

# A Randomized Trial of Relapse Prevention of Depression in Primary Care

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**Background:** Despite high rates of relapse and recurrence, few primary care patients with recurrent or chronic depression are receiving continuation and maintenance-phase treatment. We hypothesized that a relapse prevention intervention would improve adherence to antidepressant medication and improve depression outcomes in high-risk patients compared with usual primary care.

**Methods:** Three hundred eighty-six patients with recurrent major depression or dysthymia who had largely recovered after 8 weeks of antidepressant treatment by their primary care physicians were randomized to a relapse prevention program (n=194) or usual primary care (n=192). Patients in the intervention group received 2 primary care visits with a depression specialist and 3 telephone visits over a 1-year period aimed at enhancing adherence to antidepressant medication, recognition of prodromal symptoms, monitoring of symptoms, and development of a written relapse prevention plan. Follow-up assessments were completed at 3, 6, 9, and 12

months by a telephone survey team blinded to randomization status.

**Results:** Those in the intervention group had significantly greater adherence to adequate dosage of antidepressant medication for 90 days or more within the first and second 6-month periods and were significantly more likely to refill medication prescriptions during the 12-month follow-up compared with usual care controls. Intervention patients had significantly fewer depressive symptoms, but not fewer episodes of relapse/recurrence over the 12-month follow-up period.

**Conclusions:** A relapse prevention program targeted to primary care patients with a high risk of relapse/recurrence who had largely recovered after antidepressant treatment significantly improved antidepressant adherence and depressive symptom outcomes.

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OVER THE LAST decade clinicians and researchers have recognized that for most patients major depression will have either a relapsing/remitting or chronic course much like asthma. Researchers have found that the risk of relapse after having experienced 1 episode of major depression is 50% and after 2 is 80%.<sup>1,2</sup> Moreover, about 10% to 20% of patients have a chronic depressive course.<sup>3</sup> The recognition of the high degree of relapse and/or chronicity in many patients has led to specialty-based trials of continuation and maintenance antidepressant medication.

Continuation of antidepressant medication for 4 to 6 months after acute-phase treatment has been shown to significantly decrease relapse rates.<sup>4</sup> Efficacy trials testing maintenance antidepressant medication vs placebo for a 2-year period in patients with recurrent depression have found that active treatment mark-

edly decreases risks of recurrence.<sup>5,6</sup> Based on these continuation and maintenance trials, a course of 6 to 9 months of antidepressant medication is recommended for all patients with major depression and maintenance treatment of 2 years or more has been recommended for patients with significant residual symptoms and a history of chronic disorder and those with recurrent depressive episodes.<sup>4,7</sup> Despite these recommendations, few primary care patients with major depression continue to receive antidepressants for 6 to 9 months and even fewer patients with a high risk of relapse receive maintenance treatment.<sup>8,9</sup>

The long-term efficacy trials that have been completed involved intensive follow-up of highly selected specialty care patients. For instance, most maintenance studies have treated patients with acute-phase antidepressant medication with weekly follow-up over 12 weeks. The 70% who respond to acute-phase antidepressant

## SUBJECTS AND METHODS

### SUBJECTS

The settings for this study were 4 large primary care clinics of Group Health Cooperative of Puget Sound (GHC), a health maintenance organization serving more than 400 000 persons in western Washington. The 4 clinics, with a population of 88 000 enrollees, are staffed by 73 board-certified family physicians.

Based on automated prescription data, patients between the ages of 18 and 80 years from 1 of 4 primary care clinics who received a new antidepressant prescription (no prior 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 patients received a letter from their primary care physician inviting their participation in the study and informing them that they would receive a telephone call from the study team.

At 8 weeks, patients received a call from the telephone survey team who sought verbal informed consent for a 15-minute telephone-screening interview to determine study eligibility. The goal was to identify patients who recovered but were at high risk for relapse (the target population of this study) as well as those at high risk for persistent depression (the target population of a separate study<sup>12</sup>). The first-stage screen included the depression section of the telephone Structured Clinical Interview for DSM-III-R (SCID),<sup>13</sup> which has high reliability with the in-person SCID ( $\kappa=0.73$ ).<sup>14</sup> Selection criteria for the second-stage interview were either having a high epidemiologic risk of relapse (see criteria below) or 4 or more residual major depressive symptoms.

