Pain Predicts Longer Time to Remission During Treatment of Recurrent Depression

Jordan F. Karp, M.D.; John Scott, M.A.; Patricia Houck, M.S.H.; Charles F. Reynolds III, M.D.; David J. Kupfer, M.D.; and Ellen Frank, Ph.D.

Introduction: Pain and depression are mutually exacerbating. We know that both of these syndromes predict the future occurrence of the other. It has not been shown, however, whether the presence of pain slows the effect of treatment for depression. We hypothesized that greater pain and somatic scores prior to treatment with imipramine and interpersonal psychotherapy would predict a slowed time to remission from depression.

Method: We performed secondary data analyses of an archived study. Subjects (N = 230) were between 21 and 65 years of age and were enrolled in a study of maintenance treatment for recurrent unipolar depression. Patients had to meet Research Diagnostic Criteria (RDC) for a major depressive episode and historical requirements for at least 3 prior episodes and clear remissions (according to RDC). Patients were also required to have a minimum Hamilton Rating Scale for Depression score of 15 and a minimum score of 7 on the Raskin Severity of Depression Scale. This report describes the acute treatment phase, during which all subjects received combination therapy consisting of imipramine hydrochloride (150 to 300 mg) and interpersonal psychotherapy. Pain and somatization were measured with the Hopkins Symptom Checklist.

Results: Higher levels of both pain and somatization predicted a longer time to remission. After controlling for baseline severity of depression, only pain was still significant in predicting a longer time to remission. Headache and muscle soreness were the 2 variables from the pain index whose presence independently predicted a slower remission. Both pain and somatization improved during acute treatment. Subjects with more pain and somatization, after controlling for severity of depression, reported more suicidality. Women reported more pain than men.

Conclusions: Pain, but not somatization, predicted a longer time to remission and may be a marker of a more difficult-to-treat depression. Adults with recurrent depression should be screened for the presence of pain prior to treatment, as the presence of these symptoms may require more aggressive treatment or may be a marker for suicidality or the use of dual-mechanism antidepressants.

(J Clin Psychiatry 2005;66:591–597)

Received May 26, 2004; accepted Oct. 5, 2004. From the Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pa.

Supported in part by grants MH29618, MH30915, AG00972, P30-MH52247, and T32-MH19986 from the National Institute of Mental Health (Bethesda, Md.).

Dr. Karp serves on the speakers bureau for Pfizer. Dr. Reynolds has received grant/research support from Forest, Pfizer, and GlaxoSmithKline. Dr. Kupfer is a consultant to Servier Amerique and serves on the advisory board for Pfizer, Eli Lilly, Forest, and Hoffman-LaRoche. Dr. Frank is a consultant to Eli Lilly, Pfizer, and Pfizer Italia and has received grant/research support from Forest.

Corresponding author and reprints: Jordan F. Karp, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213 (e-mail: karpjf@upmc.edu).

The relationship between pain and depression has been observed for years. It has been reported that both syndromes are mutually exacerbating[1]: pain worsens depression, and depression worsens the experience of pain. The clinical implications of this phenomenon are reflected in a recent review of the pain-depression literature,[2] which determined that the presence of pain negatively affects the recognition, experience, and treatment of depression. The review also emphasized that (1) 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 and (2) depression in patients with pain is associated with more pain complaints and greater impairment.

Despite reports of the therapeutic effects of antidepressants, in particular the tricyclics, on somatic and pain complaints,[3–9] interest in the analgesic effect of antidepressants decreased during the 1980s and 1990s, as the antinociceptive properties of the selective serotonin reuptake inhibitors (SSRIs) were in general found to be unremarkable.[10–13] With the emergence of the serotonin-norepinephrine reuptake inhibitors (SNRI), which have pharmacologic effects similar to tricyclics, interest in the analgesic effects of antidepressants has increased, and pain is now being assessed systematically in trials with these agents. A report of data from animal and human experimental studies on pain relief with antidepressants supports the superior efficacy of dual-mechanism antidepressants in providing analgesia, especially for neuropathic pain syndromes.[14]

Neuropathic pain is defined by the International Association for the Study of Pain as pain initiated or caused by

a primary lesion or dysfunction in the nervous system.[15] Patients with neuropathic pain may complain of "pins and needles" or "burning feet." This type of pain is in contrast to nociceptive pain, which involves the activation of the nociceptive system by noxious stimuli such as pressure, temperature, tissue inflammation, mechanical deformation, distention of a hollow organ, or disruption of membrane integrity. Nociceptors are found in skin, muscle, joints, and viscera.[16]

