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Remission in Major Depression: Results from a Geriatric Primary Care Population

Armin R. Azar^{1,2,3}, Mohit P. Chopra^{2,4,3}, Lydia Y. Cho^{2,3,4}, Eugenie Coakley⁵, and James L. Rudolph^{2,1,3,*}

¹Division of Aging, Brigham and Women's Hospital, Boston, Massachusetts

²VA Boston Healthcare System, Boston, Massachusetts

³Harvard Medical School, Boston, Massachusetts

⁴Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts

⁵John Snow, Inc., Boston, Massachusetts

Abstract

OBJECTIVES—While a recent task force report recommended that remission from major depression be defined according to DSM criteria, most previous work has used depressive symptom rating scales. The current study sought to identify baseline factors associated with treatment outcome in major depression, diagnosed according to DSM-IV criteria.

METHODS—Data from the Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISM-E) study were utilized. This analysis focused on 792 geriatric primary care patients with major depression at baseline, who were randomized to services by a mental health professional in primary care or specialty settings. Major depression was diagnosed according to DSM-IV criteria based on a structured interview at baseline and six months. The primary outcome was the absence of any DSM-IV depressive disorder at six-month follow-up. Association with baseline demographic characteristics, comorbid anxiety disorder, “at risk” drinking, number of co-occurring medical conditions, and depressive symptom severity was examined using multiple logistic regression modeling.

RESULTS—Remission occurred in 228 (29%) patients with completed follow-up assessments, while 564 (71%) did not remit. Factors which increased the odds of non-remission included comorbid anxiety (OR=1.60, 95% CI 1.11–2.31), female sex (OR=1.49, 95% CI 1.04–2.15), general medical comorbidity (OR=1.15, 95% CI 1.07–1.24), and increased baseline depressive symptom severity (OR=1.04, 95% CI 1.03–1.06).

CONCLUSIONS—The findings underscore the importance of using DSM criteria to define remission from major depression, and suggest that concurrent measurement of depression severity, comorbid anxiety and medical comorbidity are important in identifying patients requiring targeted interventions to optimize remission from major depression.

Keywords

depression; remission; primary care; aged

*Correspondence to: Dr. James L. Rudolph, VA Boston Healthcare System, GRECC (182JP), 150 South Huntington Avenue, Jamaica Plain, MA 02130. Tel #: 857-364-6812, Fax #: 857-364-4544, jrudolph@partners.org.

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Introduction

Depression is a common mental health problem in older adults, and is linked with increased medical comorbidity, disability, and mortality, underscoring the importance of complete treatment of depression to remission (Blazer, 2003; Bruce, 2001; Schulz *et al.*, 2000). Improvement in major depression that results in residual symptoms, often referred to as response, has been shown to be associated with earlier relapse and recurrence of depression, continued functional disability, and mortality in the elderly (Steffens *et al.*, 2003; Lenze *et al.*, 2005; Ganguli *et al.*, 2002). Because most patients are treated for depression in the primary care setting, identifying predictors of poor outcome may provide clinicians with valuable information on those patients requiring close follow-up and monitoring (Schulberg *et al.*, 1998).

Some of the factors shown to be associated with non-response and non-remission in previous treatment studies include comorbid anxiety symptoms or disorder and medical comorbidity (Alexopoulos *et al.*, 2005; Andreescu *et al.*, 2007; Steffens and McQuoid, 2005; Oslin *et al.*, 2002; Reynolds *et al.*, 2006). However, most of these studies examined response (Alexopoulos *et al.*, 2005; Andreescu *et al.*, 2007; Steffens and McQuoid, 2005; Oslin *et al.*, 2002; Reynolds *et al.*, 2006; Lenze *et al.*, 2003), as defined by an improvement in depressive symptoms using a threshold on a depression rating scale, rather than remission (i.e., the absence of any DSM depressive disorder).

