ORIGINAL CONTRIBUTION

Optimized Antidepressant Therapy and Pain Self-management in Primary Care Patients With Depression and Musculoskeletal Pain

A Randomized Controlled Trial

Kurt Kroenke, MD
Matthew J. Bair, MD, MS
Teresa M. Damush, PhD
Jingwei Wu, MS
Shawn Hoke, BA
Jason Sutherland, PhD
Wanzhu Tu, PhD

Context Pain and depression are the most common physical and psychological symptoms in primary care, respectively. Moreover, they co-occur 30% to 50% of the time and have adverse effects on quality of life, disability, and health care costs.

Objective To determine if a combined pharmacological and behavioral intervention improves both depression and pain in primary care patients with musculoskeletal pain and comorbid depression.

Design, Setting, and Patients Randomized controlled trial (Stepped Care for Affective Disorders and Musculoskeletal Pain [SCAMP]) conducted at 6 community-based clinics and 5 Veterans Affairs general medicine clinics in Indianapolis, Indiana. Recruitment occurred from January 2005 to June 2007 and follow-up concluded in June 2008. The 250 patients had low back, hip, or knee pain for 3 months or longer and at least moderate depression severity (Patient Health Questionnaire 9 score ≥10).

Intervention Patients were randomly assigned to the intervention (n=123) or to usual care (n=127). The intervention consisted of 12 weeks of optimized antidepressant therapy (step 1) followed by 6 sessions of a pain self-management program over 12 weeks (step 2), and a continuation phase of therapy for 6 months (step 3).

Main Outcome Measures Depression (20-item Hopkins Symptom Checklist), pain severity and interference (Brief Pain Inventory), and global improvement in pain at 12 months.

Results At 12 months, 46 of the 123 intervention patients (37.4%) had a 50% or greater reduction in depression severity from baseline compared with 21 of 127 usual care patients (16.5%) (relative risk [RR], 2.3; 95% confidence interval [CI], 1.5-3.2), corresponding to a much lower number of patients with major depression (50 [40.7%] vs 87 [68.5%], respectively; RR, 0.6 [95% CI, 0.4-0.8]). Also, a clinically significant (≥30%) reduction in pain was much more likely in intervention patients (51 intervention patients [41.5%] vs 22 usual care patients [17.3%]; RR, 2.4 [95% CI, 1.6-3.2]), as was global improvement in pain (58 [47.2%] vs 16 [12.6%], respectively; RR, 3.7 [95% CI, 2.3-6.1]). More intervention patients also experienced benefits in terms of the primary outcome, which was a combined improvement in both depression and pain (32 intervention patients [26.0%] vs 10 usual care patients [7.9%]; RR, 3.3 [95% CI, 1.8-5.4]).

Conclusion Optimized antidepressant therapy followed by a pain self-management program resulted in substantial improvement in depression as well as moderate reductions in pain severity and disability.

Trial Registration clinicaltrials.gov Identifier: NCT00118430

JAMA. 2009;301(20):2099-2110 www.jama.com

PAIN IS THE MOST COMMON PRESENTING somatic symptom in medical outpatients,[1] and depression is the most common mental disorder.[2] Pain complaints account for more than 40% of all symptom-related outpatient visits,[3] and depression is present in 10% to 15% of all patients attending primary care. Two-thirds of pain-related outpatient visits are due to musculoskeletal pain, accounting for nearly 70 million outpatient visits in the United States each year.[3] Back and joint pain result in an estimated 200 million lost work days per year.[4] Moreover, pain and depression frequently coexist (30%-50% co-occurrence) and have an additive effect on adverse health outcomes and treatment responsiveness of one another.[5]

Two types of treatment (one pharmacological and the other behavioral) could prove synergistic in the treatment of comorbid musculoskeletal pain and depression. Antidepressants are a well-established therapy for depression, and there is also evidence for at least moderate efficacy in pain, which may vary by type of painful disorder and antidepressant class.[6,7] Pain self-management programs have proven efficacious for both low back pain and osteoarthritis (most commonly located in

Author Affiliations are listed at the end of this article.
Corresponding Author: Kurt Kroenke, MD, Regenstrief Institute Inc, Sixth Floor, 1050 Wishard Blvd, Indianapolis, IN 46202 (kkroenke@regenstrief.org).

the hip and/or knee),[8,9] with possible secondary benefits in reducing psychological distress.[10-12] While literature syntheses have suggested that self-management programs may have a smaller effect on outcomes in musculoskeletal conditions than in other diseases such as diabetes, hypertension, and asthma,[13,14] others argue that outcomes such as pain and function are more complex as are the components of pain self-management targeting painful conditions.[15,16]

The Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study was a randomized clinical trial consisting of 12 weeks of optimized antidepressant therapy (step 1) followed by 6 sessions of a pain self-management program delivered over 12 weeks (step 2), and a 6-month continuation phase in which symptoms were monitored and treatments reinforced (step 3). The study population comprised primary care patients with chronic musculoskeletal pain and comorbid depression. The co-primary outcomes were depression and pain severity at 12 months.

METHODS

Study Sample

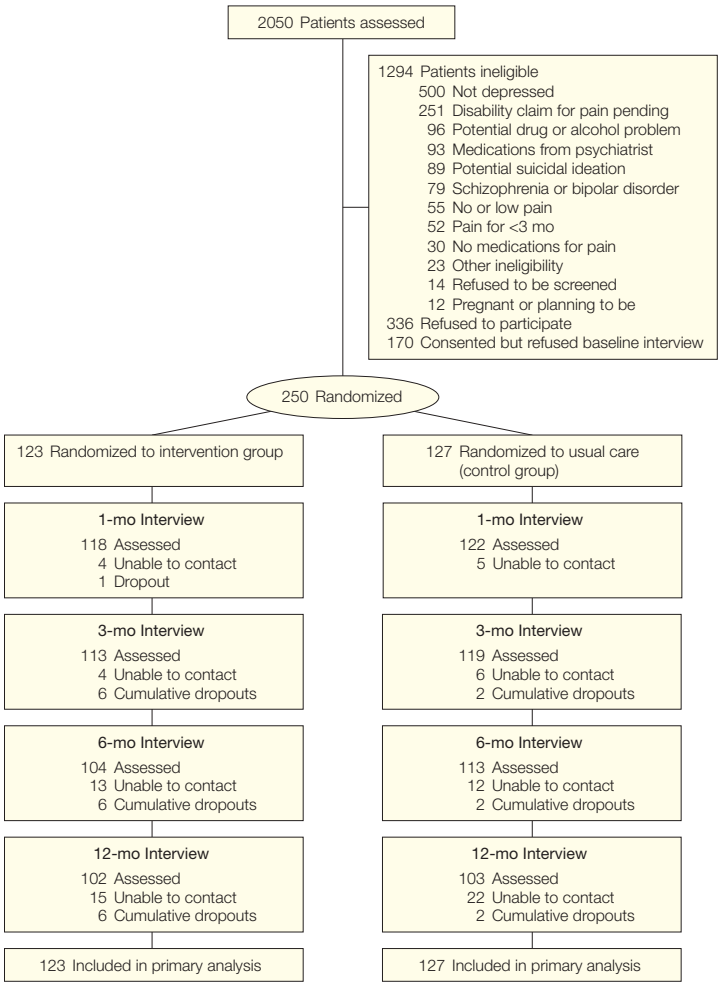
Details of the SCAMP trial design, study population, and outcome measures have been previously described.[17] Patients were recruited from January 2005 to June 2007 from 2 primary care clinical systems in the Indianapolis metropolitan area: the Indiana University Medical Group Primary Care system (6 community-based clinical sites) and the Richard L. Roudebush VA Medical Center (5 general medicine clinics). The Indiana University institutional review board approved the study and all enrolled patients gave written informed consent.

