REVIEW ARTICLE

# Depression and Pain Comorbidity

## *A Literature Review*

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Because depression and painful symptoms commonly occur together, we conducted a literature review to determine the prevalence of both conditions and the effects of comorbidity on diagnosis, clinical outcomes, and treatment. The prevalences of pain in depressed cohorts and depression in pain cohorts are higher than when these conditions are individually examined. The presence of pain negatively affects the recognition and treatment of depression. When pain is moderate to severe, impairs function, and/or is refractory to treatment, it is associated with more depressive symptoms and worse depression outcomes (eg, lower quality of life, decreased work function, and increased health care utilization). Similarly, depression in patients with pain is associated with more pain complaints and greater impairment. Depression and pain share biological pathways and neurotransmitters, which has implications for the treatment of both concurrently. A model that incorporates assessment and treatment of depression and pain simultaneously is necessary for improved outcomes.

*Arch Intern Med. 2003;163:2433-2445*

Individually, depression and pain symptoms are highly prevalent conditions encountered by primary care physicians and specialists. Epidemiologic studies indicate that the lifetime prevalence of pain symptoms (eg, joint pain, back pain, headache, chest pain, arm or leg pain, and abdominal pain) ranges from 24% to 37%[1] and that physical symptoms such as pain are the leading reason that patients seek medical care.[2,3] Major depression is also common, with prevalence in primary care patients of 5% to 10%.[4] This underestimates the true impact of depression, since many more people have depressive symptoms but do not fully meet the major depressive disorder diagnostic criteria of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for duration or number of symptoms. Depression has become the fourth leading cause of disability worldwide and is projected to become even more burdensome in the future.[5]

A growing body of literature has focused on the interaction between depression and pain symptoms. This interaction has been labeled by some authors as the depression-pain syndrome[6] or depression-pain dyad, implying that the conditions often coexist, respond to similar treatments, exacerbate one another, and share biological pathways and neurotransmitters.[7,8] Patients with depression often present with a complex set of overlapping symptoms, including emotional and physical complaints. Physical complaints typically include medically unexplained pain.[9] Although it is generally understood that depression and painful symptoms are common comorbidities and that their combination is costlier and more disabling than

*For editorial comment see page 2415*

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**Table 1. Pain Symptoms in Patients With Depression**

| Source | No. of Patients | Study Setting | Pain Type | Patients With Pain, % |
|---|---|---|---|---|
| Bair et al[21] | 573 | Primary care | Mulitple pain sites | 69 |
| Delaplaine et al[22] | 29 | Psychiatric inpatients | Multiple pain sites | 51 |
| Diamond[23] | 432 | Neurology clinic | Headache | 85 |
| Hollifield et al[24] | 29 | Outpatient clinic | "Pain" complaints | 59 |
| Lindsay and Wyckoff[6] | 196 | Private practice | Chronic pain >3 mo | 59 |
| Mathew et al[25] | 51 | Research institution | Physical symptoms | 77 (Headache), 37 (chest pain) |
| Merskey and Spear[26] | 85 | Psychiatric patients | Pain sites | 56 |
| Pelz et al[27] | 22 | Psychiatric patients | Multiple pain sites | 41 |
| Singh[28] | 150 | Depressed outpatients | "Physical complaints" | 65 |
| Vaeroy and Merskey[29] | 28 | General practice | Pain problem | 43 |
| von Knorring[30] | 40 | Psychiatric inpatients | "All types" | 60 |
| von Knorring et al[31] | 161 | Psychiatric inpatients | "Aches and pain" | 57 |
| Ward et al[32] | 16 | Respondents to newspaper advertisement | Multiple pain sites | 100 |
| Watts[33] | 100 | Psychiatric patients | Variety | 15 |

either condition alone, their interaction is not fully understood. Understanding this relationship has become more important, given that primary care physicians fail to accurately diagnose at least 50% of patients with major depression,[10] and at least 2 studies have shown that patients with depression who present with physical symptoms such as pain are particularly likely to receive an inaccurate diagnosis.[11,12] Patients with depression have significantly more unexplained physical symptoms such as pain and fatigue and utilize more health resources than nondepressed patients. The new emphasis on pain as the fifth vital sign by the Joint Commission on Accreditation of Healthcare Organizations and the Veterans Health Administration highlights the importance of a better understanding of the likely reciprocal links between depression and pain.

The present review addresses the following 6 questions: (1) What is the prevalence of pain symptoms in patients with depression and, conversely, what is the prevalence of depression in patients with pain complaints? (2) Does the presence of pain affect provider recognition and treatment of depression? (3) Does the presence of pain affect depression outcomes such as functional limitations, quality of life, health care costs and utilization, and treatment efficacy? (4) Does the presence of depression affect these same clinical outcomes in patients treated for pain? (5) Is antidepressant treatment for painful symptoms and comorbid depression effective? and (6) What are the common biological pathways and implications for treatment choice when depression and pain coexist?

## METHODS

We searched the MEDLINE database from 1966 through July 30, 2002, using the combined search terms *depression or depressive disorders* and *pain*. Articles were also identified by a manual search of bibliographies from all retrieved articles. Studies were limited to human studies reported in English. A few abstracts, studies not published in full, and book chapters were included. Two of us (M.J.B. and K.K.) independently screened titles and abstracts and reached agreement on which articles to retrieve. All primary and review articles were examined for information pertinent to our questions.

Studies were eligible for inclusion if they addressed both depression and pain symptoms. Specific symptoms (eg, headache, back pain, neck pain, extremity/joint pain, chest pain, pelvic pain, abdominal pain, and others) as well as general pain (ie, studies that used pain measures but did not specify pain location) were included in the analysis. Articles were included if they had primary data derived from clinical trials or longitudinal or cross-sectional studies. Excluded studies were those addressing pain due to specific disease processes (eg, peripheral neuropathy, rheumatoid arthritis, or cancer pain) or symptom syndromes (eg, fibromyalgia, irritable bowel syndrome, or migraine headache) because these conditions have been the subject of previous reviews.[13-20]

Because of the broad scope of depression and painful symptoms, the variety of measures used to assess depression, and the different study definitions of pain, formal meta-analytic methods were precluded. Instead, this review is a qualitative and semiquantitative synthesis of the relevant, representative, and evidence-based literature.

