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## Association of Depression and Anxiety Alone and in Combination with Chronic Musculoskeletal Pain in Primary Care Patients

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### Abstract

**OBJECTIVE**—To assess the relationship between depression and anxiety comorbidity on pain intensity, pain-related disability, and health-related quality of life (HRQL).

**METHODS**—Analysis of baseline data from the Stepped Care for Affective disorders and Musculoskeletal Pain (SCAMP) Study. All patients (N = 500) had chronic pain ( $\geq 3$  months duration) of the low back, hip or knee. Patients with depression were over-sampled for the clinical trial component of SCAMP and thus represented 50% of the study population. Patients were categorized according to pain comorbid with depression, anxiety, or both. We used ANOVA and MANOVA models to assess relationships between independent and dependent variables.

**RESULTS**—Participants had a mean age of 59 years; were 55% women, 56% white and 40% black. Fifty-four percent (n=271) reported pain only, 20% (n=98) had pain and depression, 3% (n=15) had pain and anxiety, and 23% (n=116) had pain, depression, and anxiety. Patients with pain and both depression and anxiety experienced the greatest pain severity ( $p < .0001$ ) and pain-related disability ( $p < .0001$ ). Psychiatric comorbidity was strongly associated with disability days in the past 3 months ( $p < .0001$ ), with 18.1 days reported by patients with pain only, 32.2 days by those with pain and anxiety, 38.0 days by those with pain and depression, and 42.6 days in those with all three conditions. We found a similar pattern of poorer HRQL ( $p < .0001$ ) in those with pain, depression, and anxiety.

**CONCLUSIONS**—The added morbidity of depression and anxiety with chronic pain is strongly associated with more severe pain, greater disability, and poorer HRQL.

### Keywords

chronic pain; depression; anxiety; comorbidity; outcomes; primary care

## INTRODUCTION

Pain is a significant public health problem, with a third (1) to more than half (2) of adults in population-based surveys suffering from chronic or recurrent pain. Pain is the most pervasive symptom reported in the community and primary care setting (3–5) and accounts for nearly 20% of all ambulatory visits in the US (6). Pain costs an estimated \$100 billion each year in health care and lost productivity (7). Chronic pain is one of the most common reasons for temporary and permanent work disability (8) and is frequently accompanied by psychiatric comorbidity (e.g. depressive and anxiety disorders) (9). Depression and anxiety symptoms often present together with chronic pain in primary care.

Depression is one of the most common mental health problems in the general medical setting (10,11); present in 10% to 15% of patients. Depression produces substantial disability and decrements in health-related quality of life, often exceeding the impairment seen in patients with chronic medical disorders such as heart disease, diabetes, arthritis, and low back pain (12). Major depression is the fourth leading cause of disease burden worldwide and projected to move into second place by 2020 (13). Depression costs an estimated \$83 billion annually in the US (14), of which more than half represents lost work productivity (15). Anxiety disorders afflict more than 30 million Americans in their lifetime (16), and cost the US an estimated \$42 billion dollars per year in direct and indirect costs (17). Anxiety disorders often impair work, social, and physical functioning (18). Anxiety and depression frequently co-exist; complicating management and adding to health care utilization and costs (19).

The linkage between chronic pain and its affective components (i.e. depression and anxiety) has been known since the ancient Greeks (20). Recent reviews report a 30 to 60% co-occurrence rate for pain and depression (9,21). McWilliams et al. found in a nationally representative sample that anxiety disorder was present in 35% of persons with chronic pain versus 18% of the general population (22). Additionally, studies have shown that anxiety and depression frequently coexist in patients with chronic pain (23,24). Pain, depression, and anxiety symptoms often overlap in general medical inpatients (25). Among 1,000 enrollees of a large health maintenance organization, those with at least one pain condition had more depression and anxiety symptoms than persons without a pain condition (26).

Research has provided evidence of a central pain modulation system that can either dampen or amplify nociceptive signals from the periphery (27). Both serotonin and norepinephrine may dampen peripheral pain signals. This may explain how depression and anxiety, which are associated with dysregulation of these modulating neurotransmitters along shared neuroanatomical pathways, may contribute to the frequent presence of painful symptoms. Thus the decrease or dysregulation in one or both of these neurotransmitters may increase peripheral pain signals and affect how antidepressants that increase these neurotransmitters reduce pain signals (28).

