



## Treatment-Resistant Depression and Risk of Suicide

PAUL N. PFEIFFER, MD, HYUNGJIN M. KIM, ScD, DARA GANOCZY, MPH, KARA ZIVIN, PHD, AND MARCIA VALENSTEIN, MD

We evaluated whether treatment-resistant depression (TRD) as measured by the Massachusetts General Hospital (MGH) staging method was associated with suicide in a large U.S. health system. Data from the Veterans Health Administration and the National Death Index were used to conduct a case-control study of patients newly diagnosed with depression who received antidepressant treatment between 2003 and 2006. Suicide cases ( $N = 499$ ) were matched with nonsuicide controls ( $N = 1994$ ). Conditional logistic regression was used to assess whether MGH stage at time of suicide (or matched date) was associated with case status, adjusting for patient demographic characteristics, comorbidity, and service use. Results indicated 11.6% of suicide cases had MGH stage 3 or greater (indicating at least two antidepressant trials) compared to 6.4% of controls ( $p < .001$ ). In adjusted analyses, suicide was not significantly more likely among patients with stage 3 or greater (OR 1.52; 95% CI: 0.98, 2.37) or stages 1.5–2.5 (OR 1.19; 95% CI: 0.91, 1.55) compared to patients with stage 1 or less (<10 weeks of antidepressant medication). Staging TRD using MGH criteria is unlikely to substantially improve suicide risk assessment of depressed patients beyond existing measures contained in health system records.

Treatment-resistant depression (TRD) has been broadly defined as a major depressive disorder that fails to remit despite an adequate course of antidepressant medica-

tion treatment (Berman, Narasimhan, & Charney, 1997; Fava, 2003; Fornaro & Giosue, 2010; Nelsen & Dunner, 1995; Souery et al., 2007). TRD has been reported to occur in at least one-third of depressed patients and has been associated with prolonged functional impairment, earlier relapse if remission is eventually achieved, and increased health care costs compared to treatment responders (Fava & Davidson, 1996; Gibson et al., 2010; Rush et al., 2006). Whether TRD similarly confers a greater risk of suicide has important clinical and public health implications, particularly if these patients can be proactively identified from health system records.

Individuals with affective disorders such as depression have a twofold to fourfold increased risk of suicide compared to other patients, but it remains difficult to predict the

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PAUL N. PFEIFFER, HYUNGJIN M. KIM, DARA GANOCZY, KARA ZIVIN AND MARCIA VALENSTEIN, Department of Veterans Affairs, National Serious Mental Illness Treatment Resource and Evaluation Center and Health Services Research and Development (HSR&D) Center for Clinical Management Research, Ann Arbor, MI, USA, and Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI, USA.

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Address correspondence to Paul N. Pfeiffer, North Campus Research Complex, 2800 Plymouth Road, Ann Arbor, MI 48109; E-mail: pfeiffe@umich.edu

approximately 2% to 5% of those with affective disorders who will die by suicide (Bostwick & Pankratz, 2000; Ilgen et al., 2010). Patient characteristics associated with an increased risk of suicidal behavior among depressed patients include a history of prior suicide attempt, comorbid anxiety, and comorbid alcohol-use disorders (Oquendo, Currier, & Mann, 2006; Pfeiffer, Ganoczy, Ilgen, Zivin, & Valenstein, 2009). Treatment patterns may also identify subgroups of depressed patients at greater risk for suicide; for example, patients with a recent psychiatric hospitalization are at nearly five times greater risk than those receiving general depression care (Valenstein et al., 2009). There have been concerns that initiation of antidepressant medication treatment may not only be a marker of suicide risk but may play a causal role in increasing suicidal behaviors, particularly among children and adolescents (Hammad, Laughren, & Racoosin, 2006). However, meta-analysis of randomized controlled trials, population-level studies of suicide and antidepressant prescribing, and longitudinal follow-up of mood disorder patients suggests antidepressant treatment does not play a causal role with regard to suicide risk (Angst, Stassen, Clayton, & Angst, 2002; Gibbons, Hur, Bhaumik, & Mann, 2006; Khan, Khan, Kolts, & Brown, 2003).

