Stepped Collaborative Care for Primary Care Patients With Persistent Symptoms of Depression

A Randomized Trial

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Background: Despite improvements in the accuracy of diagnosing depression and use of medications with fewer side effects, many patients treated with antidepressant medications by primary care physicians have persistent symptoms.

Methods: A group of 228 patients recognized as depressed by their primary care physicians and given antidepressant medication who had either 4 or more persistent major depressive symptoms or a score of 1.5 or more on the Hopkins Symptom Checklist depression items at 6 to 8 weeks were randomized to a collaborative care intervention (n = 114) or usual care (n = 114) by the primary care physician. Patients in the intervention group received enhanced education and increased frequency of visits by a psychiatrist working with the primary care physician to improve pharmacologic treatment. Follow-up assessments were completed at 1, 3, and 6 months by a telephone survey team blinded to randomization status.

Results: Those in the intervention group had significantly greater adherence to adequate dosage of medication for 90 days or more and were more likely to rate the quality of care they received for depression as good to excellent compared with usual care controls. Intervention patients showed a significantly greater decrease compared with usual care controls in severity of depressive symptoms over time and were more likely to have fully recovered at 3 and 6 months.

Conclusions: A multifaceted program targeted to patients whose depressive symptoms persisted 6 to 8 weeks after initiation of antidepressant medication by their primary care physician was found to significantly improve adherence to antidepressants, satisfaction with care, and depressive outcomes compared with usual care.

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Over the last decade, multiple studies have shown that there is a high prevalence of major depression in primary care (6%-10%). There has been substantial evidence demonstrating that depression is associated with multiple unexplained medical symptoms, impairment in functioning and quality of life, and high medical costs. There is also accumulating evidence that more intensive, organized treatment that integrates mental health practitioners into primary care improves outcomes of depressed patients. However, changes brought on by health system reform have tended to decrease the availability of specialty mental health care to primary care patients. These opposing trends make it imperative that scarce specialty resources are used when and where they are most needed. This study tests a population-based collaborative care model that attempts to use specialty resources in the most efficient way to reduce the burden of depression.

Collaborative care is a systematic approach that improves patient education and integrates mental health professionals or other care extenders, such as nurses, into the primary care clinic to help primary care physicians provide treatment in conformity with evidence-based guidelines. Collaborative care models have been shown to improve outcomes of patients with major but not minor depression. In the initial 2 randomized trials testing collaborative care, about 74% of intervention patients with major depression achieved a 50% reduction in depressive symptoms compared with 44% for patients receiving usual care. In a cost-effectiveness analysis of collaborative care for patients with major depression, the cost per case successfully treated was lower for collaborative care than for usual care because the success rate of treatment was increased more than the
PATIENTS AND METHODS

PATIENTS

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

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 Group Health Cooperative automated registration, pharmacy, and visit data. Patients between the ages of 18 and 80 years 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 patient received an approach letter from the primary care physician inviting participation in a study to improve the quality of care for various conditions and informing the patient that he or 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 a member of the telephone survey team, who sought verbal informed consent for a 15-minute telephone screening interview. 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 study described elsewhere).11 The first-stage screening included the telephone Structured Clinical Interview for DSM-III-R.14 Criteria for selection for the second-stage interview were having 4 or more residual major depressive symptoms, recurrent depression (2 or more prior episodes), or dysthymia.

Exclusion criteria included having a screening score of 2 or more on the CAGE alcohol screening questionnaire,13 being pregnant or currently nursing, planning to disenroll from the Group Health Cooperative insurance plan within the next 12 months, currently seeing a psychiatrist, having limited command of English, and recently using lithium or antipsychotic medication.

Eligible 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 for a face-to-face baseline interview. Inclusion criteria for the persistence study obtained during the baseline interview included having 4 or more major depressive symptoms on the Structured Clinical Interview for DSM-III-R and a score of 1.0 or greater on the 20 depression items of the Hopkins Symptom Checklist (SCL-20),16 or having fewer than 4 DSM-IV major depressive symptoms but with a score of 1.5 or greater on the SCL-2016. The recruitment procedure and the study protocol were approved by the institutional review boards of the University of Washington and the Group Health Cooperative.

RANDOMIZATION

Eligible patients were stratified into severe (>2.0) and moderate (1.0-2.0) depression groups based on their SCL-20 scores. Within each stratum, patients were randomized to the 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 the usual care group in blocks of 8. Within each block, the randomization sequence was computer-generated.

