

Predictors of Outcome in a Primary Care Depression Trial

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OBJECTIVE: Previous treatment trials have found that approximately one third of depressed patients have persistent symptoms. We examined whether depression severity, comorbid psychiatric illness, and personality factors might play a role in this lack of response.

DESIGN: Randomized trial of a stepped collaborative care intervention versus usual care.

SETTING: HMO in Seattle, Wash.

PATIENTS: Patients with major depression were stratified into severe ($N = 149$) and mild to moderate depression ($N = 79$) groups prior to randomization.

INTERVENTIONS: A multifaceted intervention targeting patient, physician, and process of care, using collaborative management by a psychiatrist and primary care physician.

MEASUREMENTS AND MAIN RESULTS: Patients with more severe depression had a higher risk for panic disorder (odds ratio [OR], 5.8), loneliness (OR, 2.6), and childhood emotional abuse (OR, 2.1). Among those with less severe depression, intervention patients showed significantly improved depression outcomes over time compared with those in usual care ($z = -3.06$, $P < .002$); however, this difference was not present in the more severely depressed groups ($z = 0.61$, NS). Although the group with severe depression showed differences between the intervention and control groups from baseline to 3 months that were similar to the group with less severe depression (during the acute phase of the intervention), these differences disappeared by 6 months.

CONCLUSIONS: Initial depression severity, comorbid panic disorder, and other psychosocial vulnerabilities were associated with a decreased response to the collaborative care intervention. Although the intervention was appropriate for patients with moderate depression, individuals with higher levels of depression may require a longer continuation phase of therapy in order to achieve optimal depression outcomes.

KEY WORDS: depression; primary care; intervention; treatment resistance.

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The development of the Agency for Health Care Policy (AHCPR) Guidelines for Treatment of Depression¹ has stimulated researchers to test new intervention models that attempt to improve the process and outcomes of care for primary care patients with major depression. Controlled, randomized trials of implementation of the ACHPR guidelines for antidepressant therapy have demonstrated that the guideline recommendations, which were based largely on specialty clinic efficacy studies, can be extended into primary care settings.²⁻⁴

One of the important differences between primary care and specialty clinic settings is the wider range in severity of depression present in patients in primary care.⁵ More patients with milder forms of major depression are likely to be enrolled in primary care studies, and these patients are likely to have less psychiatric comorbidity.^{5,6} The wider range of depression severity in primary care settings may increase the potential variability of outcomes. Important differences in outcomes between severe and less severe forms of illness may be obscured unless this variability is taken into account. Even in psychiatric populations, there appear to be differences in outcome between treatment trials with patients having mild and severe forms of major depression. This was illustrated in the National Collaborative Study of Depression where patients with milder forms of major depression responded to both active and placebo treatments, while those with more severe forms of illness had significantly greater clinical improvement with medications or psychotherapy.⁷

Most antidepressant or psychotherapy intervention trials have found that approximately one third of depressed patients have persistent symptoms or treatment resistance.^{8,9} Little is known about the predictors of this nonresponse in primary care settings. In a previous primary care study, we found that the best predictors of negative outcomes for patients with depression were the initial severity of depression based on the 20 depression items of the Hopkins Symptom Checklist and higher neuroticism scores.^{3,4} Clinical studies of patients with major depression have also shown that depression severity and neuroticism may also be associated with additional comorbidity such as panic disorder and adverse experiences in childhood.¹⁰

Using an intent-to-treat analysis, we recently reported that our collaborative care intervention resulted in improved depressive outcomes, compared with usual primary care in patients with persistent symptoms approximately 2 months after initiating treatment with their family doctor.¹¹ Because of prior research describing variability in outcome by severity of depression,^{3,12} we modified the

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current primary care clinical trial by using a stratified randomization scheme that balanced severity of SCL-20 ((Hopkins) Symptom Checklist-20) depression between intervention and control groups, using a mean item score of 2.0 as the cut point. We hypothesized that compared with patients with higher depression scores, those with lower depression scores would have significantly greater intervention versus control differences in depression outcomes. We also collected baseline information about early family environment, current stressors, family history of psychiatric illness, the personality trait of neuroticism, and social support. We further hypothesized that early adverse experiences (e.g., childhood maltreatment) as well as sequelae frequently associated with these traumas (e.g., anxiety, loneliness, and high neuroticism) would be associated with higher SCL scores.

METHODS

Setting

The settings for this study were four large primary care clinics of Group Health Cooperative of Puget Sound (GHC), an HMO serving over 400,000 persons in western Washington. These four clinics, with a population of 88,000 enrollees, are staffed by 73 full- and part-time board-certified family physicians. The GHC enrollment has an age and income distribution generally representative of the area population.

