ORIGINAL ARTICLE

A Randomized Effectiveness Trial of Collaborative Care for Patients With Panic Disorder in Primary Care

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Background: Effectiveness studies have tested interventions to improve quality of care for depression in primary care, but none, to our knowledge, have been completed for panic disorder (PD) in this setting. This study sought to test the clinical effectiveness of PD pharmacotherapy embedded in a disease management framework of "collaborative care" (CC).

Methods: One hundred fifteen patients with PD from 3 primary care clinics were randomized to CC or "usual care" (UC). Patients in CC (n=57) received educational videotapes and pamphlets; pharmacotherapy with the selective serotonin reuptake inhibitor paroxetine; 2 psychiatrist visits and 2 telephone calls in the first 8 weeks; and up to 5 telephone calls between 3 and 12 months' follow-up. Usual care patients (n=58) were treated by their primary care physician. Telephone assessments of panic, anxiety sensitivity, depression, and disability variables were performed at 3, 6, 9, and 12 months' follow-up. Adequacy of pharmacotherapy was assessed with an algorithm based on a review of efficacy studies.

Results: Patients in CC were more likely to receive adequate (type, dose, duration) medication and more likely to adhere to this medication at 3 and 6 months. Random regression analyses showed that CC patients improved significantly more over time compared with UC patients on anxiety, depression, and disability measures, with the greatest effects at 3 and 6 months.

Conclusions: Compared with UC, CC interventions significantly improved both quality of care and clinical and functional outcomes in primary care PD patients. Clinical differences were greatest in the first 6 months, corresponding to the greater quality of care and the greater intensity of intervention.

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PANIC DISORDER (PD) is a prevalent[1] and disabling[2] psychiatric condition affecting 3% of the US population at some point during a lifetime. Because the dramatic physical manifestations of a panic attack often mimic a variety of cardiorespiratory,[3] gastrointestinal,[4] and otoneurologic[5] illnesses, a large proportion of PD patients (80% according to one estimate[6]) initially receive treatment in the general medical setting.[7,8] The current prevalence of PD in primary care is estimated at 4% to 6%.[9] These patients use primary care services at several times the rate of other patients, including those with depression[10] and those with comparable medical illness severity,[11] and are overrepresented among cohorts of distressed patients who frequently use health care services.[12] Despite this pattern of frequent utilization and expensive health care cost, PD is often not recognized[9] by primary care physicians and, even when recognized, is inadequately treated. The few available studies suggest that fewer than 1 in 4 patients receives adequate pharmacotherapy, and only 1 in 8 receives adequate psychotherapy.[13,14] These rates are lower than rates recently reported for depressed patients in primary care.[15,16]

Throughout the past decade, several studies have addressed the gap between scientific knowledge of antidepressant treatment and the quality of care that patients with depression receive in primary care by developing and testing a variety of approaches to improving primary care treatment for depression. Using strategies that seek to overcome patient, physician, and process-of-care barriers to mental health treatment, along with judicious use of specialty consultation and close and sustained follow-up of patients, these approaches have demonstrated superior clinical care and greater cost-effectiveness compared with care as usual in the primary care setting.[15,17-19] More recently, a quality improvement strategy, using principles derived from these approaches to change the care process in primary care systems on a larger scale, has been shown to improve depression outcomes compared with care as usual.[20] In contrast to the progression from efficacy studies to effectiveness studies to system-wide quality improvement studies in primary care depressive illness, there have

SUBJECTS AND METHODS

SUBJECTS

Settings for this study were 3 Seattle, Wash, primary care clinics. Two university-associated internal medicine clinics cared for 8000 and 6000 patients, respectively (50%-60% with private insurance) with 30 attending physicians providing 70% of care and rotating medical residents providing the rest. The third clinic, a community family medicine clinic, part of a multisite health care system, cared for 10 000 patients (80%-90% with private insurance), with 8 attending physicians.

Patients had to be between age 18 and 65 years and meet *DSM-IV* criteria for PD, with at least 1 panic attack in the past month. We accepted all psychiatric and physical comorbidities except those that were potentially life-threatening (eg, active suicidal ideation or terminal medical illness) or those that would limit patient participation or adherence (psychosis, current substance abuse, dementia, and pregnancy). Patients had to be English-speaking and have a telephone to participate in follow-up assessments. We excluded patients currently receiving psychiatric treatment and patients currently receiving or applying for disability benefits. All physicians were informed about the study, and referrals from physicians were encouraged. However, we also recruited patients in the waiting room using a highly sensitive 2-question PD screen.[21] All positive screens and referrals received a telephone diagnostic interview to determine final eligibility. The study procedure was approved by the Institutional Review Board of the University of Washington Medical School, Seattle.