Patients who fail to respond to antidepressant treatment, however, may be at greater risk for suicide. Patients with TRD are more likely to report a prior suicide attempt than treatment responders, although suicide-related outcomes subsequent to the development of TRD are less well understood (Malhi, Parker, Crawford, Wilhelm, & Mitchell, 2005; Nelsen & Dunner, 1995).

We sought to determine whether patients who are identified as having TRD based on the Massachusetts General Hospital (MGH) method have an increased risk of suicide mortality. The MGH method is calculated based on the number and adequacy of antidepressant trials, augmentations, and receipt of electroconvulsive therapy (ECT; Fava, 2003). It can be used to measure TRD

along a continuum or to define important treatment milestones, and the method has been validated in clinical settings by predicting continued nonremission from depression (Gibson et al., 2010; Petersen et al., 2005; Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). If TRD stages as measured by the MGH method predict suicide, this could potentially assist clinicians and health systems in identifying high-risk subgroups that may benefit from additional services.

## METHODS

### *Data Source*

Patient data used in our analyses were obtained from the Veterans Health Administration's (VHA) National Registry of Depression (NARDEP), which contains inpatient and outpatient treatment records, including diagnoses at clinical encounters, pharmacy records, and demographic information, on all patients receiving treatment for depression within the VHA (Blow, Owen, & Valenstein, 2003). Data on cause of death were obtained from the National Death Index (NDI), a high quality, national mortality database suitable for research purposes, which was merged with NARDEP (Cowper, Kubal, Maynard, & Hynes, 2002). Data were obtained from fiscal year 2003 through 2008. The study was conducted in concordance with institutional review board approval at the Veterans Affairs Ann Arbor Health System.

### *Case-Control Patient Selection and Matching*

We used a case-control design to assess differences in MGH stages of TRD between patients who did or did not die by suicide. The case-control design was chosen to allow for variable follow-up periods to measure TRD scores and covariates. To ensure comparable starting points for TRD measurement, cases and controls were patients with new episodes of depression that

included new antidepressant treatment. Specifically, patients had (1) an index depressive disorder diagnosis (*International Classification of Diseases [ICD-9-CM]* codes 293.83, 296.2x, 296.3x, 296.90, 296.99, 298.0, 300.4, 301.12, 309.0, 309.1, 311) at an outpatient clinical encounter between fiscal years 2003 and 2006 without a depressive disorder diagnosis in the prior 6 months, and (2) an index antidepressant prescription either 30 days prior or 14 days after the index depressive disorder diagnosis but otherwise with no antidepressant treatment in the prior 6 months. We excluded patients with a diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder in the 2 years following the index diagnosis. Patients with a psychiatric hospitalization in the 6 months prior to the index depression diagnosis were excluded to avoid misclassifying outpatient depression treatment as new when it began in the inpatient setting.

Cases included all suicide deaths in the 2 years following the initiation of antidepressant treatment and were identified from the cause of death fields contained in the NDI using the *ICD-10* codes X60-X84 and Y87.0 [World Health Organization (WHO), 2004]. We selected 2 years as the follow-up period to allow adequate time to measure treatment resistance while decreasing the likelihood of measuring recurrent episodes. For each case, up to four individually matched controls were randomly selected from patients whose index antidepressant prescription occurred within 1 week of the case index antidepressant prescription and who were still alive when the case patient died by suicide. Case and controls were further matched by gender and age (within 5 years).

### Measures

Treatment-resistant depression stage and other patient characteristics potentially associated with suicide risk were measured from the index depression diagnosis or index antidepressant fill, whichever came first, to the time of suicide death (cases) or