A recent report by the American College of Neuropsychopharmacology (ACNP) Task Force on response and remission in major depression highlighted two points: 1) the target outcome for treatment of major depression is remission, as opposed to response; and 2) the definitions of remission should include all nine of the DSM-IV TR (American Psychiatric Association, 2000) core symptoms used to diagnose a major depressive episode (Rush *et al.*, 2006). Further, the Task Force noted concerns in utilizing rating scales where certain criterion symptoms may not be included (e.g., concentration/decision-making). Given these concerns and the noted clinical differences in remission versus response, the present study sought to examine factors related to treatment outcome of older adults with major depression in primary care, where the absence or presence of a depressive disorder was based on DSM criteria using a structured diagnostic psychiatric interview.

The Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISM-E) study was a randomized clinical trial that compared enhanced referral mental health services to an integrated mental health and substance abuse model of care for older primary care patients with depression, anxiety, or at-risk alcohol use (Levkoff *et al.*, 2004). The primary outcome of the study found that older patients, including those with a depressive disorder, were more likely to use collaborative mental health treatment within a primary care clinic (Bartels *et al.*, 2004). That said, remission rates in all depressive disorders, including major depression, did not differ across treatment models (Krahn *et al.*, 2006). However, patients with major depression enrolled in the enhanced referral model arm did demonstrate a greater reduction in depression severity as measured by a depression rating scale. Importantly, the prior analyses used reduction in symptom severity, rather than DSM criteria, as the primary outcome. Using the PRISM-E, our study sought to identify factors associated with major depression outcome (according to DSM-IV diagnostic criteria) at six months. We hypothesized that the presence of comorbid anxiety disorders, increasing general medical illness burden as well as depressive symptom severity would be related to non-remission in this study-sample. In examining demographic and clinical factors related to outcome in major depression, we hope to identify those patients at greatest risk for a chronic course.

Methods

A secondary analysis of patients with major depression from the PRISM-E study was conducted. Details regarding this sample, data collection, and consent procedures are described elsewhere (Levkoff *et al.*, 2004; Bartels *et al.*, 2004; Krahn *et al.*, 2006). Briefly, primary care clinics from which patients were recruited included five VA Medical Centers, three community health centers, and two hospital networks. Patients were randomly assigned to one of two models of care. In the integrated model, mental health services, substance abuse services, or both were provided in a primary care clinic by a mental health professional. The enhanced specialty referral model provided mental health services, substance abuse services, or both in a specialty setting that was physically separate from the primary care clinic and designated as a mental health or substance abuse clinic. Modalities of treatment across integrated and enhanced specialty referral sites predominately included individual therapy and pharmacotherapy. Exclusion criteria included the presence of significant cognitive impairment, psychotic disorder, or receiving formal treatment for a mental health disorder at the time of enrollment. All study participants provided written informed consent according to local institutional review board (IRB) approval.

Sample

Baseline data from the overall sample was available for 2,243 primary care patients aged 65 and older (Figure 1). Inclusion criteria for the current analysis included: baseline major depression diagnosis and randomization into one of the two treatment models upon conclusion of the baseline evaluation. As such, 1,195 participants without a major depression diagnosis were excluded. Of the remaining participants, those not randomized at baseline (n=93) were also excluded. Thirty participants were excluded due to missing data (i.e., incomplete interview), as were those with a diagnosis of hypomania (n=6) and psychotic syndrome (n=1). Further, participants already receiving mental health or substance abuse treatment at the time of the baseline evaluation (n=18) were also excluded. In an effort to increase generalizability to older primary care patients, those with a comorbid anxiety disorder (n=309) or at-risk alcohol use (n=70) were not excluded from the final sample. The current study's final sample consisted of 900 elderly primary care patients with baseline diagnosis of major depressive disorder and randomization into one of the study interventions (i.e., integrated, enhanced specialty referral), of which 108 (12%) were lost to all follow-up. Compared with the final analytic sample (n=792), those lost to follow-up were more often male and African-American (results not shown).

