Impact of Second-Generation Antipsychotics and Perphenazine on Depressive Symptoms in a Randomized Trial of Treatment for Chronic Schizophrenia

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Background: According to the American Psychiatric Association Clinical Practice Guidelines for schizophrenia, second-generation antipsychotics may be specifically indicated for the treatment of depression in schizophrenia. We examined the impact of these medications on symptoms of depression using the data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), conducted between January 2001 and December 2004.

Method: Patients with *DSM-IV*–defined schizophrenia (N = 1,460) were assigned to treatment with a first-generation antipsychotic (perphenazine) or one of 4 second-generation drugs (olanzapine, quetiapine, risperidone, or ziprasidone) and followed for up to 18 months (phase 1). Patients with tardive dyskinesia were excluded from the randomization that included perphenazine. Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS). Mixed models were used to evaluate group differences during treatment with the initially assigned drug. An interaction analysis evaluated differences in drug response by whether patients had a baseline score on the CDSS of ≥ 6, indicative of a current major depressive episode (MDE).

Results: There were no significant differences between treatment groups on phase 1 analysis, although there was a significant improvement in depression across all treatments. A significant interaction was found between treatment and experiencing an MDE at baseline ($P = .05$), and further paired comparisons suggested that quetiapine was superior to risperidone among patients who were in an MDE at baseline ($P = .0056$).

Conclusions: We found no differences between any second-generation antipsychotic and the first-generation antipsychotic perphenazine and no support for the clinical practice recommendation, but we did detect a signal indicating a small potential difference favoring quetiapine over risperidone only in patients with an MDE at baseline.

Trial Registration: clinicaltrials.gov Identifier: NCT00014001

J Clin Psychiatry 2011;72(1):75–80

Submitted: *March 31, 2009; accepted July 21, 2009.*
Online ahead of print: *September 21, 2010 (doi:10.4088/JCP.09m05258gre).*
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Since their introduction in the 1990s, second-generation antipsychotics (SGAs) have become the drugs of choice in the treatment of schizophrenia, despite a lack of conclusive evidence of superior efficacy as assessed by measures of general psychopathology.[1–5] One meta-analysis has, however, suggested that not all SGAs are equivalent.[6]

Depression is a common symptom over the course of schizophrenia.[7,8] It is a predictor of attempted suicide and suicide[9,10] and is an important determinant of quality of life.[11] When depressive symptoms meet the syndromal criteria for major depressive disorder, antidepressants have been suggested as adjunctive treatment to antipsychotics.[12]

Early suggestions that first-generation antipsychotics (FGAs) might have antidepressant properties notwithstanding,[13] depression has been identified as a potential treatment target for which SGAs were suggested to have a differential effect in comparison to FGAs.[14–17] The American Psychiatric Association Clinical Practice Guidelines assigned a level II evidence for a recommendation on the use of SGAs for the treatment of depression in schizophrenia not associated with relapse.[12] While some studies suggest a specific antidepressant effect for SGAs, and for olanzapine in particular, mediated through 1 or more non-D_2 pathways,[15] others have suggested that the difference detected in some studies may have reflected akinesia due to a lack of prophylactic anticholinergic medication in the FGA arm of the studies involving moderate to high doses of the high-potency drug haloperidol.[18] It has also been suggested that in drug-naive patients, depression in schizophrenia is related to low presynaptic dopamine function.[19] In contrast to trials that have not consistently demonstrated clinical superiority of SGAs over FGAs, clozapine has more consistently been more effective than other antipsychotics including SGAs in the treatment of refractory schizophrenia.[20,21] More specifically, in the treatment of symptoms of depression, clozapine has been shown to be more effective than risperidone in reducing symptoms of depression in a study of people with treatment-resistant schizophrenia.[22] Thus, the only antipsychotic that has consistently shown evidence of superior efficacy in terms of the positive symptoms of schizophrenia has also shown increased effectiveness against symptoms of depression.

