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Treatment Adequacy and Adherence as Predictors of Depression Response in Primary Care

Jo Anne Sirey, Ph.D.,
Department of Psychiatry, Weill Cornell Medical College

Alexandra Woods, Ph.D.,
Department of Psychiatry, Weill Cornell Medical College

Nili Solomonov, Ph.D.,
Department of Psychiatry, Weill Cornell Medical College

Lauren Evans, Ph.D.,
Department of Healthcare Policy & Research, Weill Cornell Medicine

Samprit Banerjee, Ph.D.,
Department of Healthcare Policy & Research, Weill Cornell Medicine

Paula Zanotti, BA,
Department of Psychiatry, Weill Cornell Medical College

George Alexopoulos, M.D.,
Department of Psychiatry, Weill Cornell Medical College

Helen C. Kales, M.D.
Department of Psychiatry and Behavioral Sciences, University of California at Davis

Abstract

Objective: Primary care is the de facto mental health system in the United States where physicians treat large numbers of depressed older adults with antidepressant medication. This study aimed to examine whether antidepressant dosage adequacy and patient adherence are associated with depression response among middle-aged and older adults prescribed with antidepressants by their primary care provider.

Design: A secondary analysis was conducted on a sample drawn from a randomized controlled trial comparing Treatment as Usual to Treatment Initiation Program, an adherence intervention. Treatment Initiation Program improved adherence but not depression compared to Treatment as Usual (Sirey et al., 2017). For this analysis, we examined dosing adequacy and adherence at 6 and 12 weeks as predictors of depression response in both groups at 12 and 24 weeks.

Send correspondence and reprint requests to Jo Anne Sirey, Ph.D., Department of Psychiatry, Weill Cornell Medical, 21 Bloomingdale Rd., White Plains, NY 10605. jsirey@med.cornell.edu.

AUTHOR CONTRIBUTIONS

JS and HCK were the principal investigators on the two R01 grants supporting the research. JS and HCC designed the study. AW oversaw its implementation and supervised the research assessments. PZ helped prepare the data and review accuracy. NS, LE, SB analyzed the data, and JS, HCC, GSA, AW, NS, PZ, and SB interpreted the findings and were involved in writing the text. All authors revised and approved the paper before submission.

Setting: Primary care practices.

Participants: One hundred eighty-seven older adults with depression prescribed an antidepressant for depression by their primary care provider.

Measurements: Depression response was defined as 50% reduction on the Hamilton Rating Scale for Depression. Adherence was defined as taking 80% of doses at follow-up interviews (6 and 12 weeks). Patient-reported dosage and duration of antidepressant therapy was collected using the Composite Antidepressant Score (adequacy score of >3) at follow-up.

Results: Greater adherence, but not receipt of adequate dosage, was associated with higher likelihood of treatment response at both 12 (Odds ratio (OR) =2.63; 95% Confidence Interval (CI), 1.19—5.84) and 24 weeks (OR = 3.09; 95% CI, 1.46—6.55).

Conclusion: As physicians prescribe antidepressants to the diverse group of adults seen in primary care, special attention to patients' views and approach to adherence may improve depression outcomes.

Keywords

Depression; adherence; primary care

OBJECTIVE

Depression among older adults is associated with suicide,[1] nonsuicide mortality,[2] higher rates of falls,[3] and greater rates of health service utilization.[4] The majority of depression care for adults of all ages is delivered in primary care, with a notable increase in primary care visits among the young old (65—74) and the oldest old (≥85).[5] In primary care, 8.1% of older adults screen positive for depression.[6] Their depressive syndromes have heterogeneous clinical presentation[7] and the rates of treatment vary in older primary care patients.[8] Medical service utilization increases as depressive symptoms burden increases from no depression to minor to major depression.[7] Antidepressants continue to be the first-line treatment for depression in primary care settings.[9]