Exclusion criteria included having a screening score of 2 or more on the CAGE (C Have you ever felt the need to cut down on your drinking? A Have you ever felt annoyed by criticism of your drinking? G Have you ever felt guilty about your drinking? E Have you ever taken a drink [eye-opener] first thing in the morning?) alcohol screening questionnaire,<sup>15</sup> being pregnant or currently nursing, planning to disenroll from GHC within the next 12 months, currently seeing a psychiatrist, having limited command of English, and recently using 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. This interview included the 20-item Hopkins Symptom Checklist (SCL-20) depression scale.<sup>16</sup> Inclusion criteria for the relapse prevention study obtained during the baseline interview included patients with fewer than 4 DSM-IV major depressive symptoms and a history of 3 or more episodes of major depression or dysthymia or 4 residual depressive symptoms but with a mean SCL-20 depression score of less than 1.0 and a history of major depression/dysthymia. After baseline interview, patients who met criteria for the relapse prevention study were provided a written informed consent statement that described randomization to a program of enhanced care of depression or to continued usual primary care.

The recruitment procedure and the study protocol were approved by the institutional review boards of the University of Washington and GHC. Patients were randomized

to the relapse prevention intervention (I) vs usual care (UC) in blocks of 8. Within each block, the randomization sequence was computer-generated.

A total of 2699 letters were mailed to eligible patients in the 4 GHC primary care clinics. A total of 2051 (76.1%) completed the screening interview: 336 (12.4%) refused the interview, 171 (6.3%) were found to be ineligible, and 141 (5.2%) were unable to be contacted. Patients agreeing to be interviewed did not differ from patients refusing the interview on age ( $47.8\pm 14.9$  compared with  $47.6\pm 15.7$  [ $t_{2385}=-0.20$ ]) or sex (72.3% female in both groups [ $\chi^2_1=0.0$ ]).

Of the 2051 patients completing the screening interview, 702 (34.2%) were eligible for the baseline interview for the relapse prevention study based on first-stage screening. A total of 1349 (66.3%) were not eligible for the relapse prevention study; 264 (12.9%) were ineligible because of having 4 or more major depressive symptoms on the SCID depression module and an SCL-20 depression score greater than 1.0, 766 (37.3%) had 0 to 3 symptoms but no risk factors for relapse, and 319 patients (15.5%) were ineligible for other reasons.

Of the 702 eligible for the baseline interview for the relapse prevention study, 24 (3.4%) were unable to be contacted, 56 (8.0%) refused the baseline interview, 87 (12.4%) were ineligible because of lack of time to attend potential I visits, and 55 (7.9%) were ineligible for other reasons. Baseline interviews were completed with 480 patients (68.4%). Patients refusing baseline interviews or who were ineligible for participation in the trial did not differ on age, sex, medical comorbidity, number of current depressive symptoms on the SCID, or prior mental health utilization compared with those successfully randomized.

Of the 480 patients completing baseline interviews for the relapse study, 386 patients (80.4%) were successfully randomized to the relapse prevention study; 69 patients (14.4%) accepted randomization to a separate persistence study<sup>12</sup> based on having 4 DSM-IV symptoms and an SCL-20 depression score greater than 1.0; and 25 (5.2%) refused randomization.

### USUAL CARE

In most cases, UC for depression provided by GHC family physicians in the 4 primary care clinics involved prescription of an antidepressant medication, 2 to 4 visits over the first 6 months of treatment, and an option to refer to GHC mental health services. Both I and UC patients could also self-refer to a GHC mental health provider.

### RELAPSE PREVENTION INTERVENTION

A multifaceted intervention was developed that included patient education, 2 visits with a depression specialist, and telephone monitoring and follow-up.

### PATIENT EDUCATION

Before the first study visit, the I patients were provided a book and videotape developed by the study team entitled, *Depression (Recurrent and Chronic): Self-Care Companion for Better Living*<sup>17,18</sup> that was aimed at increasing patient education and enhancing self-treatment of their depression.

## VISITS WITH DEPRESSION SPECIALISTS

They were also scheduled for 2 visits with a depression specialist (one 90-minute initial session and one 60-minute follow-up session) in the primary care clinic. Three depression prevention specialists (a psychologist, a nurse practitioner with a master's degree in psychosocial nursing, and a social worker) received a 60-page training manual<sup>19</sup> and participated in 2 half-day training sessions with a psychiatrist (W.K.), primary care physician (E.L.), and psychologist (E.J.L.).