The published reports on the treatment of depression in schizophrenia with antipsychotics usually examine depression as a secondary outcome measure. A recent meta-analysis of SGAs for people with both schizophrenia and depression included only 3 methodologically rigorous studies for which

depression was the primary outcome.[23] The conclusion of this review was that there were insufficient data to guide patients, prescribers, caregivers, or policy makers and that further studies were warranted.

In 1999, the National Institute of Mental Health initiated the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which used an experimental study design to compare the effectiveness of 1 FGA (perphenazine) and all 4 SGAs (olanzapine, risperidone, quetiapine, and ziprasidone) other than clozapine, that were available in the United States in January 2002 for the treatment of chronic schizophrenia. A report on the primary clinical outcomes from CATIE, considering only treatment on the initial randomly assigned drug (phase 1), found that patients treated with olanzapine remained on treatment with their medicine longer than those treated with quetiapine or risperidone and were less likely than all of those receiving other drugs to switch drugs for lack of efficacy.[5] None of the second-generation drugs showed statistically significantly greater efficacy or tolerability than the first-generation drug, perphenazine, nor were there any significant differences on measures of neurologic side effects. Weight gain with olanzapine was substantial, averaging 2 lb per month, with concomitant increases in hemoglobin A_{1c}, cholesterol, and triglycerides.

The clinical outcome assessments used in the CATIE study were selected to represent all symptoms and outcomes of relevance to clinical practice, including depression.[24] In this study, we examine the differential impact of 4 second-generation drugs and perphenazine on symptoms of depression in the overall CATIE study sample and evaluate whether there are differences in drug effects in the subsample who met criteria for a major depressive episode (MDE) on the primary measure of depressive symptoms (Calgary Depression Scale for Schizophrenia [CDSS]).

METHOD

Study Setting and Design

CATIE was conducted between January 2001 and December 2004 at 57 US sites and included an algorithmically determined series of treatment phases. The study is registered with ClinicalTrials.gov (NCT00014001). Patients were initially assigned to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions. However, patients with tardive dyskinesia (TD) (15% of the sample) were not considered in the randomization that included perphenazine and thus were not available for comparisons involving that drug. Although not reported here, patients who discontinued their first treatment were invited to further random assignment to other SGAs, including clozapine, if they so desired. Open treatment was also offered to patients who refused a second blind assignment or whose treatment failed after a second assignment (phase 3), when a small number chose FGAs.

Participants

The study was approved by an institutional review board at each site. Patients 18 to 65 years of age with a diagnosis of schizophrenia[25] who were able to take oral antipsychotic medication were eligible. Patients or their guardians provided written informed consent. Patients were excluded if they had a diagnosis of schizoaffective disorder or mental retardation or other cognitive disorders, an unstable serious medical condition, past adverse reactions to a proposed treatment, or treatment-resistant schizophrenia or if they were in their first episode of schizophrenia, pregnant, or breastfeeding.

Interventions

Identical capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg), or ziprasidone (40 mg). Ziprasidone was approved for use by the US Food and Drug Administration during the trial and was added in January 2002, after 40% of the sample had been recruited. Medications were flexibly dosed with 1 to 4 capsules daily, as judged by the study doctor. Concomitant medications were permitted, except for additional antipsychotic agents. Further details about blinding, later phases of treatment, and modal dosing have been presented elsewhere.[5,26]

Measures

A full description of the measures used in this study is reported elsewhere.[24] The outcome of primary interest for this analysis is depression, which was assessed with the CDSS.[27] The CDSS is a measure of depression specifically designed to assess depression in schizophrenia separate from negative symptoms.[28] It has been validated in independent studies[29,30] and recommended as the gold standard for assessing depression in schizophrenia for clinical trials.[31]

For the purpose of this analysis, patients with a baseline score of ≥ 6 on the CDSS were identified as meeting CDSS criteria for an MDE and thus most likely to benefit from treatment. This level of depression has been previously identified as an appropriate cutoff for the prediction of a major depressive disorder, with a specificity of 77% and sensitivity of 92%.[32]