Eligibility for Randomization

The research team developed a program of population-based screening to examine short-term outcomes among all primary care patients beginning antidepressant treatment for depression. Potentially eligible patients were identified using GHC automated registration, pharmacy, and visit data. Patients between the ages of 18 and 80 years from one of the four primary care clinics who received a new antidepressant prescription (no prescriptions within the last 120 days) from a primary care physician for the diagnosis of depression or anxiety were eligible for the study. Five weeks after the prescription, the patient received an approach letter from his/her primary care physician inviting his/her participation in a study to improve the quality of care for various conditions and informing the patient that he/she would receive a telephone call from the study team.

At 6 to 8 weeks (mean 48.7 days), the patient received a call from the telephone survey team, who sought verbal informed consent for a 15-minute telephone screening interview to determine if he/she was eligible for a study to improve treatment of depression within the primary care clinic. The goal was to identify patients at high risk for persistent depression (the target population of this study) as well as those who recovered but were at

high risk for relapse (the target population for a separate study¹³). The first-stage screen included the telephone Structured Clinical Interview for DSM-IV (SCID).¹⁴ Criteria for selection for the second stage interview were either having four or more residual major depressive symptoms or recurrent depression (three or more prior episodes) or dysthymia.

Patients were excluded if they had a screening score of 2 or more on the CAGE alcohol screening questionnaire,¹⁵ were pregnant or currently nursing, planned to drop the Group Health insurance plan within the next 12 months, were currently seeing a psychiatrist, had limited command of English, or recently used lithium or antipsychotic medication.

Eligible and willing patients were informed that a research assistant would telephone them within the next week to arrange a second interview and explain the study in more detail. The research assistant called the patient, sought verbal informed consent, and arranged a convenient time and location for a baseline interview.

Inclusion criteria for the persistence study obtained during the baseline interview included four or more DSM-IV major depressive symptoms on the SCID, and a score of 1.0 or more on the 20 depression items of the SCL-20; or no more than 3 DSM-IV major depressive symptoms, and a score of 1.5 or more on the SCL-20.¹⁶

The recruitment procedure and the study protocol were approved by the institutional review boards of the University of Washington and GHC. After complete description of the study to the subjects, written informed consent was obtained. Consenting patients were randomly assigned to a collaborative model of care provided by both a psychiatrist (W.K., E.W., G.S., or J.U.) and their primary care physician or to "usual care" provided by their primary care physician.

Usual Care

Patients randomized to the usual care arm received treatment for depression from their primary care physicians in one of the four clinics. In most cases, usual care for depression, provided by GHC family physicians, involved prescription of an antidepressant medication, two to three visits over the first 3 months of treatment, and an option to refer to GHC off-site mental health services. During the course of recruitment, Group Health began integrating a small group of mental health practitioners into the primary care clinics to provide on-site, short-term mental health consultation and treatment. The specialty treatment provided by nonstudy mental health clinicians usually involved short-term psychotherapy by a masters-level therapist, but it could include psychiatric consultation. Both intervention and usual care patients could also self-refer to a GHC mental health provider. We tracked and reported these out-of-study mental health referrals and visits.

Stepped Collaborative Care Intervention

A multifaceted intervention was developed that targeted patient, physician, and process of care. Each patient received a book and companion videotape developed by the study team that reviewed the biology of depression, the relationship to stress, and the physical and emotional symptoms; how medications and psychotherapy help depression; and how to become involved as an active partner with his/her physician in care of his/her depressive illness. After the baseline interview and randomization, the research assistant scheduled two sessions for intervention patients with a psychiatrist (one 50-minute initial session and one 25-minute follow-up session) in the primary care clinic. Additional visits with the study psychiatrist were provided based on clinical response to treatment. The first visit was 7 to 10 days after baseline interview, and the second visit was 2 weeks after the initial session.

Visits were usually spaced 2 weeks apart, with a brief telephone call to review progress between the first and second visits and, if necessary, between the third and fourth visits. All patients had started antidepressant medication approximately 8 to 9 weeks before the first intervention visit. The psychiatrist reviewed the course of the current depressive episode, current symptoms, prior individual and family history of psychiatric illness, current stressful life events, medical history, social and vocational history, and current medication adherence and side effects. When severe side effects or treatment resistance occurred, the psychiatrist helped the patient and primary care physician alter the dosage or choose an alternative medication. Patients with severe psychosocial stressors were encouraged to seek psychotherapy or were referred to support groups (e.g., Alanon). Primary care physicians received immediate verbal consultation about their patients' progress and a typed psychiatric consultation note within 1 week. After the final psychiatrist visit, both the patient and primary care physician were given a standardized note describing the name and the dosage of the antidepressant prescribed, the recommended duration of treatment, residual depressive symptoms, and recommendations for psychotherapy based on chronic stressors.