Briefly, potential participants were primary care patients with comorbid musculoskeletal pain and depression. The pain had to be (1) located in the low back, hip, or knee; (2) persistent for 3 months or longer despite conventional analgesic treatment (defined as use of ≥2 different analgesics); (3) at least moderate in severity (defined as a Brief Pain Inventory [BPI] score of ≥5).[18,19] The depression had to be of at least moderate severity (Patient Health Questionnaire 9 [PHQ-9] score ≥10) and endorsement of depressed mood and/or anhedonia. More than 90% of patients fulfilling this PHQ-9 criterion have been shown in previous studies to have major depression and/or dysthymia, and the remaining patients have clinically significant depression with substantial functional impairment.[20,21] Patients who were taking antidepressants but who still met the entry criterion for clinical depression were eligible if they had been taking an adequate dose of the antidepressant for at least 12 weeks.[22,23]

Excluded were individuals with severe cognitive impairment, bipolar disorder, substance use disorder, schizophrenia, a pain-related disability claim currently under adjudication, plans to become pregnant in the next year, a life expectancy of less than 12 months, or inability to speak English. This trial was monitored by an independent SCAMP data and safety monitoring board.

FIGURE 1 outlines the participant enrollment and follow-up in the SCAMP trial. Of 2050 patients screened, 1294 were not eligible, most often because they were either not depressed (n=500) or had pain that was minimal, of short duration, or did not require analgesics (n=137). Of the 756 eligible patients,

Figure 1. Flow of Individuals in the SCAMP Trial



SCAMP indicates Stepped Care for Affective Disorders and Musculoskeletal Pain.

250 enrolled (33%) in the trial by providing informed consent and completing a baseline interview after which they were randomized to 1 of the 2 study groups.

Randomization and Blinding

Individuals were randomized to the intervention group or the usual care (control) group with randomization stratified by pain location (back vs leg) and clinic site (university vs Veterans Affairs medical center). Randomization lists were computer generated and treatment assignments were supplied in sealed opaque envelopes. The nurse care manager obtained patient consent and revealed the randomization assignment for each participant by opening the next envelope in the sequence after completion of baseline assessment. All baseline and follow-up outcome assessments were conducted by a research assistant blinded to treatment allocation and uninvolved in the care management of the participants.

Outcome Assessment

Depression diagnoses were established with the Primary Care Evaluation of Mental Disorders, which categorizes individuals into the 3 *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic subgroups of major depression, dysthymia, and other depression.[24] Depression severity was assessed, as a primary outcome, with the 20-item Hopkins Symptom Checklist (HSCL-20), which has established sensitivity to change[25] and is widely used in effectiveness trials of depression among primary care patients.[21-23,26,27] Pain outcomes were based on the chronic pain domains recommended in the guidelines from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[28] The BPI was the primary pain outcome measure.[29] The BPI includes a 4-item severity scale (current pain and worst, least, and average pain in past week) and a 7-item interference scale (the degree to which pain interferes with general activity, mood, walking, work, sleep, relationships with other people, and enjoyment of life). Global change in pain was assessed with a 7-point scale with the options being worse, the same, or a little, somewhat, moderately, a lot, or completely better. Secondary outcome measures of pain included the Graded Chronic Pain Scale (GCPS) and the Roland Disability Scale. In addition to its pain severity and pain disability scales, the GCPS also asks how many days in the past 3 months usual activities have been limited by pain.[30] The Roland Disability Scale is a 24-item pain-specific measure of physical disability validated in patients with back pain[31] and chronic noncancer pain.[32]

Several scales or items from the Short-Form 36 (SF-36)[33,34] assessed social functioning, vitality, bodily pain, and a single general health perceptions item that has been shown to predict long-term health outcomes.[35] Anxiety was assessed by the 7-item Generalized Anxiety Disorder (GAD-7) scale, a screening and severity measure validated for the 4 most common anxiety disorders of generalized anxiety, panic, social anxiety, and posttraumatic stress disorder.[36,37] Because pain treatment and pain outcomes may vary by race or ethnicity,[38] race/ethnicity (identified by the patient from preselected options) also was included as a demographic characteristic.

Medication refill (ie, antidepressants and analgesics) and health care use data were extracted from electronic medical records for all participants for the 12-month study period following their enrollment interview. The one exception was that antidepressant use in the intervention group was extracted from care manager logs because intervention patients were provided antidepressants by the study rather than through a prescription. Most patients receive all or most of their medications from the pharmacies inputting prescription information into these electronic medical records. To assess additional cointerventions, a treatment survey asked participants about any treatments they received for pain and depression during the preceding 3 months at baseline and at the 3-, 6-, and 12-month follow-up interviews. Follow-up concluded in June 2008.

Intervention

The intervention model in the SCAMP trial is based on a depression care management team consisting of a nurse care manager supervised by a physician depression specialist, which has been proven effective in multiple depression trials among primary care patients.[39] The first 3 months consisted of optimized antidepressant therapy actively managed by the nurse care manager (step 1), followed by 6 sessions of a pain self-management program delivered every other week during the second 3 months (step 2). The final 6 months of the study was a continuation phase focused on relapse prevention. The protocol called for 5 in-person contacts (baseline, 6, 12, 16, and 20 weeks) and 8 telephone contacts (1, 3, 9, 14, 18, and 22 weeks, and at 8 and 10 months). Extra contacts could occur depending on treatment changes or a patient's clinical needs.

Step 1: Optimized Antidepressant Therapy (Weeks 1-12). For intervention patients already taking an antidepressant at baseline, dose adjustments or medication changes were considered because despite receiving antidepressant therapy, the patients remained clinically depressed. For patients not taking an antidepressant or requiring antidepressant changes, TABLE 1 outlines the antidepressant algorithm for the SCAMP trial (the rationale for which has been previously described[17]). The SCAMP trial was not designed to test any particular antidepressant but instead analyzed optimal medication management, which is both effective and tolerated in an individual patient.[40,41] A serotonin-norepinephrine reuptake inhibitor (SNRI) was offered first in the algorithm because of evidence suggesting that norepinephrine reuptake inhibition (which occurs to a greater degree with tricyclic antidepressants or SNRIs than with selective serotonin reuptake inhibitors [SSRIs]) may be particularly important in descending inhibitory pathways related to pain.[7] Venlafaxine was

Table 1. Antidepressant Selection and Dosing Details in SCAMP Trial

Priority	Indications and Precautions	Class	Drug	Dose, mg	
				Initial	Possible Increases
1	Avoid if cardiovascular disease, abnormal electrocardiogram, or hypertension not well controlled	Serotonin-norepinephrine reuptake inhibitor	Venlafaxine	75	150, 225
2	Selective serotonin reuptake inhibitor of choice	Selective serotonin reuptake inhibitor	Fluoxetine	20	30, 40
2	Selective serotonin reuptake inhibitor of choice if cardiovascular disease	Selective serotonin reuptake inhibitor	Sertraline	50	100, 150
3	If treatment failed with first selective serotonin reuptake inhibitor (fluoxetine or sertraline)	Selective serotonin reuptake inhibitor	Citalopram	20	30, 40
4	If obese or have weight gain or sexual adverse effects	Other	Bupropion	200	300, 400
4	If insomnia a problem; avoid if obese	Other	Mirtazapine	15	30, 45
5	Avoid if cardiovascular disease, abnormal electrocardiogram, or hypertension not well controlled	Tricyclic antidepressant	Nortriptyline	25	50, 75

Abbreviation: SCAMP, Stepped Care for Affective Disorders and Musculoskeletal Pain.

selected for the SCAMP trial because it was the most commonly used SNRI at the beginning of the trial and also was scheduled to become generic by the time of study completion.