## TELEPHONE MONITORING AND FOLLOW-UP

Three additional telephone visits at 1, 4, and 8.5 months from session 2 with the depression specialist and 4 personalized mailings (2, 6, 10, and 12 months) were scheduled over the following year. The mailed personalized feedback contained a graph of patients' Beck Depression<sup>20</sup> scores over the course of the I program and checklists for patients to send back to the depression specialist, including early warning signs of depression and whether they were still adhering to their medication plan. The depression specialist reviewed monthly automated pharmacy data on antidepressant refills and alerted the primary care physician and telephoned the patients when mailed feedback or automated data indicated they were symptomatic and/or had discontinued medication.

At the initial visit, the depression specialist reviewed the course of the current depressive episode as well as a complete biopsychosocial history. The intervention had the following specific self-treatment goals: to improve long-term adherence to antidepressants, to increase awareness of prodromal symptoms and the use of self-monitoring strategies to identify recurrence, and to increase proactive steps, such as early help seeking, in response to early warning signs. The other goals included increasing the daily use of depression treatment techniques, such as increasing pleasant activities, exercise, and socializing, and identifying potential high-risk situations to promote problem-solving ability, coping, and self-efficacy for managing depression. The ultimate aim of the intervention was to have each patient complete and follow a 2-page written personal relapse prevention plan, which was also shared with his/her primary care provider. Follow-up telephone calls and personalized mailings were geared toward monitoring progress and adherence to each patient's plan. Primary care physicians were notified if their patient was in I vs UC and received intermittent verbal and written consultation about their I patients' progress.

The self-treatment intervention protocol and goals were designed to build on general principles of motivational interviewing<sup>21,22</sup> as well as cognitive-behavioral theories of relapse prevention.<sup>23</sup> In line with principles of motivational interviewing, depression prevention specialists helped patients clarify the potential rewards of engaging in self-treatment behaviors as well as the risks of not doing so, acknowledging patients' personal choice with respect to changing their behavior.

## STUDY MEASURES

Patients' adherence to antidepressant medication and depressive symptoms were assessed at 3, 6, 9, and 12 months after randomization by a telephone interviewer blinded to the patients' randomization status. The baseline and follow-up telephone interviews included the SCL-20 depression items

(scored on a 0-4 scale),<sup>15</sup> the dysthymia and current depression modules of the SCID,<sup>12</sup> the NEO Personality Inventory Neuroticism Scale,<sup>24</sup> and the Longitudinal Interval Follow-up Evaluation<sup>25</sup> to measure incidence and duration of episodes within each 3-month block of time. The SCL-20 has been found to have high reliability and validity in multiple studies with medical patients and to be sensitive to change in depressed primary care patients.<sup>16</sup> A score of 1.72 on the SCL-20 has been shown to have the highest positive predictive value for major depression.<sup>26</sup>

Based on computerized automated data from prescription refills, patients were rated as adherent at the 3-, 6-, 9-, and 12-month follow-up periods as well as whether they received adequate dosage of antidepressant medication for 90 days or more during the 1-year period. The lowest dosages in the ranges recommended in the Agency for Health Care Policy and Research guidelines<sup>27</sup> and in guidelines developed for newer agents<sup>28</sup> were used to define a minimum dosage standard. The ranges of therapeutic dosages in Agency for Health Care Policy and Research guidelines were 75 to 300 mg for imipramine, amitriptyline, doxepin, and desipramine; 40 to 200 mg for nortriptyline hydrochloride; 10 to 40 mg for fluoxetine and paroxetine; 100 to 300 mg for amoxapine, maprotiline, and venlafaxine; 150 to 500 mg for trazodone; 50 to 200 mg for sertraline and fluvoxamine; and 30 to 60 mg for mirtazapine.

Medical comorbidity was assessed using the health maintenance organization's computerized prescription refill records. The Chronic Disease Score is a measure of chronic medical illness derived from the patient's use of prescription medications over a 6-month period that has been found to have a high correlation with physician ratings of severity of medical illness.<sup>29</sup>

Telephone and in-person baseline interviewers received 3 to 6 hours of training before the first interview, plus individual practice sessions with the supervisor (a master's-level clinician with extensive training in structured interviews) lasting 3 hours. Each interviewer was tested against either the supervisor or project director during practice interviews until agreement exceeded 90% for each interview question.