The psychiatrist reviewed automated pharmacy data on antidepressant refills monthly to monitor the patient's adherence to the acute and continuation phases of treatment and alerted the primary care physician and/or telephoned the patient if premature discontinuation of medication occurred.

Study Measures

Patients' adherence to antidepressant medication, satisfaction with care, perceived improvement, and level of distress were assessed at 1, 3, and 6 months after ran-

domization by a telephone survey team blinded to the patients' randomization status.

Depression Severity. The SCL-90 items that measure depression include 20 questions scored on a 0 to 4 measure of severity.¹⁶ We report the average item score of the 20 SCL items (range, 0 to 4.0). The SCL has been used in numerous studies of medical patients and has been found to have high reliability and validity.¹⁶

We used the SCID to diagnose current depression and anxiety.¹⁴ A test-retest reliability study has found excellent agreement between in-person and telephone administration of the SCID.¹⁷

Psychosocial Risk Factors. Seven items from the NEO neuroticism scale¹⁸ were used in this study because these items have been found to predict persistence of depressive symptoms in a primary care population,¹⁸ when controlling for depression severity.

We included seven items from the Childhood Trauma Questionnaire¹⁹ to screen for a history of early childhood maltreatment. These items were chosen on the basis of having had the highest item-total correlations with each of their respective subscales (physical, emotional, and sexual abuse as well as physical and emotional neglect) in a previous factor analysis of data from 1,225 randomly selected women from the same HMO in which the current study was conducted.²⁰ The items were felt to provide an adequate screen for adverse childhood experiences of abuse and neglect. Additional questions on current stress, social support, and vulnerability were added from the Interpersonal Support Evaluation List²¹ and the modified Social Adjustment Scale²² (see Table 2).

Medication Adequacy and Adherence. Adherence to antidepressant medication was assessed at the 1-, 3- and 6-month follow-up by telephone interview. Patients were asked if they were still taking an antidepressant medication and were considered adherent if they reported having taken this medication at least 25 of the last 30 days. High reliability has been shown between this self-rating of adherence and automated GHC data based on pharmacy refills of medication.⁴ Based on computerized automated data from prescription refills, patients were also rated on whether they received adequate dosage of antidepressant medication for 90 days or more.²³ The lowest dosages in the ranges recommended in the AHCPR guidelines and in guidelines developed for newer agents were used to define a minimum adequate dosage standard.¹

Comorbid Medical Conditions. Medical comorbidity was assessed using the HMO's computerized prescription refill records. The Chronic Disease Score (CDS) is a measure of chronic medical illness derived from the patient's use of prescription medications over a 6-month period.²⁴ The CDS has been found to have high stability over a 1-year period and to have a high correlation with physician ratings of severity of medical illness.

Randomization

Eligible patients with major depression were stratified into groups based on their SCL-20 scores: severe (>2.0; $N = 149$) and moderate depression (1.0 to 2.0; $N = 79$). Within each stratum, patients were randomized to the intervention or usual care group in blocks of 8. Within each block, the randomization sequence was computer-generated. The SCL score of 2.0 was chosen because it is similar to mean scores for patients with major depression in our previous trials.³

Statistical Analyses

Patients in the two depression severity strata were compared on categorical variables using χ^2 analyses with corrections for continuity and on continuous variables with t tests. In order to summarize these results, variables that had significant univariate differences between the strata ($P < .05$) were included in a logistic regression. The resulting model included only the significant and nonredundant variables that best characterize differences between the SCL strata.

Random regression models for longitudinal data were used to determine if there were different rates of change in SCL scores over the course of the study between the care as usual (controls) and intervention groups. This analysis was performed separately for each depression severity group. The repeated measure of time had four assessments (baseline, 1, 3, and 6 months), the between-group factor was intervention or control group, and the covariates used were age, gender, neuroticism score, and chronic disease score. A significant group-by-time interaction indicates differential rates of change between the care as usual and intervention groups over the course of the study. In the event of a significant interaction,

planned post hoc tests of group differences at each time point were performed using the same set of covariates.

Finally, intervention and care as usual group differences in adherence and adequacy of antidepressant use (dose and duration) between the intervention and control groups within strata were tested using χ^2 analyses.