Before participating in the randomized trial, physicians received a 1-hour didactic on the recognition and treatment of PD and a medication algorithm[22] detailing medication types and dosing strategies for PD to improve knowledge and reduce an overfocus on medical problems. Previous CC studies[15,17,18] showed intervention-UC differences despite provision of this type of information to all physicians.

Patients were randomized using a random number table either to the CC model or to UC treatment. Because randomization was by patient, the same physician could have patients in CC and UC arms of the study. Randomization was stratified according to whether patients had been referred or screened, based on greater panic severity in referred patients,[23] and whether they had an additional comorbid axis I diagnosis. Medications were provided free to all patients and were obtained at hospital pharmacies (2 university clinics) or in the clinic (family medicine clinic).

INTERVENTION

A multifaceted intervention targeted patient, physician, and process-of-care variables. Patients were provided with an initial psychiatric visit (one psychiatrist covered each clinic), at which time they were prescribed the selective serotonin reuptake inhibitor (SSRI) paroxetine based on prior agreement with SmithKline Beecham Pharmaceuticals, Philadelphia, Pa, who funded the study, unless they had shown previous nonresponse or intolerance to this medication, in which case another SSRI was prescribed. Paroxetine was started at 10 mg daily, increased to 20 mg as tolerated in the second week, and, if no response was reported by the fourth week and the patient was able to tolerate it, 40 mg. On the day of randomization, CC patients were also mailed an educational videotape describing the nature of PD, its ability to mimic other medical illnesses, the time course and effectiveness of medication treatment, and a model of how medications work in the brain,[24] along with an educational pamphlet about the medication and its adverse effects. These points were systematically reemphasized during psychiatrist visits at which psychiatrists also addressed negative attitudes toward taking medications in general, receiving treatment for panic in particular, or having the PD diagnosis. Two follow-up psychiatric telephone calls and a second visit were offered to address problems with adverse effects or further address clinical issues. Although no formal cognitive therapy was offered, patients were encouraged to expose themselves, as tolerated, to any feared and avoided situations.

A schedule of extended care aimed to overcome the usual lack of planned follow-up and monitoring that occurs in acute care–oriented primary care[19] (1-hour psychiatric visit during week 1; 10- to 15-minute telephone call, week 2; 30-minute visit, week 4; telephone call between weeks 6 and 8). Selected patients were occasionally seen for extra sessions. The primary care physician received a typed consultation note after each psychiatric visit. Between months 3 and 12, psychiatrists attempted to telephone patients 5 times at equal intervals to reinforce the importance of medication adherence and address any other pertinent issues. The psychiatrist throughout the course of this study made all medication adjustments (P.P.R.-B., D.S.C., W.K.).

USUAL CARE

Usual care patients received treatment as usual (ie, pharmacotherapy) from their primary care physician in the clinic, who received the results of the initial diagnostic telephone assessment to eliminate nonrecognition of panic and associated disorders as a factor in outcome. Usual care patients could also be referred to university or community

been no attempts to adapt proven efficacious PD treatments to the primary care setting using an effectiveness treatment model.

To address this gap, a study tested the clinical effectiveness of PD pharmacotherapy embedded in a disease management framework of "collaborative care" (CC), a model shown to improve primary care outcomes for major depression.[15,17,18] The following questions were addressed: (1) Will CC patients have greater utilization of "adequate" pharmacotherapy (ie, correct drug type, dose and duration of treatment) compared with patients receiving care as usual? (2) Can this program improve clinical and functional outcomes compared with "usual care" (UC), acutely and over the longer-term 12-month period? (3) Will patients involved in this program be more satisfied with their care than patients treated with care as usual by primary care physicians?

RESULTS

Of 7875 patients (7765 encountered in the waiting room; 110 referrals), 3797 were eligible, and 3035 agreed to be

mental health practitioners, although only a small proportion, about 25%, were referred during the study.

