Published in final edited form as:
Psychosom Med. 2008 October ; 70(8): 890–897. doi:10.1097/PSY.0b013e318185c510.

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

Matthew J. Bair, M.D., M.S.[1,2,3,4], **Jingwei Wu, M.S.**[5], **Teresa M. Damush, Ph.D.**[1,2,3,4], **Jason M. Sutherland, Ph.D.**[6], and **Kurt Kroenke, M.D.**[1,2,3,4]

[1] VA Health Services Research & Development Center of Excellence on Implementation of Evidence-Based Practices, Indiana University School of Medicine, Indianapolis, IN

[2] Roudebush VA Medical Center, Indiana University Center for Health Services and Outcomes Research, Indiana University School of Medicine, Indianapolis, IN

[3] Regenstrief Inc., Indiana University School of Medicine, Indianapolis, IN

[4] Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[5] Division of Biostatistics, Indiana University School of Medicine, Indianapolis, IN

[6] Center for The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Hanover, NH

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 (≥ 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 asess 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

Corresponding author: Matthew J. Bair, M.D., M.S.., mbair@iupui.edu, 317-988-2258.

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% to15% 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 ≥ 10 and endorsement of the cardinal symptoms of depressed mood and/or anhedonia. PHQ-9 scores ≥ 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 ≤ 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 stongly 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 magnitute 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 disabiling 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 diability 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 consisent 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 persons' 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 reuptate 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 pregablin 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).

Acknowledgments

Funding: This study was supported by a grant from the National Institute of Mental Health to Dr. Kroenke (MH-071268) and a Veterans Affairs Health Services Research & Development Career Development Award to Dr. Bair.

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, 9th 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

Reference List

1. Mantyselka PT, Turunen JH, Ahonen RS, Kumpusalo EA. Chronic pain and poor self rated health. JAMA 2003;290:2435–42. [PubMed: 14612480]
2. Peter, D. America Speaks: Pain in America. Hart Research Associates; 2003.
3. Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. Am J Med 1989;86:262–6. [PubMed: 2919607]
4. Kroenke K, Price RK. Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993;153:2474–80. [PubMed: 8215752]
5. Verhaak PFM, Schellevis FG, Nuijen J, Volkers AC. Patients with a psychiatric disorder in general practice: determinants of general practitioners' psychological diagnosis. Gen Hosp Psychiatry 2006;28:125–32. [PubMed: 16516062]
6. Schappert SM. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1997. Vital & Health Statistics - Series 13: Data From the National Health Survey 1999;(143):i–iv. 1–39.
7. Turk, DC.; Okifuji, A.; Kalauolalani, D. Clinical outcome and economic evaluation of multidisciplinary pain centers. In: Block, AR.; Kremer, EF.; Fernandez, E., editors. Handbook of pain syndromes: Biopsychosocial perspectives. Mahway, NJ: Erlbaum; 1999. p. 77-98.
8. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Fam Pract 2001;18:292–9. [PubMed: 11356737]
9. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–45. [PubMed: 14609780]

10. Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV III, Hahn SR, Brody D, Johnson JG. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 1994;272:1749–56. [PubMed: 7966923]
11. Leon AC, Olfson M, Broadhead WE, Barrett JE, Blacklow RS, Keller MB, Higgins ES, Weissman MM. Prevalence of mental disorders in primary care. Implications for screening. Arch Fam Med 1995;4:857–61. [PubMed: 7551133]
12. Schonfeld WH, Verboncoeur CJ, Fifer SK, Lipschutz RC, Lubeck DP, Buesching DP. The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder. J Aff Disord 1997;43:105–19.
13. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436–42. [PubMed: 9164317]
14. Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey Lisle PK. The economic burden of depression in the United States: how did it change between 1990 and 2000? J Clin Psychiatry 2003;64:1465–75. [PubMed: 14728109]
15. Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among US workers with depression. JAMA 2003;289:3135–44. [PubMed: 12813119]
16. Regier DA, Boyd JH, Burke JD Jr, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ. One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1988;45:977–86. [PubMed: 3263101]
17. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry 1999;60:427–35. [PubMed: 10453795]
18. Beck, AT.; Emery, G.; Greenberg, RL. Anxiety Disorders and Phobias: A Cognitive Perspective. New York: Basic Books; 1985.
19. McLaughlin TP, Khandker RK, Kruzikas DT, Tummala R. Overlap of anxiety and depression in a managed care population: Prevalence and association with resource utilization. J Clin Psychiatry 2006;67:1187–93. [PubMed: 16965195]
20. Fernandez, E. Anxiety, Depression, and Anger in Pain. Dallas: Advanced Psychological Resources, Inc; 2002.
21. Gallagher RM, Verma S. Managing pain and comorbid depression: A public health challenge. Semin Clin Neuropsychiatry 1999;4:203–20. [PubMed: 10498788]
22. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain 2003;106:127–33. [PubMed: 14581119]
23. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33:335–43. [PubMed: 7726811]
24. Krishnan KR, France RD, Pelton S, McCann UD, Davidson J, Urban BJ. Chronic pain and depression. II. Symptoms of anxiety in chronic low back pain patients and their relationship to subtypes of depression. Pain 1985;22:289–94. [PubMed: 3162136]
25. Levenson JL, Hamer R, Silverman JJ, Rossiter LF. Psychopathology in medical inpatients and its relationship to length of hospital stay: a pilot study. Int J Psychiatry Med 1986;16(3):231–6. [PubMed: 3804584]
26. Fields H. Pain modulation: expectations, opioid analgesia and virtual pain. Prog Brain Res 2000;122:245–253. [PubMed: 10737063]
27. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30–36. [PubMed: 11212591]
28. Von Korff M, Dworkin SF, Le RL, Kruger A. An epidemiologic comparison of pain complaints. Pain 1988;32:173–83. [PubMed: 3362555]
29. Kroenke K, Bair MJ, Damush TM, Hoke S, Nicholas G, Kempf C, Huffman M, Wu J, Sutherland JM. 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;29:506–517. [PubMed: 18022044]
30. Cleeland, CS. Measurement of pain by subjective report. In: Foley, KM., editor. Advances in Pain Research and Therapy. 1989.

31. 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;74:1587–9. [PubMed: 14617727]
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13. [PubMed: 11556941]
33. Kroenke K, West SL, Swindle R, Gilsenan A, Eckert GJ, Dolor R, Stang P, Zhou XH, Hays R, Weinberger M. Similar effectiveness of paroxetine, fluoxetine, and sertraline in primary care: a randomized trial. JAMA 2001;286:2947–55. [PubMed: 11743835]
34. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. Med Care 2002;40:771–81. [PubMed: 12218768]
35. Hanson, RW.; Gerber, KE. Coping with Chronic Pain: A Guide to Patient Self-Management. New York: Guilford; 1990. Models of Pain; p. 15-44.
36. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38. [PubMed: 8080219]
37. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133–7. [PubMed: 15042521]
38. 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;8:141–4. [PubMed: 6222486]
39. 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;50:15762.
40. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133–49. [PubMed: 1408309]
41. 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;31:247–63. [PubMed: 8450681]
42. Ware, JE., Jr; Kosinski, M.; Keller, SD. A User's Manual. Boston: The Health Institute, New England Medical Center; 1994. SF-36 Physical and Mental Health Summary Scales.
43. Katon W, Robinson P, Von Korff M, Lin E, Bush T, Ludman E, Simon G, Walker E. A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry 1996;53:924–32. [PubMed: 8857869]
44. Unutzer J, Katon W, Callahan CM, Williams JW Jr, Hunkeler E, Harpole L, Hoffing M, la Penna RD, Noel PH, Lin EH, Arean PA, Hegel MT, Tang L, Belin TR, Oishi S, Langston C. IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 2002;288:2836–45. [PubMed: 12472325]
45. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. Psychosom Med 2004;66:17–22. [PubMed: 14747633]
46. Katon W, Von Korff M, Lin E, Walker E, Simon GE, Bush T, Robinson P, Russo J. Collaborative management to achieve treatment guidelines. Impact on depression in primary care. JAMA 1995;273:1026–31. [PubMed: 7897786]
47. Spitzer RL, Kroenke K, Williams JBW, Lowe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 2006;166:1092–7. [PubMed: 16717171]
48. Kroenke K, Spitzer RL, Williams JBW, Monahan PO, Lowe B. Anxiety Disorders in Primary Care: Prevalence, Impairment, Comorbidity, and Detection. Ann Intern Med 2007;146:317–25. [PubMed: 17339617]
49. Perkins AJ, Kroenke K, Unutzer J, Katon W, Williams JW, Hope C, Callahan CM. Common comorbidity scales were similar in their ability to predict health care costs and mortality. J Clinical Epidemiology 2004;57:1040–1048.
50. Symreng I, Fishman SM. Anxiety and pain. Pain Clinical Updates XII [7]. 2004
51. Fishbain DA, Goldberg M, Meagher BR, Steele R, Rosomoff H. Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria. Pain 1986;26:181–97. [PubMed: 3763232]