RESULTS

As shown in Table 1, patients with mean item SCL scores greater than 2.0 were significantly younger ($t_{226} = 2.46$, $P = .02$), had higher neuroticism scores ($t_{225} = 2.09$, $P = .04$), had the onset of their first depressive episode at an earlier age ($t_{226} = 3.47$, $P < .001$), and were significantly more likely to have comorbid panic disorder ($\chi^2_1 = 13.79$, $P < .001$) compared with patients with SCL scores from 1.0 to 2.0. As would be expected, patients in the two SCL strata had significantly different baseline SCL scores ($t_{226} = 19.31$, $P < .001$). The SCL severity groups did not differ in gender, education, employment, race, chronic disease score, or percent of patients with recurrent depression or dysthymia.

Patients with SCL scores greater than 2.0 rated themselves as having significantly more stress over the past 3 months ($t_{225} = 2.44$, $P = .02$) and stated that the stress interfered with their daily activities more than patients with less-depressive severity ($t_{226} = 2.86$, $P = .004$) (Table 2). They also rated themselves as significantly more lonely ($t_{226} = 4.03$, $P < .001$) and as having more childhood emotional abuse ($t_{226} = 4.02$, $P < .001$). The groups did not differ on any other social support or vulnerability variables. There were no differences between the groups with respect to the percentage of patients seeing a mental health provider, number of primary care visits for depression, number of visits for other medical problems, or

Table 1. Demographic and Clinical Characteristics of Patients in the Depression Strata

Variable	Low SCL (n = 149)	High SCL (n = 79)
Demographics		
Mean age, y* \pm SD	48.6 \pm 14.1	43.9 \pm 12.4
Female, %	73.2	77.2
\geq 1 year of college, %	78.5	75.9
Employed full- or part-time, %	65.5	74.7
White, %	80.5	79.7
Clinical		
Chronic Disease Score, mean \pm SD	1380.3 \pm 1154.4	1090.4 \pm 1116.9
NEO Neuroticism, mean \pm SD*	22.3 \pm 5.3	23.9 \pm 5.8
SCL-Depression, mean \pm SD†	1.6 \pm 0.3	2.5 \pm 0.4
% with recurrent depression (3 or more episodes)	78.9	84.7
% with dysthymia	46.9	41.8
% with panic disorder†	4.0	20.3
% of first-degree relatives with depression, mean \pm SD	41.8 \pm 28.5	36.6 \pm 26.6
Age of onset of first depression, y† \pm SD	38.0 \pm 17.9	29.7 \pm 15.8

* $P < .05$; † $P < .01$; ‡ $P < .001$.

SCL indicates Symptom Checklist.

Table 2. Stress, Social Supports, and Vulnerability

Variable	Low SCL (n = 149)	High SCL (n = 79)
Stress		
In the past 3 months how much stress have you experienced (0 = no stress; 10 = extreme stress), mean \pm SD*	7.6 \pm 2.2	8.3 \pm 1.7
In the past 3 months how much has stress in your life interfered with your daily activities (0 = no interference; 10 = maximum interference), mean \pm SD†	5.7 \pm 2.6	6.8 \pm 2.4
Social supports		
% with a confidante they can talk to	83.2	77.2
% living or with a partner in a steady relationship	67.8	55.7
When I feel lonely, there are several people I could call and talk to (1 = not true; 5 = extremely true), mean \pm SD	3.1 \pm 1.3	3.0 \pm 1.4
Over the past 2 weeks, have you felt lonely and wished for companionship? (0 = not at all; 4 = all of the time), mean \pm SD‡	1.2 \pm 1.0	1.9 \pm 1.3
Over the past 2 weeks, have you made an effort to keep in touch with relatives? (0 = not at all; 4 = all of the time), mean \pm SD	2.0 \pm 1.2	1.8 \pm 1.4
For those with a partner, in the past 2 weeks have you ever gotten angry or argued with each other (0 = not at all; 4 = all of the time), mean \pm SD	1.0 \pm 1.0	1.1 \pm 1.1
For those with a partner, in the past 2 weeks have you shared with your partner the responsibility of practical matters that have arisen? (0 = not at all; 4 = all of the time), mean \pm SD	2.4 \pm 1.3	2.2 \pm 1.2
Vulnerability§		
My family was a source of strength and support	3.3 \pm 1.2	3.3 \pm 1.4
I was frightened of being hurt by someone in my family	2.3 \pm 1.4	2.5 \pm 1.6
Someone in my family hated me†	1.7 \pm 1.1	2.4 \pm 1.7
Someone tried to touch me in a sexual way or tried to make me touch them	1.8 \pm 1.3	1.8 \pm 1.3
Someone threatened to hurt me or tell lies about me unless I did something sexual with them	1.4 \pm 1.0	1.4 \pm 1.0
People in my family hit me so hard that it left me with bruises or marks	1.7 \pm 1.1	2.0 \pm 1.5
My parents were too drunk or high to take care of the family	1.6 \pm 1.1	1.5 \pm 1.1

*P < .05; †P < .01; ‡P < .001.