## RESULTS

### WHAT IS THE PREVALENCE OF PAIN SYMPTOMS IN PATIENTS WITH DEPRESSION?

To address the prevalence of depression and pain symptoms, we summarized the literature based on whether the subjects presented with depression and were then assessed for pain (14 articles) or if patients with a painful condition were assessed for depression (42 articles). Fourteen studies[6,21-33] were identified that focused on the prevalence of pain symptoms in patients with depression (**Table 1**). The prevalence of pain ranged from 15% to 100% (mean prevalence, 65%). Most of the studies were uncontrolled and performed in psychiatric settings. Only 3 studies[6,24,29] examined primary care patients, and 2 studies solicited community volunteers.[25,32] The prevalence rates do not appear to be influenced by the study setting in that there does not seem to be a different prevalence in psychiatric vs primary care settings. Sample sizes were modest, ranging from 16 to 573 patients (mean, 137). Pain was primarily assessed at the

clinical interview or self-assessed by the patient presenting with the pain complaint. The definition of pain condition, location of pain, and duration of pain complaint varied considerably among studies. Several different scales were used to assess depression.

A large longitudinal cohort study has shown that depressive symptoms predict future episodes of low back pain, neck-shoulder pain, and musculoskeletal symptoms compared with those patients without depressive symptoms at baseline.[34] Another study showed that low back pain is more than 2 times as likely to be reported by individuals with depressive symptoms compared with those without depressive symptoms.[35] In addition, the specific complaints of headache, abdominal pain, joint pain, and chest pain are frequently reported by patients with depression in primary care settings[25,36] and by elderly nursing home residents.[37]

## WHAT IS THE PREVALENCE OF MAJOR DEPRESSION IN PAIN PATIENTS?

Several reviews[38-42] have examined the prevalence of major depression in patients with pain. **Table 2** summarizes 42 studies[6,36,43-82] identified by our literature search. Fifteen studies were from pain clinics or inpatient pain programs; 9 from psychiatric clinics or psychiatric consultation; 3 from arthritis, rheumatology, or orthopedic clinics (excluding rheumatoid arthritis and fibromyalgia studies); 3 from dental/facial pain clinics; 2 from surgical patients; and 10 from primary care or population-based settings. Most studies (n=31) focused on "chronic" pain complaints of at least 6 months' duration.

The mean (range) prevalence rates for concurrent major depression in patients identified as having pain by study setting are as follows: 52% (1.5%-100%) in pain clinics or inpatient pain programs; 38% (6%-64%) in psychiatric clinics or psychiatric consultation; 56% (21%-89%) in orthopedic clinics or rheumatology clinics (excluding studies focusing on fibromyalgia or rheumatoid arthritis); 85% (35%-100%) in dental clinics addressing facial pain; 13% (12%-17%) in gynecology clinics addressing chronic pelvic pain in laparoscopy patients; 18% (4.7%-22%) in population-based settings; and 27% (5.9%-46%) in primary care clinics. In addition to the point prevalence rates listed in Table 2, two studies[54,73] also reported the lifetime prevalence of major depression in pain patients. Rates of depression increased from 12% to 32%[73] and 32.4% to 56.8%,[54] respectively. When the etiology of the pain condition is considered, studies of more defined pain disorders (eg, peripheral neuropathy) report lower occurrence of depression than studies of medically unexplained pain.[61]

A variety of instruments were used to diagnose depression, including the Beck Depression Inventory, Center for Epidemiological Studies Depression Scale, Primary Care Evaluation for Mental Disorders, Geriatric Depression Scale, Feighner criteria, and Hopkins Symptom Checklist. Pain was assessed mainly through clinical interview or different pain questionnaires. The substantial variation in prevalence rates is likely related to differences in diagnostic criteria used for depression, pain conditions examined, study designs, and subject populations.

Several studies have reported the association between depression and pain, specifically addressing how the risk of depression increases as a function of different aspects of worsening pain (eg, severity, frequency, duration, and number of symptoms). Patients with multiple pain symptoms (eg, back pain, headache, abdominal pain, chest pain, and facial pain) are 3 to 5 times more likely to be depressed than patients without pain,[81] and pain symptoms are associated with at least a 2-fold increased risk for coexisting depression.[83] Additionally, a population-based study showed that subjects with chronic pain (defined as pain for most days for at least a month) are 3 times as likely to meet depression criteria as those without chronic pain.[80] The association between depression and pain becomes stronger as the severity of either condition increases. For example, as the severity of pain increases, depressive symptoms and depression diagnoses become more prevalent.[75,77,84] Likewise, as depression symptoms increase in severity, pain complaints are reported more often.[81]

Consistent with findings in primary care patients,[36] multiple pain complaints increase the probability of depression[38] such that patients with 2 or more different pain complaints are 6 times more likely to be depressed, and patients with 3 or more pain complaints are 8 times more likely to meet depression criteria.[10] In addition, more frequent pain episodes[85] and longer pain duration are associated with depression. An international study showed that patients with pain lasting longer than 6 months were more than 4 times as likely to have a depressive disorder as those without chronic pain.[86] The long-term medical conditions most strongly associated longitudinally with the development of incident depression included back pain and migraine headaches.[87]