While the link between chronic pain, depression, and anxiety has been established, less is known how having all three disorders concurrently may adversely impact pain outcomes. Therefore, we sought to assess the association of depression and anxiety comorbidity with pain intensity, pain-related disability, and health-related quality of life (HRQL). We hypothesized that individuals with the triad of chronic pain, depression, and anxiety would have poorer pain outcomes, compared to individuals with either chronic pain and depression or chronic pain and anxiety. In other words, those with all three conditions (pain, depression, and anxiety) would be associated with more intense pain, greater pain interference, more functional limitations, more days “disabled” because of pain, and greater decrements in HRQL.

## METHODS

### Study Design and Sample

We analyzed baseline data from the Stepped Care for Affective disorders and Musculoskeletal Pain (SCAMP) Study, a randomized clinical trial conducted in parallel with a prospective cohort study. The SCAMP Study design, key hypotheses, intervention details, and sampling frame have been described elsewhere (29). In brief, SCAMP was designed to test the effectiveness of a stepped care approach using a combined medication-behavioral intervention for primary care patients with chronic musculoskeletal pain and depression. More specifically, the intervention consisted of 12 weeks of optimized antidepressant therapy (Step 1); followed by a 6-session pain self-management (PSM) program (Step 2) delivered over 12 additional weeks. Nurse care managers (supervised by two study physicians) delivered all aspects of the intervention.

The study sample consisted of 500 adult patients with musculoskeletal pain of the low back, hip, or knee. For inclusion, patients' musculoskeletal pain had to be: 1) persistent for 3 months or longer despite conventional analgesic treatment (i.e. prior use of at least two different analgesics); 2) of at least moderate severity, defined as a Brief Pain Inventory score of 5 or greater (30,31). Those who had both back and hip or knee pain were asked which pain was most bothersome.

In addition to chronic musculoskeletal pain, one-half ( $n = 250$ ) of the patients enrolled met criteria for comorbid clinical depression at baseline. Clinical depression was defined as a Patient Health Questionnaire-9 (PHQ-9) score  $\geq 10$  and endorsement of the cardinal symptoms of depressed mood and/or anhedonia. PHQ-9 scores  $\geq 10$  equate to at least moderately severe depression. Kroenke et al. have demonstrated that more than 90% of patients fulfilling this PHQ-9 criterion have major depression and/or dysthymia, and the remaining patients have clinically significant depression with substantial functional impairment (32,33).

Excluded individuals were those who: 1) did not speak English; 2) had moderately severe cognitive impairment as defined by a validated 6-item cognitive screener (34); 3) had bipolar disorder or schizophrenia; 4) had a current disability claim being adjudicated for pain; 5) had a positive screen for alcohol or drug dependence (i.e. tried to cut down on substance use in the past year); 6) currently pregnant or planning to become pregnant during the 12 months of the study; and 7) had an anticipated life expectancy  $\leq 12$  months according to their primary care provider's judgment.

Study participants were enrolled from several sites across two health care systems in Indianapolis, Indiana. One site consisted of the Indiana University (IU) Medical Group Primary Care clinics and the other site was the Richard L. Roudebush Veterans Administration (VA) Medical Center general medicine clinics. Recruitment occurred from December 2005 until June 2007. Participants were identified through the computerized medical record system using *International Statistical Classification of Diseases and Related Health Problems (ICD-9)* diagnoses of low back pain, osteoarthritis, knee pain, hip pain, or leg pain and had at least one primary care visit within the preceding 12 months. Enrollment occurred either during scheduled clinic visits or telephone contact 2 weeks following a mailed study letter.

A research assistant obtained informed consent and conducted the baseline interview and administered all the outcome measures to participants by phone or face-to-face. Patients were compensated \$25 each for the baseline and subsequent follow-up telephone assessments. The Institutional Review Boards of Indiana University and the Research and Development Committee of Roudebush VA Medical Center approved the study. All participants provided informed consent.

## Study Outcomes

The current study was a cross-sectional analysis of baseline data from SCAMP. Our analysis was guided by the biopsychosocial model of pain that contends that a more complete understanding of a patient's pain experience must take into account not only biological (i.e. physical aspects of pain), but also psychological (i.e. mental, emotional, and behavioral aspects of pain), and social factors (i.e. interactions with other people) (35). These factors often interact over time to exacerbate and maintain levels of pain and subsequent disability. We examined the association of psychological factors (depression and anxiety) on pain outcomes.

Pain severity and pain interference were our dependent variables and depression and anxiety symptoms were the main independent variables. We assessed pain outcomes with the Brief Pain Inventory (BPI)-Short Form, an 11-item multidimensional pain scale with demonstrated reliability in patients with cancer, and non-malignant chronic pain such as arthritis and other painful conditions (30,36,37). The BPI rates the intensity of pain as well as the interference of pain. Pain severity is the average of 4 items asking about worst, least, and average pain in the past week, and current pain. These items are scored from 0 (no pain) to 10 (worst imaginable pain). Pain interference is the average of 7 items (0 to 10 scale where 10 reflects "completely interferes") assessing the degree to which pain interferes with mood, physical activity, work, social activity, relations with others, sleep, enjoyment of life.