ASSESSMENTS

Patients were assessed at 3-month intervals by BA psychologist telephone interviewers blind to randomization status. Interviewers were trained using videotapes, manuals, and practice interviews monitored by an experienced interviewer to check for reliability. The interview included portions of the Composite International Diagnostic Interview (CIDI), modified for *DSM-IV*,[25] which has acceptable reliability for mood and anxiety disorder diagnoses.[26-28] Telephone structured psychiatric interviews have high concordance with in-person interviews.[29,30] The interview also included the Panic Disorder Severity Scale (PDSS), a reliable and valid scale that rates a spectrum of PD symptoms[31] and is sensitive to treatment effects[32]; the Anxiety Sensitivity Inventory (ASI), a core measure of PD apprehension and discomfort with psychological and physical symptoms of anxiety,[33] which predicts risk for panic, maintenance of panic in the absence of treatment, and long-term outcomes[34] and is about 40% heritable[35]; the Fear Questionnaire,[36] which measures phobia symptoms; the Center for Epidemiological Studies Depression Scale (CES-D),[37] a reliable and valid measure of depression; the 36-Item Short Form Health Survey (SF-36),[38] a widely used health status inventory; a single 1-5 Likert scale item from a previous study[15] that measured patient satisfaction with recent care for personal and emotional problems; the NEO (Neuroticism, Extroversion, Openness) Inventory Scale,[39] which measures a neurotic trait that predicted poor outcome in previous CC studies[40]; and the Cumulative Illness Rating Scale (CIRS),[41] which uses medical record review to measure degree of medical comorbidity. The CIRS ratings were completed independently and then jointly (resolving disagreements) by a board-certified internist and a psychiatrist (P.P.R.-B., D.S.C., W.K.).

Adequacy of antipanic medication (appropriate type, dose, and duration of 6 weeks) was rated from patient self-reports during the assessments using a previously published algorithm based on a review of PD efficacy studies.[22] We elected to use a threshold of 20 mg as an adequate dose for paroxetine because our CC protocol allowed psychiatrists to stop at 20 mg if patients had responded (consistent with recent data[42]) or had dose-limiting adverse effects. Patients were classified as "adherent" if they reported taking medication at least 25 days in the month prior to assessment. This self-report measure has high concordance with automated pharmacy refill data.[16]

STATISTICAL ANALYSIS

Baseline diagnostic, symptom severity, and functional status variables were compared between patients completing the study and those missing at least 1 follow-up interview using *t* tests for continuous data and χ^2 analyses with corrections for continuity for categorical data. Baseline demographic and diagnostic data were compared between CC and UC patients using *t* tests for continuous data and χ^2 analyses with corrections for continuity for categorical data. Analyses of covariance (ANCOVA) using age, sex, ethnicity, NEO Inventory Scale score, clinic site, and medical comorbidity were used to compare baseline symptom severity and functional status variables between the treatment groups. Treatment group differences in the quality of care with respect to medication and satisfaction with care were examined using χ^2 analyses with corrections for continuity at 3-, 6-, 9-, and 12-month assessments.

To evaluate panic severity and functional impairment, we chose 6 primary outcomes: PDSS total score, ASI total score,[33] the Agoraphobia subscale from the Fear Questionnaire,[36] the CES-D scale, and the Social Functioning and Role Impairment subscales from the SF-36. The latter subscale was created to increase sensitivity by combining the role impairment owing to physical and emotional problems subscales.[43] In the event of a significant result for the PDSS total scores, 7 post hoc analyses were performed on the individual ratings owing to their theoretical importance. Mixed-effects random regression analysis procedures were used[44] because this procedure permits inclusion of patients with 1 or more missing data points (45 of the 115 in the study) and allows for individual varying slopes and intercepts over time.[45] Clinic site, age, sex, NEO Inventory Scale score, ethnicity, and medical comorbidity scores were used as covariates. Site and ethnicity by treatment interaction terms were tested for each outcome. These interactions were not significant, so they were excluded from the final regression analyses to increase power. The procedure uses maximum likelihood estimates to evaluate group, time, and group × time interaction effects. In the event of a significant group × time interaction, post hoc ANCOVAs on each follow-up assessment (3, 6, 9, and 12 months) were computed with clinic site, age, sex, NEO Inventory Scale score, baseline scale scores, and medical comorbidity scores used as covariates. For significant findings ($\alpha \leq .05$), changes between the groups over each 6-month period were also examined using similar ANCOVAs. As a final measure of response, we compared the proportion of responders in each group by 2 distinct measures. We defined patients who were "recovered" from anxiety sensitivity as those who scored lower than a commonly reported mean posttreatment score of 20, cited in a recent review of treated samples.[35] In addition, we used a 40% reduction in PDSS total score to define a "partial" response to treatment, as done in the recently published multicenter efficacy study in panic.[32]

screened. Of those, 479 (429, waiting room; 50, referrals) were positive for PD, and 115 (71, waiting room; 44, referrals) were ultimately enrolled. Only 21 (5%) of 479 waiting room subjects who were positive for PD and later qualified refused enrollment into the study (**Figure 1**). The 115 patients enrolled were randomized to either intervention (n=57) or care as usual (n=58) groups. Of the 115 patients, 99 (86%), 92 (80%), 81 (70%), and 91 (79%) completed the 3-, 6-, 9-, and 12-month assessments, respectively. Seventy (61%) completed all assessments, 17 (15%) completed 3 of the 4 assessments, and 10 (9%), 12 (10%), and 6 (5%) completed 2, 1, or no assessments, respectively. The 45 patients missing at least 1 follow-up interview were equally distributed between the treatment and UC groups (37% and 41%) and did not differ from the 70 patients completing all follow-ups on any of the demographic or clinical variables listed in **Table 1**.