## DOES THE PRESENCE OF PAIN AFFECT PROVIDER RECOGNITION AND TREATMENT OF DEPRESSION?

Fourteen studies sought to determine whether the presence of pain affected provider recognition of depression. In depression studies not addressing pain, at least half of patients with major depression were not properly diagnosed and therefore not treated for depression in primary care settings.[11,88] Although many factors account for this problem, the most important reason relates to how the patient presents. The "typical" depression presentation in primary care is dominated by physical (somatic) complaints as opposed to psychological complaints. More than 50% of patients with depression report somatic complaints only[11,12,24,89-92] and at least 60% of these somatic complaints are pain related.[24,25,36,93] Thus, patients with depression in primary care settings are more likely to report various pain symptoms than they are to present with dysphoric mood or anhedonia. Physical (or somatic) symptoms of depression, specifically fatigue, insomnia, and pain complaints, are more numerous in patients with depression, are frequently nonspecific,[91,94] and are of-

**Table 2. Major Depression in Patients With Pain**

| Source | No. of Patients | Setting | Sample | Patients With Depression, % |
|---|---|---|---|---|
| **Pain Clinics and Inpatient Pain Programs** | | | | |
| Benjamin et al[43] | 106 | Outpatient pain clinic | Chronic pain | 33 |
| Blumer and Heilbronn[44] | 900 | Pain clinics | Chronic pain | 83 |
| Covino et al[45] | 44 | Pain clinic | Chronic pain | 100 |
| Fishbain et al[46] | 283 | Pain clinic | Pain >2 y | 4.6 |
| France et al[47] | 80 | Pain clinic | Low back pain >6 mo | 21 |
| Haley et al[48] | 63 | Pain clinic | Chronic pain | 49.2 |
| Lindsay and Wyckoff[6] | 300 | Pain clinic | Chronic pain | 87 |
| Muse[49] | 64 | Pain clinic | Pain >6 mo | 1.5 |
| Turner and Romano[50] | 40 | Pain clinic | Pain >6 mo | 30 |
| Reich et al[51] | 43 | Pain board | Chronic pain | 23.2 |
| Atkinson et al[52] | 52 | Inpatient pain program | Chronic low back pain | 44 |
| Boukoms et al[53] | 62 | Inpatient pain program | Pain >6 mo | 24.2 |
| Katon et al[54] | 37 | Inpatient pain program | Pain >1 y | 32.4 |
| Kramlinger et al[55] | 100 | Inpatient pain program | Chronic pain | 25-39 |
| Krishnan et al[56] | 71 | Inpatient pain program | Chronic low back pain | 45 |
| **Psychiatry Clinics and Psychiatry Consultation** | | | | |
| Chaturvedi[57] | 200 | Outpatient psychiatry | Chronic pain | 61 |
| Chaturvedi[58] | 203 | Outpatient psychiatry | Pain >3 mo | 6.9 |
| Katon et al[59] | 49 | Psychiatric consultation | Chronic pain | 57.1 |
| Large[60] | 50 | Psychiatric consultation | Pain >6 mo | 6.0 |
| Magni and Merskey[61] | 137 | Psychiatric consultation | Pain >6 mo | 31.3 |
| Merskey et al[62] | 32 | Psychiatric consultation | Chronic pain | 28.1 |
| Pilling et al[63] | 182 | Psychiatric patients | Chronic pain | 64 |
| Remick et al[64] | 68 | Psychiatric consultation | Atypical facial pain | 13.2 |
| Schaffer et al[65] | 20 | Psychiatry | Back pain | 50 |
| **Rheumatology and Orthopedic Clinics** | | | | |
| Atkinson et al[66] | 34 | Orthopedic clinic referrals | Low back pain >6 mo | 21.6 |
| Forrest and Wolkind[67] | 50 | Rheumatology clinic | Low back pain | 46 |
| Tilscher and Bogner[68] | 53 | Orthopedic patients | Axial pain | 89 |
| **Dental Clinic** | | | | |
| Feinmann[69] | 93 | Dental clinic | Facial pain | 35 |
| Lesse[70] | 225 | Facial pain patients | Facial pain | 100 |
| Lascelles[71] | 93 | "Face pain" clinic | Facial pain | 100 (Atypical) |
| **Gynecology Clinic** | | | | |
| Magni et al[72] | 29 | Laparoscopy patients | Pelvic pain >6 mo | 17.2 |
| Walker et al[73] | 100 | Laparoscopy patients | Pelvic pain >3 mo | 12 (32 Lifetime) |
| **Primary Care Clinics and Population-Based Studies** | | | | |
| Love[74] | 68 | Private practice clinics | Low back pain >6 mo | 25 |
| Carroll et al[75] | 1131 | Population based | Spinal pain | 22 |
| Holroyd et al[76] | 245 | General population | Chronic tension headache | 28.6 |
| Kroenke et al[36] | 1000 | Primary care | Multiple pain conditions | 34-46 |
| Lamb et al[77] | 408 | Community women older than 65 y | Knee pain | 15.4-19.1 |
| Magni[78] | 64 | Factory workers | Low back pain | 4.7 |
| Magni et al[79] | 3023 | Population based | Arthritis history | 18 |
| Magni et al[80] | 2341 | Population households | Chronic pain | 16.4 |
| Von Korff et al[81] | 1500 | HMO enrollees | Common pain conditions | 5.9-10.7 |
| Wells et al[82] | 2500 | HMO and solo practice | Somatic pain | 35 |

Abbreviation: HMO, health maintenance organization.

ten unrelated to a known organic disease process.[3]

The patient's presentation of physical complaints (and the prominence of pain symptoms) interferes with the recognition of depression for patients in primary care settings. Presentation of progressively more physical complaints reduces depression recognition[11,12] because patients and their medical providers (at least initially) often associate these symptoms with an underlying medical illness instead of an underlying depressive disorder. Previous work has shown that if all primary care patients presenting with a variety of pain conditions (eg, abdominal pain, headache, joint pain, and back pain) were evaluated for possible depression, 60% of previously undetected depression cases could have been recognized.[95] Patients having multiple presenting physical complaints, including nonspecific musculoskeletal complaints and back pain, had more underlying depressive symptoms.[96] Additionally, patients presenting with somatic complaints are more likely to have subclinical and milder cases of depression that negatively affect recognition: milder cases of de-

pression are more difficult to detect than more severe and blatant cases, and patients with milder cases are more likely to present to primary care providers than to psychiatrists.