Nonadherence to antidepressants is associated with poor clinical outcomes, higher rates of hospitalizations and emergency room visits, and greater overall medical service utilization.[10] A recent randomized controlled trial found that missing a single dose early in a medication trial was associated with treatment drop-out.[11] Analysis of a large Medicaid database documented that patients who filled an antidepressant prescription at the initial visit and refilled two-thirds of their prescriptions over the next 6 months were less likely to relapse and to have a recurrence of depression.[12] By contrast, premature discontinuation of antidepressants was associated with 77% increase in risk of relapse/recurrence.[12] In a prospective study of 241 older adults with depression, antidepressant nonadherence was associated with higher levels of depression at 12 months.[13]

Targeted interventions can improve adherence. In an early study of primary care treatment for depression, Katon et al. (1995) demonstrated that a behavioral treatment could improve medication adherence and significantly reduce depression over time compared with usual care.[14] Recently, in a randomized controlled trial, we demonstrated that our Treatment

Initiation and Participation (TIP) program, a brief personalized intervention focused on identification of barriers to adherence, could significantly improve adherence among middle-aged and older adults treated for depression in primary care.[15]

Along with adherence, the dosage of antidepressant therapy and the duration of treatment are key components of successful treatment for depression[16] and may increase the rate of remission even among older adults with cognitive deficits.[17] A meta-analyses of 10 trials found that 44% of older adults (age >60) responded to antidepressant therapy.[18] In our own prior community based sample, we found that adequate treatment as defined by dose prescribed and duration of antidepressant use predicted depression response.[19] However, other data suggest a more limited impact of antidepressant therapy in late-life depression,[20] especially among older adults with executive impairment.[21] In an early randomized controlled trial of a stepped collaborative care intervention, the combination of antidepressant adherence and 3 months of psychiatric consultation was associated with initial change in depressive symptoms between baseline and 3 months.[22] However, these differences disappeared during the 3—6-month follow-up period among patients with more severe depression despite maintaining significantly improved medication adequacy and adherence in the intervention group at 6 months as measured by refill patterns and self-report data. These data suggest that improved pharmacotherapy alone may be insufficient in maintaining good outcomes. There are many challenges to providing effective treatment for depression in primary care settings.[23,24] Structured care management improved response and remission rates and reduced suicidal ideation during a 24-month follow-up in primary care patients.[25,26] Guidelines for the treatment of depression recommend pharmacotherapy and psychotherapy, or collaborative care when possible.[27]

This study investigated the role of dosing adequacy as prescribed by the physician and patient adherence to the antidepressant regimen in predicting depression response among depressed middle-aged and older primary care patients being treated in primary care.[15] We hypothesized that patients whose physicians prescribed an adequate dose of antidepressants and who were adherent to the regimen would be more likely to respond to treatment (i.e., reduction of 50% or more in depression severity) at 12 and 24 weeks after initiation of treatment. In addition, we examined age differences in adequacy, adherence, and response, because of findings suggesting lower efficacy of antidepressants in old-old patients.[20] Given that the TIP improved adherence but did not improve depression response compared to Treatment as Usual,[15] we tested our hypotheses using the full sample to identify treatment factors that affect depression outcomes in primary care.

METHODS

Study Design

The original trial was approved by the Weill Cornell Medicine and the University of Michigan IRBs. Potential participants were identified at participating primary care sites and recruited within 10 days of receiving a prescription for an antidepressant for depression. In the original study, participants were randomized to either the TIP intervention or to treatment monitoring provided by the primary care provider (PCP). The two site principal investigators oversaw the conduct and data analysis of the trial and data with an annual

review by an independent data and safety monitoring board. Additional details on the study design and CONSORT chart can be found in.[15]

Participants

Participants were consecutively recruited beginning from January 2011 to December 2014 from two primary care practices in New York and Michigan. All patients had been newly prescribed an antidepressant by their PCP for depressive symptoms. Patients were excluded if they had: 1) active suicidality; 2) current substance abuse, bipolar disorder, or psychosis; 3) significant cognitive impairment (Mini-Mental State Examination <23); 4) terminal illness or current chemotherapy; or 5) an inability to communicate in English.