PATIENT CHARACTERISTICS

Table 1 depicts patient characteristics, which were similar in intervention and UC groups. No differences reached

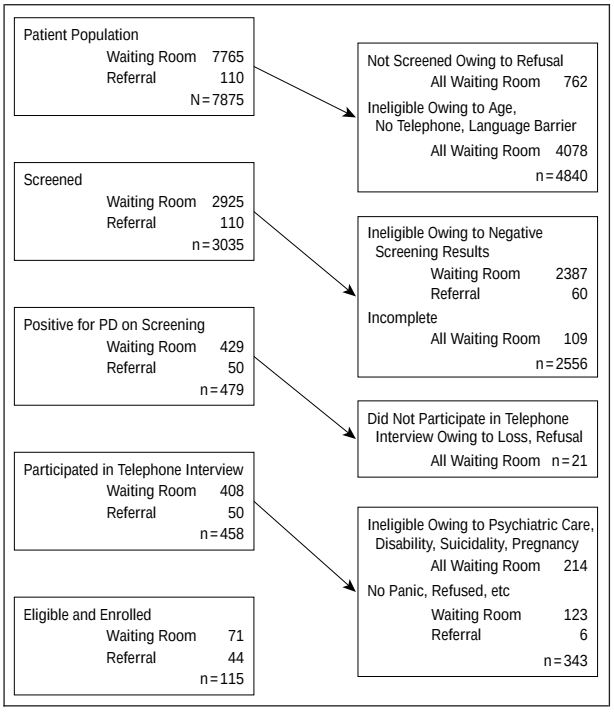

Figure 1. Flow diagram depicting patient process at each step and reasons for ineligibility or nonparticipation. PD indicates panic disorder.

statistical significance. The group was demographically heterogeneous with representative proportions of ethnic minority (37%) and indigent/unemployed (36%) patients. Average medical comorbidity was moderate, with patients having 1 to 3 medical illnesses requiring medication, but few had serious medical illnesses. Half the patients had a comorbid major depression, and one-third to one-half had a comorbid generalized or social anxiety disorder. Panic attack frequency was low, with patients averaging 1 to 2 panic attacks per week, although attacks were usually intense enough to stop activity (3 on the 4-point PDSS). Anticipatory anxiety was often present, and patients reported that it affected their lifestyle. However, they had only mild levels of phobic avoidance. Social and work impairment was rated to be moderate but manageable.

PARTICIPATION IN THE INTERVENTION PROGRAM

Of 57 patients assigned to the CC arm, 49 (86%) made at least 1 psychiatrist visit, and 43 (75%) made at least 2 visits in the initial 3-month period. Intervention patients were seen an average of 1.77±0.95 visits (mean±SD; range, 0-5 visits). During the first 3 months, patients also received an average of 2.25±1.53 follow-up telephone calls (range, 0-6 calls), with 81% receiving at least 1 telephone call. The mean±SD number of calls for the last 3 quarters of the year were 1.40±0.96, 1.12±1.10, and 0.81±0.85, with 77%, 67%, and 53% receiving at least 1 call during these time periods. The number of telephone calls decreased significantly over the course of the year ($F_{3,168}=26.48$; $P<.001$).

QUALITY OF CARE WITH RESPECT TO MEDICATION

Table 2 contains percentages for appropriate type, dose/duration, and adherence to antipanic medication during the 12-month study period. Compared with UC patients, significantly more CC patients reported receiving an appropriate type (3 months) and adequate dose duration (3 and 6 months) of evidence-based antipanic medication, and self-administering them for 25 or more days in the last month (3 and 6 months). At 9 and 12 months, these differences were no longer significant owing to declining rates over the course of the year in CC patients and continued steady but lower rates in UC patients. Throughout the year, 85% of CC patients self-administering medication received paroxetine; 10%, sertraline; and the remainder, a tricyclic or benzodiazepine. Throughout the year, 65% of the medicated UC patients received various SSRIs (including paroxetine); 20%, benzodiazepine medications; and 15%, tricyclic medications. Only 3 of 57 CC patients changed medication type during the year.

