N* (%) indicate frequencies and percents of the study sample

NS non-significant

and 6 month MPR cohorts were predominantly male (94–95%), white (72–73%), and middle aged (mean age was 52). Psychiatric comorbidities were quite prevalent, as 59–61% of patients also had a substance use disorder, 32–33% had a PTSD diagnosis, 21% had other anxiety disorders, and 13% had personality disorders.

The mean antidepressant MPR among patients with depression in the 3 month period following psychiatric inpatient discharge was 0.79 (SD = 0.37, median = 0.82, range = 0.01–2.75). Almost half (49%) of these patients had MPRs < 0.8 during this period, indicating less than ideal adherence, and 27% of patients had MPRs < 0.5 during this period. The mean MPR in the 6 month period following psychiatric inpatient discharge was 0.66 (SD = 0.40, median = 0.66, range = 0.01–4.77); 60% of patients had MPRs < 0.8, indicating poor adherence over a 6-month period, and 41% of patients had MPRs < 0.5 during the same period.

Patient demographic and clinical predictors (expressed as odds ratios with 95% confidence intervals) of poor adherence (MPR < 0.8) in the 3 and 6 months post-discharge are presented in Table 2. In bivariate analyses, patients with poor adherence were significantly more likely to have substance use disorders and personality disorders, whereas patients with high levels of adherence were more likely to have PTSD and an additional anxiety disorder ($P < 0.01$ for all comparisons).

After controlling for demographic and clinical characteristics, male gender, younger age, non-white and unknown race, substance abuse, and personality disorder were all significantly associated with poor adherence at 3 months, whereas PTSD and other anxiety disorders were significantly associated with good adherence. These findings were replicated for adherence at 6 months except that having a personality disorder was no longer significantly associated with adherence. Given our large sample size, we specifically note characteristics most strongly associated with adherence (e.g. have odds ratios <0.8 or >1.3 which may be less likely to be false positive identifications of predictive factors), which include age, black or unknown race, substance abuse, PTSD, and other anxiety disorders.

Discussion

This study provides new information on rates of antidepressant adherence from a national sample of depressed patients recently discharged from a psychiatric hospitalization. Although the mean MPR was 0.79 at 3 months, almost half of the patient population had MPRs < 0.8

Table 2 Predictors of antidepressant adherence post-discharge among patients with 3 and 6 month MPRs

	3 Month predictors of poor adherence (MPR < 0.80)				6 Month predictors of poor adherence (MPR < 0.80)			
	OR unadjusted	95% CI	OR adjusted	95% CI	OR unadjusted	95% CI	OR adjusted	95% CI
Male (reference = female)	1.24	(1.10, 1.40)*	1.31	(1.15, 1.48)*	1.13	(1.01, 1.27)*	1.27	(1.12, 1.43)*
Age (reference = 18–44)								
45–64	0.71	(0.66, 0.76)*	0.78	(0.73, 0.83)*	0.58	(0.55, 0.62)*	0.65	(0.61, 0.70)*
65+	0.48	(0.44, 0.52)*	0.70	(0.63, 0.77)*	0.36	(0.33, 0.40)*	0.54	(0.49, 0.59)*
Race (reference = white)								
Black	2.32	(2.17, 2.48)*	2.02	(1.88, 2.16)*	2.56	(2.39, 2.74)*	2.18	(2.03, 2.34)*
Other	1.25	(1.05, 1.50)*	1.23	(1.02, 1.48)*	1.15	(0.96, 1.36)	1.12	(0.93, 1.33)
Unknown	1.64	(1.33, 2.02)*	1.45	(1.17, 1.80)*	2.11	(1.68, 2.66)*	1.83	(1.45, 2.31)*
Hispanic	0.98	(0.87, 1.10)	1.14	(1.01, 1.28)*	1.02	(0.91, 1.15)	1.22	(1.08, 1.37)*
Substance abuse	2.18	(2.06, 2.31)*	1.86	(1.75, 1.97)*	2.36	(2.23, 2.49)*	1.94	(1.83, 2.05)*
PTSD	0.79	(0.74, 0.83)*	0.81	(0.76, 0.87)*	0.68	(0.64, 0.72)*	0.70	(0.66, 0.75)*
Personality disorder	1.19	(1.10, 1.29)*	1.13	(1.04, 1.23)*	1.15	(1.06, 1.24)*	1.04	(0.96, 1.13)
Other anxiety disorder	0.68	(0.63, 0.72)*	0.76	(0.71, 0.81)*	0.65	(0.61, 0.69)*	0.74	(0.69, 0.79)*

* Indicates significance at the $P < 0.05$ level

indicating problematic adherence. The mean MPR at 6 months was only 0.66 and 60% of patients had MPRs < 0.8 over a 6 month period.