STEPPED COLLABORATIVE CARE INTERVENTION

A multifaceted intervention was developed that targeted patient and process of care.

Patient

Prior to the first study visit, the intervention patients were provided a book and videotape developed by the study team.17,18 The book and videotape reviewed the biology of depression, the relationship to stress, physical and emotional symptoms, how medications and psychotherapy help depression, and how to become involved as active partners with their physician in care of their depressive illness. They were instructed to take the videotape home and watch it with their significant other(s). After the baseline interview and randomization, the research assistant scheduled 2 sessions with a psychiatrist for intervention patients within a 4-week period (one 30-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.

Process of Care

Psychiatric 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 were prescribed antidepressant medication approximately 8 to 9 weeks before the first intervention visit. The psychiatrist reviewed the course of the current depressive episode, prior individual and family history of psychiatric illness, current stressful life events, medical history, social 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 (eg, Al-Anon). Primary care physicians received immediate verbal consultation about their patient’s progress and a typed psychiatric consultation note within 1 week. Both primary care physicians and the psychiatrist had previewed the videotape and book and total costs of treatment per case.11 For patients with minor depression (2-4 DSM-IV major depressive symptoms), treatment by the primary care physician alone was more cost-effective, since direct collaborative care costs were higher than usual primary care depression treatment costs and the outcomes were similar.

The results suggested that targeting collaborative care for patients with major depression would increase its cost-
were encouraged to discuss patient reactions to and questions about these educational materials.

The psychiatrist reviewed monthly automated pharmacy data on antidepressant refills 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.

**USUAL CARE**

Patients randomized to the usual care arm received treatment for depression from their primary care physician in 1 of the 4 clinics. In most cases, usual care for depression, provided by Group Health Cooperative family physicians, involved prescription of an antidepressant medication, 2 or 3 visits over the first 3 months of treatment, and an option to refer to Group Health Cooperative mental health services. Both intervention and usual care patients could also self-refer to a Group Health Cooperative mental health provider. We tracked and reported these out-of-study mental health referrals and visits.

**STUDY MEASURES**

Patients' adherence to antidepressant medication, satisfaction with care, and level of distress was assessed at 1, 3, and 6 months after randomization by a telephone survey team blinded to the patients' randomization status. The baseline and follow-up telephone interviews included the 20 depression items in the SCL-90 measured by severity (range, 0-4); the telephone version of the Structured Clinical Interview for DSM-IV diagnosis current depression module and the section on the most severe depressive episode in the last 2 years; a measure of satisfaction with the treatment of depression that rated treatment as poor to excellent on a 5-point ordinal scale; and the 7 items from the NEO neuroticism scale that can predict persistence of depressive symptoms in a primary care population.

Patients were asked if they were still taking an antidepressant medication and were considered adherent if they reported having taken this medication for at least 25 of the last 30 days. Computerized pharmacy records were also used to examine antidepressant use (rates of refill and whether they received an adequate dosage of antidepressant mediation for 90 days or more). The lowest doses in the ranges recommended in the Agency for Health Care Policy and Research guidelines were as follows: 75 to 300 mg of imipramine hydrochloride, amitriptyline hydrochloride, doxepin hydrochloride, or desipramine hydrochloride; 40 to 200 mg of nortriptyline hydrochloride; 10 to 40 mg of fluoxetine hydrochloride or paroxetine; 100 mg of amoxapine, maprotiline hydrochloride, trazodone hydrochloride, or venlafaxine hydrochloride; 50 mg of sertraline hydrochloride or fluvoxamine maleate; and 30 mg of mirtazapine.

Telephone and in-person baseline interviewers received 3 to 6 hours of training prior to the first interview, plus individual practice sessions with the supervisor (a clinician with a master's degree and extensive training in structured interviews) lasting 2 to 3 hours. Each interviewer was tested against either the supervisor or project director during a practice and study interview, with reliability exceeding 90% for each interview question.

Computerized pharmacy records were also used to compute the chronic disease score, a measure of chronic medical comorbidity based on prescription drug use.