matched time period (controls). Thus, measurement periods varied across cases but were equivalent (within 1 week) between cases and their matched controls. TRD was measured using the MGH method (Fava, 2003). Patients received 1 point for each antidepressant medication for which they obtained at least a 6-week supply with at least one refill. Patients who never met these criteria for any antidepressant received a 0. For each antidepressant medication meeting these initial criteria, patients received an additional 0.5 points each if they received at least a 10-week continuous supply of the antidepressant medication or received the maximum dose for at least 6 weeks. To meet duration criteria, patients were required to refill their medications such that their supply on hand was not less than 80% of a continuous supply. Although not specified in the initial description of the MGH method, 80% is a validated cutoff for adequate medication coverage in psychiatric populations (Valenstein et al., 2002). An additional 0.5 points was given if any of the following augmentation agents were added to an antidepressant: buspirone, lithium, a stimulant, an atypical antipsychotic, or a second antidepressant. Patients who received electroconvulsive therapy received an additional 3 points. To facilitate clinical interpretation, we constructed three MGH stage categories a priori based on clinical relevance and previously established cutoffs (Gibson et al., 2010): MGH stages 0 and 1 were combined to represent a subadequate antidepressant trial (e.g., no antidepressant trial reached 10 weeks duration or longer); MGH stages 1.5–2.5 were combined to represent adequate (e.g., 10 weeks duration or longer) to optimal treatment (e.g., maximum dose with augmentation) with an initial antidepressant, while stages 3 and above were combined because these stages typically represent two or more adequate antidepressant medication trials. MGH stages of 3 or more generally represent the presence of TRD when comparing to dichotomous paradigms (Gibson et al., 2010).

Demographic characteristics in addition to age and gender (for matching) included marital status, Hispanic ethnicity, and race (White, Black, Other, Unknown). "Other" race includes patients of Asian, Native Hawaiian, Pacific Islander, or Native American race/ethnicity, and patients who are multiracial. We also included the region of the United States where the patient received most of their care (West, Northeast, Upper Midwest, South).

We measured patient characteristics available in the administrative data that have previously been associated with suicide or that might confound the relationship between antidepressant use and suicide (Pfeiffer et al., 2009; Zivin et al., 2007). Clinical diagnoses based on *ICD-9-CM* codes entered at provider encounters were used to determine whether patients received a diagnosis of major depressive disorder (*ICD-9-CM* codes 296.2x, 296.3x) versus other depressive disorder diagnoses prior to suicide. Comorbid psychiatric conditions were similarly assessed, including posttraumatic stress disorder (PTSD), other anxiety disorders (i.e., generalized anxiety disorder, panic disorder, social phobia, anxiety disorder not otherwise specified), any substance use disorder, and any personality disorder. Prescription of any benzodiazepine medication during the follow-up period was determined from outpatient pharmacy records as this is likely an indicator of undiagnosed but significant comorbid anxiety symptoms and is associated with suicide mortality among depressed VHA patients (Pfeiffer et al., 2009). Prescription of benzodiazepines is not included in MGH staging. General medical comorbidity was determined using a modified Charlson Comorbidity Index score greater than 0 (Quan et al., 2005). The Charlson Comorbidity Index is scored based on the presence of 17 different medical conditions and is associated with mortality (Charlson, Pompei, Ales, & MacKenzie, 1987). We also measured any psychiatric hospitalization, and total outpatient mental health encounters subsequent to the index depression diagnosis or antidepressant fill.

### Analyses

We tested for differences in patient characteristics, including the mean MGH stage and MGH stage categories between cases and controls using generalized linear models accounting for clustering within matched sets of cases and controls. We then conducted a conditional logistic regression model to predict case status using MGH category dummy variables as primary predictors. The model included all demographic characteristics, comorbidities, and mental health service use variables as covariates. To further assess the role of an MDD diagnosis as a confounder, we constructed two additional post hoc case-control samples: one including patients with an MDD diagnosis and another of patients with depressive disorder diagnoses other than MDD. We included three additional years of data in each sample to maintain statistical power similar to the main analyses. We repeated the above conditional logistic regression analyses in both samples. Alpha was set at 0.05 for all comparisons. All analyses were conducted in SAS version 9.3.

## RESULTS

Among patients with new episodes of antidepressant treatment for depression, we identified 499 cases of suicide within 2 years of their index antidepressant fill and matched these cases to 1994 controls. Among cases, the mean time from index antidepressant fill to suicide was 327 (*SD* 213) days. Consistent with a sample drawn from the VHA veteran population, the mean age was 56 years old, and 97% of patients were male. In unadjusted analyses, there were statistically significant differences in all measured variables between cases and controls except for U.S. region and comorbid PTSD (Table 1).