52. Varni JW, Rapoff MA, Waldron SA, Gragg RA, Bernstein BH, Lindsley CB. Chronic pain and emotional distress in children and adolescents. J Dev Behav Pediatr 1996;17:154–61. [PubMed: 8783061]
53. Ferguson RJ, Ahles TA. Private body consciousness, anxiety and pain symptom reports of chronic pain patients. Beh Res Ther 1998;36:527–35.
54. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7. [PubMed: 16717171]
55. Porro CA. Functional imaging and pain: behavior, perception, and modulation. Neuroscientist 2003;9:354–69. [PubMed: 14580120]
56. Charney DS. Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Neurol Scand Suppl 2003:38–50.
57. Casey KL. Imaging pain. Pain Clinical Updates VIII [4]. 2000
58. Picavet HS, Vlaeyen JW, Schouten JS. Pain catastrophizing and kinesiophobia: predictors of chronic low back pain. Am J Epidemiol 2002;156:1028–34. [PubMed: 12446259]
59. Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004;45:17–28. [PubMed: 14709757]
60. Dunner DL, Goldstein DJ, Mallinckrodt C, Lu Y, Detke MJ. Duloxetine in treatment of anxiety symptoms associated with depression. Depress Anxiety 2003;18:53–61. [PubMed: 12964171]
61. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524–34. [PubMed: 14623723]
62. Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom 2000;69:205–15. [PubMed: 10867588]
63. McCracken LM, Turk DC. Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. Spine 2002;27:2564–73. [PubMed: 12435995]
64. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. Int J Psychiatry Med 2006;36:13–34. [PubMed: 16927576]
65. Mergl R, Seidscheck I, Allgaier AK, Moller HJ, Hegerl U, Henkel V. Depressive anxiety, and somatoform disorders in primary care: prevalence and recognition. Depress Anxiety 2007;24:185–95. [PubMed: 16900465]
66. Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics. (in press).
67. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737–44. [PubMed: 10568646]
68. Kessler D, Lloyd K, Lewis G, Gray DP. Cross sectional study of symptom attribution and recognition of depression and anxiety in primary care. BMJ 1999;318:436–9. [PubMed: 9974461]
69. Spitzer RL, Kroenke K, Linzer M, Hahn SR, Williams JB, deGruy FV III, Brody D, Davies M. Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 Study. JAMA 1995;274:1511–7. [PubMed: 7474219]
70. Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, Hoven C, Farber L. Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry 1997;154:1734–40. [PubMed: 9396954]
71. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. Arch Intern Med 2006;166(19): 2087–93. [PubMed: 17060538]
72. Linton SJ. A review of psychological risk factors in back and neck pain. Spine 2000;25:1148–56. [PubMed: 10788861]

73. Fishbain DA. Approaches to treatment decisions for psychiatric comorbidity in the management of the chronic pain patient. Med Clin North Am 1999;83:737–60. [PubMed: 10386123]

74. Koenig TW, Clark MR. Advances in comprehensive pain management. Psychiatr Clin North Am 1996:589–611. [PubMed: 8856818]