Few studies focused on how pain plays a role in depression treatment considerations. For example, patients often attribute their painful physical symptoms to an underlying medical illness and want treatment for their pain. Health care providers frequently accept the patient's request for pain treatment, while neglecting treatment for the patient's underlying depression. Fritzsche et al[97] noticed that patients with depression and pain who lacked psychological attribution to their illness were offered less psychosocial treatment, experienced worse outcomes, and received more medications and physical therapy.

Only older studies addressed how specific medication practices were influenced by pain in patients with depression. For example, opioid analgesics were more commonly prescribed than antidepressants in a sample of patients with depression and chronic pain,[98] and there were no differences in sedative and antidepressant medications used in chronic pain patients with and without depression.[48] As a result, patients with chronic pain are at risk for polypharmacy, adverse drug events, and narcotic and/or benzodiazepine dependence or addiction.[99,100]

## DOES THE PRESENCE OF PAIN AFFECT DEPRESSION OUTCOMES?

Outcomes included depression severity and secondary measures such as functional status, quality of life, health care costs and utilization, and treatment efficacy. Unfortunately, most depression and pain studies have either been cross-sectional or have assessed the prognostic value of depression for poor pain outcomes. Relatively few studies have specifically addressed how the presence of pain affects depression outcomes. Most work in this area has been performed by Von Korff et al[81] showing that the presence of up to 5 different pain complaints (abdominal pain, headache, back pain, chest pain, and facial pain) is associated with increased symptoms of depression. Further study demonstrated that progressive pain severity at baseline was associated with poor depression outcomes, including more severe depression, more pain-related functional limitations, worse self-rated health, higher unemployment rate, more frequent use of opioid analgesics, and more frequent pain-related doctor visits (at baseline and 1-year follow-up).[101] Interference with daily activities due to pain, the number of days in pain (within a 6-month period), and the diffuseness of pain (or number of pain sites) also predicted the severity of depression.[102] Unimproved back pain at short-term (7-week) and long-term (2-year) follow-up was associated with significantly more depressive symptoms and chronic depression when compared with patients whose back pain improved.[101,103,104] Over the long term, improvement in pain symptoms was associated with a decrease in depressive symptoms to nearly normal.[81]

When evaluated by changes in physical symptoms, psychiatric symptoms, and functional outcomes, patients without painful physical symptoms were found to have better depression outcomes.[105] In a sample of 217 patients with depression, pain was experienced on more than half the days over a 3-month period, producing 16 days when usual activities were curtailed, 4 days missed from school or work, and at least 1 visit with a physician or clinical nurse.[106] Retrospective studies suggest that patients with depression have significantly more clinic visits, phone calls to the clinic, and hospitalizations for pain-related symptoms in the months leading up to a diagnosis of depression.[107,108] A population-based study found that persons with depression and concomitant pain initiated 20% more visits to medical providers and their total medical costs were higher than persons with depression but without pain.[109] Although some studies suggest that patients with depression and comorbid chronic low back pain respond just as well (eg, fewer depression symptoms) to antidepressants and cognitive behavioral therapy as depressed patients without back pain, little is known about how or if pain complicates depression outcomes.[110,111] Bair et al[21] suggest that baseline pain reduces the benefits of antidepressant therapy at 12 weeks in terms of depression and other quality-of-life outcomes, but more prospective studies are needed to better quantify this.

The goal of depression treatment is complete symptom resolution or remission. Lingering physical symptoms in patients with depression may prevent patients from achieving remission of their depression. Currently, up to 70% of patients respond to treatment but fail to achieve complete resolution of their emotional and physical symptoms.[112,113] A recent clinical study[114] found that 76% of compliant depressed patients with lingering symptoms of depression relapsed within 10 months. Of these patients who experienced lingering symptoms, 94% had mild to moderate physical complaints.[114]

## DOES THE PRESENCE OF DEPRESSION AFFECT CLINICAL OUTCOMES IN PATIENTS TREATED FOR PAIN?

We identified 22 studies* that addressed how depression or depressive symptoms affect outcomes in patients with pain (**Table 3**). Ten of the studies were based in managed care or other primary care settings, 6 in pain and/or specialty clinics, 4 were population-based, 1 study was conducted at a worksite, and 1 in surgical patients. The most common pain condition examined was low back pain. Depression was associated with an array of poor pain outcomes and worse prognosis. Patients with pain and comorbid depression experienced more pain complaints,[89] more intense pain,[77] more amplification of pain symptoms,[82] and longer duration of pain.[116] Unfortunately patients with both conditions were more likely to have persistent pain[116,120,123,125] and nonrecovery.[120] Future episodes of pain, such as low back pain, chest