There have been few prior studies that have examined antidepressant adherence after psychiatric hospitalization, even though this is a time of particular vulnerability for patients. Our findings indicate that interventions to address adherence to antidepressant medications may be an important area in which care can be improved for these severely ill patients during the high risk period following discharge.

In line with models of adherence behaviors that emphasize the importance of patient perceptions of illness severity on medication taking behaviors, antidepressant adherence among higher acuity patients after hospitalization appears to be somewhat higher than less acute patients treated in outpatient settings (Aikens et al. 2005; Demyttenaere et al. 2008; Horne and Weinman 1999). Studies examining adherence in outpatient settings have reported adherence rates between 37 and 73% over 6 months, with several studies indicating outpatient antidepressant adherence as less than 50% during this period (Akincigil et al. 2007; Bambauer et al. 2006, 2007; Burra et al. 2007; Cantrell et al. 2006; Demyttenaere et al. 1998; Keene et al. 2005; Maidment et al. 2002; White et al. 2003).

Higher rates of adherence immediately following hospitalization are congruent with conceptual models adherence behaviors, such as Leventhal's self-regulatory model (SRM) (Brown et al. 2005; Leventhal et al. 1992) or Becker and Maiman's health belief model (HBM) (Adams and Scott 2000; Becker and Maiman, 1975). Both of these models indicate that patients' beliefs may influence adherence, such as their perceptions about an illness' causes, consequences and controllability (SRM) or the benefits and barriers associated with adherence as well as the likelihood of relapse or perceived illness severity (HBM). However, even though providers may be encouraged that recently discharged patients have somewhat higher levels of adherence with antidepressant treatment, they must still stay vigilant regarding poor adherence even in these high acuity patients.

More research is needed to determine the reasons that so many patients have relatively low rates of adherence after hospitalization, even though they are presumably in greater need of treatment. Potentially, patients with depression who have been hospitalized may have more difficulty organizing their daily schedules in a manner that facilitates adherence, and they may have less energy and motivation to continue with medications. These patients may also be more resistant to antidepressant treatment and be less adherent as a result. Additional targeted assistance with adherence may be needed post-discharge, including more vigorous educational efforts, closer clinical monitoring, and potentially the use of adherence aids such as specialized packaging or other tailored reminders.

An interesting finding from this study is the relationship between adherence and psychiatric comorbidity. In this study, depressed patients who had a psychiatric hospitalization had a substantial degree of psychiatric comorbidity. However, while we hypothesized that psychiatric comorbidity would be associated with poorer adherence, we found that some psychiatric comorbidities were associated

with poorer adherence (e.g., substance abuse), while others were associated with better adherence (e.g., PTSD and other anxiety disorders). The existing literature is rather limited and mixed with respect to the relationship between depression, psychiatric comorbidity, and antidepressant adherence.

We note that antidepressants are now frequently used and are even the preferred treatment for anxiety disorders in addition to their indication for depression (Beck et al. 2005; Devane et al. 2005). Prior research indicates that there are similar rates of antidepressant adherence among patients with either depression or anxiety (Sheehan et al. 2008). While having an anxiety disorder and/or PTSD in addition to depression can cause greater impairment than depression alone (Mittal et al. 2006) our findings are consistent with several studies that found depression comorbid with anxiety to be associated with greater adherence than in depression alone (Busch et al. 2004; Sheehan et al. 2008; Stein et al. 2006). However, at least one study reported decreased adherence and increased dropout from treatment among patients with comorbid depression and anxiety (Lenze 2003) and another study indicated that reported anxiety is a common reason for antidepressant discontinuation (Goethe et al. 2007). It is unknown what the specific mechanism is that contributes to increased adherence to antidepressants among depressed patients with comorbid anxiety; however, prior research suggests that patients with comorbid anxiety may have more severe symptoms and a poorer outcome than patients with depression alone, requiring more aggressive treatment (Ballenger 2000; Stein et al. 2006). In our study population, we have also found higher rates of suicide among depressed patients with comorbid anxiety disorders (Pfeiffer et al. 2009).