Measures

Psychiatric Disorder—The Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998), a structured diagnostic psychiatry interview for DSM-IV and ICD-10 psychiatric disorders, was used to establish the following diagnoses of interest: major depression, dysthymia, minor depression, depression NOS, panic disorder, generalized anxiety disorder (GAD), anxiety NOS, and “at risk” drinking. Of particular note, the MINI assessed all nine criterion symptoms for a major depressive episode according to DSM-IV diagnostic criteria. The MINI further follows DSM-IV diagnostic criteria for major depression by evaluating symptoms in the past two weeks. For dysthymia, symptoms occurring for the last two years were evaluated according to DSM criteria. Duration of symptoms for depression NOS and minor depression was at least two and four weeks, respectively. At-risk alcohol use was defined as any of the following: a) ≥ 14 drinks in the previous week for men and ≥ 12 drinks in the previous week for women, b) ≥ 4 binges in the previous 3 months, in which a binge was defined as ≥ 4 drinks in one day, or c) use of alcohol-targeted medication and ≥ 7 drinks in the previous week for men and women. The MINI, administered in-person at all assessment points, has been shown to be a valid and

reliable measure of psychiatric disorders (Sheehan *et al.*, 1997). Based on the administration protocol of the MINI, there was no attempt to establish the primacy of either major depressive disorder or another psychiatric disorder at enrollment.

Depression Severity—The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) is a 20-item self-report measure of depressive symptoms in the past week. With a possible range of 0 to 60, higher scores are suggestive of greater depressive symptom severity.

General Medical Illness—Assessment of medical comorbidity was based on self-report of 20 medical conditions (e.g., diabetes, arthritis/rheumatism, liver trouble/jaundice, and cancer). The presence or absence of the medical conditions was summed to form a composite score, with higher scores indicating greater medical burden. Previous research has found good agreement between self-reports and medical records for select medical conditions (Bush *et al.*, 1989).

Outcome

The primary outcome for this analysis was remission of major depression at the six-month PRISM-E follow-up, as assessed by the MINI. In particular, remission was defined as the absence of a DSM-IV depression diagnosis (i.e., major depression, dysthymia, minor depression or depression NOS) at the six-month follow-up. As such, non-remission was defined as the presence of any DSM-IV depression diagnosis at the final assessment point. For patients who did not complete the six-month assessment, the three-month follow-up was used ($n=72$). These 72 patients, when compared to those with six-month data, were more often men and endorsed lower, but still clinically significant, levels of baseline depressive symptoms (CES-D: 3m completers= 25.57 ± 9.95 , 6m completers= 28.60 ± 9.89 ; $p=0.014$).

Statistical Analysis

Bivariable analyses compared demographic and clinical characteristics of participants attaining remission at follow-up to those who did not remiss using chi-square tests for dichotomous variables and *t*-tests for continuous measures. Demographic variables of interest included: age, gender, race/ethnicity, and education. Clinical characteristics included: anxiety disorder diagnosis, “at risk” drinking, depressive symptom severity, and general medical illness burden at baseline.

Variables on which the two groups differed significantly in bivariable analyses ($p<0.05$) were selected for entry into a multivariable logistic regression model using a likelihood-ratio (LR) backward elimination approach. This model allowed for the removal of variables failing to make significant independent contributions to the prediction model (exclusion criteria $p=0.15$). Despite PRISM-E not demonstrating a difference in rates of remission between the treatment arms, the randomization group (i.e., integrated, enhanced referral) was included in multivariable modeling as subgroup analysis found that patients with major depression randomized into enhanced referral care had improved depressive symptom severity (Krahn *et al.*, 2006). To improve clinical utility of the findings, we also examined percent remission by baseline depression severity quartile.

Results

Of the 792 patients with major depression included in the final analytic sample, 29% ($n=228$) attained remission (i.e., progressed from major depression to no depression diagnosis), while 71% ($n=564$) were non-remitters (i.e., maintained a DSM-IV depression diagnosis).