Statistical Methods

For consistency and comparability, the statistical methods used in the analysis of continuous measures in this study were the same as those used in the original publication from CATIE.[5] The main analyses are limited to the period of treatment with the initially assigned drug (phase 1). The central analysis was a paired comparison between treatment groups of average CDSS scores from all timepoints using a mixed model including terms representing treatment group, the baseline value of the CDSS, time (treated as a classification variable for months 1, 3, 6, 9, 12, 15, and 18), site, a history of recent clinical exacerbation, and baseline-by-time interactions. The baseline-by-time term adjusts for baseline differences in characteristics of patients who dropped out early and thus are less well represented at later timepoints. Treatment-by-time interactions to evaluate differences in time trends between groups were also tested. A random

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subject effect and a first-order autoregressive covariance structure were used to adjust standard errors for the correlation of observations from the same individual.

Two hundred thirty-one patients with TD were excluded from assignment to perphenazine, and ziprasidone was added to the trial after 40% of the patients had been enrolled. Randomization occurred under 4 separate regimens: including and excluding patients with TD, and including and excluding ziprasidone. Analyses were thus conducted on 4 different datasets with overlapping membership. Each dataset included only patients with an equal chance of being randomly assigned to the treatments under comparison. Perphenazine-treated patients, in particular, were compared only to equivalent patients who did not have TD at baseline.

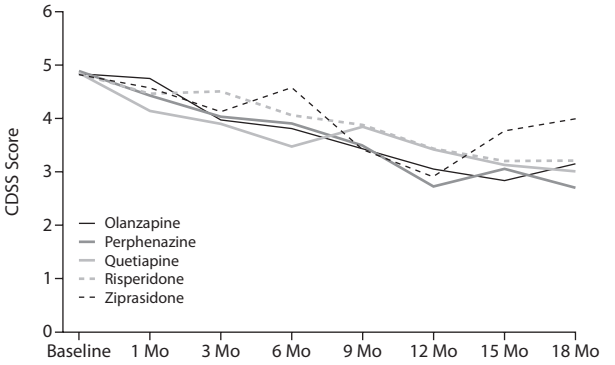
The primary comparison between the 4 treatments available at the beginning of the trial was an overall 3 degrees of freedom test. This test was performed on analytic dataset 1, excluding both patients with TD and those randomly assigned to ziprasidone. If the overall test was significant at $P < .05$, the 3 second-generation drugs were compared with perphenazine with a Hochberg adjustment for multiple comparisons[33] in which the smallest P value was compared to $.05/3 = .017$ and the largest to $P = .05$.

Next, with the use of dataset 2, which excludes perphenazine and includes TD patients, the 3 second-generation drugs were compared to each other via step-down testing. If the overall 2 degrees of freedom test was significant at $P < .05$, an α of $P < .05$ was applied for all comparisons.

Datasets 3 and 4 were used to compare ziprasidone to the other 4 drugs among patients randomized after ziprasidone became available, but with TD patients excluded from the perphenazine comparison. Hochberg adjustment for 4 pairwise comparisons was used to compare ziprasidone and perphenazine in dataset 3 and ziprasidone to the other 3 drugs in dataset 4. The smallest P value was considered significant if $P = .05/4 = .013$.

Because the impact of these medications on depressive symptoms may have been different among patients who met criteria for an MDE at the time of study entry than among patients who did not, a set of interaction analyses was conducted within each of the 4 strata. Within each stratum, an interaction term was modeled representing the interaction of treatment group by a dichotomous variable indicating whether the patient had met criteria for depression using 2 criteria: a categorical criterion of a major depressive disorder using the CDSS cutoff score of ≤ 6 or greater at baseline and a continuous criterion level of depression assessed on the CDSS. These analyses allowed us to determine whether there were differences between treatment effects among patients who met these a priori criteria for depression and patients who did not. If the interaction term was significant, paired comparisons between treatments were conducted among patients who met the criterion for depression and among patients who did not. Because these analyses were descriptive in nature, an α level of $P < .05$ was used to test paired comparisons.