PANIC SEVERITY AND FUNCTIONING INTERVENTION OUTCOMES

The mixed-effects random regression procedure revealed a significant treatment group × time interaction for the PDSS total score, ASI, SF-36 Role Function, and CES-D scales (**Table 3**). Although CC patients scored lower at all time points, on the PDSS, the difference was only significant at 6 months ($F_{1,83}=9.31$; $P=.003$) (**Figure 2**). Post hoc random regression analyses of the individual PDSS items showed that the significant treatment group × time interaction was owing to a significant interaction on the item-assessing severity of anticipatory anxiety. In contrast, for the ASI total score, the CC group scored significantly lower than the UC group at the 3-month ($F_{1,90}=5.32$; $P=.002$), 6-month ($F_{1,80}=11.10$; $P<.001$), and 12-month follow-ups ($F_{1,82}=4.60$; $P=.035$) (**Figure 3**). Similarly, for the CES-D, the CC group had significantly decreased depression severity at all follow-up assessments.

Follow-up, mo	F Test	*P* Value
3	$F_{1,90}=10.72$	.002
6	$F_{1,80}=8.27$	.005
9	$F_{1,72}=4.59$	.036
12	$F_{1,80}=5.81$	.02

Finally, for SF-36 role functioning, the CC group only showed significantly greater improvements at 12 months ($F_{1,81}=6.16$; $P=.015$). The Agoraphobia subscale from the Fear Questionnaire and the Social Functioning scale from the SF-36 did not show any significant effects. In all the outcomes with significant time × group interactions, the rate of change was significantly greater for the CC group compared with the UC group from baseline to 6 months but not from 6 months to 1 year. The effect sizes for CC vs UC for the decrease in severity during the first 6-month period were 1.01 for the ASI, 0.69 for the PDSS total, 0.57 for the CES-D, and 0.42 for the SF-36 Role Functioning scale. This indicates that, despite an overall improve-

Table 1. Baseline Demographic and Clinical Characteristics*

Variable	Care as Usual (n = 58)	Intervention (n = 57)	Total (n = 115)
Demographics		Percentage	
Age, mean (SD)	41.9 (10.4)	39.6 (10.2)	40.8 (10.3)
Female	63.8	50.9	57.4
White	62.5	71.9	67.3
Employed	63.8	63.2	63.5
Psychiatric diagnosis			
Agoraphobia	42.1	35.1	38.6
Major depression	49.1	52.6	50.9
Dysthymia	12.3	12.3	12.3
GAD	42.1	43.9	43.0
OCD	19.3	14.0	16.7
PTSD	21.1	8.8	14.9
Social phobia	40.4	36.8	38.6
Clinical characteristics		Mean (SD)	
CIRS, total score	1.5 (0.54)	1.3 (0.72)	1.4 (0.64)
CES-D	27.2 (10.9)	26.6 (9.7)	26.9 (10.3)
Panic Disorder Severity Scale, total	12.4 (5.7)	13.0 (5.3)	12.7 (5.5)
Panic attack frequency	1.9 (1.0)	1.7 (1.1)	1.8 (1.0)
Distress from panic attacks	2.8 (0.9)	3.0 (1.0)	2.9 (1.0)
Severity of anticipatory anxiety	1.6 (1.0)	2.0 (1.0)	1.8 (1.0)
Agoraphobic avoidance	1.4 (1.3)	1.4 (1.2)	1.4 (1.3)
Panic-related sensation fear	1.3 (1.2)	1.1 (1.1)	1.2 (1.1)
Impairment/interference in work owing to panic disorder	1.7 (1.1)	1.8 (1.1)	1.7 (1.1)
Impairment/interference in social functioning owing to panic disorder	1.7 (1.3)	1.9 (1.3)	1.8 (1.3)
Anxiety Sensitivity Index	28.2 (12.3)	30.0 (11.9)	29.3 (12.1)
Fear Questionnaire			
Total	2.6 (1.5)	2.4 (1.4)	2.5 (1.4)
Agoraphobia subscale	2.0 (1.9)	1.6 (1.6)	1.8 (1.8)
Bodily Injury subscale	2.5 (2.0)	2.4 (1.9)	2.4 (1.9)
Social Phobia subscale	2.7 (1.7)	2.5 (1.6)	2.6 (1.7)
SF-36			
General health	52.2 (24.6)	50.7 (27.1)	51.4 (25.8)
Physical functioning	73.7 (27.4)	77.9 (25.8)	75.8 (26.6)
Mental health	51.0 (21.5)	51.2 (20.0)	51.1 (20.7)
Bodily pain	36.6 (21.3)	36.2 (19.8)	36.4 (20.4)
Vitality	36.1 (20.5)	34.1 (20.0)	35.1 (20.1)
Social functioning	58.3 (28.9)	56.8 (33.1)	57.5 (31.0)
Role dysfunction, emotional problems	34.5 (39.5)	40.9 (41.3)	37.7 (40.3)
Role dysfunction, physical problems	45.7 (44.2)	48.2 (42.2)	47.0 (43.1)