Secondary study outcomes included functional limitations, disability days, and health-related quality of life (HRQL). We assessed functional limitations with the Roland Disability Scale, a 24-item pain-specific measure of physical limitations validated in patients with back pain (38) and nonmalignant pain problems (39). A single item from the Graded Chronic Pain Scale (40) was used to assess disability days in the last 3 months. The item asks respondents: "About how many days in the last three months have you been kept from your usual activities (work, school or housework) because of pain?" HRQL was assessed by several subscales of the SF-36 (41,42), including social functioning, vitality, and general health perceptions.

## Independent variables

Our primary independent variables were depression and anxiety symptoms. Depression severity was assessed by the Symptom Checklist 20 (SCL-20), a modified subscale of the Hopkins Symptom Checklist and Brief Symptom Inventory. This scale has been used extensively to assess depression outcomes in primary care trials (43,44). The 20 items are scored and averaged to provide a measure of overall depression severity from 0 to 4, with higher scores representing more severe depression. Patients with clinical depression were defined by a SCL-20 score greater than 1.3: a cut point that has been used in previous primary care depression studies (45,46). Anxiety was assessed by the GAD-7, a screening and severity measure validated for the most common anxiety disorders in primary care: generalized anxiety, panic, social anxiety, and posttraumatic stress disorder (47,48). Higher scores on the GAD-7 represent more severe anxiety symptoms. Clinical anxiety was defined at a GAD-7 score greater than 10; a cut point validated in previous studies (47,48).

## Covariates

Covariates included: age (analyzed as a continuous variable); sex (male or female); race/ethnicity (black or white/other); education (less than or equal to high school vs. high school or above), employment (employed or unemployed/disabled or retired); marital status (married or not married), pain location (back or knee/hip), study site (University or VA), and medical comorbidity (presence or absence of 9 common medical conditions scored from 0 to 9). Medical comorbidity was assessed using a previously validated checklist shown to predict hospitalization, costs, and mortality (49).

## Analysis

For comparison, four clinically defined groups were formed according to the presence or absence of pain, depression, and/or anxiety. The four groups were: *pain only*--P (neither depression nor anxiety), *pain and depression*--PD (no anxiety), *pain and anxiety*--PA (no depression), and all three conditions: *pain, depression, and anxiety*--PDA. The mean and standard deviation were estimated for continuous variables, while frequencies and percentages were used to describe categorical variables. An analysis of variance (ANOVA) model was used to assess the relationship between our dichotomized independent (i.e. depression and/or anxiety) and dependent variables (i.e. pain intensity, pain interference, functional limitations, disability days, and HRQL). These bivariate analyses were adjusted for demographic characteristics, medical comorbidity, pain location, and study site. Pair-wise comparisons were conducted across groups

Multivariate analysis of variance (MANOVA) was used to model BPI pain severity and pain interference simultaneously because of their moderate correlation with one another coupled with the fact they measure related but nonetheless distinct and important dimensions of pain. The independent variables, depression and anxiety, were included in the model as continuous measures. We controlled for age, sex, race/ethnicity, education, employment, marital status, medical comorbidity, pain location, and study site. From this model, beta-coefficients and their 95% confidence intervals (CI) were estimated. Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC). All hypothesis testing was conducted at the .05 significance level (two-tailed).

## RESULTS

### Overall Sample Characteristics

Overall, the sample (N = 500) was 55% women with a mean age of 59 years, and a racial distribution of 56% white, 40% black, and 4% other. Participants' work status was 25% employed, 41% unemployed or unable to work, and 34% retired. Pain location was about equally distributed between back (53%) and hip or knee (47%). About two-thirds of the subjects were enrolled from the University primary care clinics and about one-third from the VA clinics. The 250 participants with clinical depression at baseline had a mean SCL-20 score of 1.9, representing a moderately severe level of depression. Nearly all of these clinically depressed participants met the criteria for major depression (76.3%) or dysthymia (18.4%), while 5.3% met criteria for minor depression.

### Characteristics by Clinically Defined Groups

As shown in Table 1 patients in the PDA group were younger ( $P < .001$ ), less educated ( $P = 0.018$ ), and more likely to be retired and unemployed ( $P < .0001$ ) compared to the other three groups. Furthermore, there was a trend for the PDA group to be more likely female ( $P = 0.05$ ) and married ( $P = .05$ ). There was no association between group status and race.