Figure 1. CDSS Least-Squares Means for Each Treatment Group, Corrected for Baseline Levels of Depression



Abbreviation: CDSS = Calgary Depression Scale for Schizophrenia.

RESULTS

Characteristics and Disposition

The baseline demographic and clinical characteristics of the patients have been described in a previous publication and showed no significant differences between treatment groups on baseline measures.[5] Although 1,493 patients were enrolled in the study, all data from 1 site (33 patients) were excluded prior to analysis due to concerns about data integrity, and 17 patients never took study drug. A total of 448 (30.69%) patients had a CDSS score of ≤ 6 at baseline and were considered to be in a current MDE. Patients with an MDE were more often white ($P = .04$), female ($P = .006$), and younger ($P = .02$) and had fewer years of treatment ($P = .02$).

The total CDSS score improved over time in all groups (Figure 1). The mixed models, however, revealed no overall significant differences between treatments within any of the 4 strata (Table 1). There were also no significant treatment-by-time interactions indicating differences in rates of change in depressive symptoms.

Interaction analyses of treatment group by MDE at baseline showed interactions between the presence of major depressive disorder at baseline and treatment group in 2 of the analytic strata. The first interaction was observed in dataset 1, the stratum that included patients without TD assigned perphenazine, olanzapine, quetiapine, or risperidone ($P < .02$), but examination of paired comparisons showed no significant differences involving perphenazine.

An interaction was also observed in dataset 2, the stratum that included all patients randomly assigned to olanzapine, risperidone, or quetiapine ($P = .05$). Further paired comparisons of CDSS scores among patients meeting criteria for MDE showed a small but statistically significant difference between quetiapine and risperidone (mean = 8.52 for quetiapine vs 9.06 for risperidone, $P = .0056$), indicating that patients receiving quetiapine had lower depression scores than those receiving risperidone, specifically among patients who met criteria for MDE (Figure 2). Further examination of paired differences between these drugs at specific timepoints showed that lower depression scores with quetiapine

Table 1. Mixed-Model Analyses of CDSS Least-Squares Means Across Treatment Groups and Interaction Between Treatment and Being in a Major Depressive Episode (MDE) at Baseline[a]

						Main Effect of Treatment Group		Interaction of Treatment Group by MDE		Paired Comparison[b]	
	Olanzapine (O)	Perphenazine (P)	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	*F*	*P*	*F*	*P*	*F*	*P*
Total n	328	256	326	332	182						
Dataset 1 (*df* = 3): P vs O, Q, and R (excluding patients with tardive dyskinesia and those taking Z)											
n	263	256	261	269							
Mean CDSS											
Total sample	3.80	3.80	3.67	3.96		0.79	.50	3.32	.02		
No MDE	2.28	2.44	2.35	2.33							
MDE	8.95	8.71	8.51	9.11							NS
Dataset 2: O vs Q vs R (including patients with tardive dyskinesia but excluding those taking Z or P)											
n	328		326	332							
Mean CDSS											
Total sample	3.73		3.73	3.97		1.43	.24	2.90	.05		
No MDE	2.28		2.12	2.42							
MDE	8.78		8.52	9.06						2.9; Q < R	.0056*
Dataset 3: Z vs P (excluding patients with tardive dyskinesia but including those taking Z)											
n		146			150						
Mean CDSS											
Total sample	3.23	3.73	3.84	3.84	4.23	1.30	.27	1.86	.11		
No MDE	2.45	2.53	2.27	2.47	2.48						
MDE	9.07	8.63	8.55	8.70	9.34						NS
Dataset 4: Z vs O, Q, and R (including patients with tardive dyskinesia and those taking Z)											
n	177		181	174	178						
Mean CDSS											
Total sample	3.86		3.68	3.77	3.89	0.37	.77	0.75	.15		
No MDE	2.41		2.28	2.41	2.32						
MDE	8.88		8.61	8.91	9.29						NS

[a]Least-squares means of CDSS scores from months 1, 3, 6, 9, 12, 15 (4,816 patient month observations for data set 1; 4,480 for data set 2; 1,285 for data set 3; and 3,802 for data set 4).
[b]All pairwise *P* values < .05 are presented.
*Statistically significant using criteria for multiple comparisons.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, NS = nonsignificant.

were observed at only 4 of 7 timepoints: months 3, 6, 9, and 18 (Figure 2).