## STATISTICAL METHODS

### Depression Outcomes

Statistical analyses focus on the intervention's effect on depression severity (SCL-20) during the year after baseline assessment, with secondary analyses examining effects on episodes of major depression. We used regression models to estimate the effect of treatment while adjusting for patient characteristics that we believe are related to both depression severity and the probability of relapse: age, sex, physical comorbidity (Chronic Disease Score), neuroticism (NEO), and baseline SCL-20. These models accounted for correlation in longitudinal assessments across the 4 follow-up times using an unstructured correlation matrix, with estimation carried out using generalized estimating equations. Linear regression models implemented by SAS PROC MIXED<sup>30,31</sup> were used to model semicontinuous SCL-20 scores. Logistic regression models implemented by the SAS GLIMMIX macro<sup>32</sup> were used to model major depression. Regression models include an overall effect of intervention, a linear time

Continued on next page

effect, and an interaction between time and intervention. The main effect of intervention estimates differences at 3 months, and the interaction between intervention and time estimates differences in change over time. If we found no evidence of a group  $\times$  time interaction, we dropped this effect, testing for a sustained effect of intervention during follow-up. If we found no evidence of a time effect, we dropped this, testing for overall (average) differences between randomization groups over the follow-up period.

#### Differential Dropout and Treatment of Missing Data

We found differences in follow-up rates for I and UC groups, with follow-up more likely among I than UC patients. Across all interviews, 10.1% of follow-up interviews were missing, 6.2% in the I group and 12.5% in the control group. The percentage of missing interviews increased over the follow-up period, and at the 12-month follow-up 10.3% of the I group and 20.8% of the UC group missed interviews. We assumed that missingness depended only on observed outcomes and used observed data to account for differential dropout via multiple imputation with propensity-score matching of missing to observed cases.<sup>33,34</sup> We adjusted only for unit-nonresponse (ie, missing interviews) because there was very little item nonresponse. Propensity scores were estimated separately for each time point using logistic regression models with completely observed baseline covariates (randomization group, married [yes/no], lives alone, single parent [yes/no], college graduate, panic attack in the last 2 weeks, self-rated health, self-reported high stress, satisfaction with health maintenance organization care, physical comorbidity [Chronic Disease Score], and baseline SCL-20). Propensity score matching was stratified by I group, quartile of propensity score, and interview. We imputed data for entire cases but imputed

data separately for each missed follow-up time, thus incorporating the cross-sectional correlation of outcome and covariate data, but ignoring between-time correlation of outcomes. Probabilities of nonresponse based on this set of variables achieved good prediction of missingness at each follow-up. For example, at the 12-month follow-up the estimated probability of nonresponse exceeded 25% for 13% of subjects actually interviewed vs 40% of subjects who were missing.

#### Process Outcomes

We examined 3 types of process outcomes: visits, antidepressant refills, and antidepressant adequacy of dosage. Between-group differences in process outcomes were estimated using regression models that adjusted for patient age, sex, physical comorbidity, baseline neuroticism, and baseline SCL-20. Visit data were summarized for the 12 months after randomization. Mental health specialty visits were dichotomized as any/none because few subjects made more than 1 visit. Refill rates (any refill vs none) were summarized quarterly for the year after randomization. Antidepressant adequacy for 90 days or more (yes vs no) was summarized in the two 6-month periods after randomization. Linear regression was used to test for between-group differences in the number of visits. Logistic regression was used to test for between-group differences in mental health visits, antidepressant refills, and treatment adequacy. Models for antidepressant refills and treatment adequacy were estimated via generalized estimating equations, as described above, to account for repeated measures within subjects. Analysis of process outcomes did not require application of imputation methods because these outcomes were based on automated data so that data were missing for only a few patients (n=9) who disenrolled from the health maintenance organization.

treatment are then monitored with at least monthly follow-up for 3 to 6 months. Those who remain in full remission are then randomized to maintenance antidepressant treatment vs placebo and then followed up monthly for 2 years. This intensity of treatment is in marked contrast with primary care, in which the mean number of visits for depression treatment is approximately 4 to 6 visits per year.<sup>10,11</sup> There is a need to develop effectiveness models of continuation and maintenance treatment of primary care patients with recurrent or chronic depression that are less restrictive in selecting patients and less time-intensive and costly.