Baseline demographic and clinical characteristics for those with and without DSM-IV depression at follow-up are presented in Table 1. Sex, education, comorbid anxiety disorder, baseline depressive symptom severity, and general medical comorbidity were found to significantly differ between those who had remitted at follow-up and those who maintained a depression diagnosis. “At risk” drinking was not found to significantly differentiate depression status. Results did not significantly change when study participants with “at risk” drinking (n=70) were excluded from all analyses (results not shown). Compared to Caucasian patients, African-American (p=0.504), Hispanic (p=0.950) and Other (i.e., Native American, Asian, and Other) patients (p=0.063) were no more likely to remiss at the study’s conclusion.

Logistic regression analysis, presented in Table 2, found the following to be significant predictors of non-remission: baseline anxiety disorder diagnosis, sex, general medical comorbidity, and depressive symptom severity at baseline: final model, $X^2 = 62.83$, $df = 4$, $p < 0.001$, overall correct classification = 71.6%. The presence of a comorbid anxiety disorder increased the odds of non-remission by a factor of 1.6 (95% CI 1.11 – 2.31, $p = 0.012$). Similarly, women had 1.5 greater odds of non-remission than men in this study-sample (95% CI 1.04 – 2.15, $p = 0.032$). General medical comorbidity predicted non-remission, such that the presence of each additional medical condition was associated with increased odds of non-remission by a factor of 1.2 (95% CI 1.07 – 1.24, $p < 0.001$). Odds of non-remission increased by a factor of 1.0 (95% CI 1.03 – 1.06, $p < 0.001$) for each point increase on the CES-D, the self-report measure of depressive symptom severity. Underscoring the significant relationship between depressive symptom severity and outcome in major depression, CES-D quartiles scores at baseline were calculated and compared on rates of remission. As presented in Figure 2, rates of remission were found to decrease linearly as a function of increasing baseline CES-D quartile scores ($X^2 = 36.54$, $df = 3$, $p < 0.001$). Model of treatment (i.e., integrated, specialty referral) and education were not found to independently predict outcome in the final logistic regression model.

The mean ($\pm$ SD) follow-up CES-D score for those who reached remission was 7.40 ($\pm$ 4.41), which was significantly lower than the mean score (24.73 ± 10.39) of the group that did not achieve remission at follow-up ($t(2, 772) = -23.54$, $p < 0.001$).

Given the final analyses included 72 study participants with only three-month data and no six-month assessment, bivariable and multivariable analyses were re-run excluding those patients with incomplete data at six months. In the bivariable analyses, results were unchanged with the exception of education, which no longer reached statistical significance ($p=0.068$). Further, results remained unchanged in the final logistic regression model, where baseline anxiety disorder diagnosis, sex, general medical comorbidity, and depressive symptom severity at baseline continued to predict six-month depression status (results not shown). Finally, the two groups (3 and 6 month completers) were not found to significantly differ in rates of remission ($p=0.150$).

Discussion

The current project sought to identify baseline factors related to major depression outcome in older primary care patients enrolled in mental health treatment. Results indicated that baseline anxiety disorder, female sex, increased medical comorbidity, and baseline depressive symptom severity independently predicted non-remission at six months. Clinically, these findings are significant as they point toward the added challenge in treating depression within primary care when accompanied by psychiatric and medical comorbidity. Given the negative health consequences associated with depression, failure to attain

remission following mental health treatment places these patients at an even greater risk for additional morbidity and possible mortality.

This study expands the previous literature by defining remission in major depression as the absence of DSM-IV diagnostic criteria for *any* depressive disorder. Classifying remission according to criterion symptoms is clinically significant as even residual symptoms of depression have been linked with shorter time to relapse and impaired functioning, even in the elderly (Chopra *et al.*, 2005; Cui *et al.*, 2008). This criteria is not only more stringent, but serves as a good goal for treatment. However, our finding that depression severity was an independent predictor of remission suggests that a baseline measure of depression severity is beneficial in determining the possibility of remission. Thus, while only using DSM-IV criteria for the diagnosis of major depression in older primary care patients may describe who has depression, it will likely miss the opportunity to identify patients who will not remiss and require additional care due to a more severe depression.