Suicide cases had a mean MGH stage of 1.43 compared to 1.13 for controls ( $p < .001$ ). Among cases, 11.6% had an MGH stage of 3 or greater compared to

6.4% of controls ( $p < .001$ ). MGH stage of 3 or greater indicated receipt of at least two adequate antidepressant trials. MGH stage greater than 5, generally indicating three or more antidepressant trials, occurred in <1% of the total sample (1.8% of cases and 0.6% of controls). The maximum MGH stage, reached by a single suicide case patient, was 9. Case patients compared to controls were more likely to receive each individual component of the MGH staging algorithm, including 6 weeks of an antidepressant medication (71.9% vs. 65.3%;  $p < .01$ ), 10 weeks of an antidepressant medication (58.1% vs. 52.8%;  $p = .02$ ), maximum antidepressant dose (12.2% vs. 7.2%;  $p < .001$ ), an augmentation agent (22.4% vs. 11.9%;  $p < .001$ ), and ECT (0.40% vs. 0.05%;  $p = .09$ ), although the difference in ECT was not statistically significant.

In analyses adjusted for demographic and clinical characteristics, neither MGH stage of 3 or more (OR 1.52; 95% CI: 0.98, 2.37) nor stage 1.5–2.5 (OR 1.19; 95% CI: 0.91, 1.55) was associated with case status compared to stage 1 or less. Comorbid substance use disorders (OR 2.06; 95% CI: 1.52, 2.77), personality disorders (OR 1.70; 95% CI: 1.00, 2.87), benzodiazepine use (OR 2.55; 95% CI: 1.96, 3.33), major depressive disorder diagnosis (OR 1.65; 95% CI: 1.27, 2.12), and psychiatric hospitalization (OR 3.33; 95% CI: 2.34, 4.76) were associated with an increased risk of suicide. Comorbid PTSD (OR 0.63; 95% CI: 0.45, 0.88), Black race (OR 0.21; 95% CI: 0.12, 0.37), and being married (OR 0.56; 95% CI: 0.44, 0.71) were associated with decreased risk of suicide. In unadjusted analyses of samples restricted to patients with or without an MDD diagnosis, MGH stage 3 or greater was associated with suicide among patients with an MDD diagnosis (OR 1.73; 95% CI: 1.21, 2.47) but not among patients with other depressive disorder diagnoses (OR 1.42; 95% CI: 0.88, 2.29). In adjusted analyses, MGH stage 3 or greater was not associated with suicide for patients with an MDD diagnosis (OR 1.14; 95% CI: 0.63, 1.24) or those with other

depressive disorder diagnoses (OR 1.26; 95% CI: 0.67, 2.35).

## DISCUSSION

Although a depressive disorder diagnosis is a well-established risk factor for suicide, suicide among depressed patients still remains a rare event at less than 100 suicide deaths per 100,000 person years (Arsenault-Lapierre, Kim, & Turecki, 2004; Ilgen et al., 2010; Zivin et al., 2007). Further risk stratification is therefore needed to identify depressed patients at greatest risk who may benefit from additional suicide prevention interventions. This study found that TRD, as measured by an MGH stage of 3 or more, was more common among patients who died by suicide than matched nonsuicide controls, but MGH stage 3 or more was not a significant predictor of suicide after adjusting for other known risk factors.

Prior studies have evaluated suicide risk (e.g., recent suicidal ideation or a history of suicide attempt) among those with TRD (Malhi et al., 2005; Nelsen & Dunner, 1995; Souery et al., 2007); however, this is the first study to our knowledge that has assessed a method for measuring TRD among patients who have died by suicide. MGH stage was associated with suicide in unadjusted but not adjusted analyses, suggesting that the constructs measured by the MGH method overlap with other indicators of illness severity included in the regression model, such as a major depressive disorder diagnosis or psychiatric hospitalization. It is important to note that this study does not negate the potential association between TRD and increased suicide risk, particularly among patients with a major depressive disorder diagnosis, but it does show that TRD as measured by MGH method is not independently associated with increased risk. TRD staging may also be sensitive to a heterogeneous group of unmeasured underlying constructs, of which only some may be related to suicide, thereby diminishing the association between broad measures of