### Pain outcomes across clinically defined groups

As shown in Figure 1, the P group had the least pain severity and interference, the PDA group had the greatest severity, and the PD and PA groups had intermediate severity. Notably, depression and anxiety were strongly associated with the number of pain-related disability days in the past 3 months ( $P < .0001$ ) with the mean being 18.1 days in the P group, 32.2 days in the PA group, 38.0 days in the PD group, and 42.6 days in the PDA group. This association between psychiatric comorbidity and pain-related functional limitations was corroborated by Roland disability scores of 12.6, 15.1, 17.9, and 18.3 in the P, PA, PD, and PDA groups, respectively, consistent with moderate to severe limitations

We found similar associations ( $P < .0001$ ) across the groups in terms of worse scores on several other pain measures that assessed pain self-efficacy, fear of movement, and coping attitudes. Figure 2 shows a similar pattern regarding an association with poorer function on multiple domains of HRQL, including social functioning, vitality, and mental health.

### Relationship between psychiatric comorbidity and pain using MANOVA

Table 2 displays the results from the MANOVA model testing the relationship of depression and anxiety, individually and in combination, with pain severity and pain interference. We controlled for demographics, pain location, clinic site, and medical comorbidity. This model explained 25% and 48% of the variance, for pain severity and pain interference, respectively. Consistent with our hypothesis, the interaction between depression and anxiety was associated with greater pain severity and pain interference ( $F$  value = 5.88,  $df = 2, 482$ ;  $P = 0.003$ ). Other factors significantly associated with greater pain severity and pain interference included: lower educational attainment, being unemployed, and University clinic site. The location of pain was not significantly related to pain intensity and interference. In pair-wise comparisons among the 4 groups, the PDA group had significantly worse pain severity than the other 3 groups. Also, both the PDA and PD groups had significantly worse pain interference than the PA and P groups.

## DISCUSSION

Our study demonstrates that the added morbidity of both depression and anxiety with chronic musculoskeletal pain is strongly associated with more severe pain and greater pain interference with daily activities than those with pain only, pain and depression, or those with pain and anxiety. Depression and anxiety were also associated with adverse main and interactional effects on the number of disability days in the last 3 months and multiple domains of health-related quality of life (HRQL).

This study extends our understanding of how depression and anxiety influence pain severity and pain interference. Patients with co-existing pain, depression, and anxiety experienced more severe pain (1.25 points more on a 0 to 10 scale) and greater pain interference with activities (2.8-points more on a 0 to 10 scale) compared to patients with pain only. The magnitude of these differences equate to moderate (BPI pain severity score = 5.3) to moderately-severe (BPI pain severity score = 6.6) pain levels and from moderate to severe interference with daily activities. Patients with either pain and depression (PD) or pain and anxiety (PA) experienced more severe pain than those with pain only (P), but less pain than those with all three conditions (pain, depression, and anxiety—PDA).

We also found an association that musculoskeletal pain is much more disabling when depression and anxiety were both present (i.e. PDA group). Patients with pain only reported 18.1 disability days in the past 3-months, while those with PA and PD reported 32.2 and 38.0 disability days, respectively. Those in the PDA group reported more than twice the number of disability days (i.e. 42.6 days) from their pain compared to those without any concurrent clinical depression or anxiety. Furthermore, among those with PDA, SF-20 domain scores (vitality, general health perception, social functioning) were significantly lower (i.e. worse quality of life) compared to those patients with pain and depression, pain and anxiety, or pain only.

Several studies and reviews have assessed the impact of depression on pain outcomes. They have established that concurrent depression and pain have a much greater impact than either disorder alone (9,21). In patients with pain, depression is associated with more pain sites, greater pain intensity, longer duration of pain, and greater likelihood of poor treatment response (9). Previous studies have also shown that comorbid depression and pain are associated with additive impairments in social and work function as well as other functional limitations. The

reciprocal relationship between pain and depression has been documented. Williams et al. (31) found that 25% of patients in a neurology clinic setting had comorbid pain and depression at baseline. At 12-month follow-up, depression and pain persisted in the majority of patients afflicted at baseline. The strongest independent predictor of pain severity at follow-up was the severity of depression at baseline and the degree of depression improvement over time. Likewise, the strongest predictor of depression severity at follow-up was baseline pain severity and the degree of pain improvement over time.