**References 34, 35, 55, 67, 76, 77, 82, 89, 103, 115-127.*

**Table 3. Effect of Depression on Patients With Pain**

| Source | No. of Patients | Setting | Sample | Depression Diagnostic Tool | Pain Measure | Comments |
|---|---|---|---|---|---|---|
| Betrus et al[89] | 237 | Nursing clinic | Women treated for physical disorder | SCL-90 | Health history | ↑Physical complaints, ↑disability, ↑functional limitations, ↑use of health care services |
| Blanchard et al[115] | 91 | Psychology department | Chronic headaches | BDI | Headache index | Depression associated with less improvement in headache index |
| Burton et al[116] | 252 | Primary care | Low back pain | Modified ZDI | MPQ | Persistent pain symptoms, functional impairment |
| Cherkin et al[103] | 219 | Primary care | Low back pain (initial episode) | "SCL-6" | "Symptom satisfaction" | Depression associated with poor outcome at 7 wk and at 1 y |
| Croft et al[35] | 4501 | General population | Low back pain | GHQ | Record review, pain survey | Psychological symptoms predict later onset of low back pain |
| Dionne et al[117] | 1213 | HMO | Back pain in primary care | SCL-90-R | Telephone interview | Depression was one of the strongest predictors of long-term functional limitations |
| Dolce et al[118] | 63 | Pain management program | Chronic pain | BDI | Pain scale (0-10) | Depression predicted less return to work |
| Engel et al[119] | 1059 | Primary care | Back pain | SCL-90R | CPSP | ↑Depressive symptoms associated with ≥2 back pain follow-up visits, ≥2 back pain radiographs, ≥8 pain medication refills, ↑total costs |
| Forrest and Wolkind[67] | 50 | Rheumatology clinic | Low back pain | Middlesex Survey | Health history | Depressed group more likely to have "poor response" |
| Gureje et al[120] | 3197 | Primary care | Persistent pain syndromes | CIDI | Pain survey | Depressive disorder at baseline marginally predicted pain nonrecovery, predicted onset of persistent pain |
| Holroyd et al[76] | 245 | General population | Chronic tension headache | BDI/PRIME-MD | Headache assessment | Daily headaches with depression frequently impaired on one SF20 subscale |
| Kerns and Haythornthwaite[121] | 131 | Pain rehabilitation program | Chronic pain | BDI | MPQ | No difference in depressed and nondepressed group in pain outcomes |
| Kramlinger et al[55] | 100 | Pain center | Chronic pain conditions | Hamilton Scale | Pain scale (0-10) | More work loss in patients with pain and depression |
| Lamb et al[77] | 769 | Community women >65 y | Knee pain | GDS | WOMOI | Depression ↑pain and effect on walking ability/limited mobility |
| Leino and Magni[34] | 607 | Metal plant | Employees with musculoskeletal symptoms | Depressive symptoms | Musculoskeletal survey | Depressive symptoms predict future musculoskeletal symptoms and findings in men |
| Painter et al[122] | 50 | Pain center | Chronic pain conditions | MMPI | Pain scales | Depression more common in treatment failure group |
| Potter and Jones[123] | 45 | Primary care | Musculoskeletal pain (new onset) | GBQ | MPQ | Depression on screening was associated with development of chronic pain |
| Power et al[124] | 571 | British birth cohort | Low back pain | "Malaise Inventory" | Back pain history | Depression doubled risk of incident low back pain |
| Reis et al[125] | 219 | Family practice | Low back pain (new onset) | 3-item Depression Tool | Low back pain complaint | Depression was strong predictor of chronicity |
| Taenzer et al[126] | 40 | Surgical patients | Gallbladder surgery | BDI | Postoperative pain | Significant correlation between depression score and postoperative pain |
| Von Korff et al[127] | 803 | HMO enrollees | Common pain symptoms | SCL-90R | Pain interview | Moderate to severe depressive symptoms predicted new onset of chest pain and headache; nonsignificant onset rates for back pain, abdominal pain, and TMD pain |
| Wells et al[82] | 2554 | HMO and solo practice | Patients with depressive symptoms | Depressive symptoms/DIS | Survey | Major depression causes ↑ pain symptoms, ↑ functional disability, and ↓ social function |

Abbreviations: BDI, Beck Depression Inventory; CIDI, Composite International Diagnostic Interview; CPSP, Chronic Pain Scale and Persistence; DIS, Diagnostic Interview Schedule; GBQ, Goldberg's Brief Questionnaire; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HMO, health maintenance organization; MMPI, Minnesota Multiphasic Personality Inventory; MPQ, McGill Pain Questionnaire; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCL-6, Symptom Checklist–6 items; SCL-90, Hopkins Symptoms Checklist, 90 items; SCL-90R, SCL-90 Revised; SF20, 20-Item Short-Form Health Survey; TMD, temporomandibular disorder; WOMOI, Western Ontario McMaster Osteoarthritis Index; ZDI, Zung Depression Index; ↑, increased; ↓, decreased.

pain, headache, and musculoskeletal complaints were predicted by the presence of depression.[34,35,124,127]

Functional limitations (eg, limited mobility, activity restrictions) and resulting disability, such as days in bed ill and hospitalizations, were increased in patients with pain and depression.[77,82,89,116,117] Similarly, depression and pain produced additive impairments in social functioning,[76,82] higher unemployment rates,[42,55,67,118] and diminished patient satisfaction.[103] Engel et al[119] showed that increased depressive

symptoms in patients with low back pain also increased health care utilization. Higher depressive symptoms were associated with more primary care follow-up visits for back pain, more back pain–related radiographs, more pain medication refills, and higher total costs.[89] "Poor outcomes" were observed at short-term (7 weeks) and long-term (1 year) follow-up.[103] In surgical patients, those with higher preoperative depression scores experienced greater postoperative pain.[126]

Some studies[35,116] and a literature review by Linton[128] have suggested that depression has a greater impact than other clinical factors on outcomes, especially functional impairment, in patients with pain, and that neglecting to treat the depression accounts for some of the pain treatment failures.[38,52] Patients with depression and chronic pain were less likely to comply with pain rehabilitation and thus more likely to relapse following treatment.[121,122] Although most studies (Table 3) support the finding that patients with pain and depression have poorer overall response to treatment than pain patients without depression, a few did not report such a relationship.[55,121,129,130]