This study will address the following questions in a more representative sample of high-risk primary care patients with recurrent major depression or chronic depression who were randomized to a low-intensity relapse prevention program vs usual primary care: (1) Is the relapse prevention program associated with improved adherence to antidepressant medication and less depressive symptoms over a 1-year period? (2) Is the relapse program associated with less relapse/recurrence of major depressive episodes over a 1-year period?

## RESULTS

### PATIENT CHARACTERISTICS AND PARTICIPATION IN THE INTERVENTION PROGRAM

The only significant difference between I and control patients on any demographic or clinical variable (**Table 1**) was that a higher percentage of UC patients had a major depressive episode within the last 2 years compared with I patients ( $\chi^2_1=5.1$ ,  $P=.02$ ). High rates of patients with recurrent depression and dysthymia were seen, reflecting the selection of these patients into the relapse prevention trial.

Of the 194 patients randomized to the I arm, 188 (96.9%) made at least 1 visit to the depression specialist and 181 (93.3%) attended both visits. Patients in the I arm of the study had a mean of  $1.9 \pm 0.39$  visits and a mean of  $3.4 \pm 0.12$  follow-up telephone calls with the depression specialist, with 155 (79.9%) completing all of the 3 telephone call follow-ups. Thirteen patients (6.7%) had a consultation with a study psychiatrist because of having persistent depressive symptoms.

**Table 1. Demographic and Clinical Characteristics of Depressed Patients\***

	Intervention (n = 194)	Control (n = 192)
Age, mean ± SD	46.4 ± 11.9	45.6 ± 13.3
Female, %	75.4	71.9
>1 Year of college, %	88.2	87.0
White, %	92.3	88.0
Married, %	61.0	55.0
Employed full- or part-time, %	78.0	78.1
SCL depression, mean ± SD	0.83 ± 0.39	0.84 ± 0.35
Chronic Disease Score, mean ± SD	1051.4 ± 1228.0	1009.2 ± 994.5
NEO Neuroticism, mean ± SD	3.03 ± 0.72	3.03 ± 0.73
Recurrent depression (≥3 episodes)	75.4	75.4
Major depression within last 2 years, %	78.5	87.5
Dysthymia, %	52.6	45.7
Comorbid panic, %	13.6	11.5
Given antidepressant medications at baseline, %	81.5	81.3

\*SCL indicates the 20-item Hopkins Symptom Checklist (range, 0-4); NEO Neuroticism, NEO Personality Inventory neuroticism subscale.  
†P = .01.

**Table 2. Intervention vs Usual Care: Observed Percentage of Patients Who Filled Antidepressant Prescriptions at Follow-up**

Period, mo	Usual Care, % (95% CI)	Intervention, % (95% CI)
0-3	65.6 (58.8-72.38)	80.7 (75.1-86.3)
3-6	58.2 (51.2-65.2)	71.9 (65.5-78.2)
6-9	55.6 (48.5-62.7)	68.4 (61.8-75.0)
9-12	49.7 (42.6-56.9)	63.2 (56.3-70.0)

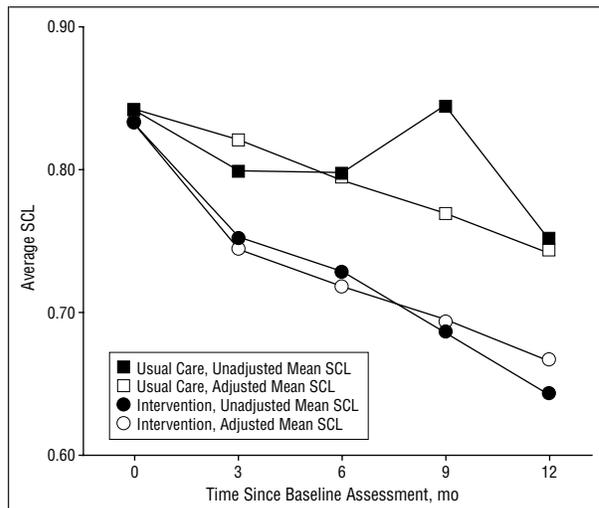
\*CI indicates confidence interval.