While the deleterious impact of depression on pain is well known, much less is known regarding the association between anxiety and pain. However, the limited evidence suggests a strong reciprocal relationship between anxiety and pain and that the overlap between the two conditions is common (50). Anxiety disorders may be present in up to 60% of patients with chronic pain (51). Varni et al. found that more severe chronic pain was associated with more severe anxiety symptoms (52). Ferguson and Ahles have shown that the presence of anxiety leads to more frequent reports of pain (53).

To our knowledge this is the only study that has assessed the individual as well as combined effects of depression and anxiety on pain outcomes. Our results are consistent with and extend the findings seen in a previous primary care study by Spitzer et al. (54) In 2740 primary care patients, depression and anxiety frequently overlapped and were associated with independent and additive impairments of patients' ability to perform important daily activities. As seen in this study, those with both depression and pain had the most significant decrements in quality of life as assessed by the SF-20.

Our understanding of the triadic relationship between pain, depression, and anxiety is far from complete. Biologic explanations point towards the shared neurobiology and neuroanatomical pathways common to these conditions. Relevant and contributory (as least partly) to the development of pain, depression, and anxiety are the monoamines (i.e. serotonin and norepinephrine), gamma-amino-butyric-acid (GABA), glutamate, adenosine, cannabinoids, and many other neuropeptides (50). Neuroimaging studies using functional MRI of subjects with chronic pain and depression (or anxiety) have shown common areas of brain activation (55) suggesting relevant pathways between these conditions (55–57). Activation of the sympathetic nervous system, involvement of the hypothalamic-pituitary-axis, and down-regulation of benzodiazepine receptors in the frontal cortex are additional mechanisms that may at least partially explain the link between pain, depression, and anxiety (50).

Psychological mechanisms have also been proposed to explain the relationship between pain, depression, and anxiety. Catastrophizing and hypervigilance may mediate the relationship between all three conditions and lead to amplification of physical and psychological symptoms. As a result, a person's perception of pain may be heightened in the context of depression and anxiety (20). Picavet et al. have found that kinesiophobia or the fear of exacerbating pain by movement and pain catastrophizing predict more severe pain and disability in patients with chronic low back pain (58).

The relationship between pain, depression, and anxiety extends to the area of treatment, since similar approaches are used to treat these conditions. Tricyclic antidepressants and the serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine and duloxetine) have been found to be effective in the context of chronic pain and depression (9,59) and when depression and anxiety overlap (60). Anticonvulsants such as gabapentin and pregabalin have also shown promise as co-analgesics that may also improve a patient's affective state (61). Psychological treatments, especially cognitive behavior therapy have strong evidence for its effectiveness for pain and depression (62–64) by providing behaviors and coping skills to minimize symptoms. A variety of behavioral and cognitive approaches have been studied for chronic pain and

anxiety. These include breathing control, muscle relaxation, exposure in vivo, attention-diversion, desensitization, and hypnosis (50,64).

Because SCAMP oversampled patients with depression, the group with pain and anxiety only was quite small. Therefore, the trend we found towards an independent effect of anxiety would require further testing in a larger sample of pain patients with anxiety but not depression. Similar to another primary care study (65), we found that depression and anxiety commonly co-existed. Mergl et al. (65) suggest that the independent constructs of depression and anxiety may be artificial and are “variations of a common theme.” Depression and anxiety may be partial representations of a common underlying pathology, involving genetic predisposition to these conditions. Of note, one previous study did suggest that the association between anxiety and pain is independent of depression (66). Our findings regarding an interaction between depression and anxiety on pain outcomes are stronger due to the large group of patients with combined depression and anxiety.

Our study has several limitations. First, the cross-sectional nature of the analyses limits causal inferences regarding the relationship between depression, anxiety, and pain outcomes. However, the study findings are consistent with the current literature and suggest that the relationship between pain, depression, and anxiety is robust. Second, the number of patients with pain plus anxiety was small ( $n = 15$ ) limiting the ability to draw conclusions about this group relative to the other clinical subgroups. Third, depression and anxiety was assessed with self-report measures rather than standardized clinical interviews to diagnose specific mental disorders. However, the SCL-20 and GAD-7 are well-validated measures of depressive and anxiety symptom severity, respectively. Fourth, since SCAMP was conducted among two health care systems at a single academic medical center, the generalizability of our findings needs to be confirmed in other settings.

Nonetheless, our study demonstrates several important findings that increase our understanding of the burden of depression and anxiety among primary care patients with musculoskeletal pain. This increased understanding is particularly important given that depression and anxiety are the two most common mental health problems seen in the primary care setting (67), often co-occur, and are frequently under-recognized and under-treated (68). Both produce substantial disability and decrements in health-related quality of life, often exceeding the impairment seen in patients with chronic medical disorders (69,70).