Another example of the efficacy of antidepressants in the treatment of reported pain in depressed patients is a treatment study using the SNRI duloxetine, recently approved by the U.S. Food and Drug Administration (FDA). This report demonstrated the favorable efficacy of duloxetine versus placebo in improving pain and in achieving remission of major depressive disorder.[17] Patients who achieved remission of depression with duloxetine 60 mg daily were noted to have more than 3 times the improvement in overall pain severity versus placebo. Other reports support the use of venlafaxine (another SNRI that is FDA approved for the treatment of both major depressive disorder and generalized anxiety disorder) in the treatment of pain.[18–23] It has been postulated that the higher remission rates achieved with SNRIs versus SSRIs may be due to an efficacy profile that addresses a wider range of depression symptoms: the physical along with the psychological.[24,25]

Recent work has suggested that patients being treated for depression who also report increased levels of bodily pain have a more difficult time achieving antidepressant response. For example, Fava[26] showed that responders who had not achieved remission had significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. However, to our knowledge there are no reports of the effect of the presence of reported pain prior to beginning antidepressant treatment on time to remission from depression. We hypothesized that in a well-characterized sample of adults with recurrent depression, higher levels of reported bodily pain at baseline would predict a delayed time to remission in response to treatment with imipramine and interpersonal psychotherapy (IPT).

METHOD

We performed secondary data analyses of an archived study[27] to test this hypothesis. Method and study design have been described in detail elsewhere[27] but will be briefly reviewed. The original protocol from which our sample was drawn was designed to explore the relative efficacy of 5 maintenance treatment strategies in preventing or delaying recurrences in a sample of patients with highly recurrent unipolar depression.[27,28] To enter the Maintenance Therapies in Recurrent Depression protocol, subjects between ages 21 and 65 years were required to have a minimum 10-week remission between the index episode (3rd or greater episode) and the immediately prior episode, according to Research Diagnostic Criteria (RDC).[29] A minimum Hamilton Rating Scale for Depression (HAM-D)[62] score of 15 and a minimum score of 7 on the Raskin Severity of Depression Scale[30] were also required for study participation. Eligible patients were then evaluated using the Schedule for Affective Disorders and Schizophrenia.[31] Those patients who met both RDC for a major depressive episode and the historical requirements for previous episodes and clear remissions were entered into the protocol. After complete description of the study to the subjects, written informed consent was obtained.

Table 1. Somatic and Pain Items of the Hopkins Symptom Checklist

Somatic symptom
Headaches
Pains in heart or chest
Pains in lower back
Soreness of your muscles
Faintness or dizziness
Nausea or upset stomach
Trouble getting your breath
Hot or cold spells
Numbness or tingling in parts of your body
A lump in your throat
Feeling weak in parts of your body
Heavy feelings in your arms or legs
Pain symptom
Headaches
Pains in heart or chest
Pains in lower back
Soreness of your muscles

Prior to entering the maintenance phase of the study, all patients (N = 230) received acute treatment consisting of a combination of imipramine hydrochloride (150 to 300 mg) and IPT.[32] At baseline, in addition to the depression severity criteria described above, both self-reported somatic and pain symptoms were assessed with the Hopkins Symptom Checklist (SCL-90).[33] Each item of the SCL-90 is rated on a 5-point Likert scale, and is a response to the question, "How much were you bothered by . . . ?" The time assessed is the past 7 days. The somatic domain of the SCL-90 was used to determine the somatic score. We created a pain domain from the SCL-90 by selecting the 4 questions that were pain specific. The items that make up both the somatic and pain scores are shown in Table 1. The domain score is an average of the items, with a higher score indicating greater symptomatology.

Treatment sessions were scheduled weekly for 12 weeks, then biweekly for 8 weeks, and then monthly. Remission was defined as achieving both a HAM-D score of less than or equal to 7, and a Raskin score of less than or equal to 5, for 3 consecutive weeks. When these criteria were met, patients entered the continuation phase of the study.