### HEALTH CARE VISITS EXCLUDING DEPRESSION SPECIALIST VISITS

During the year after randomization, UC patients made significantly more primary care visits for reasons other than depression (UC: 3.94 vs I: 3.13; mean adjusted difference, 0.90; 95% CI, 0.18-1.63;  $P = .02$ ), and made fewer primary care visits for depression (UC: 1.15 vs I: 1.46; mean adjusted difference, -0.31; 95% CI, -0.61 to 0.00;  $P = .05$ ). We found no difference in the percentage of patients who made at least 1 visit to a nonstudy mental health specialist (UC: 24.2% vs I: 31.9%; adjusted odds ratio for I: control, 0.69; 95% CI, 0.43-1.09;  $P = .11$ ).

### MEDICATION ADHERENCE

As shown in **Table 2**, I patients were significantly more likely to refill antidepressant medication prescriptions than UC patients during the 1-year follow-up (adjusted odds ratio for I: control, 1.91; 95% CI, 1.37-2.65;  $P < .001$ ). Intervention patients were also more likely to receive adequate dosage of antidepressant treatment compared with UC patients during the 1-year follow-up period (ad-



**Figure 1.** Observed and estimated average Hopkins 20-Item Symptom Checklist (SCL-20) scores in intervention (N=194) vs usual care patients (N=192) over time. Estimated SCL-20 scores are based on fitted values for an average group of subjects: aged 45.9 years, 26.2% male, baseline Chronic Disease Score of \$1030, baseline Neuroticism score of 3.034, and baseline SCL-20 of 0.84.

**Table 3. Intervention vs Usual Care Outcomes on the 20-Item Hopkins Symptom Checklist (SCL) Depression Items and Percentage With Major Depression\*†**

Parameter	SCL, Regression Coefficient (95% CI)	Major Depression, Estimated Odds Ratio (95% CI)
Age	0.000 (-0.003 to 0.004)	1.00 (0.98-1.02)
Male	-0.08 (-0.16 to 0.002)	0.87 (0.56-1.02)
Physical comorbidity	0.02 (-0.02 to 0.06)	0.97 (0.80-1.18)
Baseline neuroticism	-0.09‡ (-0.15 to -0.04)	0.86 (0.63-1.16)
Baseline SCL	0.43‡ (0.31 to 0.55)	1.98§ (1.09-3.60)
Intervention group	-0.08§ (-0.15 to -0.003)	1.00 (0.68-1.49)
Time	-0.03§ (-0.05 to -0.005)	

\*CI indicates confidence interval.

†Regression results for depression outcomes based on 25 imputed data sets.

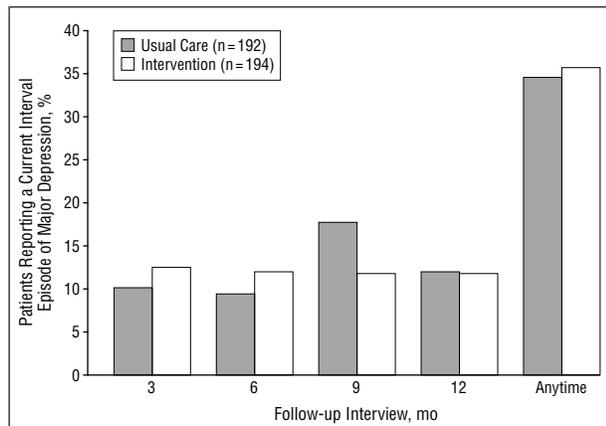
‡ $P < .001$ .

§ $P < .05$ .

justed odds ratio for I: control, 2.08; 95% CI, 1.41-3.06;  $P < .001$ ).

### DEPRESSIVE SYMPTOM OUTCOMES

As shown in **Figure 1**, the UC group had higher unadjusted average SCL-20 scores at follow-up than the I group. Based on regression models, we found no evidence of an I × time interaction, and therefore this term was not included in final models (**Table 3**). There was, however, evidence of change in average SCL-20 scores over time ( $P = .02$ ), with a modest but sustained I effect ( $P = .04$ ). Across follow-up times, I patients had SCL-20 scores that were, on average, 0.08 points below UC patients. There were no differences in patient SCL-20 outcomes across the 3 depression specialists at 6, 9, or 12 months; at 3 months, there was a significant difference in patient depression outcome between 2 of the depression specialists.