**TABLE 1**  
*Characteristics of Suicide Cases and Matched Controls<sup>a</sup> among Veterans Health Administration Patients with New Episodes of Antidepressant Treatment for Depression*

Variable	Suicide Cases (N = 499) %	Matched Controls (N = 1994) %	p Value <sup>b</sup>
<b>MGH Stage of TRD</b>			
Continuous Stage, <i>M (SD)</i>	1.43 (1.29)	1.13 (1.06)	<.001
Categorical Stage, %			<.001
Stage 0–1	39.1	45.6	
Stage 1.5–2.5	49.3	47.9	
Stage ≥ 3	11.6	6.4	
<b>Demographic characteristics</b>			
Age, <i>M (SD)</i>	55.9 (14.2)	56.0 (13.9)	matched
Male sex, %	96.8	96.9	matched
Race, %			<.001
White	73.0	72.7	
Black	3.6	13.8	
Other	1.8	3.0	
Unknown	21.6	10.6	
Hispanic ethnicity, %	3.4	5.2	<.001
Married, %	37.9	54.2	<.001
U.S. region, %			.28
Northeast	17.8	17.1	
Upper Midwest	25.1	23.2	
West	21.8	19.6	
South	35.3	40.1	
<b>Clinical factors</b>			
Major depressive disorder, %	44.9	30.3	<.001
Posttraumatic stress disorder, %	16.4	19.9	.08
Other anxiety disorder, %	29.1	18.7	<.001
Benzodiazepine prescription, %	43.1	22.0	<.001
Substance use disorder, %	35.7	19.2	<.001
Personality disorder, %	8.6	2.9	<.001
Charlson comorbidity index > 0, %	41.1	46.9	<.001
Psychiatric hospitalization, %	23.7	7.1	<.001
Outpatient mental health visits, <i>M (SD)</i>	8.2 (15.2)	6.4 (19.7)	<.01

<sup>a</sup>Matched on age, gender, and time from index antidepressant fill.

<sup>b</sup>General linear model accounting for clustering between matched sets of cases and controls.

TRD and suicide. Potential such contributors to TRD include genetically mediated pathophysiologic subtypes of depression, brain changes following under treatment of chronic early life depression and differences in drug metabolism and pharmacodynamics (Bertilsson, 2007; Greden, Riba, & McInnis, 2011; Judd et al., 2000; McMahon et al., 2006; Nierenberg, 2003; Van, Schoevers, & Dekker, 2008). Erroneous or arti-

factual progression to advanced stages of TRD as measured by the MGH method could also occur due to misdiagnosis or by patient behaviors that lead to greater antidepressant prescribing independent of actual treatment resistance (e.g., lower tolerance for mild symptoms, greater self-advocacy) (Nelsen & Dunner, 1995). Further study is needed to determine the relative contribution of the above factors to

**TABLE 2**  
*MGH Stage as a Predictor of Suicide Cases (N = 499) versus Nonsuicide Controls (N = 1,994) among Patients with Depression Matched on Age, Gender, and Time from Initiation of Antidepressant Treatment*

Variable	AOR <sup>a</sup> (95% CI)
MGH Stage, vs. 1 or less	
1.5–2.5	1.19 (0.91, 1.55)
3 or more	1.52 (0.98, 2.37)
Demographic characteristics	
Race, vs. White	
Black	<b>0.21 (0.12, 0.37)</b>
Other	0.92 (0.42, 2.02)
Hispanic ethnicity	1.03 (0.57, 1.88)
Married	<b>0.56 (0.44, 0.71)</b>
U.S. Region, vs. West	
Northeast	1.14 (0.78, 1.65)
South	0.82 (0.59, 1.12)
Upper Midwest	1.08 (0.76, 1.53)
Additional clinical characteristics	
Major depressive disorder	<b>1.64 (1.27, 2.12)</b>
Posttraumatic stress disorder	<b>0.63 (0.45, 0.88)</b>
Other anxiety disorder	1.14 (0.85, 1.54)
Benzodiazepine prescription	<b>2.55 (1.96, 3.33)</b>
Substance use disorder	<b>2.06 (1.52, 2.77)</b>
Personality disorder	<b>1.70 (1.00, 2.87)</b>
Charlson comorbidity > 0	0.80 (0.62, 1.02)
Psychiatric hospitalization	<b>3.33 (2.34, 4.76)</b>
Outpatient mental health visits	1.00 (0.99, 1.00)