Table 2. Baseline Characteristics of Subjects Enrolled in a Study of Maintenance Treatment for Recurrent Depression

Variable	N	Mean	SD	Median
Hopkins Symptom Checklist score				
Pain	221	0.84	0.76	0.75
Somatic	211	0.65	0.57	0.50
17-item Hamilton Rating Scale for Depression score	221	21.36	4.93	21.00
Global Assessment Scale score	221	50.70	9.50	51.00
Education, y	179	13.56	2.35	13.00
Age, y	230	39.47	10.57	38.00
Age at onset of depression, y	224	26.92	10.33	24.50
No. of previous episodes	228	6.22	5.96	4.00
Duration of index episode, wk	225	23.89	18.09	18.00
	N	%		
Gender				
Female	180	78		
Male	50	22		
Race				
African American	10	4		
White	219	95		
Asian	1	0.4		

Statistical Analyses

We used Cox proportional hazards models to test the effect of baseline pain and somatic symptoms on time to remission. Covariate-adjusted survival curves for the effect of pain on time to remission, controlling for severity of depression, were produced using the corrected group prognosis method.[34] Paired t tests were used to determine whether there was significant improvement in pain and somatic symptom scores from baseline to remission (i.e., completer analyses). Item analysis of the pain scale, using proportional hazards modeling, was performed to determine the effect on time to remission of each of the 4 items. Spearman correlation coefficients were used to explore the relationship between pain and somatic scores at baseline and other demographic and clinical characteristics (i.e., Global Assessment Scale [GAS][35] scores). The Wilcoxon rank-sum test was used to compare pain and somatization scores as a function of gender and race. Statistical significance was set at $p \leq .05$)

RESULTS

Effect of Pain and Somatic Symptoms on Time to Remission

Table 2 describes the baseline characteristics of the entire sample. Pain and somatic scores were dichotomized into groups of patients who endorsed either an (1) average item score of less than "a little bit" or (2) average item severity ranging from "a little bit" to "extreme." This decision to dichotomize the groups left a substantial number of patients in each group (85 in the higher-pain group, 136 in the lower-pain group, 60 in the higher-somatic group, and 151 in the lower-somatic group) and effectively split the group into those with and without somatic and pain complaints. Higher pain ($\chi^2 = 7.5$, df = 1, p = .006, hazard ratio = .61) and somatic ($\chi^2 = 4.8$, df = 1, p = .03, hazard ratio = .65) scores were significantly associated with longer time to remission in proportional hazards models.

Since pain and somatic symptoms at baseline are probably related to severity of depression (which is supported by the substantial correlation between HAM-D score and the SCL-90 domain scores), we reanalyzed the proportional hazards models for time to remission, this time controlling for baseline HAM-D score. Greater pain was still significantly associated with longer time to remission after controlling for severity of depression ($\chi^2 = 4.1$, df = 1, p = .04, hazard ratio = .69), but somatic scores no longer were ($\chi^2 = 1.1$, df = 1, p = .29, hazard ratio = .80). Table 3 shows the distribution of the different pain item scores at baseline.

The Kaplan-Meier estimate of median time to remission was 17 weeks (remission rate = 68%) for subjects in the group reporting pain and 12.3 weeks (remission rate = 79%) for patients not reporting pain. For the somatic scores, the estimated median time to remission was 19.1 weeks for patients in the group reporting somatic symptoms versus 12.9 weeks for patients not reporting somatic symptoms. Figure 1 illustrates the effect of pain on time to remission after correcting for baseline depression severity.

Each of the 4 individual pain items measured at baseline were entered individually into a univariate proportional hazards model. Both headache ($\chi^2 = 5.3$, df = 1, p < .02) and muscle soreness ($\chi^2 = 5.5$, df = 1, p < .02) were associated with a slowed time to remission. Chest pain and low back pain were not statistically significant.

Change in Pain and Somatic Scores During Treatment

Paired t tests were used to determine whether there was significant improvement in pain and somatic symptom scores from baseline to remission (i.e., completer analyses). There was highly significant improvement on both measures (pain scores: from a mean of 0.8 to 0.3, t = 8.3, df = 148, p < .0001; somatic scores: from a mean of 0.7 to 0.3, t = 8.7, df = 148, p < .0001).

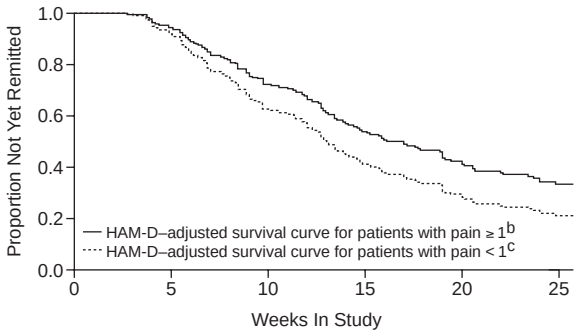
Relationship of Pain and Somatic Scores to Measures of Depression Severity at Baseline