Clinical response was assessed at 3 weeks and, if there was not a clinically meaningful response (defined as a 5-point drop in PHQ-9 score[25]), a dose increase occurred. Participants who did not achieve a PHQ-9 score of less than 10 and a 50% reduction in PHQ-9 score at 6 weeks were switched to a different antidepressant. Of note, depression rather than pain response dictated antidepressant adjustments. The target PHQ-9 score was less than 5, which approximates depression remission.[42]

Patients randomized to the usual care group were informed they had depressive symptoms and that they should seek advice about treatment. There were no other attempts by study personnel to influence depression or pain management unless a psychiatric emergency (eg, suicidal ideation) arose.

Step 2: Pain Self-management Program (Weeks 13-26). The pain self-management sessions were modeled after the successful Stanford self-management program[8,9,43] and were based on social cognitive theory,[44] which focuses on increasing self-efficacy and social support to self-manage low back pain or arthritis symptoms. Participants learn to modify their behavior through use and discussion of behavioral plans and problem-solving techniques to sustain behavioral change. The nurse care manager conducted the pain self-management sessions using a standardized, written protocol adapted from our previous work with musculoskeletal pain.[45,46] Details of the pain self-management program including care manager training and procedures to ensure fidelity are detailed elsewhere.[17]

Briefly, patients learn about chronic pain including triggers and flare-ups; coping with fear and other negative emotions; and strategies for physical activity, muscle relaxation, deep breathing, distraction, sleep hygiene, and working with clinicians and employers. During each session, the nurse care manager introduces new strategies for patient self-management, assists the patient in choosing strategies, and supervises the patient as he/she practices the chosen strategy. To promote perceived self-efficacy, patients receive individualized feedback about their progress.

Step 3: Continuation Phase (Weeks 27-52). Intervention patients received scheduled nurse care manager calls at 8 and 10 months to assess symptoms and to evaluate antidepressant and pain self-management adherence. The care manager assessed current self-management strategies and assisted patients with new behavioral plans. Patients with a PHQ-9 score of 5 or greater could have their antidepressant dose increased or be switched to a different antidepressant if they had not yet had trials of 2 different antidepressants. Those experiencing treatment failure with 2 different antidepressants were offered a referral to see a psychiatrist. Only those refusing referral to a psychiatrist could be given several more antidepressants during the 12-month study. If antidepressant changes did occur, additional nurse care manager calls were scheduled as in step 1.

Analysis

Analyses were based on the intention-to-treat method in all randomized participants. The primary outcome was a composite depression-pain response at 12 months defined as both an improvement of 50% or greater in depression and an improvement of 30% or greater in pain, which are the standard thresholds for moderate improvement in depression and pain clinical trials.[47,48] This composite outcome used the HSCL-20 and BPI total scores; the latter was the average of the 4 BPI severity and the 7 BPI interference items because both dimensions are considered essential in assessing outcomes of chronic pain therapy.[28] The internal reliabilities of the BPI total, severity, and interference scores were similar in the sample (Cronbach α level of .89, .88, and .83, respectively). With 97 individuals per group, 80% power was projected to detect a 20% absolute difference in response rates with a 2-tailed α level of less than .05. Enrolling 250 individuals allowed up to a 25% attrition rate.

The resulting sample size also provided 80% power to detect a moderate treatment effect size of 0.4 SD on depression or pain as individual outcomes.

While the prespecified analysis was to compare groups primarily at 12 months and secondarily at intermediate time points, repeated measures analyses also were conducted on the primary depression (HSCL-20) and pain (BPI) outcomes using mixed-effects regression models. Analyses were not adjusted for multiple comparisons. This does not affect interpretation of the primary outcomes, but findings for secondary outcomes should be interpreted cautiously unless they are highly significant ($P < .001$). Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Baseline characteristics were reported and comparisons were made between the 2 treatment groups. Categorical data were reported as frequencies (percentages); and differences between groups were compared with χ^2 tests. Continuous data were reported as the mean and standard deviation (SD), and differences between groups were tested using 2-sample *t* tests.

There was no difference in the magnitude of missing data between the treatment groups. Furthermore, logistic regression models showed that intervention and control participants for whom 12-month data were missing did not differ in terms of age, sex, pain location, clinic site, depression, or pain severity. Missing outcomes during the follow-up period were imputed using the last-observation carried forward method. To assess the robustness of the analytical results under alternative imputation methods, analyses were repeated on all outcomes using multiple regression imputation as well as available data only (no imputation). Results did not differ between these 2 methods and last-observation carried forward; thus, the results from last-observation carried forward are reported because it is the most conservative imputation strategy and also allows straightforward imputation of categorical as well as continuous variables.

Using the 1-, 3-, 6-, and 12-month follow-up data, between-group differences were reported as mean (95% confidence interval [CI]) differences for continuous variables and relative risks (RRs) with 95% CIs for categorical variables.[49] For key pain and depression continuous outcomes, standardized effect sizes were calculated as the mean group difference divided by the pooled SD for the measure at baseline. For key binary outcomes, the number needed to treat (NNT) was calculated as the reciprocal of the difference in the response rates.[50]

RESULTS

Baseline Characteristics of Study Sample

As shown in TABLE 2, there were no significant baseline differences between the intervention and usual care groups. Overall, the mean age of the 250 participants was 55.5 years; 52.8% were women; 60.4% were white, 36.4% were black, and 3.2% were classified as other. Work status was 25.6% employed, 31.6% unemployed or unable to work, and 42.8% retired. The site of pain was the back in 60.4% of individuals and the hip or knee in 39.6%.

As shown in TABLE 3, intervention and usual care patients also were simi-

Table 2. Baseline Characteristics of the 250 Participants in the SCAMP Trial

	No. (%) of Participants[a]		
	Intervention Group (n = 123)	Usual Care Group (n = 127)	*P* Value
Age, mean (SD), y	55.2 (12.6)	55.8 (11.1)	.70
Female sex	69 (56)	63 (50)	.30
Race			
White	75 (61)	76 (60)	.29
Black	42 (34)	49 (39)	
Other[b]	6 (5)	2 (2)	
Education			
<High school	28 (23)	32 (25)	.65
High school degree	54 (44)	48 (38)	
Some college or trade school	41 (33)	46 (36)	
Married	48 (39)	44 (35)	.47
Employment status			
Employed	36 (29)	28 (22)	.35
Unemployed or unable to work	39 (32)	40 (31)	
Retired	48 (39)	59 (46)	
Pain location			
Back	76 (62)	75 (59)	.66
Hip or knee	47 (38)	52 (41)	
Clinical site			
Veterans Affairs	50 (41)	52 (41)	.96
University clinic	73 (59)	75 (59)	
Duration of pain, median (interquartile range), y[c]	8 (3-21)	10 (4-20)	.81
No. of medical illnesses, mean (SD)	2.7 (1.6)	2.7 (1.4)	.62
Baseline medications[d]			
Opioid analgesics	63 (52)	49 (42)	.12
Nonopioid analgesics	88 (72)	85 (72)	.99
Tricyclic antidepressants	29 (24)	16 (14)	.04
Non–tricyclic antidepressants	28 (23)	17 (14)	.09
Nonpharmacological treatments for pain	31 (25)	28 (22)	.56
Prior mental health specialist visit	51 (41)	59 (46)	.43

Abbreviation: SCAMP, Stepped Care for Affective Disorders and Musculoskeletal Pain.
[a] Unless otherwise indicated. Data may not equal 100% due to rounding.
[b] Includes 3 American Indians and 5 not specified.
[c] Middle 50% range of values (ie, difference between first and third quartiles or 25th-75th percentiles).
[d] Data were available for 122 intervention patients (99%) and 118 usual care patients (93%). These numbers were used as the denominators for calculating the proportion of patients taking various medications.

lar in terms of baseline depression and pain measures. In terms of depression diagnoses, 74.8% of the sample met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for major depression, 20.8% for dysthymia only, and 4.4% for minor depression. The mean HSCL-20 score of 1.89 (on a 0-4 scale) represents moderately severe depressive symptoms. Likewise, the mean BPI severity and interference scores of 6.15 and 6.97 (on a 0-10 scale), respectively, represent moderately severe pain. This level of disability is confirmed by a Roland disability score of 17.4 (on a 0-24 scale, in which a higher score indicates greater pain-related disability) and an SF-36 bodily pain score of 26.8 (on a 0-100 scale, in which 0 represents the worst pain-related impairment).