Measures

Research assessments were conducted at baseline, 6, 12, and 24 weeks by trained research assistants blind to group assignment. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition was administered to confirm a diagnosis of depression.[28] The 24-item Hamilton Rating Scale for Depression (HAM-D) was used to assess the severity of depressive symptoms[29] and depression response (defined as a 50% reduction on the HAM-D). The Cornell Services Index (CSI) was used to document service utilization at the 12 and 24 follow up assessment.[30]

Adherence, Adequacy, and Depression Outcomes

Adherence was measured using the Brief Medication Questionnaire, which is a self-report measure, validated against MEMS caps data, and used extensively in studies of older adults.[31, 32] Adequate antidepressant adherence was defined as 80% adherence to assure that a majority of doses are taken to achieve a biological effect.[33] Participants were considered adherent if they were taking the prescribed antidepressant medication 80%—100% of the time at both the 6th and the 12th week of follow-up. Patients who discontinued their antidepressant were classified as nonadherent.

Adequacy of prescribed antidepressant dosage was ascertained using the Composite Antidepressant (CAD) score,[34] which classifies the intensity of antidepressant dosing for older adults on a 0—4 scale such that a score of 3 or greater is consider adequate.[34,35] For example, Sertraline 50—100 mg, Bupropion 200—300 mg, Escitalopram 10—15 mg receive a CAD score of 3. The intensity of the antidepressant prescription is based on the medication's prescribed dosage and frequency and does not include what was actually taken by the patient.

Depression response was defined using the standard criterion of 50% reduction in depressive symptoms on the HAM-D from baseline.[26] Since the inclusion criterion was PCP initiation of a new treatment of depression with an antidepressant rather than a formal diagnosis of major depression, the severity of depression at baseline had a wide range.

Statistical Analyses

In separate logistic models, we examined the effect of main variables of interest (dosage adequacy and adherence) on achieving depression response at 12 and 24 weeks. Treatment

characteristics included in these models were antidepressant therapy dosing adequacy (adequate dose versus inadequate dose/no dose), adherence to antidepressants (adherent versus nonadherent), and study site (University of Michigan versus Weill Cornell Medicine).

Of the 187 participants with complete data on the depression remission status assessed at 12 and 24 weeks, 11 (5.9%) had missing data on one of the predictors used in the regression models. We examined the relation of age and depression severity on depression. Missing variables were imputed using the fully conditional method for multiple imputation.[36,37] All significance tests are two-tailed. Statistical analyses were conducted with the SAS software, version 9.4 (SAS Institute, Inc.).

RESULTS

Sample Characteristics

Approximately half of the sample was recruited from the Michigan study site (49.2%) and half from the New York study site (50.8%). Among 231 patients who completed the baseline assessment, 187 (81%) had complete data on treatment response (HAM-D) assessed at 12 and 24 weeks. Participants with complete data on treatment response at the 12- and 24-week assessments (n = 187) did not significantly differ from participants without follow-up data on these assessments (n = 44). We compared the two groups on demographic (age, sex, race/ethnicity, marital status, occupation status, education level, self-reported financial hardship) and baseline clinical characteristics (cognitive status, baseline depression level, or adequacy of their antidepressant medication dose). Sample characteristics are described in Table 1.

During follow-up, 31.6% (n = 59) of the sample had achieved response of depression by 12 weeks and 42.3% (n = 79) by 24 weeks. At both the 6- and 12-week assessments, a total of 40.6% (n = 76) were receiving an adequate dosage of antidepressant medication, and 62.6% (n = 117) reported that they were fully adherent to the medication at both the 6- and 12-week assessments. There were no significant differences in the number of medical visits made in the 12 week and 24 week follow up assessments on the CSI. Treatment response from baseline to 12 weeks and from baseline to 24 weeks was modeled in two separate multivariate models.

Prior to hypothesis testing, we examined whether there were age differences in medication adequacy, and treatment response. For these analyses, age was dichotomized into younger (<75 years) and older groups (≥75 years). We chose this criterion based on evidence showing that depression may be more challenging to detect among the “old-old” primary care patients and they may be offered differential treatments due to their increased medical burden and disabilities.[38] In addition, there are data suggesting that there may be lower efficacy of antidepressants in old—old patients.[20] Participants aged 75 years and older were less likely to be at an adequate dose at 6-week follow-up (chi =5.00, p = 0.03), but not at the 12th week. There were no differences in the rates of response between the younger participants and older participants at 12 or 24 weeks.