**Figure 2.** Percentage of intervention vs control patients reporting a current or interval episode of major depression at follow-up (results based on 25 imputed data sets).

## RELAPSE/RECURRENCE

**Figure 2** shows the prevalence of patients who either had a current episode of depression at the 3-, 6-, 9-, and 12-month follow-up or who did not meet criteria for a current episode based on the SCID, but had an interval episode based on the Longitudinal Interval Follow-up Evaluation. We found no evidence of a time  $\times$  I or an overall time effect, so these terms were dropped from the model. The final model showed no differences in the overall odds of an episode of major depression during the follow-up period for I vs control patients. Overall rates of relapse were similar for I (35%) and UC groups (34.6%).

## COMMENT

The relapse prevention program was associated with a significant improvement in adherence to antidepressants as well as a significant decrease in depressive symptoms but not relapse/recurrence over time compared with usual primary care. A more intensive relapse prevention program may be needed to decrease relapse rates. The more robust differences in relapse rates reported in specialty continuation and maintenance trials may be because of patients being randomized to continued antidepressant care vs placebo. For instance, at each follow-up time point between 49% and 65% of UC patients had evidence of a refill of antidepressant medications, a much higher rate than anticipated in planning this trial. Moreover, patients in specialty maintenance trials are highly selected because of being required to be in remission for 3 to 6 months and to receive monthly visits, which probably explains the higher rate of medication adherence in specialty intervention patients. We selected patients who were often still symptomatic after 8 weeks of primary care treatment as evidenced by SCID symptoms and a mean baseline SCL-20 score of 0.83 to 0.84 (an SCL-20 score of  $<0.5$  approximates a Hamilton-Depression remission score of  $<8$ ). Patients in psychiatry trials also may have higher relapse rates (often as high as 50% to 80% over a 1- to 2-year period)<sup>5-7</sup> compared with the relapse rate of 35% to 36% found in this trial.

The higher than anticipated rates of longitudinal use of antidepressant medication in UC patients may reflect the fact that these patients had generally experienced multiple episodes of depression or chronic depression that may have convinced them and their primary care physicians about the importance of long-term treatment. It also may be because of the modern era, where almost all patients are prescribed serotonin reuptake inhibitors, which have less adverse effects than previously used antidepressant agents, making patients and physicians less reticent about long-term medication use.

The relapse prevention program is a low-intensity intervention that included enhanced patient education, 2 visits with the depression specialists, 3 to 4 telephone calls, and symptom monitoring over the 12-month period.<sup>19</sup> The program blended seamlessly into busy primary care practices and was well accepted by a more representative sample of patients than those studied previously in specialty maintenance trials. More than 90% of patients adhered to the 2 in-person visits with the depression clinical specialist and almost 80% received the 3 scheduled telephone visits. Depression specialist backgrounds were diverse (master's-level social worker, psychiatric nurse, and doctoral-level psychologist), with no important clinician difference in outcomes. Weekly supervision with a psychiatrist to review patient history, medication adherence, adverse effects, and clinical outcomes may have helped standardize antidepressant medication treatment regimens.

Primary care systems need to begin to adapt services to improve care of patients with recurrent and chronic medical and psychiatric illness. Primary care has been better organized historically to treat acute illness and systematic changes will need to occur to improve chronic illness management.<sup>35</sup> These changes would ideally include patient education and activation, monitoring of adherence and outcomes of treatment, and referral of selected treatment-resistant patients.<sup>35,36</sup> The relapse prevention program tested here sought to extend research on the "collaborative care model"<sup>11,36</sup> from acute-phase treatment to improving continuation and maintenance phases of treatment.

Limitations of this research included the sample studied and our ability to accurately adjust our findings for missing data. We relied on imputation models that assumed that we could reasonably predict nonresponse using baseline data. Although these assumptions are untestable, we believe they are reasonable and that our results offer a more realistic estimate of intervention effects than analyses that completely ignore missing data. Our sample included patients from one region of the country with high rates of employment and 1 or more years of college who were members of a single, large organized system of health care with only family practice physicians. The results in this sample may not generalize to more diverse racial and ethnic groups, patients from lower socioeconomic status, and other types of primary care settings. However, effectiveness trials have shown successful adaptation of the collaborative model of care to patients with diverse racial and socioeconomic backgrounds, and to diverse practice settings.<sup>37</sup>

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