*GAD indicates generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; CIRS, Cumulative Illness Rating Scale; CES-D, Center for Epidemiological Studies Depression Scale; and SF-36, the 36-Item Short Form Health Survey. All means are adjusted from analyses of covariance with age, sex, ethnicity, the NEO (Neuroticism, Extroversion, Openness) Inventory Scale score, clinic, and CIRS as covariates.

ment with time in each group, there was a significant intervention effect. There were no sex or racial differences in outcome.

Another test of treatment effectiveness is whether patients meet a predefined level of clinical recovery or improvement. At 3 months, the higher proportion of CC patients reaching these levels was only significantly different using the ASI recovery criteria (40% vs 15%) but not the PDSS improvement criteria (61% vs 42%). However, by 6-months' follow-up, the rate of both recovery and improvement in the CC group was more than twice the rate in the UC group (ASI, 49% vs 17%; PDSS, 76% vs 38%). At 9 months the differences in the rate of recovery on the ASI (33% vs 24%) and PDSS (82% vs 60%) were no longer significant. At the 12-month assessment, significantly more CC patients were both improved and recovered on the PDSS (80% vs 59%) and the ASI (47% vs 20%).

Follow-up, mo	Scale	χ^2_1	*P* Value
3	ASI	7.63	.004
	PDSS	2.89	.089
6	ASI	8.40	.004
	PDSS	11.51	.001
9	ASI	0.78	.37
	PDSS	3.36	.067
12	ASI	7.97	.005
	PDSS	3.90	.048

SATISFACTION WITH TREATMENT

At the 6- and 12-month follow-up interviews, more CC than UC patients were satisfied or very satisfied with the quality of care they received for emotional problems (6 months: 82% vs 43%, $\chi^2_1=13.71$, $P<.001$; 12 months: 76% vs 52%, $\chi^2_1=4.28$, $P=.039$).

Table 2. Quality of Care With Respect to Medication*

	Receiving Appropriate Type of Medication, %			Receiving Adequate Dose and Duration, %			Adherent >25 Days, %		
Month	CC	UC	χ^2_1	CC	UC	χ^2_1	CC	UC	χ^2_1
Baseline	33	48	2.07	14	19	0.21	10	12	0.01
3	77	52	7.06†	61	34	7.03†	53	28	6.51†
6	67	52	2.07	56	29	7.40†	49	26	5.69†
9	58	47	1.06	47	29	3.24	40	26	2.11
12	58	48	0.72	47	33	1.98	44	31	1.51

*CC indicates collaborative care; UC, usual care. All figures denote percentage of patients with appropriate type, dose duration, and adherence to antipanic medication based on overall intent-to-treat sample of 115, regardless of whether patients were assessed at certain time points. Appropriate type and adequate dose are as defined in reference 26. A duration of 6 weeks was required for adequate duration.

†$P<.05$.

‡$P<.01$.

COMMENT

Our findings indicate that compared with care as usual, CC approaches, previously shown to be effective for depressed primary care patients,[15,17,18] improved the symptomatic and functional outcomes of patients with PD in primary care. These differences were most consistent and pronounced over the initial 6-month period of the study, corresponding to both the more intensive nature of the disease management intervention during this period, as well as the greater rates of utilization of and adherence to "effective" antipanic medication regimens during this same time. Patients in the CC group were also significantly more satisfied with the care they received for their mental and emotional problems.

Although both groups improved over time (as seen in most clinical trials), patients receiving the CC intervention had greater improvements over the 6-month period in overall panic severity on the PDSS, largely owing to significant changes in anticipatory anxiety. Differences between CC and UC patients were most consistent and pronounced for anxiety sensitivity, with statistical significance at 3 of 4 assessment points. The 10-point difference in improvement in this measure at 6 months is particularly noteworthy, since this core underlying feature of PD is an important determinant of the transition from nonclinical sporadic panic attacks to PD,[35] where the fear of internal bodily sensations often results in hypochondriacal preoccupation. More than twice as many CC as UC patients reached "normal" levels of this measure, a clinically important finding. These pronounced effects and the absence of effects on panic attack frequency (which decreased substantially in both groups) may be related to the absence of any disease management in UC patients but the presence of some, albeit lower quality, pharmacotherapy (which would preferentially affect panic frequency more than anticipatory anxiety). Sustained effects on depressive symptoms were also consistently noted. Intervention patients also had significant improvements in work (SF-36) disability compared with UC patients.