In summary, among primary care patients with chronic musculoskeletal pain, depression and anxiety have independent as well as additive adverse effects on pain severity, pain interference, functional limitations, disability days, and HRQL. The clinical implications of the relationship between pain, depression, and anxiety are noteworthy. Sullivan et al. (71) found that depression, anxiety, and drug abuse predicted the initiation and ongoing regular use of opioid analgesics in patients with chronic pain. Linton (72) has suggested that psychological factors such as depression and anxiety are more strongly associated with adverse pain outcomes than clinical factors (e.g. radiographic findings). Because depression and anxiety further complicate the management of patients with pain and are associated with poorer outcomes, future studies are needed to test integrated and comprehensive approaches to the assessment and treatment of these common conditions (73,74).

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## ACRONYMS

ANOVA	Analysis of variance
BPI	Brief Pain Inventory
CI	Confidence interval
GABA	gamma-amino-butyric-acid, GAD-7, Generalized Anxiety Disorder 7-item scale
HRQL	Health-related quality of life
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9 <sup>th</sup> edition
IU	Indiana University
MANOVA	Multivariate analysis of variance
MRI	Magnetic Resonance Imaging
PA	Pain and anxiety
PD	Pain and depression
PDA	Pain, depression, and anxiety
PHQ-9	Patient Health Questionnaire-9
PO	Pain only
SCAMP	Stepped Care for Affective Disorders and Musculoskeletal Pain
SCL-20	Hopkins Symptom Checklist-20
SF-36	Medical Outcomes Study Short Form-36
VA	Veterans Affairs