§Items are all scored 1 (never true) to 5 (very often true).

number of visits or telephone calls related to the intervention over the 6-month time period.

To summarize the univariate findings, age, neuroticism, stress level and interference from stress, comorbid panic disorder, age of onset of first depression, loneliness, and childhood emotional abuse were allowed to enter in a stepwise fashion into a logistic regression model predicting SCL depression group severity strata. Both backwards and forwards methods were employed. Both techniques produced the same model with three significant independent predictors of SCL severity status: comorbid panic disorder (Wald's $t = 11.14$, $P < .001$), loneliness (Wald's $t = 9.46$, $P < .002$), and childhood emotional abuse (Wald's $t = 5.42$, $P < .02$). Patients in the high severity SCL group were more likely to have comorbid panic disorder (odds ratio [OR], 5.8), to feel more lonely (OR, 2.6), and to have experienced childhood emotional abuse at least "sometimes" (OR, 2.1), compared with patients in the lower SCL group.

As seen in Figure 1, intervention patients in the lower SCL severity group were significantly more likely to improve over time compared with usual care patients ($z = -3.06$, $P < .002$). Conversely, Figure 2 shows that in the more severely ill depression group, there was no signifi-

cant group-by-time effect ($z = 0.61$, $P = \text{NS}$), although both intervention and usual care groups had a significant decrease in depressive symptoms over time ($z = -7.09$, $P < .001$). Interestingly, in the more severe group, collaborative care appears to produce a more significant change in first 3 months (similar to the differences found between the less severe intervention vs control groups), yet that difference disappears between 3 and 6 months.

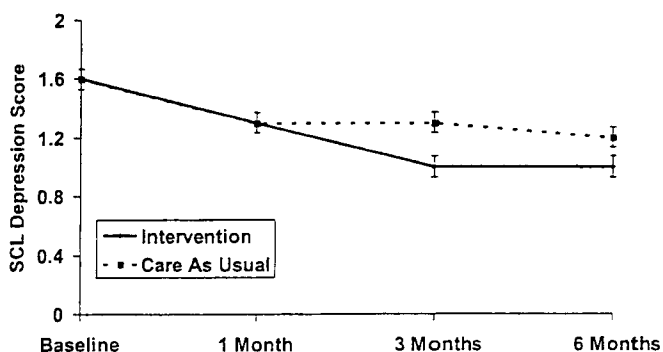


FIGURE 1. SCL depression adjusted means (adjusted for age, gender, chronic disease score, and neuroticism) with standard errors for patients in the high severity strata.

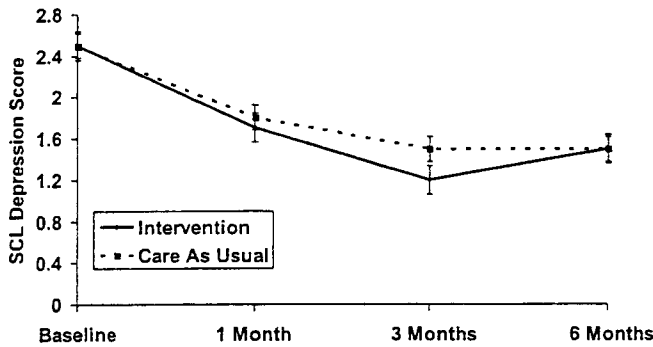


FIGURE 2. SCL depression adjusted means (adjusted for age, gender, chronic disease score, and neuroticism) with standard errors for patients in the low severity strata.

Table 3 presents the percentages of adequacy of antidepressant dose, adherence to medications, and the percentage of patients taking selective serotonin reuptake inhibitors (SSRIs) in the care as usual and the intervention groups classified by depression severity. Adequacy is shown in both the lowest dose, consistent with ACHPR guidelines, and twice the lowest dose. Intervention patients in both severity groups received more intensive pharmacotherapy and were significantly more likely to receive an adequate dose of antidepressants for 90 days or more compared with usual care controls. Despite the lack of significant effects on depressive symptoms between intervention and usual care patients in the high severity group, self-report data show that the intervention patients in the high severity group were significantly more likely to have taken medication for 25 or more days during the prior month at the 6-month follow-up. Compared with the usual care patients, the intervention patients in the high

severity group were also more likely to be taking SSRIs at the 6-month follow-up.