Additionally, our finding linking comorbid anxiety and non-remission in major depression is consistent with some (Steffens and McQuoid, 2005), but not all previous research (Lenze *et al.*, 2003). In a naturalistic study of older adults receiving treatment for depression and comorbid symptoms of generalized anxiety disorder, Steffens and McQuoid (2005) found the presence of generalized anxiety disorder (GAD) symptoms to be associated with a longer time-to-remission, when compared with depression alone. Similarly, in a separate study, older adults receiving pharmacotherapy and interpersonal psychotherapy for the treatment of major depression were found to have slower rates of response when also presenting with elevated levels of anxiety (Andreescu *et al.*, 2007). Participants with comorbid anxiety were also more likely to have a recurrence of depression within two years. While the aforementioned studies found comorbid anxiety to be linked with poorer outcomes in older adults with depression, Lenze and colleagues (2003) failed to find differences in rates of response in older adults with and without comorbid anxiety receiving treatment for depression. While these mixed findings point toward the need for additional research in comorbid anxiety and depression, particularly in later life, our results suggest that the presence of anxiety needs to be assessed at baseline in patients who are being initiated on treatment for major depression.

These findings need to be highlighted in the demographic and ethnic diversity of the enrolled population. While 63% of the study sample was non-Caucasian, we found no differences in remission from DSM-IV depression with respect to ethnicity. This is consistent with a prior PRISM-E project that examined differences in service use and outcome, as defined by CES-D scores (Areán *et al.*, 2008). Our finding is novel and extends this previous work by examining race differences in DSM-IV major depression outcome within a diverse sample. The current project's finding that women were less likely to achieve remission than men is consistent with some studies (Thase *et al.*, 2005), though others have failed to identify gender differences in treatment response (Quitkin *et al.*, 2002). Our results are surprising given that previous research has shown older men to utilize less mental health care than women in the treatment of depression (Unützer *et al.*, 2003). That said, the finding of female sex as a predictor of non-remission needs to be interpreted cautiously as female sex and education (i.e., less than 12 years), which was found to differentiate remission from non-remission in bivariable analyses, were highly correlated.

This study has several strengths. First, the study utilized a large, ethnically and geographically diverse sample of older primary care patients in the PRISM-E dataset, thereby making the results more generalizable. Second, the use of the MINI provided a standardized structured diagnostic psychiatric interview to assess for major depression and additional psychiatric disorders including anxiety and other depressive disorders. Further, in

using the MINI to define outcome rather than a percentage decline on the CES-D, we adhered to DSM criteria while also extending the work of previous PRISM-E projects. Finally, while enrollment was restricted to those not in treatment at baseline, only 18 of 1,048 (1.7%) patients with major depression at enrollment were receiving current mental health or substance abuse treatment, thereby precluding them from study participation. The PRISM-E, however, did successfully target and improve access to treatment for a vulnerable group that historically did not receive mental health care (i.e., older adults). As a result, the initial treatment (of either arm) was likely to improve the baseline mood disorder in this study sample.