## IS ANTIDEPRESSANT TREATMENT FOR PAINFUL SYMPTOMS AND COMORBID DEPRESSION EFFECTIVE?

Feinmann[131] has previously reviewed studies that reported pain relief associated with depression symptom relief. We identified 22 studies[6,71,132-151] that examined antidepressant efficacy for treating pain symptoms and subsequent depression response (**Table 4**). We did not include studies of symptom syndromes (eg, fibromyalgia, irritable bowel syndrome, migraine headaches) or studies excluding patients with depression or organic pain (eg, diabetic neuropathy, cancer pain) because these conditions have been reviewed previously, and antidepressants were found to be effective.[18-20,152,153] The primary outcome in all the studies in Table 4 was pain relief or other pain outcomes, while depression symptom relief was one of the secondary outcomes. Sample sizes were relatively small, ranging from 14 to 253. Only 4 studies[6,132,137,141] were conducted in a primary care setting, with the remainder situated in pain, psychiatric, and specialty clinics. The intervention arm of each selected study usually involved tricyclic antidepressants, and only 4 studies involved selective serotonin reuptake inhibitors (SSRIs)[135,138,143,145] to assess pain and depression. While most of the studies demonstrated improvement in both pain and depression symptoms, a few of the studies[132,142,147] failed to show symptom relief. Whether SSRIs improve painful symptoms associated with depression is unsettled. Most studies were uncontrolled, of short duration (averaging 9 weeks), and used doses that were subtherapeutic for adequate depression treatment.

Anecdotal reports note that when depression is successfully

**Table 4. Effect of Antidepressants on Pain and Comorbid Depression Outcomes**

| Source | No. of Patients | Setting | Sample | Medication(s) | Outcome | |
|---|---|---|---|---|---|---|
| | | | | | Pain | Depression |
| Alcoff et al[132] | 50 | Family practice | Chronic low back pain | Imipramine | No change | No change |
| Blumer et al[133] | 104 | Pain clinic | Chronic pain | Amitriptyline, imipramine, loxapine, carbamazepine | 57% Improved | Improved |
| Cannon et al[134] | 60 | National Institutes of Health | Chest pain | Imipramine | Improved | No change |
| Dickens et al[135] | 98 | Rheumatology clinic | Low back pain | Paroxetine, placebo | No difference | No difference |
| Feinmann et al[136] | 93 | Oral surgery clinic | Psychogenic facial pain | Dothiepin | Improved | Improved |
| Gringras[137] | 55 | General practice | Rheumatic pain | Tofranil | Improved | Improved |
| Gourlay et al[138] | 20 | Pain clinic | Chronic pain | Zimelidine | No difference | No difference |
| Hameroff et al[139] | 30 | Pain clinic | Low back pain, cervical pain | Doxepin | Improved | Improved |
| Hameroff et al[140] | 60 | Pain clinic | Low back pain, cervical pain | Doxepin | Improved | Improved |
| Hill and Blendis[141] | 27 | Outpatient practice | "Nonorganic" abdominal pain | Amitriptyline, imipramine | 100% Improved | 100% Improved |
| Jenkins et al[142] | 44 | Rehab unit | Low back pain | Imipramine | No change | No change |
| Johansson and von Knorring[143] | 40 | Pain clinic | Chronic pain | Zimelidine, placebo | Improved | No difference |
| Lascelles[71] | 40 | "Face pain" clinic | Atypical facial pain | Phenelzine | 75% Improved | Improved |
| Lindsay and Wyckoff[6] | 116 | Private practice | "Recurring benign pain" | Amitriptyline, imipramine, desipramine, doxepin | 83% Improved | Not mentioned |
| Loldrup et al[144] | 253 | Multisite | Chronic idiopathic pain | Clomipramine, mianserin | No change | 75% Improved |
| Manna et al[145] | 40 | Psychiatry clinic | Chronic tension headache | Fluvoxamine, mianserin | Improved | Improved |
| Merskey and Hester[146] | 30 | Psychiatry clinic | Various pain syndromes | "Antidepressants," phenothiazines, antihistamines | 70% Improved | Improved |
| Pilowsky et al[147] | 32 | Pain clinic | Pain of unknown origin | Amitriptyline | No change | No change |
| Sherwin[148] | 14 | Neurology clinic | Headache | Amitriptyline, perphenazine | 70% Improved | Improved |
| Singh and Verma[149] | 60 | Psychiatry clinic | Pain, no etiology | Amitriptyline, imipramine | 80% Improved | Improved |
| Tyber[150] | 34 | "Private practice" | Shoulder pain | Amitriptyline, lithium | Improved | Improved |
| Ward et al[151] | 36 | Newspaper ad respondents | Chronic back pain | Doxepin, desipramine | 50% Improved | 70% Improved |