More research is needed to determine whether differences in efficacy, underlying illness, or patient population might result in differences in adherence among depressed patients with comorbid anxiety. Such research could include seeking to identify different attitudes and motivation for treatment among these patients, differential diagnosis approaches to identifying depression with and without comorbid anxiety, and differential patterns of adherence to antidepressants among patients with anxiety disorders.

Other psychiatric disorders such as substance use and personality disorders appear to be associated with decreased antidepressant adherence. This finding is easier to understand and explain, given that substance use or long standing maladaptive patterns may impair patients' ability and willingness to adhere to prescribed medication regimens. Consistent with our findings, prior research has demonstrated that depression and comorbid alcohol or substance use is associated with decreased antidepressant adherence following new antidepressant starts (Akincigil et al. 2007; Busch et al. 2004). Patients with comorbid depression and substance use may also be more likely to have treatment-resistant depression, which involves more antidepressant switches (Crown et al. 2002). There is less published information on depression and personality disorders; however, personality disorder has been shown to be associated with lower adherence to antidepressants (Sirey et al. 2001) and increased risk of suicide when associated with depression (Hansen et al. 2003). Our study found only a modest relationship between comorbid personality disorder and antidepressant adherence.

While this study provides new information on post discharge antidepressant adherence, there are some important limitations of note. MPRs, like many adherence measures, are an imperfect measure of adherence (Valenstein et al. 2006) although, they yield similar results as compared to other adherence measures (Cantrell et al. 2006). MPRs are not accurate for patients with less than 90 days of outpatient follow-up. MPRs also do not provide information on medication ingestion and it is possible that patients may repeatedly refill medications but fail to take them regularly. MPRs may also provide inaccurate information about adherence of patients who fill medications outside the VA health system (Valenstein et al. 2006). However, for patients using mental health services, rates of cross-system use outside the VA are low (Desai et al. 2001; Desai and Rosenheck 2002; McCarthy et al. 2008). We note that we did not examine whether patients were taking antidepressants prior to hospitalization and among those patients who were, whether they were more or less adherent to their medications prior to hospitalization. We chose instead to focus on an understudied high-risk period post hospitalization, as there has been substantial literature focused on antidepressant adherence in the absence of hospitalization. We might expect that hospitalization could increase adherence initially upon discharge compared to prior adherence, but this hypothesis should be empirically tested.

We also required patients to have at least one outpatient visit during the 3 and 6 month follow-up periods, as a conservative approach to ensure that patients were in outpatient VA settings prior to discharge. In sensitivity analyses (data not shown) we removed this restriction and found slightly lower rates of adherence. Clinical and demographic correlates of adherence did not change.

Finally, we did not account for patients taking other medications, either for psychiatric disorders or medical conditions. While we did not examine patients taking more than one type of antidepressant during the study period, in sensitivity analyses, we found that the results were similar (e.g., the same predictors were significant in the same direction) for patients taking only one, or more than one antidepressant during the study period, and the large majority

of patients took only one antidepressant during the study follow up periods. Furthermore, while patients had been hospitalized, we don't know their level of depression severity, or their history of antidepressant use, psychotherapy, or psychiatric hospitalization, or whether they had any caregivers or social supports that might have influenced antidepressant adherence. These factors may also play a role in antidepressant adherence, as well as other factors discussed earlier, such as side effects, attitudes, and education about adherence, which were not measured in this study.

Conclusions

Our data indicate that a substantial proportion (49–60%) of recently hospitalized depressed patients, who are at high risk for adverse outcomes including suicide, is poorly adherent to antidepressant medications. Although most prior literature and adherence interventions have addressed poor adherence among less severely ill outpatients, our findings emphasize the potential importance of adherence enhancing interventions for patients in the periods immediately following hospital discharge. We note that more frequent clinical visits, adherence aids, or strategies that have been adopted to improve depression care among newly diagnosed patients in outpatient settings, such as depression care management, may also improve adherence among these high-risk patients. Depression care managers could address patient side effects, treatment needs, health beliefs, and address questions between physician visits in a timely manner, and potentially decrease early antidepressant discontinuation. Interventions to improve adherence should also focus on particular subgroups of depressed patients, such as those with comorbid substance use disorders, who may need additional supports to increase adherence to antidepressant treatment (e.g., discussions of psychotropic medication adherence incorporated into substance abuse treatment groups). Innovative interventions to increase adherence and future research to evaluate their effectiveness must be a priority.

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Appendix 1: Patient Depression and Other Psychiatric Disorder ICD-9 Codes and Corresponding Diagnoses

See Tables 3 and 4.