Impact of Medication Adherence and Medication Adequacy on Treatment Response

Improvements in depressive symptoms from baseline to 12 weeks and from baseline to 24 weeks were significant among those who were adherent to their medication at both the 6- and 12-week assessments. Greater adherence was associated with a higher likelihood of treatment response at both 12 weeks (odds ratio, 2.63; 95% Confidence Interval (CI), 1.19—5.84) and 24 weeks (odds ratio, 3.09; 95% CI, 1.46—6.55; Table 2). Study site significantly affected the likelihood of treatment response, and it was included in the multivariate models. There were important site differences. The New York primary care practices had more minority participants and this group was less likely to achieve treatment response compared to participants in the Michigan primary care practices at both 12 weeks (odds ratio, 0.54; 95% CI, 0.28—1.05) and 24 weeks (odds ratio, 0.46; 95% CI, 0.25—0.86).[15] However, there were no site differences in dosing adequacy.

Classifying antidepressant therapy into adequate versus inadequate or none demonstrated that taking an adequate dosage of antidepressant at both the 6- and 12-week assessments was not a significant predictor of treatment response at 12 weeks (odds ratio, 0.55; 95% CI, 0.27—1.11 or at 24 weeks (odds ratio, 1.26; 95% CI, 0.65—2.45). Rates of responses for the three groups and the overall three-group comparison are reported in Table 3. To determine if being adherent to an adequate dose predicted a greater likelihood of response, a between-group comparison was conducted (adherent to adequate dosing, adherent to less than adequate dosing, and nonadherent); the comparison found no differences in response based on adequate dosing among the adherent participants. A main effect term for treatment and interaction terms (Treatment*Time, and Site*Dosing adequacy interactions) were found to be nonsignificant and dropped from the final models. The meaningful differences remained between being adherent and nonadherent.

DISCUSSION

In this study, we examine the impact of antidepressant adherence and adequacy of dose of the prescribed antidepressant medication on depression response among middle-aged and older adults receiving pharmacotherapy for depression in primary care settings. Our hypothesis that both good adherence at 6 and 12 weeks and adequate dose levels of antidepressant therapy would predict a better treatment response was partially confirmed. Patients who were adherent to their antidepressants were more likely to respond than those patients who were nonadherent. However, adherent patients who were prescribed an adequate dosage did not have a significantly greater likelihood of improving than those patients who were adherent to lower doses of antidepressant medication.

The results of this study highlight the importance of patient adherence to achieve depression response. In “real-world” settings, we can improve patients’ adherence to antidepressant medication in primary care with brief and focused interventions, which in turn may contribute to reduction in depression severity. To date, low-cost medication reminders developed to address forgetfulness have not been found to improve adherence.[39] Instead, adherence interventions that provide education, target barriers and help patients identify goals of treatment[40] or those interventions that include person-centered planning and collaborative documentation[41] may be better suited to tackle the variation and complexity of

medication nonadherence. Importantly, while adequacy of dosage is determined by community physicians and may be based on many factors, adherence to medication is an individual choice and can be facilitated by evidence-based brief behavioral interventions, such as TIP.[15]

The treatment response rates in this real-world study were consistent with those documented in the literature among older adults. A meta-analysis of 51 randomized controlled trials including patients age 55 and older showed a 48% response rate across all classes of antidepressants,[42] compared with 54% at 12 weeks and 46% at 24 weeks in this study. We were not able to see a higher response among those adherent participants who received adequate antidepressant dosing as compared to those adherent participants on doses rated as inadequate. Some individuals may respond to doses less than the established therapeutic dose. There is evidence that depressed individuals who are poor metabolizers of antidepressant and patients on drugs suppressing the metabolism of antidepressants may respond to dosages lower than those considered therapeutic.[43] This may account for why adequate dosing was not a significant factor in predicting response. Although there is some evidence that antidepressants are not as effective with increasing age,[20] we did not see different response rates in adults aged 75 years or older. This may reflect the characteristics among older adults seen in primary care versus specialty services, or a cohort effect of a decade.