Clinical Outcomes

As shown in Table 3, the intervention group had significantly better HSCL-20 depression outcomes; the difference between groups at baseline and 12 months was –0.11 and –0.55, respectively. Accounting for baseline differences, this resulted in a net between-group difference of –0.44 (95% CI, –0.62 to –0.26). This equates to a standardized treatment effect size of 0.67 (0.44 divided by the pooled SD for the HSCL-20 at baseline of 0.65). FIGURE 2 illustrates the substantial intervention effect that occurred by 1 month and was sustained over the 12-month trial. The intervention group also was much more likely to experience depression response (46 of 123 intervention patients [37.4%] vs 21 of 127 usual care patients [16.5%]; RR, 2.3 [95% CI, 1.5 to 3.2]) and complete remission (22 [17.9%] vs 6 [4.7%], respectively; RR, 3.8 [95% CI, 1.6 to 7.6]) at 12 months, corresponding to a much lower number of patients with major depression (50 [40.7%] vs 87 [68.5%], respectively; RR, 0.6 [95% CI, 0.4 to 0.8]). The NNT for depression response was 1/(0.374–0.165) or 4.8 (95% CI, 3.4 to 8.3).

Table 3 also shows the effectiveness of the intervention on pain outcomes.

Table 3. Last-Observation Carried Forward Primary Depression and Pain Outcomes

	Intervention Group (n = 123)	Usual Care Group (n = 127)	Between-Group Difference or RR (95% CI)	*P* Value
Depression Outcomes				
HSCL-20 for depression, mean (SD) (range, 0-4)				
Baseline	1.83 (0.66)	1.94 (0.65)	–0.11 (–0.27 to 0.06)	.20
6-mo follow-up	1.16 (0.77)	1.64 (0.70)	–0.47 (–0.66 to –0.29)	<.001
12-mo follow-up	1.14 (0.69)	1.69 (0.74)	–0.55 (–0.73 to –0.37)	<.001
Major depressive disorder, No. (%)				
Baseline	90 (73.2)	97 (76.4)	0.9 (0.8 to 1.1)	.56
12-mo follow-up	50 (40.7)	87 (68.5)	0.6 (0.4 to 0.8)	<.001
Depression responder, No. (%)[a]				
6-mo follow-up	47 (38.2)	18 (14.2)	2.7 (1.8 to 3.8)	<.001
12-mo follow-up	46 (37.4)	21 (16.5)	2.3 (1.5 to 3.2)	<.001
Pain Outcomes				
BPI severity, mean (SD) (range, 0-10)				
Baseline	6.16 (1.76)	6.14 (1.78)	0.02 (–0.42 to 0.46)	.92
6-mo follow-up	5.24 (2.51)	5.86 (2.20)	–0.63 (–1.22 to –0.04)	.04
12-mo follow-up	5.08 (2.54)	6.03 (2.08)	–0.95 (–1.53 to –0.38)	.001
BPI interference, mean (SD) (range, 0-10)				
Baseline	6.84 (2.15)	7.09 (1.97)	–0.25 (–0.76 to 0.26)	.34
6-mo follow-up	5.05 (2.84)	6.30 (2.53)	–1.25 (–1.92 to –0.58)	<.001
12-mo follow-up	4.96 (2.75)	6.48 (2.43)	–1.52 (–2.16 to –0.87)	<.001
BPI total, mean (SD), (range, 0-10)[b]				
Baseline	6.62 (1.85)	6.77 (1.74)	–0.15 (–0.60 to 0.30)	.51
6-mo follow-up	5.04 (2.57)	6.14 (2.31)	–1.11 (–1.72 to –0.50)	<.001
12-mo follow-up	4.94 (2.54)	6.33 (2.18)	–1.39 (–1.98 to –0.80)	<.001
Pain responder, No. (%)[c]				
6-mo follow-up	47 (38.2)	22 (17.3)	2.2 (1.4 to 3.0)	<.001
12-mo follow-up	51 (41.5)	22 (17.3)	2.4 (1.6 to 3.2)	<.001
Composite Outcome				
Composite responder, No. (%)[d]				
6-mo follow-up	29 (23.6)	10 (7.9)	3.0 (1.6 to 5.1)	<.001
12-mo follow-up	32 (26.0)	10 (7.9)	3.3 (1.8 to 5.4)	<.001

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; HSCL-20, 20-item Hopkins Symptom Checklist; RR, relative risk.
[a] Defined as 50% or greater decrease in HSCL-20 from baseline.
[b] The BPI total is the average of the 11 items of the BPI for severity (4 items) and BPI for interference (7 items) scales.
[c] Defined as 30% or greater decrease in BPI total from baseline.
[d] Defined as 50% or greater decrease in HSCL-20 and 30% or greater decrease in BPI total from baseline.

The intervention group had significantly better BPI severity (net between-group difference of –0.98 [95% CI, –1.48 to –0.47]) and BPI interference (net between-group difference of –1.27 [95% CI, –1.88 to –0.66]) scores at 12 months. This represented standardized effect sizes of 0.54 for BPI severity and 0.62 for BPI interference. FIGURE 3 illustrates the significant intervention effect on BPI interference and BPI severity occurring by 1 month and sustained over the 12-month trial. Although both dimensions of pain improved significantly, the reductions in pain interference were even greater than in pain severity The intervention group also was much more likely to experience a reduction of 30% or greater in pain at 12 months (51 intervention patients [41.5%] vs 22 usual care patients [17.3%]; RR, 2.4 [95% CI, 1.6 to 3.2]). This corresponds to a NNT of 4.1 (95% CI, 3.0 to 6.5)

In terms of the trial's primary and most conservative outcome, the intervention group was significantly more likely to experience a composite response, defined a priori as a reduction of 50% or greater in depression and a reduction of 30% or greater in pain. This difference in composite response rates was significant at both 6 months (23.6% for intervention patients vs 7.9% for usual care patients; RR, 3.0 [95% CI, 1.6-5.1]) and 12 months (32 [26.0%] vs 10 [7.9%], respectively; RR, 3.3 [95% CI, 1.8-5.4]). This corresponds to a NNT of 5.5 (95% CI, 3.7-10.9). Finally, the statistical significance of the intervention effect was similar when fitting mixed-effects regression models for the repeatedly measured primary outcomes (ie, HSCL-20 depression score, BPI severity, and BPI interference).

Intervention patients were much more likely than usual care patients to report overall improvement in their pain at 6 months (61 [49.6%] vs 19 [15.0%], respectively; RR, 3.3 [95% CI, 2.2-5.2]), which was sustained at 12 months (58 [47.2%] vs 16 [12.6%]; RR, 3.7 [95% CI, 2.3-6.1]). Correspondingly, there were fewer patients in the intervention group compared with the usual care group who were worse (15 vs 44, respectively) and unchanged (50 vs 67) at 12 months. Of the 58 intervention participants whose pain was better at 12 months, 8 were a little better, 21 were somewhat or moderately better, and 29 were a lot or completely better. In contrast, only 16 usual care participants reported improved pain at 12 months, of whom 3 were a little better, 6 were somewhat or moderately better, and 7 were a lot or completely better.