*Note.* Bolded values are where the confidence interval (95% CI) does not cross 1.0.

<sup>a</sup>Adjusted odd ratios (AOR) from conditional logistic regression model including all variables simultaneously.

TRD and their independent associations with suicide.

The associations between patient characteristics other than MGH stage (e.g., race, comorbid substance use disorders) and suicide are largely consistent with prior studies of suicide risk among VHA patients, although the case and control patients in this study were drawn from a cohort that overlaps with the cohorts used in these

prior studies (Pfeiffer et al., 2009; Zivin et al., 2007). The decreased risk for suicide associated with PTSD among depressed patients may be counter-intuitive, but prior VHA studies suggest patients with PTSD have a lower suicide risk than patients with depression (Desai, Dausey, & Rosenheck, 2005; Ilgen et al., 2010). PTSD comorbid with depression may mitigate the risk associated with depression rather than have an additive effect. The availability of specialized treatment programs for PTSD and compensation for PTSD service-connected disabilities could also contribute to this finding (Zivin et al., 2007).

Our finding regarding the prevalence of TRD (MGH stage 3 or more) at 11.6% of suicide cases is in contrast to the greater than 30% prevalence reported in other settings (Fava & Davidson, 1996; Rush et al., 2006; Souery et al., 2007). The lower prevalence could relate to the case-control study design, such that among suicide cases, treatment was cut short by suicide and therefore the course of depression treatment was not long enough to demonstrate TRD; however, the mean time to suicide of 327 days was sufficient for a large majority of patients to undergo a second antidepressant trial. Alternatively, the lower prevalence of TRD likely relates to differences in depression treatment in routine clinical settings such as the VHA compared to care delivered to clinical research participants in prior studies. In routine practice, patients may be less likely to persist in treatment beyond an initial antidepressant trial, and clinicians may not be as vigilant or supported in recognizing TRD and advancing beyond initial treatment plans. Unusually high remission rates to depression treatment as an explanation for low TRD prevalence are unlikely based on high comorbidity rates and clinical trial experience in the VHA (Mohr et al., 2011).

Our study demonstrates the feasibility of applying the MGH method to health system administrative data sets. Additional studies based on the MGH scoring algorithm could adjust the relative weights of initial antidepressant trials, augmentations,

dose optimizations, and ECT to potentially improve the algorithm's predictive ability. Although less than 1% of patients received ECT, adjustments to the algorithm might also consider excluding ECT for severe or high-risk depression in the absence of prior treatment failures.

Very large data sets are necessary to study rare events such as suicide death. However, these data sets are limited in that they do not contain measures of depression symptom severity or remission status. Our findings are also limited in that diagnoses of depression were made clinically as opposed to the use of standardized, structured interviews, and we are unable to account for depression treatments that occurred prior to or outside of VHA services. We do note that only 20% of VHA patients who also use non-VA services receive mental health care in both settings, and dual use is not associated with differences in depression symptoms (Liu et al., 2009). Medication use was also measured from pharmacy refills, which may be different than patients' actual

ingestion of medication. However, we did require patients to refill their medications within time frames consistent with adequate adherence. Finally, differences between the VHA patient population and other depressed patient populations may limit generalizability.

## CONCLUSION

We applied the MGH method for staging TRD to health system records and found that TRD stage was not associated with suicide after adjusting for patient demographic and other clinical characteristics. Future work should examine the various factors that contribute to TRD and their associations with suicide independent of other measures of depression severity. Whether TRD is broadly associated with suicide could be further explored through testing optimizations of the MGH method or alternative TRD staging methods.

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