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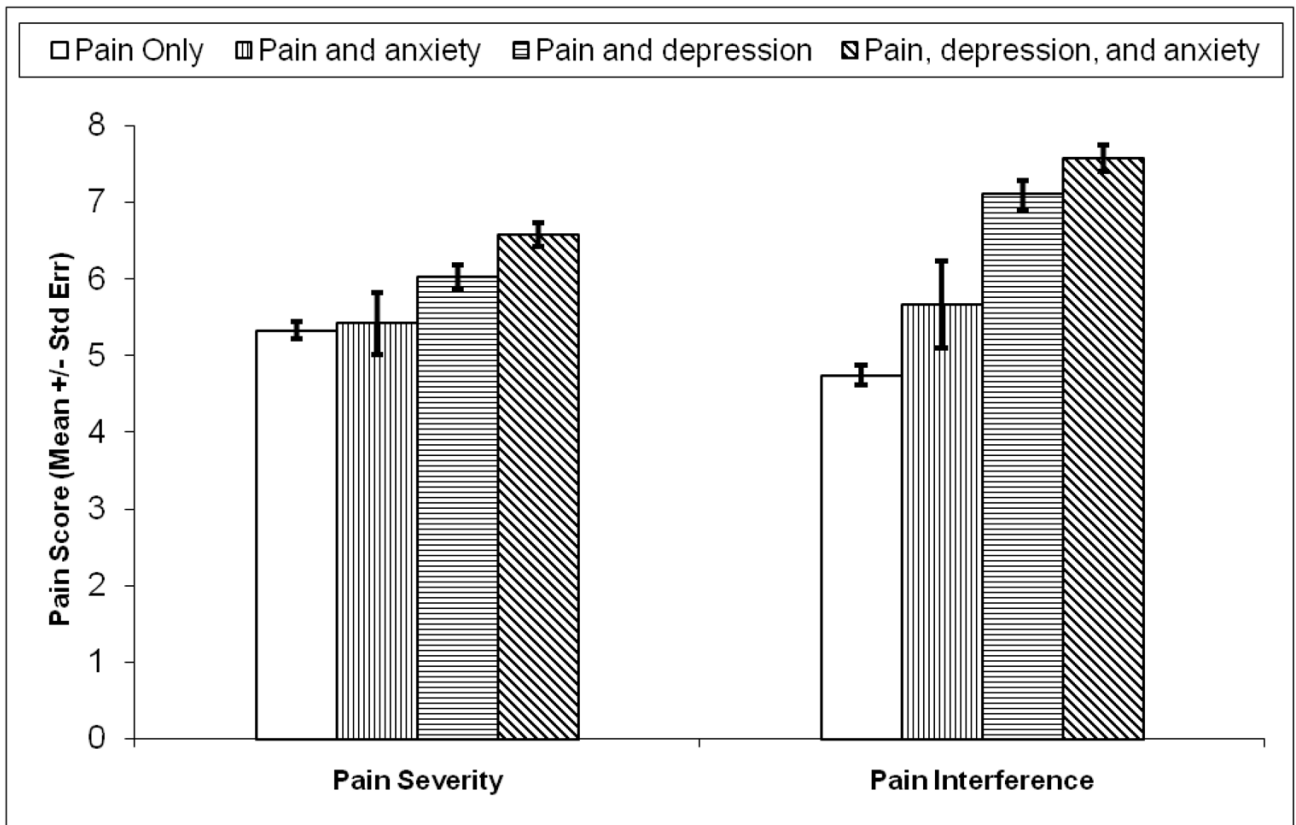
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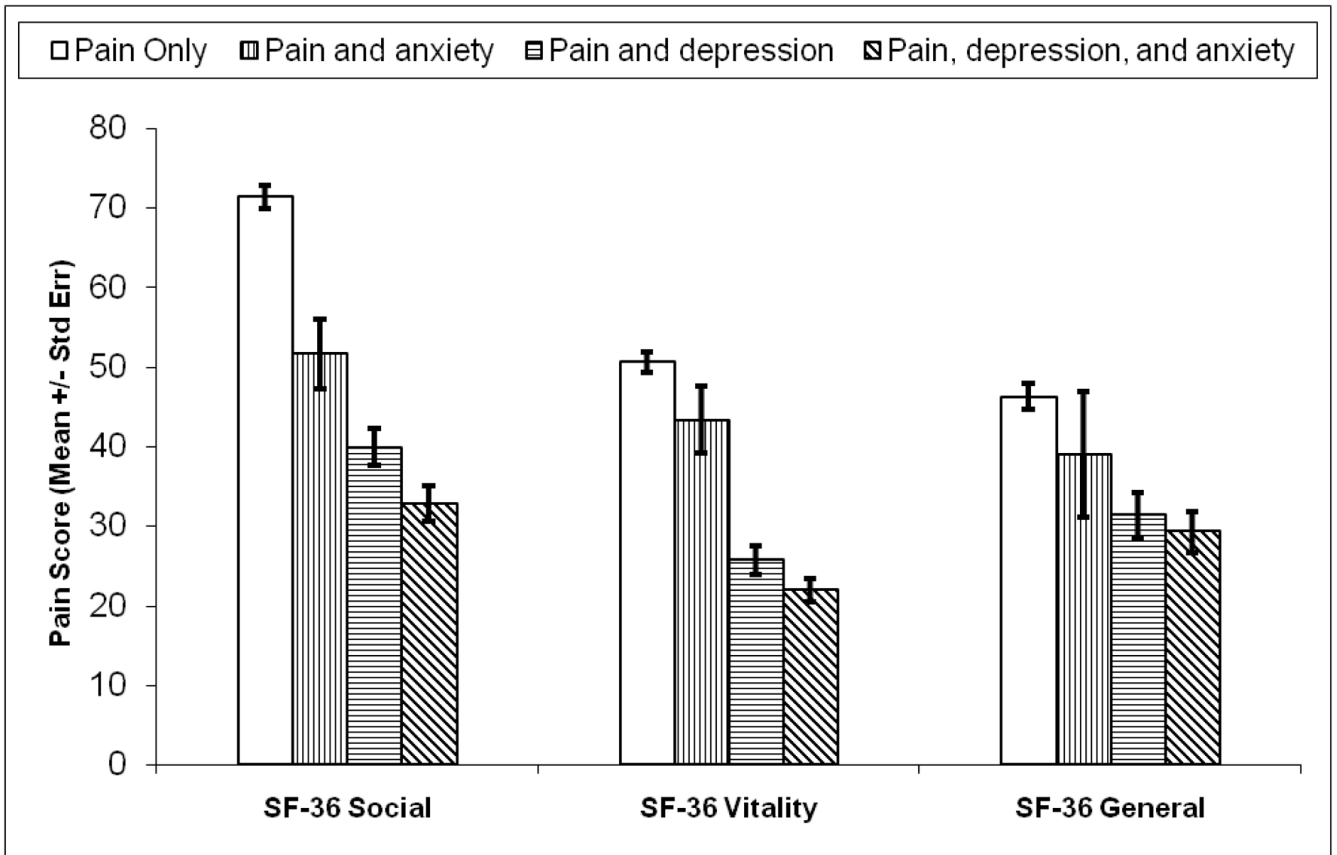


**Figure 1. Pain severity and pain interference by pain only and pain with psychiatric comorbidity groups**

\* Unadjusted group means with standard errors (displayed as error bars) comparing pain severity and pain interference across four clinically defined groups using analysis of variance (ANOVA) tests; main effect of group status (pain only, pain and anxiety, pain and depression, and pain, depression, and anxiety). For pain severity and interference, the overall  $F$  test value is significant ( $P < 0.001$ ) for increasing severity and interference when pain is comorbid with depression and/or anxiety.