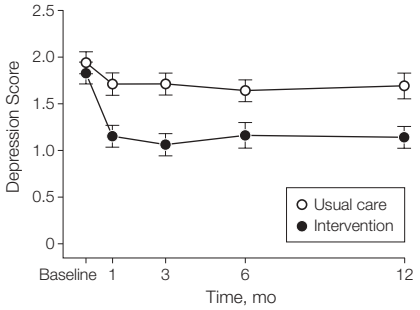
TABLE 4 compares the groups in terms of other pain and quality-of-life outcomes. The intervention group had better outcomes in terms of secondary pain measures (ie, Roland pain disability, GCPS pain scores, and SF-36 bodily pain), less severe anxiety (GAD-7 scale), and better health-related quality life (SF-36 vitality and general health perception scores).

Care Manager Contacts and Antidepressants Taken in the Intervention Group

The intervention protocol called for 5 in-person care manager contacts and 8 telephone contacts over 12 months, with extra contacts allowed depending on treatment changes or a patient's clinical needs. The mean (SD) number of in-person contacts that actually occurred was 2.5 (1.3) and the mean (SD) number of telephone contacts was 11.5 (5.1). Thus, the average intervention patient had 14 contacts over the 12-month study period, 82% of which were by telephone. The variability was due to early dropout by some intervention patients, extra contacts required for others, and substitution of telephone contacts when an in-person contact was not feasible for the patient.

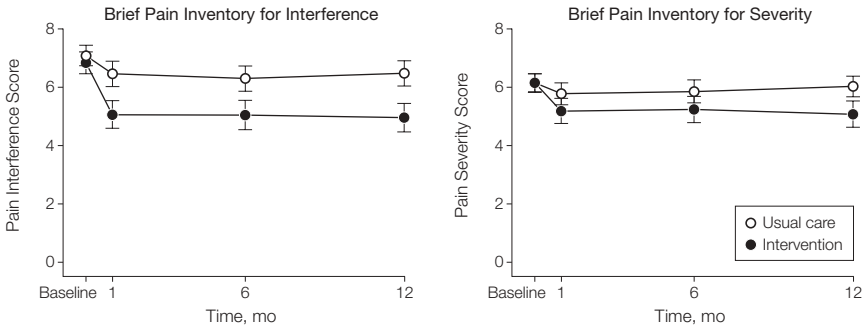
The antidepressant initiated or continued at baseline was venlafaxine in 75 of the intervention patients (61%), an SSRI in 39 patients (32%), or another antidepressant including pharmacotherapy combinations in 9 patients (7%). At 12 months, there were 26 intervention patients (21%) taking venlafaxine, 36 patients (29%) taking an SSRI, 22 patients (18%) taking other antidepressants including combinations, 16 patients (13%) not taking an antidepressant, and 23 patients (19%) for which the information was not

Figure 2. Mean 20-Item Hopkins Symptom Checklist Depression Scores



Depression scores can range from 0 to 4. Error bars indicate standard errors. All study participants were included in each time point because last-observation carried forward imputation was used.

Figure 3. Mean Brief Pain Inventory Scores for Pain Interference and Pain Severity



The Brief Pain Inventory scores can range from 0 to 10. Error bars indicate standard errors. All study participants were included in each time point because last-observation carried forward imputation was used.

known. Of the 100 intervention patients whose antidepressant status was known at 12 months, 41% had continued taking their initial antidepressant, 43% had switched to a different antidepressant (n=38) or combination pharmacotherapy (n=5), and 16% were not taking an antidepressant. Thus, at a minimum, 43 of the 123 patients (35%) in the intervention group had an antidepressant switched or added during the study. The mean dose for the 79 patients known to be receiving antidepressant monotherapy at 12 months was 147 mg for venlafaxine (n=26), 140 mg for sertraline (n=24), 295 mg for bupropion (n=10), 36 mg for mirtazapine (n=7), 27 mg for fluoxetine (n=6), 40 mg for citalopram (n=4), and 15 mg for paroxetine (n=2).

12-Month Medication and Health Care Use

TABLE 5 summarizes the antidepressant and analgesic use information as well as health care use for all intervention and usual care participants during the 12-month study period following their enrollment interview. All data were derived from the electronic medical records, except antidepressant use in the intervention participants because they were provided antidepressants free of charge as part of the study. Patients in the intervention group were taking antidepressants during the 12-month study for a much longer period compared with the usual care patients (9.2 vs 2.0 months, respectively; $P<.001$). Notably, 82 participants in the intervention group (66.7%) were taking antidepressants all 12 months of the study compared with only 6 participants in the usual care group (4.7%). Of the 52 usual care participants for whom there was electronic medical record data showing any antidepressant use, only 9 (17%) had electronic medical record evidence of an antidepressant being switched or added during their 12 months in the study. There were no significant group differences in terms of low-dose tricyclic antidepressant or opioid or non–opioid analgesic use.

Intervention participants had slightly more mental health visits (not including care manager contacts), emergency department visits, and hospital days and slightly fewer medical specialty visits. Removing extreme outli-

Table 4. Last-Observation Carried Forward Secondary Pain and Quality-of-Life Outcomes

Clinical Outcome	Mean (SD)		Between-Group Difference, Mean (95% CI)	*P* Value
	Intervention Group (n = 123)	Usual Care Group (n = 127)		
Roland Pain Disability Scale score (range, 0-24)				
Baseline	17.3 (4.5)	17.6 (4.1)	–0.3 (–1.4 to 0.8)	.57
12-mo follow-up	14.0 (6.5)	17.2 (5.3)	–3.2 (–4.7 to –1.8)	<.001
Graded Chronic Pain Scale				
Severity score (range, 0-100)				
Baseline	72.7 (17.7)	72.8 (15.4)	–0.1 (–4.2 to 4.1)	.97
12-mo follow-up	67.8 (22.8)	74.7 (17.2)	–6.9 (–12.0 to –1.9)	.007
Disability score (range, 0-100)				
Baseline	67.8 (25.0)	70.2 (24.8)	–2.4 (–8.6 to 3.8)	.45
12-mo follow-up	52.5 (31.6)	66.1 (27.3)	–13.6 (–20.9 to –6.2)	<.001
Duration of disability from pain in past 3 mo, d (range, 0-90)				
Baseline	34.9 (33.4)	38.0 (33.1)	–3.1 (–11.4 to 5.2)	.46
3-mo follow-up	33.2 (32.3)	41.5 (33.2)	–8.3 (–16.5 to –0.1)	.05
6-mo follow-up	28.2 (31.5)	31.1 (30.9)	–2.8 (–10.6 to 5.0)	.47
12-mo follow-up	31.4 (33.2)	38.1 (31.8)	–6.8 (–14.9 to 1.3)	.10
Generalized Anxiety Disorder scale score (range, 0-21)				
Baseline	8.7 (4.5)	9.1 (4.4)	–0.4 (–1.5 to 0.7)	.48
12-mo follow-up	5.8 (5.0)	8.0 (5.1)	–2.2 (–3.5 to –0.9)	<.001
Short-Form 36 (range, 0-100)				
General health perceptions score				
Baseline	33.1 (27.9)	28.4 (26.6)	4.7 (–2.1 to 11.5)	.18
12-mo follow-up	35.2 (29.7)	24.2 (25.5)	11.1 (4.2 to 18.0)	.002
Social functioning score				
Baseline	38.0 (25.2)	40.5 (26.2)	–2.5 (–8.9 to 4.0)	.45
12-mo follow-up	53.1 (30.9)	47.0 (28.5)	6.1 (–1.3 to 13.5)	.11
Bodily pain score				
Baseline	26.5 (16.0)	27.2 (14.1)	–0.7 (–4.5 to 3.0)	.70
12-mo follow-up	37.3 (21.1)	28.8 (16.9)	8.5 (3.8 to 19.1)	<.001
Vitality score				
Baseline	25.8 (16.6)	24.6 (17.3)	1.2 (–3.0 to 5.4)	.57
12-mo follow-up	36.6 (22.7)	27.8 (18.9)	8.8 (3.6 to 14.0)	.001

Abbreviation: CI, confidence interval.

ers from the analyses did not change the results. Although statistically significant, the absolute magnitude of these differences was small.