Spearman correlation coefficients were used to explore the relationship between pain and somatic scores at baseline and other demographic and clinical characteristics. As reported earlier, both pain and somatic scores were substantially and significantly correlated with baseline HAM-D scores ($\rho = .32$ and $\rho = .44$, respectively, p < .0001 in both cases). There were smaller but significant correlations between baseline pain and the HAM-D suicide item (item 3) score ($\rho = .13$, p = .05). Pain was not correlated with age ($\rho = -.06$, p = .38). Baseline somatic scores were also associated with the HAM-D sui-

Table 3. Distribution of Scores on Hopkins Symptom Checklist Pain Items at Baseline for Subjects Enrolled in a Study of Maintenance Treatment for Recurrent Depression (N = 221)

How much were you bothered by…?	0 = Not at all N (%)	1 = A little bit N (%)	2 = Moderately N (%)	3 = Quite a bit N (%)	4 = Extremely N (%)
Headaches	63 (29)	64 (29)	34 (15)	45 (20)	15 (7)
Pains in heart or chest	169 (77)	31 (14)	15 (7)	5 (2)	1 (1)
Pains in lower back	136 (62)	30 (14)	28 (13)	20 (9)	7 (3)
Soreness of muscles	134 (61)	39 (18)	27 (12)	15 (7)	6 (3)

Figure 1. Baseline Hamilton Rating Scale for Depression (HAM-D)–Adjusted Survival Curves for Time to Remission by Degree of Pain in Subjects Enrolled in a Study of Maintenance Treatment for Recurrent Unipolar Depression (N = 221)[a]



[a]Truncated at 26 weeks, which retained 15% of the sample in the analysis.
[b]Pain score ≥ 1 = "a little bit" to "extreme"; median time to remission = 17 weeks; rate of remission = 68%.
[c]Pain score < 1 = less than "a little bit"; median time to remission = 12.3 weeks; rate of remission = 79%.

cide item score (ρ = .20, p = .004), the GAS score (ρ = –.18, p = .01), and fewer years of education (ρ = –.17, p = .03).

Differences by Race or Gender on Pain and Somatic Scores

Wilcoxon rank-sum tests were used to determine if baseline pain and somatic scores differed significantly depending on gender or race of the subjects. There were significant differences between women and men on both pain (z = –3.0, p = .003) and somatic scores (z = –3.0, p = .003), with women reporting more severe symptoms in both cases. There were no significant differences between white (N = 219) and African American (N = 10) patients on either pain (z = 1.0, p = .31) or somatic scores (z = 1.1, p = .26).

DISCUSSION

As hypothesized, we found that more reported pain at baseline predicted a longer time to remission. Despite item overlap, this relationship was not significant for the more general somatic domain once we adjusted for depression severity. We feel these findings are unique and significant because the presence and severity of pain were measured before treatment was initiated, and could be distinguished from somatic distress more generally with respect to treatment response variability. This finding is clinically useful, because patients who report more pain prior to receiving antidepressant treatment, for example at their initial psychiatric evaluation, may have a more difficult-to-treat depression. In other words, these patients may require more aggressive treatment, or longer treatment, to achieve remission. This point may be particularly salient in primary care, where many patients present with both pain and nonspecific somatic complaints as part of, or a prelude to, a depressive syndrome.[36]

These findings complement those of Fava,[26] who found that patients who reported more somatic complaints after 8 weeks of treatment with fluoxetine had not responded to treatment as well as patients with fewer somatic symptoms. Both studies suggest that pain and somatic symptoms are associated with a lower response rate. Unlike our report, however, the symptoms were measured after acute treatment, the symptoms were nonspecific somatic complaints, and the antidepressant was an agent that only modulates the serotonergic system. Our results show that symptoms of pain are treatable. We hypothesize that their presence requires higher doses of medication, dual-mechanism agents, and longer exposure to treatment to achieve remission.

The antidepressant imipramine has several interesting characteristics of relevance to this discussion. Imipramine, a tricyclic antidepressant, blocks the reuptake of norepinephrine and serotonin at nerve terminals, preventing their degradation and increasing their availability. This results in a decreased turnover of these amines in selective neurons. Both norepinephrine and serotonin appear to exert analgesic effects via descending pain pathways and therefore play a modulating role in pain. This mechanism of action is in addition to the analgesia caused by direct sodium channel blockade at the neuronal level.[37] The tricyclics are no longer first-line therapy for the treatment of affective disorders. They are, however, prototypical SNRIs, and data from antidepressant research studies from the past 30 years still have much to offer in helping us to understand the relationship between pain, depression, and dual-action antidepressants.