**STATISTICAL ANALYSES**

We performed a χ² analysis, with corrections for continuity to examine group differences on categorical variables (ie, intervention vs control, patients refusing interviews vs screened patients, patients completing all assessments vs patients missing at least 1 follow-up). Independent group t tests were used for continuous variables. Treatment group differences in medication adherence were assessed using mixed-effects ordinal regression analysis for longitudinal data. This procedure uses a logistic function to test whether there is a difference in medication adherence between intervention and control patients over time after adjusting for relevant covariates. Marginal maximum likelihood methods were used to generate maximum likelihood estimates for group, time, and group time interaction effects. These effects were evaluated using a z statistic (maximum likelihood estimate divided by its SE). This procedure permits inclusion of patients with missing data and allows for individual varying slopes and intercepts over time. This approach allowed us to use the data from all 228 patients in an intent-to-treat analysis rather than the 167 patients who completed all follow-up assessments. We employed a model with uncorrelated errors (no autocorrelation terms). Age, sex, NEO score, and chronic disease score were used as fixed covariates for each analysis. For significant interaction or group effects, χ² analyses with corrections for continuity were examined to determine at which assessment the groups differed. To evaluate the continuous outcomes of SCL-20 depression, a mixed-effects regression analysis procedure was used. This procedure has all the advantages of the mixed-effects ordinal regression analysis described above. This model is used for normally distributed response data and can be used for analysis of longitudinal designs with missing data. The procedure also used maximum likelihood estimates to evaluate group, time, and group time interaction effects. In the event of a significant interaction or group effect, univariate analysis of covariances were used to determine where the groups differed in their rate of change. Because of the nonnormality of the utilization data, nonparametric Kruskal-Wallis tests were used to test group differences in the number of health care visits. A 2-tailed α level of .05 was used to determine significance.
treatment (step 1) who were stepped up to collaborative care (step 2) would receive more adequate pharmacotherapy based on Agency for Health Care Policy and Research guidelines for dose and duration of antidepressant therapy, be more satisfied with their care, and achieve more favorable depression outcomes over 6 months.

RESULTS

A total of 2699 letters were mailed to eligible patients in the 4 Group Health Cooperative primary care clinics; rates of refusal, ineligibility, and lack of successful contact are described in Figure 1. Patients agreeing to be interviewed did not differ from patients refusing to be interviewed in age (mean ± SD, 47.8±14.9 years for patients agreeing to participate compared with 47.6±15.7 years for those refusing [t<sub>2385</sub> = −0.20]) or sex (72.3% female in both groups; χ<sup>2</sup> = 0.0).

Of the 2051 patients (76.1%) completing the screening interview, 272 (13.3%) were eligible for the persistence study after baseline interviews. Of these, 149 were randomized within the block scoring 1.0 to 2.0 on the SCL-20 depression items and 79 were randomized in the block scoring more than 2.0 on the SCL-20 depression items.

Of the 228 patients randomized, 209 (91.7%) completed the 1-month follow-up; 193 (84.6%) completed the 3-month follow-up, and 192 (84.2%) completed the 6-month follow-up. Eighty-seven intervention patients (76.3%) vs 80 usual care patients (70.2%) completed all 3 follow-up interviews. There were no significant differences on any demographic or clinical variables listed in the Table between the 61 patients who missed completing at least 1 follow-up interview and the 167 patients who completed all 3 follow-up interviews.

PATIENT CHARACTERISTICS

The only significant difference between intervention and control patients on any demographic or clinical variable (Table) was that there was a higher percentage of female subjects in the control arm of the study (χ<sup>2</sup> = 5.20; P = .02), which was one of the covariates controlled for when analyzing differences in outcomes between the 2 groups. High rates of dysthymia (50%-60%) and recurrent major depression (76%-83%) were seen, probably reflecting the selection of patients who had persistent symptoms 6 to 8 weeks after initiation of antidepressant treatment.

PARTICIPATION IN THE INTERVENTION PROGRAM

Of the 114 patients randomized to the intervention arm, 108 (94.8%) made at least 2 visits to the psychiatric consultant. Intervention patients were seen for 2.75 ± 1.47

<table>
<thead>
<tr>
<th>Demographic and Clinical Characteristics of Patients With Depression*</th>
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<tbody>
<tr>
<td>Intervention (n = 114)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Demographic Characteristics</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female, %‡</td>
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<tr>
<td>&gt;1 y of college, %</td>
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<tr>
<td>Employed full or part time, %</td>
</tr>
<tr>
<td>White, %</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
</tr>
<tr>
<td>Chronic disease score†</td>
</tr>
<tr>
<td>NEO neuroticism score†</td>
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<tr>
<td>SCL-depression†</td>
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<tr>
<td>Recurrent depression (≥3 episodes), %</td>
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<tr>
<td>Dysthymia, %</td>
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<td>Panic disorder, %</td>
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* SCL indicates Hopkins Symptom Checklist.
†Values are mean ± SD.
‡P < .05.