Patient-Reported Cointerventions

Participants were asked to report treatments received for pain or depression since their last interview at 3, 6, and 12 months. Patients were classified as having each type of treatment either not at all or at least once during the 12-month period. Intervention patients were slightly less likely than usual care patients to report changes in their pain medicine (52% vs 63%, respectively; $P = .02$) but did not differ significantly in their likelihood of visiting a pain clinic (34% vs 28%) or having pain-related emergency department visits (22% vs 30%), hospitalizations (10% vs 8%), x-rays (41% vs 49%), or laboratory tests (20% vs 31%; $P = .06$). There were no differences in self-reported visits to a psychiatrist, psychologist, or counselor (11% for intervention patients vs 13% usual care patients), or to specialists for pain such as physical therapists, orthopedists, rheumatologists, neurologists, or complementary medicine clinicians. Intervention and usual care participants were equally likely (50% vs 49%, respectively) to report a change in their medication for mood, nerves, or depression.

COMMENT

The SCAMP trial has several important findings. First, optimized antidepressant therapy coupled with a pain self-management program produced substantial reductions in depression severity as well as enhanced response and remission rates. Second, the intervention also resulted in moderate reductions in both pain severity and pain-related disability. Third, the benefits on both depression and pain outcomes were sustained over the 12 months of the trial, including the 6-month continuation phase.

The effect size of the SCAMP intervention on depression outcomes was similar to that seen in patient populations without chronic pain. In a systematic review of 28 randomized controlled trials of multicomponent interventions for primary care patients receiving acute phase treatment for depression, Williams et al[39] found an 18.4% median absolute increase in patients with a 50% improvement in symptoms (range, 8.3%-46%) and a median absolute increase of 16.7% (range, 10.6%-40%) in remission from depression. The median absolute increases in SCAMP were 20.9% for a 50% improvement in symptoms (ie, 37.4% in the intervention group vs 16.5% in the usual care group) and 13.2% for remission (17.9% vs 4.7%, respectively). Also, the NNT of 4.8 to achieve a treatment response for depression is similar to the NNT of 4 in a Cochrane review of antidepressants compared with placebo or no treatment in medically ill adults.[51]

Some of the reasons for improved depression outcomes in the SCAMP trial may be that intervention patients were taking antidepressants longer than usual care patients (9.2 vs 2.0 months, respectively), were more likely to be taking an antidepressant all 12 months of the study (66.7% vs 4.7%), and were more likely to have an antidepressant switched or added during the study (35% vs 17%). Continuing to take an antidepressant for at least 6 to 12 months is known to enhance depression outcomes, and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial and

Table 5. 12-Month Medication and Health Care Use

Variable	No. (%) of Patients With Any Use During 12 mo		Amount of Use During 12 mo				
			Intervention Group (n = 123)		Usual Care Group (n = 127)		
	Intervention (n = 123)	Usual Care (n = 127)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	*P* Value[a]
Medication use, mo							
Antidepressants	121 (98)	54 (43)	9.2 (4.2)	12 (0-12)	2.0 (3.3)	0 (0-12)	<.001
Tricyclics[b]	32 (26)	35 (28)	1.2 (2.7)	0 (0-12)	1.2 (2.6)	0 (0-12)	.98
Other psychotropics	20 (16)	16 (13)	0.7 (2.2)	0 (0-12)	0.7 (2.2)	0 (0-12)	.89
Opioid analgesics	67 (54)	67 (53)	3.5 (4.6)	1 (0-12)	3.0 (4.2)	1 (0-12)	.35
Other analgesics[c]	74 (60)	82 (65)	2.5 (3.1)	1 (0-12)	2.8 (3.4)	1 (0-12)	.44
Health care use, No.							
Outpatient visits							
Primary care	115 (93)	119 (94)	6.3 (5.8)	5 (0-35)	5.9 (5.3)	4 (0-33)	.16
Medical specialty	52 (42)	53 (42)	1.3 (2.3)	0 (0-16)	1.6 (2.8)	0 (0-19)	.03
Surgical specialty	77 (63)	86 (68)	2.7 (4.0)	1 (0-24)	2.4 (3.5)	1 (0-26)	.10
Mental health	31 (25)	21 (17)	1.6 (7.9)	0 (0-82)	0.7 (2.9)	0 (0-24)	<.001
Other	45 (37)	53 (42)	1.4 (3.4)	0 (0-23)	1.2 (2.4)	0 (0-18)	.16
Emergency department visits	61 (50)	59 (46)	1.8 (3.5)	0 (0-27)	1.2 (2.1)	0 (0-14)	<.001
Time in hospital, d	25 (20)	18 (14)	1.5 (5.9)	0 (0-49)	0.8 (2.5)	0 (0-15)	<.001

[a] Group differences between means while taking medication were tested using *t* test and on health care use using Poisson modeling.
[b] Typically low-dose level (<100 mg amitriptyline or equivalent) rather than antidepressant dose level.
[c] May be underestimated because simple analgesics are often obtained without a prescription and would not be captured by electronic prescribing data.

other trials have shown that an inadequate response to the initial antidepressant is not uncommon and may require a change in medication.[39,52] The assessment of antidepressant use may have been more accurate in intervention patients whose medication was provided by the nurse care manager and documented in the study logs, while antidepressant use in usual care patients depended entirely on refill information in the electronic medical record. However, it is unlikely that group differences as large as we found for antidepressant use are entirely due to ascertainment bias.

The effect size of the SCAMP intervention on pain outcomes of 0.54 for pain severity and 0.62 for pain interference was notable. Chronic pain is difficult to treat and a 30% reduction is typically judged a clinical response (as determined by patient-rated quality of life and perceptions of analgesic efficacy[53]) in contrast to the 50% reduction required for depression. Using this threshold, a clinical response in pain was much more likely in the intervention group compared with the control group (41.5% vs 17.3%, respectively, or a NNT of 4.1). Impressively, when rating overall change in pain, 47.2% of intervention patients reported improvement at 12 months compared with only 12.6% of usual care patients. Thus, the SCAMP intervention showed benefits in terms of pain severity, pain interference, and global pain improvement, which are the outcomes considered most relevant in clinical trials. It is possible that pain improvement in our trial reflected a main effect of improved mood (ie, an antidepressant effect on mood rather than an analgesic effect), and that as depression lifts, patients may experience pain as being less intense and less disabling. Conversely, it is also possible that the improvement in depression was mediated by an improvement in pain (ie, as pain improves, patients feel less depressed) or that both depression and pain lessened as a result of treatment effects on a common pathway.

The largest reductions in depression and pain were seen early (ie, during the first month of optimized antidepressant therapy) and were sustained during the remainder of the trial. Thus, the added value of the pain self-management program cannot be ascertained in the SCAMP trial. We had postulated that improvements in pain that might occur with optimized antidepressant therapy would be further enhanced with a behavioral intervention designed to improve pain coping and other self-management skills. It is possible that (without the pain self-management program) patients whose pain initially improved might have experienced a relapse. However, it is also possible that antidepressant continuation, as occurred in the SCAMP trial, is sufficient. To test whether pain self-management provides any benefits beyond optimized antidepressant therapy would require a parallel group or factorial trial design rather than the sequential approach used in the current study.

While the between-group differences (ie, treatment effect) were similar to previous depression trials,[39,54] the absolute response and remission rates in both the intervention and control groups were low compared with other depression care management studies, and closer to that seen in populations with more medical comorbidity.[22,51] Indeed, secondary analyses of 2 collaborative care interventions found that high baseline pain reduces depression improvement rates.[55,56] A secondary analysis of patients with comorbid pain in a geriatric depression trial[57] found a much more modest improvement for pain outcomes than for depression. Thus, additional interventions to co-manage pain (eg, optimized analgesic management) may be necessary to further improve response and remission rates. For example, Dobscha et al[58] recently found that a collaborative care intervention for chronic pain that included clinician education, patient education and activation, symptom monitoring, feedback and recommendations to clinicians, and facilitation of specialty care produced modest improvement in both pain and depression outcomes.