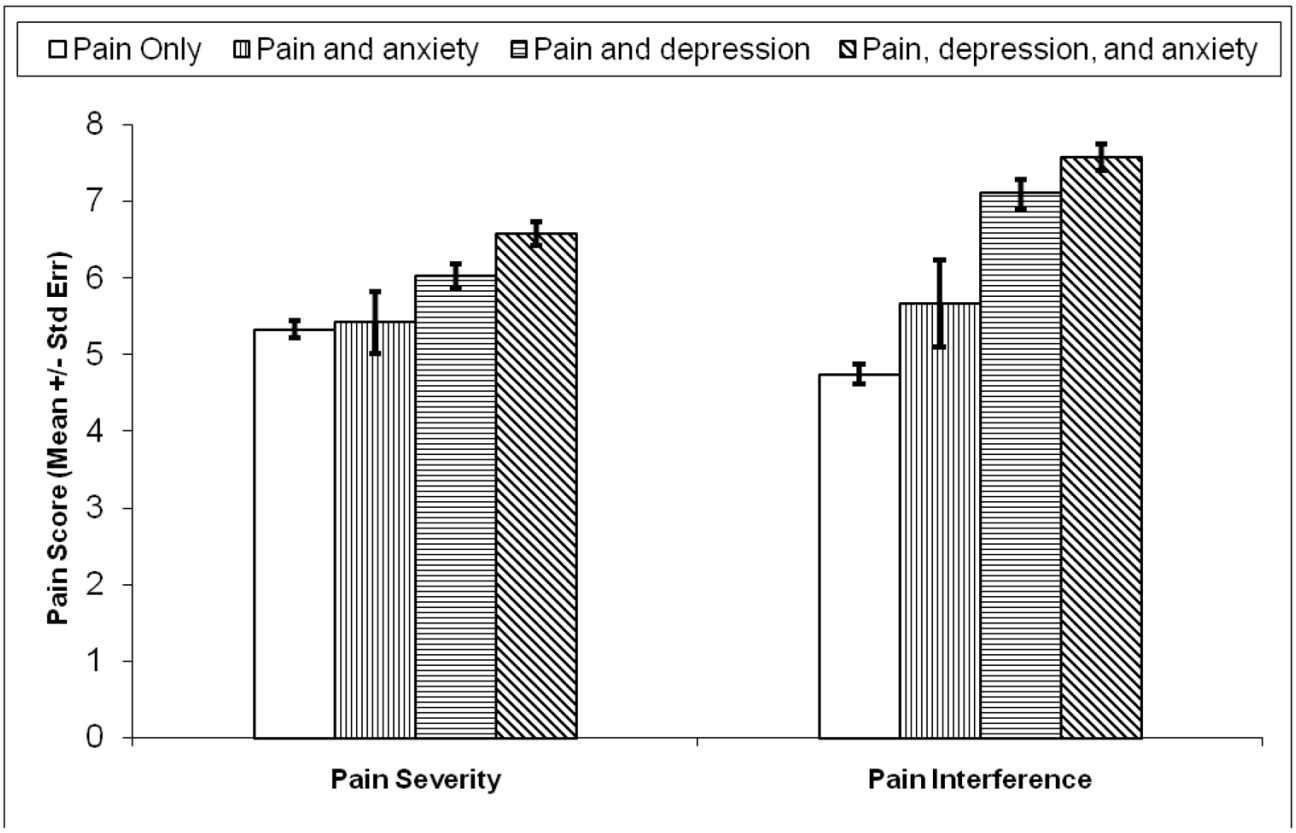

Figure 1. Pain severity and pain interference by pain only and pain with psychiatric comorbidity groups

* 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.