Because UC physicians received patient diagnosis at baseline, these intervention effects are not owing to improved screening or recognition. The provision of a panic medication algorithm and 1-hour didactic at baseline for all physicians also suggests that differences in physician knowledge about panic treatment were not a factor. Instead, the most likely factor is improved quality of care defined as adequacy of, and adherence to, antipanic medication, facilitated by disease management focusing on improving patient education and PD monitoring and follow-up. Primary care physicians received no feedback about UC patient adherence, employed no specific adherence strategies, and had little time for psychoeducation. Although CC patients received paroxetine, any other SSRI would likely be equally effective. Patients in the UC arm of the study showed slower, but detectable, improvement on a number of measures. Partial response rates at 3 months in this group are similar to the 40% response rates for depression in previous CC studies. The changes that occurred in the UC group may represent spontaneous improvement, fluctuations in the ordinary course of PD, or, in the patients receiving and adhering to appropriate treatment, a true treatment response. Unlike 8- to 12-week efficacy studies, this year-long study allows more time for both natural symptom improvement and continual care seeking and active medication treatment in UC subjects.

The effect sizes for certain core measures such as anxiety sensitivity and anticipatory anxiety, as well as full recovery using the ASI, seemed to increase slightly at 6 vs 3 months. Although intensity of the intervention was greatest between 0 and 3 months, studies suggesting that anxious patients respond more slowly to treatment provides a possible explanation for this delayed effect. Consistent with several previous studies of this approach in depression, which showed that beneficial effects of acute 3-month interventions seemed to decrease between 4 and 7 months,[18,20] the robust CC vs UC differences noted at 6 months gradually began to narrow between 6 and 12 months.

This study has a number of limitations. First, generalizability is compromised by the use of a small number of sites. However, the ethnic, socioeconomic, and health care financing mix was far broader than in previous CC studies that focused on middle class, working, white patients in health maintenance organizations, and the absence of site and racial differences suggests that beneficial effects were generalized to the entire group. Second, all subjects were provided medication free of charge, which differs from the "real world" of primary care. Third, the use of anxiety disorder specialists and university sites (in 2 of the 3 settings) may suggest it would be difficult to implement this intervention in certain rural and urban inner-city settings owing to a lack of specialists. However, this simple intervention might be carried out by well-trained physician extenders (such as nurses) with psychiatric supervision, as is being done for depression in the Kaiser Health System (Oakland, Calif).[46] Fourth, it is not possible to determine which components of the intervention were responsible for the beneficial effects since no systematic assessment of the treatment process was made. Nonetheless, it seems that the provision of skilled assessment and treatment explanations, the scheduling of regular patient-clinician contact, and the ongoing monitoring of treatment tolerance, adherence, and outcomes were most important in possibly allowing better management of medication adverse ef-

Table 3. Panic and Functioning Outcomes*

Measure	Time Effect		Treatment Effect		Time-Treatment Interaction	
	Z	*P* Value	Z	*P* Value	Z	*P* Value
Panic Disorder Severity Scale						
Total	**–6.44**	**<.001**	0.02	.98	**–1.96**	**.05**
Panic attack frequency	**–5.00**	**<.001**	−0.92	.36	−0.11	.91
Distress during panic attacks	**–4.27**	**<.001**	0.05	.96	−1.54	.12
Severity of anticipatory anxiety	**–4.39**	**<.001**	1.16	.24	**–2.58**	**.009**
Agoraphobic avoidance	**–4.28**	**<.001**	−0.13	.90	−0.99	.32
Panic-related sensation fear	**–4.53**	**<.001**	−0.47	.64	−0.49	.62
Interference in work functioning owing to panic	**–5.21**	**<.001**	0.14	.88	−1.56	.12
Interference in social functioning owing to panic	**–4.05**	**<.001**	0.52	.60	−1.90	.06
Anxiety Sensitivity Index	**–2.98**	**.004**	−0.39	.70	**–2.37**	**.018**
Fear Questionnaire						
Agoraphobia subscale	−1.20	.23	−0.66	.51	−0.42	.67
SF-36						
Role functioning	−1.56	.12	0.05	.96	**–2.17**	**.03**
Social functioning	**2.82**	**.005**	−0.11	.91	0.68	.49
CES-D	−1.52	.13	−0.57	.57	**–2.11**	**.03**

*SF-36 indicates the 36-Item Short Form Health Survey; CES-D, Center for Epidemiological Studies Depression Scale. Analysis based on mixed-effects random regression. Significant ($P<.05$) findings are in bold type. Analysis uses covariates of age, sex, clinic, the NEO (Neuroticism, Extroversion, Openness) Inventory Scale score, and medical comorbidity. Collaborative care, n = 57; usual care, n = 58.