In addition to improving depression and pain outcomes, the SCAMP intervention also demonstrated benefits in terms of secondary measures such as anxiety, functional impairment, and quality of life. There was also a nonsignificant trend toward fewer pain-related disability days. Because pain and depression are among the 2 leading causes of decreased work productivity,[59,60] interventions that improve both of these symptoms as well as their adverse effect on functional status might be particularly desirable for not only the patient but also from the employer and societal perspectives.

The SCAMP trial used an antidepressant algorithm rather than a single antidepressant, and more than half of the patients discontinued or switched from their initial antidepressant by 12 months. Therefore, the superiority of one antidepressant over another in comorbid depression and pain cannot be determined. Studies to date have failed to establish differential efficacy among antidepressants in terms of depression outcomes.[21,52] For pain, tricyclic antidepressants may be somewhat more effective than SSRI antidepressants.[6,61,62] However, head-to-head comparisons are few, previous trials are short in duration, and many trials have used lower doses of tricyclic antidepressants than are normally required for an optimal effect on depression. Several SNRI antidepressants now have indications from the US Food and Drug Administration for treating neuropathic pain and fibromyalgia[7] but their efficacy in the painful conditions studied in our trial (low back pain and osteoarthritis of the hip and knee) requires further research. Also, their relative superiority compared with other antidepressants in terms of improving pain is less certain[63] and would require active comparator trials. Notably, all antidepressants used in the SCAMP trial are now available in generic formulations.

Neither data from electronic medical records nor patient self-report suggested that group differences were significantly confounded by co-interventions. The average intervention patient averaged slightly more than 1 care man-

ager contact per month over the 12-month study, with most of these (82%) occurring by telephone. Health care use was slightly higher for intervention patients in a few categories of visits, but these differences did not appear to be clinically significant. Although we did not design our study to conduct a formal cost-effectiveness analysis, the care manager contacts together with greater antidepressant use and no decrease in health care use certainly indicates there was some added cost to achieve the improved depression and pain outcomes in the intervention group. This is consistent with many other primary care trials comparing enhanced depression care with usual care.[64,65] However, a recent multicenter trial with sophisticated cost analyses found that the cost per quality-adjusted life-year for enhanced depression care compared favorably with many other medical interventions,[66] and it is possible that increased costs incurred during the first year may be recouped with cost savings in subsequent years.[67]

Our study has several limitations. First, because patients were enrolled from urban underserved and Veterans Affairs clinics, the generalizability of our results to other primary care populations needs to be demonstrated. However, adverse socioeconomic factors more prevalent in our sample tend to make treatment of depression and pain more difficult, so the substantial effects we observed are noteworthy. Second, because only one-third of eligible patients agreed to enroll, the extent to which the benefits we found are generalizable to patients not desiring participation in a trial is uncertain. Third, SCAMP is a multicomponent effectiveness trial. Therefore, to what degree benefits can be specifically attributed to the antidepressant-behavioral intervention vs the nonspecific effects of care manager contacts cannot be precisely determined. Also, the lack of blinding in an effectiveness design may inflate the benefits specifically attributable to the intervention. However, a recent literature synthesis of depression care management trials showed that, like the SCAMP study, an effectiveness trial with a usual care control group has been the most common study design.[39] Also, a number of patients in the usual care group received antidepressants, which might tend to reduce the effect size of the intervention. Importantly, the 2 treatment groups did not differ in terms of self-reported pain or depression cointerventions over the 12-month trial. Finally, there was some discordance between patient self-report and electronic medical record data in terms of medication and health care use (eg, number of mental health visits or percentage who had changes in psychotropic medication use), suggesting that the 2 methods may capture somewhat different information.

In conclusion, the SCAMP trial showed that optimized antidepressant therapy coupled with pain self-management in patients with comorbid pain and depression can produce substantial improvements in both depression and pain. At the same time, additional interventions may be needed to produce larger improvements in pain and higher depression response and remission rates. Strategies might include optimized analgesic management, cognitive behavioral therapy,[6,68] or augmentation strategies.[41] While numerous trials have shown that enhanced care for depression is equally or more cost-effective than the treatment of chronic medical illnesses, the lack of parity for mental disorders leads some payers to insist that depression care must be cost neutral or even cost saving.[64,65] A recent trial demonstrated that depression care management improved workplace as well as clinical outcomes.[69] Because pain and depression are among the leading causes of decreased work productivity, an intervention that is effective for both conditions may further strengthen a business model. Also, an intervention that allows a care manager to cover several conditions rather than a single disorder may enhance its implementation and cost-effectiveness. Given the prevalence, morbidity, disability, and costs of the pain-depression dyad, the SCAMP trial results have important implications.

Author Affiliations: Divisions of General Internal Medicine and Geriatrics (Drs Kroenke, Bair, and Damush) and Biostatistics (Mr Wu and Dr Tu), Indiana University School of Medicine, Indianapolis; VA HSR&D Center of Excellence on Implementation of Evidence-Based Practices, Roudebush VAMC, Indianapolis, Indiana (Drs Bair and Damush and Mr Hoke); Regenstrief Institute Inc, Indianapolis, Indiana (Drs Kroenke, Bair, Damush, Tu and Mr Hoke); and the Dartmouth Institute for Health Policy and Clinical Practice, Hanover, New Hampshire (Dr Sutherland).
Author Contributions: Dr Kroenke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kroenke, Bair, Damush, Sutherland.
Acquisition of data: Kroenke, Bair, Damush, Hoke.
Analysis and interpretation of data: Kroenke, Bair, Damush, Wu, Sutherland, Tu.
Drafting of the manuscript: Kroenke, Wu, Hoke.
Critical revision of the manuscript for important intellectual content: Kroenke, Bair, Damush, Wu, Sutherland, Tu.
Statistical analysis: Kroenke, Wu, Sutherland, Tu.
Obtained funding: Kroenke.
Administrative, technical, or material support: Kroenke, Bair, Damush, Hoke.
Study supervision: Kroenke, Bair, Damush, Hoke.
Financial Disclosures: Dr Kroenke reported receiving research funding from Eli Lilly, Pfizer, and Wyeth, and honoraria as a speaker, consultant, or advisory board member from Eli Lilly, Pfizer, Wyeth, Astra-Zeneca, and Forest Laboratories. Dr Bair reported receiving one-time consultant fees from Wyeth, Abbott, and Cephalon. No other authors reported financial disclosures.
Funding/Support: This study was supported by grant R01 MH-071268 (awarded to Dr Kroenke) from the National Institute of Mental Health.
Role of the Sponsor: The sponsor provided financial support for the study only and had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the study; or in the preparation, review, or approval of the manuscript.
Additional Contributions: We gratefully acknowledge the care management provided by Carol Kempf, RN, and Gloria Nicholas, RN, and the research assistance provided by Monica Huffman, BA. The individuals listed above were compensated as study personnel for these services. We also thank Erin Krebs, MD (Roudebush VA employee; uncompensated for her role in the study) for consultation on the analysis and in the manuscript preparation.

REFERENCES

1. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res*. 2003; 12(1):34-43.
2. Spitzer RL, Kroenke K, Linzer M, et al. Health-related quality of life in primary care patients with mental disorders: results from the PRIME-MD 1000 study. *JAMA*. 1995;274(19):1511-1517.
3. Schappert SM. National Ambulatory Medical Care Survey: 1989 summary. *Vital Health Stat 13*. 1992; 13(110):10-11.
4. Sternbach RA. Survey of pain in the United States: the Nuprin Pain Report. *Clin J Pain*. 1986;2:49-53.
5. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433-2445.
6. Jackson JL, O'Malley PG, Kroenke K. Antidepressants and cognitive-behavioral therapy for symptom syndromes. *CNS Spectr*. 2006;11(3):212-222.
7. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *Gen Hosp Psychiatry*. In press.