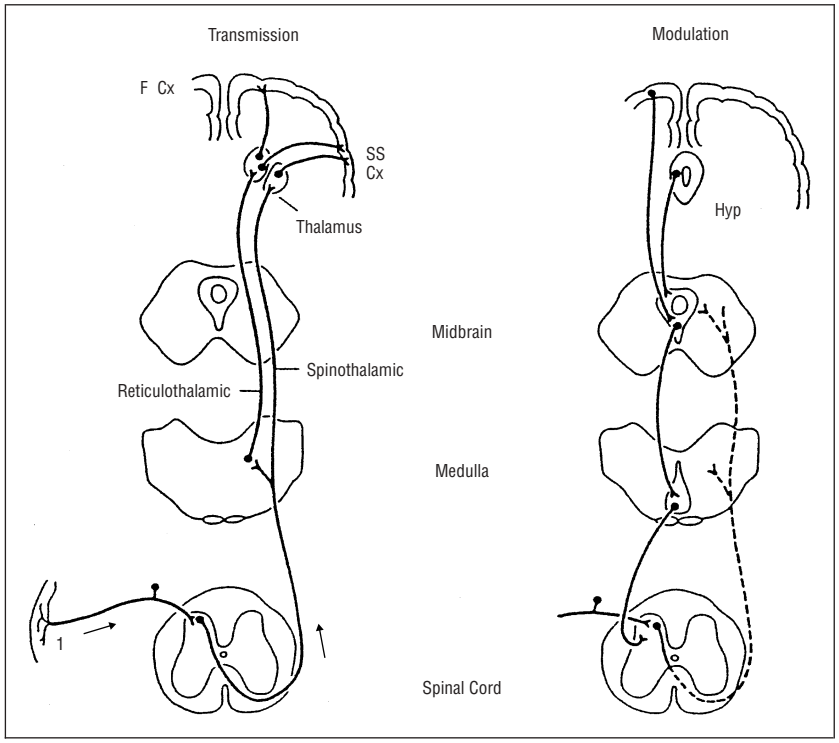
treated, the patient's somatic symptoms, particularly pain complaints, are also relieved.[59,88] In a 6-week clinical trial comparing fluoxetine with placebo, outpatients with major depression who were treated with active medication had significant improvements in functional health, including painful symptoms, compared with the placebo group.[154] However, a trial investigating a collaborative management program for depression vs usual care showed significantly fewer somatization symptoms at follow-up but no significant intervention effect on pain symptoms.[155] A relatively recent meta-analysis[153] of antidepressant use in treating symptom syndromes and unexplained symptoms found that symptom improvement did not usually correlate with depression response in the studies where both pain and depression were assessed. Only a third of studies showed improvement in physical symptoms in concert with depression response. Similarly, a review of cognitive-behavioral therapy for somatic symptoms showed an effect on somatic symptoms that appeared, at least in part, independent of an effect on psychological distress.[156] Several studies have examined the use of SSRIs in pain syndromes such as diabetic neuropathy and fibromyalgia, but few of these have assessed changes in both pain and depression.[157] On the other hand, Ward et al[32] reported that the degree of depression improvement correlated with the amount of pain relief. Other studies have suggested that the combination of antidepressants and cognitive behavioral therapy may be effective in treating patients with both chronic pain and depression.[6,44,47]

## WHAT ARE THE COMMON BIOLOGICAL PATHWAYS FOR DEPRESSION AND PAIN, AND WHAT ARE THE IMPLICATIONS FOR TREATMENT?

The biochemical theory of depression posits that depression is the result of a neurochemical imbalance or a functional deficiency of key neurotransmitters, the monoamines: serotonin, norepinephrine, and dopamine. A common theory holds that depression and painful symptoms follow the same descending pathways of the central nervous system. Eight studies described the biological link between depression and pain. Although nociceptive fibers transmitting pain signals from the periphery of the body through the dorsal horn to the medulla, midbrain, hypothalamus, thalamus, limbic cortical areas (anterior cingulate and insular cortex), somatosensory cortex, and posterior parietal cortex have been carefully mapped, there is an increasing interest in the neuroanatomy of a descending system of pain modulation.[158] The increasing knowledge about this system allows scientists and physicians to better understand mechanisms of pain modulation via medications as well as psychological mechanisms such as expectation, attention and distraction, and negative and positive affect.

The periaqueductal gray (PAG) is a key anatomic structure in the pain modulation system.[158,159] As shown in the **Figure**, the PAG is an anatomic relay from limbic forebrain and midbrain structures to the brainstem. The amygdala, hypothalamus, and frontal neocortex all send fibers to the PAG, which connects with relay systems in the pons and medulla.[159] These relay systems contain serotonergic neurons such as those in the rostral-ventromedial medulla (RVM) as well as noradrenergic neurons such as those in the dorsolateral pontine tegmentum (DLPT).[160] The RVM sends projections to the dorsal horn directly, whereas the DLPT affects dorsal horn neurons indirectly by its projections to the RVM as well as having direct connections (inhibitory only) to the dorsal horn. The RVM has 2 types of cells important in pain perception: "on cells," which facilitate pain transmission; and "off cells," which inhibit pain perception.[158]

The on and off cells in the RVM through data transmitted from the limbic forebrain and other structures transmitted through the PAG may amplify or dampen pain impulses transmitted from the periphery. Activation of the RVM off neu-




On the left is illustrated the transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction (1). The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the 2 major ascending pain pathways, the spinothalamic and spinoreticulothalamic. The message is relayed in the thalamus to both the frontal cortex (F Cx) and the somatosensory cortex (SS Cx). On the right is the pain modulation network. Inputs from the frontal cortex and hypothalamus (Hyp) activate cells in the midbrain, which control spinal pain transmission cells via cells in the medulla. (Figure reproduced from Fields HL. *Pain.* New York, NY: McGraw-Hill; 1987, with permission.)

rons or the DLPT neurons via electrical stimulation depresses the activity of nociceptive neurons in the spinal dorsal horn.[158,160] These bidirectional on/off systems determine vigilance to either external threats or sensations coming from inside the body.[158,161] Limbic structures, the PAG, and these on and off cells determine affect and attention to peripheral stimuli. Normally, this system has a modulatory effect, tending to dampen signals coming in from the body so that these signals are suppressed, allowing attention to be focused on more important events outside of the body.[159,161] However, with depletion of serotonin and norepinephrine, as occurs in depression, this system may lose its modulatory effect such that minor signals from the body are amplified, and more attention and emotion are focused on them. This explanation may tell us why patients with depression describe multiple pain symptoms and why their pain is often associated with increased attention, focus, and negative affect.