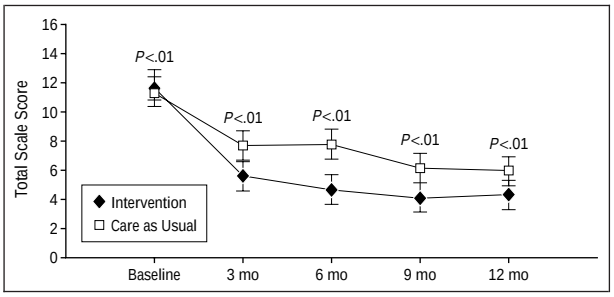

Figure 2. Adjusted means based on covariates of age, sex, clinic, NEO (Neuroticism, Extroversion, Openess) Inventory Scale score, and medical comorbidity in both groups over time. Sample sizes at baseline, 3, 6, 9, and 12 months, respectively: collaborative care patients—57, 51, 45, 43, and 45; usual care patients—58, 48, 47, 38, and 46.

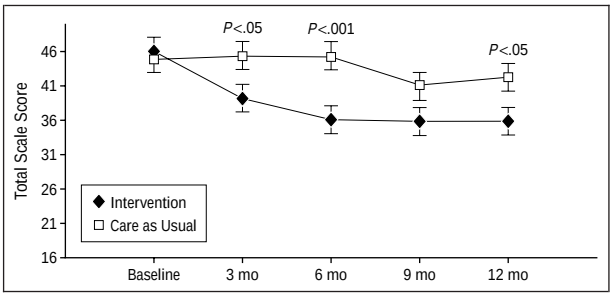

Figure 3. Adjusted means based on covariates of age, sex, clinic, NEO (Neuroticism, Extroversion, Openness) Inventory Scale score, and medical comorbidity in both groups over time. Sample sizes at baseline, 3, 6, 9, and 12 months, respectively: collaborative care patients—57, 51, 45, 43, 45; usual care patients—58, 48, 47, 38, and 46.

fects and dose adjustments. Finally, this effectiveness study, by nature, lacked certain methodologic controls common to more internally valid efficacy studies. The PDSS has not been validated for use via the telephone or by lay interviewers, and the ASI has been infrequently used as a pharmacotherapeutic outcome measure,[35] though its content is unusually well suited for primary care PD. Efficacy studies have established that 40 mg of paroxetine is the efficacious dose,[43] while our modal paroxetine dose was 20 mg, the most common dose in primary care clinics[47] (Risa B. Weisberg, PhD, Martin Keller, MD, e-mail communication, March 2001) and an effective dose for some patients.[43] Although our protocol allowed psychiatrists to stop at 20 mg, it is possible that pushing the dose higher could have increased response in CC patients.

These limitations are balanced by some important strengths not seen in efficacy studies. First, our long-term retention rate was almost 75% at 12 months, substantially higher than the approximate 40% long-term retention rate in the recent collaborative PD efficacy study by Barlow et al.[32] Second, the high level of psychiatric and medical comorbidity in our sample more accurately reflects the real world of primary care. Third, even though our comparison group received, at low but steady rates throughout the 1-year study, active medication rather than placebo, and their physicians received reports of their diagnosis and education about a potential antipanic treatment, we were still able to show that our intervention made a significant difference. Finally, related to this, we had no differential dropout in our comparison group compared with our intervention group, something that is often seen in the placebo cell of efficacy studies.

These findings demonstrate that a CC intervention for patients with PD in primary care increases patients' use of and adherence to guideline-recommended pharmacotherapy and results in greater clinical and functional improvements and greater patient satisfaction with care compared with care as usual in this setting. This "carved in" collaborative model has now been adopted to treat multiple psychiatric disorders by both university clinics in this study, and is being used by Group Health Cooperative (Seattle), Kaiser Permanente (Oakland, Calif), and the VA Hospitals primary care clinics, which collectively care for more than 20 000 patients. Now that this

intervention has been shown to be effective, future studies in this setting should consider employing the "stepped care" approach recently reported to be effective in depression.[18] In this approach, patients would first be treated by their primary care physician, and only incomplete responders or patients at high risk for relapse and or a chronic condition would receive a second "step" of CC. This mode of care would be potentially more cost-effective than the approach reported here and could address the reluctance of primary care clinics to adopt these models because of concerns about added cost,[47] despite demonstrated cost-effectiveness in depression.[19]

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