There are several limitations to this study. While antidepressant adequacy was standardized using the CAD, differences in dosing, adherence, or treatment outcome were not examined based on the specific type of antidepressant prescribed. This analysis does not identify specific medications, side effect profiles, or account for. In this study we used the criterion of a 50% reduction to determine a depression response given the applicability and relevance of this criterion to routine clinical practice. Our future work will expand the current inquiry by examining trajectories of change in depression severity over time using longitudinal modeling approaches.

Given the impact of early adherence on depression treatment outcomes, we recommend targeting adherence improvement with personalized interventions such as TIP, which can identify barriers early and build a personalized plan with effective strategies. Once a target dose is achieved and adherence is established, prescribing physicians can evaluate the impact of the antidepressant treatment and shift medications as needed. Although integration of mental health support services into primary care settings is widely recommended, there are many challenges including lack of resources, poor infrastructure, and an overwhelmed workforce with high turnover.[44] Nevertheless, this study provides additional evidence that adherence is important in improving treatment response. Clinicians can facilitate adherence by employing brief and simple strategies that could improve patients' outcomes.

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DISCLOSURE

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TABLE 1.

Baseline Characteristics of Participants With Follow-up Data at the 12- and 24-Week Assessments

Baseline Characteristics	No. (%)
Age (mean, SD), y	67.4 (8.1)
Female	133 (71.1)
Hispanic	24 (12.8)
Race/ethnicity	
Black	36 (19.3)
White	132 (70.6)
Asian	7 (3.7)
Other	12 (6.4)
Marital status	
Single	25 (13.4)
Married	82 (43.9)
Divorced/separated	53 (28.3)
Widowed	27 (14.4)
Living alone	63 (33.7)
Educational level, mean (SD), y	14.5 (3.1)
Employment status	
Full- or part-time	43 (23.0)
Unemployed	20 (10.7)
Retired	107 (57.2)
On disability	15 (8.0)
Baseline HAM-D score, mean (SD)	18.3 (9.5)
SCID diagnosis	
Major depression	83 (44.4)
Minor depression	54 (28.9)
Did not meet criteria	50 (26.7)
MMSE score, mean (SD)	27.8 (2.0)
Psychiatric hospitalization	0

Notes: Results present a total of 187 participants. HAM-D: Hamilton Depression Rating Scale; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MMSE: Mini-Mental State Examination.

TABLE 2.

Multivariate Logistic Models With Treatment Response Status at 12 and 24 Weeks as Dependent Variables for 187 Participants

Variable	Treatment Response at 12 Weeks OR (95% CI)	p Value	Treatment Response at 24 Weeks OR (95% CI)	p Value
Antidepressant therapy				
Adequate dose	0.55 (0.27—1.11)	0.10	1.26 (0.65—2.45)	0.49
Inadequate dose/no dose	1 [Reference]		1 [Reference]	
Medication adherence				
Adherent	2.63 (1.19—5.84)	0.02	3.09 (1.46—6.55)	0.003
Nonadherent	1 [Reference]			
Study site				
Cornell	0.54 (0.28—1.05)	0.07	0.46 (0.25—0.86)	0.02
Michigan	1 [Reference]			

Notes: Results describe likelihood ratio chi square (df = 1); odds ratio (OR) is estimated by logistic regression model.

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TABLE 3.

Rates of Depression Response by Three Groups

Groups	N/% of People Who Respond at 12 Weeks	% of People Who Respond at 24 Weeks
Adherent to adequate dosing at 6 and 12 weeks	21 (31.8%)	38 (57.6%)
Adherent to inadequate dosing at 6 and 12 weeks	22 (44.0%)	24 (48.0%)
Nonadherent to any dose	11 (18.33%)[a]	13 (21.7%)[b]

[a] chi-square = 8.51, df = 2, p = 0.014.

[b] chi = 17.4, df = 2, p = 0.0002.