Table 3 Depression ICD-9 codes and corresponding diagnoses

Code	Diagnosis
293.83	Organic affective syndrome
296.2x	Major depressive affective disorder single episode
296.3x	Major depressive affective disorder recurrent episode
296.90	Unspecified affective psychosis
296.99	Other specified affective psychosis
298.0	Depressive type psychosis
300.4	Neurotic depression
301.12	Chronic depressive personality disorder
309.0	Adjustment reaction with brief depressive reaction
309.1	Adjustment reaction with prolonged depressive reaction
311	Depressive disorder not elsewhere specified

Table 4 Other psychiatric disorder ICD-9 codes and corresponding diagnoses

Disorder	Code	Diagnosis
Substance use disorder	303.0x	Acute alcoholic intoxication in alcoholism (unspecified, continuous, episodic, and in remission)
	303.9x	Other and unspecified alcholic dependence (unspecified, continuous, episodic, and in remission)
	304.0x-9x	Drug dependence
		Opioid type dependence (unspecified, continuous, episodic, and in remission)
		Barbiturate and similarly active sedative or hypnotic (unspecified, continuous, episodic, and in remission)
		Cocaine dependence (unspecified, continuous, episodic, and in remission)
		Canabis dependence (unspecified, continuous, episodic, and in remission)
		Amphetamine and other psychostimulant dependence (unspecified, continuous, episodic, and in remission)
		Hallucinogen dependence (unspecified, continuous, episodic, and in remission)
		Other specified drug dependence (unspecified, continuous, episodic, and in remission)
		Combinations of opiod type drug with any other drug (unspecified, continuous, episodic, and in remission)
		Combinations of drug dependence excluding opiod type drugs (unspecified, continuous, episodic, and in remission)
		Unspecified drug dependence (unspecified, continuous, episodic, and in remission)
	291.x	Alcoholic psychoses
		Alcohol withdrawal delirium
		Alcohol amnestic syndrome
		Other alcoholic dementia

Table 4 continued

Disorder	Code	Diagnosis
		Alcohol withdrawal hallucinosis
		Idiosyncratic alcohol intoxication
		Alcoholic jealousy
		Other specified alcoholic psychosis
		Alcohol withdrawal
		Other alcoholic psychosis
		Unspecified alcoholic psychosis
	292.x	Drug psychoses
		Drug withdrawal syndrome
		Paranoid and/or hallucinatory states induced by drugs
		Drug induced organic delusional syndrome
		Drug induced hallucinosis
		Pathological drug intoxication
		Other specified drug induced mental disorders
		Drug induced delirium
		Drug induced dementia
		Drug induced amnestic syndrome
		Drug induced organic affective syndrome
		Other specified drug induced mental disorders
		Unspecified drug induced mental disorder
PTSD	309.81	Prolonged post traumatic stress disorder
Other anxiety disorders	300.00-300.02	Anxiety state unspecified
		Panic disorder
		Generalized anxiety disorder
	300.09	Other anxiety states
	300.10	Hysteria
	300.20-300.23	Phobia unspecified
		Agoraphobia with panic attacks
		Agoraphobia without panic attacks
		Social phobia
	300.29	Other isolated or simple phobias
Personality disorders	301.0	Paranoid personality disorder
	301.20	Schizoid personality disorder unspecified
	301.22	Schizotypal personality disorder
	301.7	Antisocial personality disorder
	301.83	Borderline personality
	301.50	Histrionic personality disorder unspecified
	301.81	Narcissistic personality
	301.82	Avoidant personality
	301.6	Dependent personality disorder
	301.4	Compulsive personality disorder
	301.9	Unspecified personality disorder
Bipolar disorder II	296.8x	Manic-depressive psychosis, other and unspecified
		Manic-depressive psychosis unspecified
		Atypical manic disorder
		Atypical depressive disorder
		Other manic-depressive psychosis

Appendix 2: Types of Antidepressants Included in this Study

Amitriptyline (high dose only)
Amoxapine
Atomoxetine
Buproprion
Citalopram
Clomipramine
Desipramine
Doxepin
Duloxetine
Escitalopram
Fluoxetine
Fluvoxamine
Imipramine
Isocarboxazid
Maprotiline
Mirtazapine (high dose only)
Nefazodone
Nortriptyline (high dose only)
Paroxetine
Phenelzine
Protriptyline
Sertraline
Tranylcypromine
Trazodone (high dose only)
Trimipramine
Venlafaxine

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