[1]Score range: 0 (none) to 10 (most severe) as assessed by Brief Pain Inventory

[2]Score range: 0 (no interference) to 10 (completely interferes) as assessed by Brief Pain Inventory

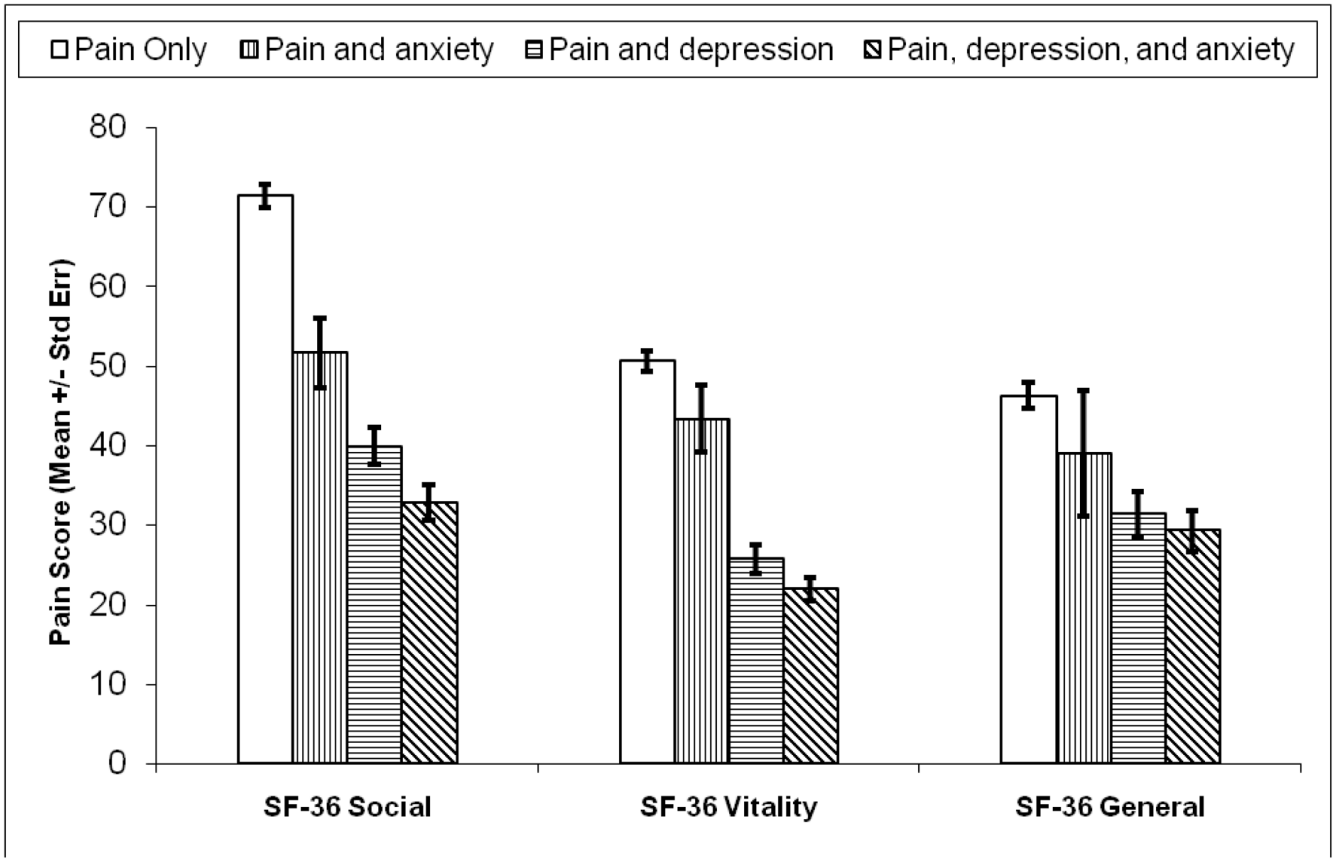

Figure 2. Health-related quality of life by pain only and pain with psychiatric comorbidity groups *

* 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

Psychosom Med. Author manuscript; available in PMC 2010 July 13.

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[†] 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
Education	**3.80**	**.02**
Employment	**4.13**	**.003**
Marital status	0.04	.96
Pain location (back vs. knee/hip)	1.82	.16
Clinic site (University vs. VA)	**6.52**	**.002**
Depression	**38.48**	**<.0001**
Anxiety	**6.27**	**0.002**
Depression * anxiety	**5.88**	**0.003**

[†]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