Figure 1. Recruitment for persistence study (228 patients were randomized). SCL indicates Hopkins Symptom Checklist.
visits (mean ± SD) by 1 of the 4 intervention psychiatrists (range, 0–7 visits), with 1.56 ± 1.61 follow-up telephone calls (mean ± SD). By 3 months, 96% of intervention patients had read at least part of the educational book and 90% had watched at least part of the videotape.

HEALTH CARE VISITS EXCLUDING PSYCHIATRY INTERVENTION VISITS

In the first 12 weeks of treatment, beginning with the date of randomization, usual care patients had 1.8 ± 1.8 visits (mean ± SD) with their primary care physician vs 1.6 ± 1.8 visits among intervention patients ($\chi^2 = 1.46; P = .23$). In the 6-month period beginning with the date of randomization, usual care patients received 3.3 ± 3.1 visits (mean ± SD) with their primary care physician compared with 3.4 ± 4.3 visits (mean ± SD) for intervention patients ($\chi^2 = 0.35; P = .55$).

In the first 12-week period, beginning with the date of randomization, 17.5% of intervention patients compared with 24.6% of usual care patients were seen at least once by a nonstudy mental health specialist reimbursed by Group Health Cooperative ($\chi^2 = 1.29; P = .26$). In the 6-month period beginning with the date of randomization, 24.6% of intervention patients vs 27.2% of usual care patients were seen by a nonstudy mental health specialist ($\chi^2 = 0.09; P = .76$). There were also no significant differences between intervention and usual care patients on their mean number of visits to a nonstudy mental health specialist in the first 12-week period (0.6 ± 1.7 vs 0.8 ± 1.9 visits; $t_{226} = 0.95; P = .34$) or in the 6-month period (1.3 ± 2.9 vs 1.3 ± 2.9 visits; $t_{226} = 0.19; P = .85$).

MEDICATION ADHERENCE

Based on the follow-up interviews, the mixed-effects ordinal regression analyses found a significant group × time interaction for medication adherence ($z = 3.26; P < .001$). Intervention patients were significantly more likely to adhere to antidepressant medication for 25 of 30 days in each of the 3 follow-up interviews over the 6-month period compared with usual care patients (Figure 2). Post hoc analyses found significant differences at 3 months (78.6% vs 62.1%; $\chi^2 = 5.52; P = .02$) and 6 months (73.2% vs 50.5%; $\chi^2 = 9.53; P = .002$) but not 1 month (77.4% vs 69.2%; $\chi^2 = 1.38; P = .24$).

Based on automated prescription data on refills, intervention patients were significantly more likely than controls to have received antidepressant medication for at least 90 days at or above the lowest dose level recommended by Agency for Health Care Policy and Research guidelines (68.8% in intervention group vs 43.8% in usual care group [$\chi^2 = 12.60; P < .0001$]) and at twice the dosage of the guideline lower range (intervention [46.8%] vs usual care [25.7%]; $\chi^2 = 9.36; P = .002$). These differences remained significant after controlling for age, sex, NEO score, and chronic disease score using logistic regression analysis.

SATISFACTION WITH TREATMENT

At the 3- and 6-month follow-up interviews, significantly more intervention patients rated the quality of care they received for depression as good to excellent compared with usual care patients (3 months: 94.5% vs 63.9%, $\chi^2 = 23.51, P < .00001$; 6 months: 79.5% vs 63.5%, $\chi^2 = 4.21, P = .04$).

CHANGES IN DEPRESSION OUTCOMES

As shown in Figure 3, the mixed-effects regression procedure found a significant group × time interaction for the SCL-20 ($z = −2.06; P = .04$). This difference in change over time between the intervention and usual care groups was caused by significant differences in rate of change in severity from the baseline to 3-month follow-up interviews ($F_{1, 186} = 12.38; P = .001$), with a nonsignificant similar trend seen from the baseline to 6-month follow-up interviews ($F_{1, 186} = 3.09; P = .08$), after controlling for age, sex, NEO score, and chronic disease score.