Studies have shown that the PAG and relay sites in the midbrain, medulla, amygdala, and dorsal horn are rich in endogenous opioids such as enkephalins.[158,162] Experimental studies have shown that morphine applied at any of the above sites of the descending pain modulatory system (limbic cortex, midbrain, medulla, or dorsal horn) blocks peripheral pain signals.[158,162] Serotonin and norepinephrine given intrathecally also block pain signals.[158,160] By increasing levels of serotonin and norepinephrine availability in key brain areas, antidepressants also have effects on modulating pain signals.[163] This effect of antidepressants may be greatest for medications that increase availability of serotonin and norepinephrine.[163]

Studies have shown that brain regions involved in the generation of emotion (eg, the medial prefrontal, insular, and anterior temporal cortex, hypothalamus, and amygdala) send many projections to brainstem structures involved in pain modulation (PAG and RVM).[158] Studies have shown that the activity of the anterior cingulate gyrus increases with peripheral pain stimuli, such as heat applied to the skin, but it also has increased activity when warm stimuli are applied if the patient is expecting hot stimuli.[158,164,165] Negative anticipation causes key brain areas to activate, and the subject then appears to focus, attend to, and rate the pain stimuli as more severe. Distraction from pain signals in experimental pain has been shown in other experiments to decrease activation of PAG and decrease pain perception.[164,165] Also, opiates excite off cells and inhibit on cells. These 2 effects help suppress pain signals. Perhaps these experiments suggest how depression, which is associated with negative expectancies, may amplify pain signals by activating brain structures such as the anterior cingulate gyrus. Depression is also associated with depletion of serotonin and norepinephrine, which may decrease the modulatory effect of this descending pain system.

## CONCLUSIONS

Several key themes emerged from our review of the relationship between depression and pain. First of all, the prevalence of pain in a depressed sample and the prevalence of depression in a pain sample are higher than the prevalence rates when the conditions are individually examined. On average, 65% of patients with depression experience one or more pain complaints, and depression is present in 5% to 85% (depending on the study setting) of patients with pain conditions. Depression is most prevalent in pain, psychiatric, and specialty clinics vs population-based or primary care studies.

Second, the presence of pain negatively affects the recognition and treatment of depression. Depression is often underrecognized and thus frequently undertreated. At least 75% of primary care patients with depression present with physical complaints exclusively[92,166] and seldom attribute their pain symptoms to depression or other psychiatric illness. These physical complaints may be due to amplification of chronic physical disease and remain medically unexplained after extensive workup. As a result, providers frequently assess for physical causes of pain and treat medically instead of exploring the pain symptoms in a broader, biopsychosocial context.

Primary care providers should recognize that pain is a common symptom of depression, that depression and painful conditions frequently coexist, and that evaluation and treatment of both are important. At least in primary care settings, the typical depression presentation is complicated more often by painful symptoms and physical complaints than emotional symptoms of sad mood or anhedonia. The patient who presents "looking depressed" is not difficult to recognize for most providers but may represent the minority of patients with depression seen in primary care.

Recognition would likely be improved by screening for depression in any patient with unexplained pain or unexplained exacerbation of a stable painful condition. Often patients are referred to specialists with expertise in treating pain or expertise in treating depression rather than to a provider who is comfortable treating both. Primary care physicians seem to be in the best position to manage both conditions but may lack the knowledge and experience to tackle this difficult but common clinical situation. Also, the short visit times, inadequate reimbursement, and competing demands on the primary care physician can interfere with optimal management of these complex conditions.[167,168]

Different aspects of pain negatively affect several depression outcomes. Increasing pain severity, pain that interferes with daily activities, frequent pain episodes, diffuse pain, and pain that is refractory to treatment are all associated with more depressive symptoms and more severe depression. Additionally, as pain severity worsens, other depression outcomes such as functional limitations, health-related quality of life, and work function are adversely affected. Pain with comorbid depression also appears to be additive in terms of an increased number of medical visits and higher health care costs. The prognosis of comorbid depression and pain is poor compared with the prognosis

for individuals with depression without pain.[169] What is not clear is whether patients with depression and pain are less responsive to usual depression management than those with depression alone.

Our literature review establishes the reciprocal nature of the depression-pain relationship. Depression complicates the management of patients with pain and is associated with poorer outcomes. In patients with pain, depression is associated with more pain complaints, greater pain intensity, longer duration of pain, and greater likelihood of nonrecovery. Additive impairments in social function, work function, and functional limitations (eg, limited mobility and restricted activity) are seen when depression and pain coexist. Depression also predicts increased health care utilization, poorer adherence to treatment, worse patient satisfaction, and future episodes of pain.

Most studies that examined antidepressant treatment of pain conditions suggested that pain and depression symptoms improved simultaneously, with the caveats that most of these studies were uncontrolled, of short duration, and designed more to measure pain response. Tricyclic antidepressants have been the predominant therapy evaluated. Preliminary data suggest that some of the newer antidepressants, including agents that act on several receptors (eg, norepinephrine and serotonin), may be useful in chronic pain.[170-173] However, larger clinical trials on non–tricyclic antidepressants in patients with comorbid depression and pain are needed. Unfortunately, very few depression treatment trials have assessed whether pain improves in concert with depression symptoms and whether greater improvement in pain or depression relates to greater improvement in the other condition. Despite the promising findings that depression and pain respond to antidepressant therapy, many patients are treated primarily with pain-relieving medications that have little intrinsic antidepressant effect.

Recent research has provided evidence of a central pain modulation system that can either dampen or amplify nociceptive signals from the periphery. Both serotonin and norepinephrine have been shown to dampen peripheral pain signals. This explains how depression, which is associated with a dysregulation of these key modulating neurotransmitters along a shared pathway, may contribute to the frequent presence of painful symptoms. Thus the decrease in one or both of these neurotransmitters may increase peripheral pain messages and affect how antidepressants that increase these neurotransmitters decrease pain signals.

In summary, the combination of depression and pain is associated with worse clinical outcomes than either condition alone. Thus, a treatment model that incorporates assessment and treatment of both depression and pain seems necessary for more optimal outcomes. More research is needed to determine if alleviation of pain helps the patients' depressive symptoms and, likewise, whether relief of depressive symptoms improves pain and its related morbidity. Inattention to pain can cause refractoriness to depression treatment and not addressing depression can preclude successful pain treatment.Dual therapy trials are needed to see if depression and pain outcomes can be improved with attention to their comorbidity.

*Accepted for publication January 31, 2003.*

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*This project was supported in part by grant T-32 PE15001 from the Health Resources and Service Administration and by funding from Eli Lilly and Company, Indianapolis, Ind.*

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