<sup>1</sup>Score range: 0 (none) to 10 (most severe) as assessed by Brief Pain Inventory

<sup>2</sup>Score range: 0 (no interference) to 10 (completely interferes) as assessed by Brief Pain Inventory



**Figure 2. Health-related quality of life by pain only and pain with psychiatric comorbidity groups**

\*

\* The decrement in subscale scores of the Medical Outcomes Study SF-20 are shown across the four clinically defined groups: pain only, pain and anxiety, pain and depression, and pain, depression, and anxiety groups. For each SF-20 subscale, the overall  $F$  test value is significant ( $P < 0.001$ ) for declining function when pain is comorbid with depression and/or anxiety

**Table 1**

Baseline characteristics across the four clinically defined groups\*

Characteristic	Pain only (P) (n = 271)	Pain and anxiety (PA) (n = 15)	Pain and depression (PD) (n = 98)	Pain, depression, and anxiety (PDA) (n = 116)	P-value
Age, yr (SD)	63.3 (13.8)	55.4 (11.1)	56.6 (11.3)	51.5 (10.5)	<.0001
Women, n (%)	129 (48%)	7 (47%)	55 (56%)	68 (59%)	0.17
Race n (%)					
White	154 (57%)	9 (60%)	63 (64%)	65 (56%)	0.64
Black	109 (40%)	6 (40%)	30 (31%)	46 (40%)	
Other	8 (3%)	0 (0%)	5 (5%)	5 (4%)	
Married, n (%)	108 (40%)	8 (53%)	32 (33%)	41 (35%)	0.33
Education, n (%)					
<= high school	151 (56%)	11 (73%)	62 (63%)	81 (70%)	0.03
> high school	120 (44%)	4 (27%)	36 (37%)	34 (30%)	
Employment, n (%)					
Employed	56 (21%)	5 (33%)	19 (19%)	37 (32%)	<.0001
Unemployed	140 (52%)	5 (33%)	37 (38%)	24 (21%)	
Retired	75 (28%)	5 (33%)	42 (43%)	55 (47%)	
Medical Diseases, mean (SD)	2.6 (1.4)	2.5 (1.6)	2.7 (1.6)	2.7 (1.4)	0.97
Clinical sites, n (%)					
University clinics	146 (54%)	9 (60%)	61 (62%)	84 (72%)	0.008
Veterans	125 (46%)	6 (40%)	37 (38%)	32 (28%)	
Pain location, n (%)					
Back	138 (51%)	7 (47%)	61 (62%)	71 (62%)	0.10
Extremity	132 (49%)	8 (53%)	37 (38%)	44 (38%)	
SCL-20 depression severity, mean (SD)	0.6 (0.4)	1.1 (0.3)	2.0 (0.4)	2.3 (0.5)	<.0001



Characteristic	Pain only (P) (n = 271)	Pain and anxiety (PA) (n = 15)	Pain and depression (PD) (n = 98)	Pain, depression, and anxiety (PDA) (n = 116)	P-value
GAD-7 Anxiety severity, mean (SD)	2.6 (2.3)	11.4 (3.9)	6.6 (2.0)	12.0 (2.5)	<.0001

**Table 2**

Multiple regression model<sup>†</sup> assessing the relationship between depression, anxiety, and their combination on pain intensity and pain interference

Variables	F Value *	P-value
Age	2.24	.11
Medical comorbidity	1.38	.25
Gender	0.49	.62
<b>Education</b>	<b>3.80</b>	<b>.02</b>
<b>Employment</b>	<b>4.13</b>	<b>.003</b>
Marital status	0.04	.96
Pain location (back vs. knee/hip)	1.82	.16
<b>Clinic site (University vs. VA)</b>	<b>6.52</b>	<b>.002</b>
<b>Depression</b>	<b>38.48</b>	<b>&lt;.0001</b>
<b>Anxiety</b>	<b>6.27</b>	<b>0.002</b>
<b>Depression * anxiety</b>	<b>5.88</b>	<b>0.003</b>

<sup>†</sup> Covariates in the multivariate analysis of variance model (MANOVA) included: age, medical comorbidity, gender, educational level, employment status, marital status, pain location (back or knee/hip pain), clinic site (University or Veterans Affairs, SCL-20 depression score, GAD-7 anxiety score, and the interaction between SCL-20 depression score and GAD-7 anxiety score

\* F-values were estimated from the MANOVA regression analysis that modeled BPI pain severity and pain interference simultaneously