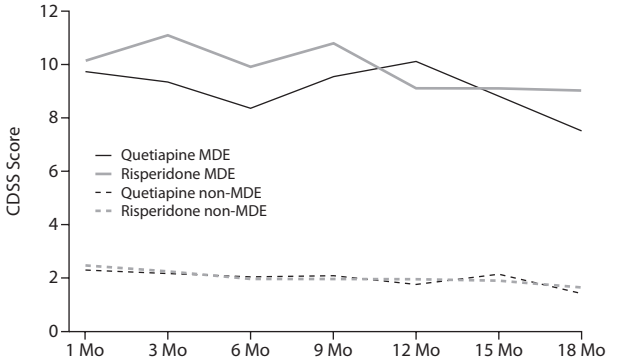
DISCUSSION

The main finding of this study is that we found no evidence of a class benefit of the use of SGAs compared with FGAs in the treatment of symptoms of depression, even in the subset that was above the baseline threshold for MDD. Depression was not the primary outcome measure for this study, and the sample size was not powered for this outcome. Thus, these analyses should be considered descriptive.

Despite this, our post hoc assessment of the results suggests that the clinical importance of the results would not be different if the sample had been larger. The standard deviation for depression scores was 5.0, and the few differences favoring SGAs are all less than 0.1 (0.026–0.04), resulting in effect sizes of less than 0.01. An effect size of 0.2 is considered small, and anything less than 0.2 is not likely to be of clinical importance.

However, in a subsample of schizophrenia patients identified as meeting criteria for MDE, those assigned to quetiapine had lower scores than those assigned to risperidone, but, again, no FGA-SGA differences were seen. These results

Figure 2. CDSS Least-Squares Means for Quetiapine and Risperidone Patient Groups Who Did and Did Not Meet Criteria for an MDE, Corrected for Baseline Levels of Depression



Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, MDE = major depressive episode.

are in contrast to studies that have reported a difference in change in depression between SGAs and haloperidol.[15–17] Furthermore, the findings do not lend empirical support to the recommendation for SGAs in schizophrenia with depression of the American Psychiatric Association Clinical Practice Guidelines, a level II recommendation meaning "Recommended with moderate clinical confidence."[12] It

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has been suggested that the findings of reduced changes in depression with haloperidol as compared to SGAs may have been due to akinetic extrapyramidal side effects (EPS) in the absence of prophylactic anticholinergics.[18] The CATIE results presented here, in contrast to earlier studies, used an intermediate-potency FGA, perphenazine, and found no significant differences among groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders or in the prescription of concomitant anticholinergic or antidepressant medications.[5] Although there were no overall differences in frequency of antidepressant prescription between antipsychotics in the original CATIE report,[5] the rate of prescription was highest in the risperidone group, 16%, and lowest in the quetiapine group, 8%, with perphenazine between these 2 SGAs, at 11%. Although the exact timing and duration of antidepressant treatment are not known, the results favoring quetiapine over risperidone are not likely to be an artifact of greater use of concomitant antidepressant treatment in the quetiapine group.

Another possible explanation of the differences in findings between this study and earlier studies is that both of the earlier studies found differences in change in positive and negative symptoms of schizophrenia or global psychopathology, as assessed by the Positive and Negative Syndrome Scale (PANSS), between SGAs and haloperidol. In contrast to those other studies, there were no differences in change in global psychopathology in the CATIE study. In studies of treatment response to antipsychotic medications, there is evidence that depressive symptoms in acute schizophrenia improve in conjunction with changes in global psychopathology.[34] Although the CATIE study was not an acute treatment study, there were statistically significant changes in global psychopathology over time. If the primary driver of reductions in depression is improvement in global psychopathology, then one would expect that treatments of equivalent efficacy in the treatment of general psychopathology would have equivalent effects on depression in schizophrenia. Such a general principle would explain the finding in studies comparing clozapine to other antipsychotics in treatment-resistant schizophrenia in which differential improvements in depression coincided with differential improvements in general psychopathology favoring clozapine.[22]