To investigate whether differences in antidepressant adherence between intervention and usual care patients might explain the disappearance of treatment response in the high depression severity intervention group (Fig. 2), we examined automated data on refills during this period. We compared intervention and controls in the high severity group with respect to gaps of 15 days or more in their antidepressant adherence for the interval between 3 months (the end of the intervention) and 6 months. We found that, compared with usual care patients, significantly fewer intervention patients in the high depression severity group had refill gaps of 15 days or more (38.7% vs 61.3%). This suggests that the intervention patients had a more continuous adherence to medications than controls between 3 and 6 months, despite having increased depression symptoms.

DISCUSSION

In a previous paper describing the main results of this randomized trial of collaborative care intervention for primary care patients with depression, we reported that the intervention was significantly more effective than usual care in adherence to guideline-level antidepressant treatment (25 days or more out of each month at each follow-up), satisfaction with care of depression, antidepressant dosing adequacy, and depression outcomes.¹² The present analysis took the next step and asked whether depression severity and psychosocial variables related to severity were factors associated with response to the intervention. By using the balanced randomization categories of the original study (low and high severity depres-

Table 3. Adequacy and Adherence Percentages for Intervention and Control Groups Within the Low and High Depression Strata

	Low SCL Group (n = 149)		High SCL Group (n = 79)		χ^2 (df = 1)	
	Controls, %	Intervention, %	Controls, %	Intervention, %	Low	High
90-day adequacy						
Low dosage	46	67	39	72	6.10*	8.23†
High dosage	25	44	28	51	5.93*	4.31*
Adherence						
Baseline	70	64	48	56	0.73	0.63
1 Month	75	79	58	75	0.25	2.25
3 Months	63	82	60	70	5.91*	0.71
6 Months	56	72	39	75	3.49	8.40†
Patients Taking SSRIs						
Baseline	61	61	45	49	0.001	0.01
1 Month	55	73	45	59	4.47*	1.04
3 Months	43	67	38	51	7.34†	1.01
6 Months	46	56	30	54	1.13	3.68*

*P < .05; †P < .01.

SSRI indicates selective serotonin reuptake inhibitor.

sion) as a classification variable, we demonstrated that the main effect of this intervention occurred in patients with lower severity depressive symptoms (Fig. 1), with no significant intervention versus usual care differences over time for patients with more severe forms of depression at baseline (Fig. 2).

Although it is not surprising that individuals with more severe affective illness might have a less robust response to the intervention, delineation of the specific factors associated with this lack of response is important in that it may lead to a better understanding of why some patients fail to improve and how to direct additional resources to their care. We found that patients with increased depression severity demonstrated not only less response to treatment but also higher risk for current comorbid panic disorder and psychosocial factors, such as decreased social support and childhood emotional abuse. These findings suggest a clinical model in which interactions with the intervention provider and the effects of pre-existing vulnerabilities might account for the decreased response in these more severely ill individuals and infer treatment approaches that could boost the intervention effect in selected patients.

The first part of the model hypothesizes that the study psychiatrists may be partially responsible for the changes shown in Figure 2. It appears that in patients with more severe depression, there is a strong trend for intervention patients to improve faster than controls between baseline and 3 months (the period during which the intervention was occurring), but between 3 and 6 months (after cessation of the psychiatrist visits), the intervention patients seem to develop worsening depressive symptoms.

The disappearance of this effect from 3 to 6 months was studied in further analyses. One possibility was that the intervention group may have decreased adherence to antidepressant medication after the psychiatry visits ended (in most cases by 3 months). However, analysis of refill patterns from automated data showed no differences in adherence (as measured by refills) between the high and low depression severity groups for the period of 3 to 6 months, suggesting that the worsening depressive symptom course in intervention patients was not due to medication adherence.

The second possibility, more consistent with the data, is that more severely depressed patients may need longer follow-up periods of specialty mental health care. In the high depression group, there was a significant improvement in intervention versus usual care patients in adequacy of pharmacotherapy for 90 days or more at both the lowest range of antidepressant medication dosage and twice the lowest range, as well as marked differences in adherence between interventions and controls at the 6 month follow-up (75% vs 39%). Intervention patients were also significantly more likely to receive SSRI prescriptions compared with usual care patients at 6 months. These differences in adequacy of pharmacotherapy coupled with

the pattern of change in Figure 2 suggest that it may be the combination of the support of the psychiatrist and antidepressant medication that may be associated with the initial change in depressive symptoms between baseline and 3 months; however, once the support of the psychiatrist was discontinued, improved pharmacotherapy alone was inadequate in maintaining improved outcomes. In contrast, patients with less severe depression (Fig. 1) seem to be able to maintain their initial significant gains with primary care visits and antidepressants alone.