The findings should be interpreted in light of the study's limitations, which stem primarily from its design of re-examining data from a project that has already been conducted. First, given that remission was defined according to depression status at one point only (six months), it is possible that patients reaching remission prior to six months may have relapsed by the assessment period, thereby not being considered in remission for purposes of the current study. Similarly, some patients categorized as non-remitters may vary from other non-remitters based on a cyclical pattern of depression status. Further, the study was unable to investigate the role of cognition, particularly executive function, on depression outcome, as the PRISM-E screened out those with cognitive impairment. This is particularly important given that executive dysfunction has been previously linked with depression, medical comorbidity, and treatment response in depression (Alexopoulos *et al.*, 2000; Lockwood *et al.*, 2002). Another limitation is the use of self-report to quantify general medical illness burden, though previous research has demonstrated good agreement between self-report and medical record review of general medical illness (Bush *et al.*, 1989). Because those who did not follow up were more likely to be male and African-American, our final cohort may not be representative of this subgroup. Further, it may be that those lost to follow up were less sick and therefore less likely to follow through with treatment. Finally, it is entirely possible that other unstudied factors (e.g., social support, socioeconomic status, access to health care) may influence the association with non-remission in major depression than the variables examined in the current project.

Conclusion

To conclude, the current study identified demographic and clinical characteristics that predict change in depression status at six months in older primary care patients enrolled in mental health treatment. The findings offer additional support for the close monitoring and follow-up of depressed older adults with comorbid psychiatric and medical conditions. Future studies could explore treatment approaches specifically targeted at populations identified through research such as the current investigation, who are at special risk for limited response to treatment for depression.

Key Points

1) Seventy-one percent of older primary care patients with DSM-IV major depression did not remit at six months. 2) Non-remission in late-life major depression was associated with psychiatric and medical factors.

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Figure 1.
Study Participant Progression

Figure 2.
% Remitted by Baseline CES-D Quartile Scores

Table 1

Baseline Demographic and Clinical Characteristics Stratified by Depression Status*

Characteristic	Remission (n=228)	Non-remission (n=564)	p-value	Included in multi-variable selection model
Age, mean (SD)	73.62 (6.19)	73.64 (6.23)	.966	
Male, n (%)	169 (74%)	366 (65%)	.012	X
Race, n (%)				
Caucasian	86 (38%)	209 (37%)	.166	
African American	63 (28%)	134 (24%)		
Hispanic	60 (26%)	144 (26%)		
Other	18 (8%)	75 (13%)		
Education, n (%)				X
< 12 years	113 (50%)	327 (58%)	.034	
≥ 12 years	113 (50%)	234 (42%)		
CES-D, mean (SD) [†]	24.90 (10.00)	29.69 (9.58)	<.001	X
Anxiety diagnosis, n (%)	56 (25%)	221 (39%)	<.001	X
“At risk” drinking, n (%)	15 (7%)	48 (9%)	.360	
GMC, mean (SD) [‡]	3.58 (2.10)	4.32 (2.32)	<.001	X
Model of Care, n (%)				X
Integrated	110 (48%)	295 (52%)	.301	
Referral	118 (52%)	269 (48%)		

* The table does not include 108 patients who were lost to follow-up. These patients were more often male and African-American.

[†] Center for Epidemiological Studies Depression Scale (CES-D). Range; 60=worst.

[‡] General medical comorbidity (GMC). Range; 20=highest comorbidity

Table 2

Multivariable Logistic Regression Predicting Non-Remission in Major Depression (N=772)

Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
<i>Baseline Model (Model 1)</i>				
Sex	0.36	0.19	1.43 (0.99 – 2.07)	.057
Education	−0.23	0.17	0.79 (0.57 – 1.11)	.173
Anxiety Disorder	0.49	0.19	1.63 (1.13 – 2.37)	.010
General Medical Comorbidity	0.14	0.04	1.15 (1.06 – 1.24)	<.001
Depressive Symptom Severity	0.04	0.01	1.04 (1.03 – 1.06)	<.001
Treatment Randomization	−0.20	0.17	0.82 (0.59 – 1.14)	.238
<i>Final Model (Model 3)</i>				
Sex	0.40	0.19	1.49 (1.04 – 2.15)	.032
Anxiety Disorder	0.47	0.19	1.60 (1.11 – 2.31)	.012
General Medical Comorbidity	0.14	0.04	1.15 (1.07 – 1.24)	<.001
Depressive Symptom Severity	0.04	0.01	1.04 (1.03 – 1.06)	<.001