Despite the finding of no general effect for SGAs, this study did find evidence of a statistically significant difference between quetiapine and risperidone. While the size of the difference is clinically small, these results are congruent with a study comparing quetiapine with haloperidol in partially responsive schizophrenia[35] that showed a differential effect of quetiapine on the PANSS depression factor compared with haloperidol despite no difference in change in global psychopathology between treatments. Positron emission tomography studies in humans suggest that risperidone and quetiapine are at opposite ends of the range of dopamine affinity.[36,37] The low and transient D_2 occupancy of quetiapine appears to account for its low potential for EPS. This would fit the theory that depression may be exacerbated either by EPS or by the high dopamine blockade that underlies EPS. In contrast to quetiapine, risperidone has the highest D_2 receptor affinity of the drugs used in this study, comparable to that of haloperidol.[38] It would also fit with a theory that the mesolimbic dopamine reward circuit plays a part in depression[39] and that higher occupancy of dopamine D_2 receptors may be associated with increased feelings of dysphoria.[40,41] The same theory might also explain the earlier findings of reduced depression in studies comparing SGAs versus relatively high doses of haloperidol, but these pharmacologic conceptualizations remain speculative. An alternative explanation might be that a metabolite of quetiapine, *N*-desalkylquetiapine, has antidepressant properties.[42]

Strengths of the study were its large sample size, long duration of follow-up, and recruitment of patients from diverse representative sites with minimal exclusion criteria—all of which increase the generalizability of the results. The investigators also selected a depression scale that was specifically designed for the assessment of depression in schizophrenia and that avoids the confounds of negative symptoms, extrapyramidal symptoms, and depression.

Limitations of this study include the use of secondary outcome data and data loss from attrition. While patients treated with olanzapine stayed significantly longer on treatment than risperidone or quetiapine, there were no differences in duration of treatment between patients treated with quetiapine and risperidone.

In contrast to some previous research and a level II APA guideline, this study of the impact of antipsychotics on depressive symptoms in patients with schizophrenia found no differences between any SGA, including olanzapine, and the FGA perphenazine, but we did detect a signal indicating a small difference favoring quetiapine over risperidone that was limited to patients with an MDE at baseline.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Davis** is an employee of Quintiles. **Dr Stroup** has been a consultant for Janssen and Eli Lilly. **Dr McEvoy** has been a consultant for Pfizer and Indevus, has received grant/research support from Sanofi and Pfizer, and has received honoraria from Eli Lilly. **Dr Swartz** has received grant/research support and honoraria from and been a speakers/advisory board member for Eli Lilly. **Dr Lieberman** receives grant/research support from Allon, Forest, Merck, and Pfizer; is an advisory board member for Bioline and Eli Lilly; and holds a patent for Repligen. In 2007–2008, he received grant/research support from AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, and Wyeth; was a consultant for Cephalon, Eli Lilly, and Pfizer; was an advisory board member for AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Otsuka, Pfizer, and Wyeth; held a patent with Repligen; and was a Data and Safety Monitoring Board member for Solvay. **Drs Addington, Mohamed,** and **Rosenheck** report no financial or other relationship relevant to the subject of this article.

Funding/support: This article was based on results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, supported by the National Institute of Mental Health

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(N01 MH90001). Medication was provided by AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Forest Pharmaceuticals, Inc; Janssen Pharmaceutica Products, LP; Eli Lilly and Company; Otsuka Pharmaceutical Co, Ltd; Pfizer Inc; and Zenith Goldline Pharmaceuticals, Inc. The Foundation of Hope of Raleigh, North Carolina, also supported this work.

Acknowledgment: This analysis was conducted with the assistance of staff of the VA Northeast Program Evaluation Center, who provided analytic support.

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