The influence of psychiatric comorbidity and pre-existing vulnerability factors is also consistent with this explanation. Patients with early childhood maltreatment are at higher risk for later psychological distress, especially anxiety, depression, low self-esteem, problematic adult social relationships, and impaired social skills.²⁵ The results of the logistic regression showing that the high severity group was significantly more lonely and had a higher likelihood of comorbid panic suggest that the combination of anxiety and loneliness may have made these patients more vulnerable to relapse after stopping the additional visits with the psychiatrist.

One of the most robust clinical predictors of differences between the two groups of patients was the presence of comorbid panic disorder. Panic disorder was approximately 5 times as prevalent in patients in the more severe depression subgroup. Several research groups have found that primary care patients with comorbid panic disorder have increased severity of depressive symptoms. For instance, Lecrubier et al.²⁶ found that primary care patients with major depression and panic disorder compared to those with major depression alone had higher General Health Questionnaire (GHQ)-28 scores (17 compared with a score of 12 for depression alone). Moreover, those with comorbid panic and/or agoraphobia and major depression had significantly more disability days per month (12 vs 7.2) than those with depression alone, had an earlier age of onset, and were more likely to have long-term disorders. Several other primary care researchers have reported that patients with comorbid panic disorder and major depression have greater physical and psychosocial functional impairment compared to those with major depression alone.²⁷⁻³¹ Brown and colleagues have shown that primary care patients with comorbid lifetime panic disorder and major depression were more likely to have a history of alcohol dependence, somatization disorders, and avoidant personality disorder.²⁷

Brown and colleagues³⁰ have also shown that the presence of comorbid panic disorder in primary care patients with major depression was a significant predictor of poor outcomes in a trial of antidepressant medication versus interpersonal therapy versus usual primary care. Depressed primary care patients with lifetime panic disorder were significantly more likely to prematurely terminate pharmacotherapy or psychotherapy during each treatment's acute phase. The presence of comorbid panic disorder in patients with major depression has also been

shown to predict negative outcomes of treatment with antidepressant medication in efficacy trials,^{31,32} and has been associated with early childhood abuse and neglect.¹⁰

There are several possible limitations of this research. We tested patients with high rates of employment, with 1 or more years of college, and who were members of an organized system of health care with limited racial and ethnic diversity. However, effectiveness trials have shown that this collaborative model of care can be successfully adapted to patients with a variety of socioeconomic backgrounds and diverse practice settings as well.^{33,34} Because referral to the study was dependent upon the accuracy of primary care physician diagnoses, the study may not be generalizable to the 40% to 50% of patients who do not receive accurate diagnosis in primary care or the patients identified by the physician as depressed but not receiving medication. In addition, the measurement of psychosocial vulnerability was a secondary goal of this study, and the findings of emotional abuse and social isolation as important contributors to poor response should be confirmed in larger well-designed studies using the full scales from which these items were derived.

Our findings suggest that the collaborative care intervention improves the care and long-term depressive outcomes for patients with persistent symptoms of moderate severity after primary care treatment. The more severely ill patients may require more intensive clinician follow-up and/or psychotherapy to achieve sustained improvement from depressive symptoms. The widely held clinical impression that patients with more severe depression may need more intensive clinical management was recently examined in a "mega-analysis" of depression treatment studies⁹ where combined antidepressant and psychotherapeutic approaches were found to be superior to either therapy alone for patients with severe, recurrent depression. These findings suggest that the testing of stepped care algorithms that move more severely depressed patients into increasingly intensive treatment protocols is the next step in the cost-effective treatment of patients with recurrent, severe major depression.