8. Lorig K. Self-management education: more than a nice extra. *Med Care*. 2003;41(6):699-701.
9. Von Korff M, Moore JC. Stepped care for back pain: activating approaches for primary care. *Ann Intern Med*. 2001;134(9 pt 2):911-917.
10. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med*. 2003;26(1):1-7.
11. Damush TM, Weinberger M, Perkins SM, et al. Randomized trial of a self-management program for primary care patients with acute low back pain: short-term effects. *Arthritis Rheum*. 2003;49(2):179-186.
12. Pariser D, O'Hanlon A. Effects of telephone intervention on arthritis self-efficacy, depression, pain, and fatigue in older adults with arthritis. *J Geriatr Phys Ther*. 2005;28(3):67-73.
13. Warsi A, LaValley MP, Wang PS, Avorn J, Solomon DH. Arthritis self-management education programs: a meta-analysis of the effect on pain and disability. *Arthritis Rheum*. 2003;48(8):2207-2213.
14. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med*. 2005;143(6):427-438.
15. Newman S, Steed L, Mulligan K. Self-management interventions for chronic illness. *Lancet*. 2004;364(9444):1523-1537.
16. Holman HR, Lorig K. Self-management education for osteoarthritis. *Ann Intern Med*. 2006;144(8):617.
17. Kroenke K, Bair M, Damush T, et al. Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study design and practical implications of an intervention for comorbid pain and depression. *Gen Hosp Psychiatry*. 2007;29(6):506-517.
18. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. *Advances in Pain Research and Therapy, Volume 12: Issues in Pain Measurement.* New York, NY: Raven Press; 1989:391-403.
19. Williams LS, Jones WJ, Shen J, Robinson RL, Weinberger M, Kroenke K. Prevalence and impact of depression and pain in neurology outpatients. *J Neurol Neurosurg Psychiatry*. 2003;74(11):1587-1589.
20. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
21. Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. *JAMA*. 2001;286(23):2947-2955.
22. Unützer J, Katon W, Callahan CM, et al; IMPACT Investigators. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA*. 2002;288(22):2836-2845.
23. Dietrich AJ, Oxman TE, Williams JW Jr, et al. Re-engineering systems for the treatment of depression in primary care: cluster randomised controlled trial. *BMJ*. 2004;329(7466):602-605.
24. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: the PRIME-MD 1000 study. *JAMA*. 1994;272(22):1749-1756.
25. Löwe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the Patient Health Questionnaire-9. *Med Care*. 2004;42(12):1194-1201.
26. Katon W, Von Korff M, Lin E, et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. *Arch Gen Psychiatry*. 1999;56(12):1109-1115.
27. Williams JW Jr, Barrett J, Oxman T, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA*. 2000;284(12):1519-1526.
28. Dworkin RH, Turk DC, Farrar JT, et al; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19.
29. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med*. 1994;330(9):592-596.
30. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133-149.
31. Roland M, Morris R. A study of the natural history of back pain, part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine*. 1983;8(2):141-144.
32. Jensen MP, Strom SE, Turner JA, Romano JM. Validity of the Sickness Impact Profile Roland scale as a measure of dysfunction in chronic pain patients. *Pain*. 1992;50(2):157-162.
33. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36), II: psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993;31(3):247-263.
34. Ware JE Jr, Gandek B; IQOLA Project Group. The SF-36 Health Survey: development and use in mental health research and the IQOLA Project. *Int J Ment Health*. 1994;23(2)):49-73.
35. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav*. 1997;38(1):21-37.
36. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.
37. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med*. 2007;146(5):317-325.
38. Cintron A, Morrison RS. Pain and ethnicity in the United States: a systematic review. *J Palliat Med*. 2006;9(6):1454-1473.
39. Williams JW Jr, Gerrity M, Holsinger T, Dobscha S, Gaynes B, Dietrich A. Systematic review of multifaceted interventions to improve depression care. *Gen Hosp Psychiatry*. 2007;29(2):91-116.
40. Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231-1242.
41. Trivedi MH, Fava M, Wisniewski SR, et al; STAR*D Study Team. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1243-1252.
42. Kroenke K, Spitzer RL. The PHQ-9: a new depression and diagnostic severity measure. *Psychiatr Ann*. 2002;32(9):509-515.
43. Lorig K, Holman H. Arthritis self-management studies: a twelve-year review. *Health Educ Q*. 1993;20(1):17-28.
44. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Englewood Cliffs, NJ: Prentice Hall; 1986.
45. Damush TM, Weinberger M, Perkins SM, et al. The long-term effects of a self-management program for inner-city, primary care patients with acute low back pain. *Arch Intern Med*. 2003;163(21):2632-2638.
46. Damush TM, Weinberger M, Clark DO, et al. Acute low back pain self-management intervention for urban primary care patients: rationale, design, and predictors of participation. *Arthritis Rheum*. 2002;47(4):372-379.
47. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA*. 2003;289(23):3152-3160.
48. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121.
49. Zhang J, Yu KF. What's the relative risk? a method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280:1690-1691.
50. Herbert RD. How to estimate treatment effects from reports of clinical trials, II: dichotomous outcomes. *Aust J Physiother*. 2000;46(4):309-313.
51. Gill D, Hatcher S. Antidepressants for depression in medical illness. *Cochrane Database Syst Rev*. 2000;(4):CD001312.
52. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
53. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88(3):287-294.
54. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med*. 2006;166(21):2314-2321.
55. Thielke SM, Fan MY, Sullivan M, Unutzer J. Pain limits the effectiveness of collaborative care for depression. *Am J Geriatr Psychiatry*. 2007;15(8):699-707.
56. Kroenke K, Shen J, Oxman TE, Williams JW Jr, Dietrich AJ. Impact of pain on the outcomes of depression treatment: results from the RESPECT trial. *Pain*. 2008;134(1-2):209-215.
57. Lin EH, Katon W, Von Korff M, et al; IMPACT Investigators. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA*. 2003;290(18):2428-2429.
58. Dobscha SK, Corson K, Perrin NA, et al. Collaborative care for chronic pain in primary care: a clustered randomized trial. *JAMA*. 2009;301(12):1242-1252.
59. Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among US workers with depression. *JAMA*. 2003;289(23):3135-3144.
60. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290(18):2443-2454.
61. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med*. 1997;12(6):384-389.
62. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci*. 2001;26(1):30-36.
63. Krebs EE, Gaynes BN, Gartlehner G, et al. Treating the physical symptoms of depression with second-generation antidepressants: a systematic review and meta-analysis. *Psychosomatics*. 2008;49(3):191-198.
64. Rubenstein LV. Improving care for depression: there's no free lunch. *Ann Intern Med*. 2006;145(7):544-546.
65. Callahan CM. Depression in primary care: encouragement and caution for the business case. *J Gen Intern Med*. 2006;21(10):1125-1127.
66. Katon WJ, Schoenbaum M, Fan MY, et al. Cost-effectiveness of improving primary care treatment of late-life depression. *Arch Gen Psychiatry*. 2005;62(12):1313-1320.
67. Unutzer J, Katon WJ, Fan MY, et al. Long-term cost effects of collaborative care for late-life depression. *Am J Manag Care*. 2008;14(2):95-100.
68. Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. *Psychother Psychosom*. 2000;69(4):205-215.
69. Wang PS, Simon GE, Avorn J, et al. Telephone screening, outreach, and care management for depressed workers and impact on clinical and work productivity outcomes: a randomized controlled trial. *JAMA*. 2007;298(12):1401-1411.