Another test of treatment effectiveness is whether patients meet a predefined level of clinical recovery at a specified time. We described the percentage of patients who were asymptomatic as defined by a Structured Clinical Interview for DSM-IV finding of 0 or 1 of the DSM-IV 9 major depressive symptoms at 3 and 6 months. At each time, significantly more intervention patients than usual...
This multifaceted intervention, providing an on-site integrated role for a psychiatrist to improve care for patients with persistent depression symptoms, surveillance of patient outcomes and medication adherence, and enhanced patient education, significantly improved the process and outcomes of care for patients with persistent DSM-IV depressive symptoms. Patients in the intervention arm of the study showed better adherence to antidepressants, reported more satisfaction with care, and had improved clinical outcomes for depression compared with patients treated with usual care. We attribute these improvements relative to usual care to the enhanced organization of care, including targeted specialty visits, and to active monitoring and follow-up care.

The stepped-care strategy used in this study targeted collaborative care for patients whose depressive symptoms persisted 6 to 8 weeks after initiation of pharmacotherapy. A critical question was whether targeting these patients with more chronic illness would reduce the effectiveness of collaborative care. The results of this study show that targeting collaborative care in this stepped-care fashion improved patient outcomes among the more difficult-to-treat cases. It is significant that the usual care control group was also being treated. All usual care patients were prescribed antidepressant medication and 27% were seen by a Group Health Cooperative mental health provider, so the improvements in outcome are beyond what was achieved with existing depression services.

The patients with persistent depressive symptoms who were randomized to this trial had a much higher prevalence of dysthymia (approximately 55% vs 30%) and slightly higher levels of recurrent major depression (76%-83% vs approximately 68%-75%) than we have seen in our previous trials in which patients were randomized at initial prescription. Patients with dysthymia and major depression and those with 3 or more major depressive episodes have been found to be at high risk of relapse both in our prior primary care samples and in the studies reviewed in the Agency for Health Care Policy and Research guidelines. Patients only received stepped-care visits with the psychiatrist during the acute phase of treatment (up to 12 weeks). After the acute phase of treatment, patients who do not improve or who relapse may need more long-term specialty treatment, since the data show optimum outcomes at 3 months but flattening of the recovery curve and a relative decrease in satisfaction with care of depression between 3 and 6 months. The recovery rate of 44% in intervention patients is also somewhat lower than that seen in specialty efficacy trials, probably reflecting both the lower intensity of the intervention (mean ± SD, 2.75 ± 1.5 visits) and the high rate of double depression. The need for prolonging specialty treatment into a continuation and maintenance phase of treatment in selected patients may be thought of as step 3 in the proposed stepped-care model.

The program that we implemented to improve the process and outcomes of depression in this study is an example of a population-based stepped-care approach. The essential elements of this program were as follows: assessing whether a favorable outcome had been achieved at a defined end point, stepping up the intensity of care for patients who had not improved, targeting use of specialty providers to ensure guideline-concordant care, and ensuring active follow-up and monitoring of the process and outcome of care. Other essential components of this population-based care approach included educating and activating patients to become collaborators in illness management and providing information systems that support proactive follow-up, adherence to treatment, and delivery of care.

Limitations of the study include the following: (1) Our patient population was predominantly white and middle-class, and the success of the intervention may not be generalizable to other socioeconomic or ethnic groups. (2) The research was completed in 4 large health maintenance organization clinics staffed by family physicians; the intervention mode used in the study may be more difficult to integrate into network models that do not integrate primary care and specialty services. (3) Since referral to the study was dependent on the accuracy of the primary care physician’s diagnosis, 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 who are not prescribed antidepressants. (4) The multifaceted intervention did not allow us to determine the specific active components of the program that were most helpful. (5) Approximately one quarter of patients in both the intervention and control groups had 1 or more visits with a nonstudy mental health specialist, probably reflecting the fact that Group Health Cooperative patients are well educated, have a small copayment for mental health visits, and can self-refer.

CONCLUSION

A multifaceted care program targeted for primary care patients whose depressive symptoms persisted for 6 to 8 weeks after initiation of usual primary care treatment was found to improve outcomes relative to usual care. This suggests that targeting collaborative care in a stepped-care fashion may be a viable option for efficient use of specialty services in the primary care setting.

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