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REFERENCES

1. Depression in Primary Care: Volumes 1 and 2. Detection and Diagnosis. Rockville, Md: U.S. Department of Health and Human Services AHCPR Publication No. 93-0551. 1993. Public Health Service Agency for Health Care Policy and Research.
2. Schulberg HC, Katon WJ, Simon GE, Rush J. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. *Arch Gen Psychiatry*. 1998;55:1121-7.
3. Katon W, Von Korff M, Lin E, et al. Collaborative management to achieve treatment guidelines: impact on depression in primary care. *JAMA*. 1995;273:1026-31.
4. Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry*. 1996;53:924-32.
5. Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry*. 1992;14:237-47.
6. Cooper PL, Crum RM, Ford DE. Characteristics of patients with major depression who received care in general medical and specialty mental health settings. *Med Care*. 1994;32:15-24.
7. Elkin I, Shea MT, Watkins JT, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Arch Gen Psychiatry*. 1989;46:971-82.
8. Wells KB, Burnam MA, Camp P. Severity of depression in prepaid and fee-for-service general medical and mental health specialty practices. *Med Care*. 1995;33:350-64.
9. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry*. 1997;54:1009-15.
10. Young EA, Abelson JL, Curtis GC, Nesse RM. Childhood adversity and vulnerability to mood and anxiety disorders. *Depress Anxiety*. 1997;5:66-72.
11. Katon W, Von Korff M, Lin EH, et al. A randomized trial of stepped collaborative care for depressed primary care patients with persistent symptoms. *Arch Gen Psychiatry*. 1999;56:1109-15.
12. Katon W, Lin E, Von Korff M, et al. The predictors of persistence of depression in primary care. *J Affective Dis*. 1994;31:81-90.
13. Katon W, Rutter C, Ludman E, et al. A randomized trial of relapse prevention of depression in primary care. *Arch Gen Psychiatry*. In press.
14. Williams JB, Gibbon M, First MB, et al. The Structured Clinical Interview for DSM-III-R: II. Multisite test-retest reliability. *Arch Gen Psychiatry*. 1992;49:630-6.
15. Mayfield D, McLeod G, Hall P. The CAGE Questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry*. 1974;131:1121-3.
16. Derogatis LR, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist: a measure of primary symptom dimensions. In: Pichot P, ed. *Psychological Measurements in Psychopharmacology: Problems in Pharmacopsychiatry*. Basel, Switzerland: Karger; 1974.
17. Simon GE, Revicki D, Von Korff M. Telephone assessment of depression severity. *J Psychiatr Res*. 1993;27:247-52.
18. Costa PT, McCrae RR. *The NEO Personality Inventory Manual*. Odessa, Fla: Psychological Assessment Resources; 1985.
19. Bernstein DP, Fink L. *Childhood Trauma Questionnaire: A Retrospective Self-Report*. San Antonio, Tex: The Psychological Corporation; 1988.
20. Walker EA, Gelfand A, Katon W, et al. Adult health status of women HMO members with histories of childhood abuse and neglect. *Am J Med*. 1999;107:332-9.
21. Cohen S, Hoberman HM. Positive events and social supports as buffers of life change stress. *J Appl Social Psychol*. 1983;13:99-125.
22. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. *Arch Gen Psychiatry*. 1976;33:1111-5.
23. Saunders K, Simon G, Bush T, Grothaus L. Assessing the accuracy of computerized pharmacy refill data for monitoring antidepressant treatment: a comparison of automated and self-report data. *J Clin Epidemiol*. 1998;51:883-90.
24. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992;45:197-203.
25. Beitchman JH, Zucker KJ, Hood JE, daCosta GA, Akman D, Cas-savia E. A review of the long-term effects of child sexual abuse. *Child Abuse Negl*. 1992;16:101-18.
26. Lecrubier Y, Ustun TB. Panic and depression: a worldwide primary care perspective. *Int J Clin Psychopharm*. 1998;13(suppl 4):S7-S11.
27. Brown C, Schulberg HC, Shear MK. Pharmacology and severity of

- major depression and comorbid lifetime anxiety disorders in primary care. *Anxiety*. 1996;2:210-8.
28. Sherbourne CD, Wells KB, Meredith LS, Jackson CA, Camp P. Comorbid anxiety disorders and functioning and well-being of chronically ill patients of general medical providers. *Arch Gen Psychiatry*. 1996;53:889-95.
29. Fifer SK, Mathias SD, Patrick DL, Mazonson PD, Lubeck DP, Buesching DP. Untreated anxiety among adult primary care patients in a health maintenance organization. *Arch Gen Psychiatry*. 1994;51:740-50.
30. Brown C, Schulberg HC, Madonia MJ, Shear MK, Houck PR. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. *Am J Psychiatry*. 1966;153:1293-300.
31. Grunhaus L, Harel Y, Krugler T, Pande A, Haskett R. Major depressive disorder and panic disorder. *Clin Neuropharmacol*. 1998;11:454-61.
32. Van Valkenburg C, Akiskal H, Puzantian V, Rosenthal T. Anxious depressions: clinical, family history and naturalistic outcomes comparisons with panic and major depressive disorders. *J Affect Disorder*. 1984;6:67-82.
33. Wells KB, Sherbourne C, Schoenbaum M, et al. Impact of disseminating quality improvement programs for depression in managed primary care: a randomized controlled trial. *JAMA*. 2000;283:212-20.
34. Hunkeler E, Meresman J, Hargreaves W, et al. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Arch Fam Med*. 2000;9:700-8.



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