For example, our finding that pain and somatic symptoms, in addition to depression symptoms, decreased during acute treatment with imipramine reinforces our understanding of imipramine as an effective antidepressant as well as "analgesic" for the pain symptoms associated with depression. We do not know for certain if the reported bodily pain was secondary to a medical condition, such as arthritis or diabetes, or to the depression. However, given the relatively young age of the sample (median = 38 years), it is unlikely that chronic painful illnesses were the etiology of the pain symptoms. In general, it is neuropathic (e.g., secondary to diabetes, postherpetic neuralgia, poststroke pain syndromes) and not nociceptive (e.g., arthritis) pain that is more responsive to treatment with tricyclic antidepressants.[38] Future antidepressant trials that also assess pain and painful chronic illnesses in a more thorough and sophisticated manner at several timepoints during acute treatment (e.g., assessing the location, severity, temporal nature, and etiology of pain, as well as cognitive and emotional responses to it) will provide insight into the nature of the pain that antidepressants are treating in psychiatric patients.

We realize that using the word "pain" generically throughout this report is simplistic; the qualities of various painful symptoms and syndromes are unique and respond differentially to disparate treatments. In addition, while not included in our analysis, it is clinically useful to acknowledge that patients with increased numbers of pain symptoms are at an elevated risk of developing depression.[39] Our examination of the 4 pain symptoms in a univariate proportional hazards model revealed both headache and muscle soreness to be correlated with a slowed time to remission.

Stress-induced muscle hyperactivity has been proposed as an etiologic factor in the production of pain in the muscles of mastication and the temporomandibular joints.[40] In that study, Lundeen et al.[40] report on 52 patients with joint or muscle pain who were evaluated for level of stress. Their results suggest an association between pain, depression, and impairment of activity in the muscle-pain group but not in the joint-pain group.

This finding may be consistent with studies of fibromyalgia, a relatively common disorder[41] (especially among women) with symptoms of chronic musculoskeletal pain and stiffness, tenderness over specific trigger points, fatigue, and disrupted sleep. It has been reported that over half of patients diagnosed with fibromyalgia have a lifetime history of depression, although active depression is present in only one third.[42,43] Fibromyalgia, however, may be directly linked with depression, via cytokines or another central mechanism.[44] Many studies of arthritis (a joint disorder), however, suggest that disability, and not merely the presence of the illness, is the mediating variable between that chronic disorder and depression.[45,46] While answering yes to a self-report probe for muscle soreness is certainly not the same as a diagnosis of fibromyalgia, it is intriguing that muscle soreness, and not chest or back pain, was found to be significantly associated with a slower time to remission in these subjects treated with imipramine.

In addition to muscle soreness, headaches were also associated with a slowed time to remission from depression on the 4 pain items. This is consistent with literature that supports a relationship between headache and depression.[47–51] While the bidirectional relationship between pain, in particular headache, and depression has been established, the effect of these symptoms on time to remission from depression is a new finding. Clinically, this finding suggests that if patients report 4 or more pain symptoms, or if they report problems with either muscle soreness or headache, their depression may be slower to respond to treatment with antidepressants and psychotherapy. We feel it may be indicated to generalize our finding to antidepressants in general and not restrict our statements to imipramine, since tricyclics are "broad-coverage" antidepressants, and, in addition to their noted analgesia, also have prominent antiheadache properties.[52–54]

The fact that we found statistically significant correlations between reported pain and suicide, assessed by the HAM-D, may have several implications. First, bodily pain may be indicative of a more severe depression, as described above, which is reflected in the greater prevalence of suicidal ideation in these subjects. Studies conducted in our own laboratory of depressed older adults who also report suicidal ideation have shown these individuals to be slower to respond to antidepressant treatment[55] than those patients who do not report suicidal ideation. Finally, it has been reported that chronic pain may be a risk factor for suicide.[56] A limitation of our pain assessment is that the SCL-90 measures pain for the past week, which does not meet the conventional definition of "chronic" pain (present for at least 3–6 months). However, our results suggest that clinicians should be more vigilant about assessing suicidality in the presence of reported pain.

Race was not associated with pain and somatization. However, given the relatively few number of African American patients enrolled in the study (N = 10), our power is too low to draw any conclusions. We did find, however, that women reported more severe symptoms in both of these domains. This finding is supported by numerous reports of lower pain thresholds, greater pain severity, and more pain-related disability in women versus men.[57–60] Of note, in a study conducted by Unruh et al.,[61] women tended to report both more pain located in the head and more somatic problems. These women also reported significantly more intense pain than men. These findings suggest that clinicians should carefully assess for symptoms of pain in women with recurrent major depression, as these complaints are more common than in male

patients and, if present, may predict a slower response to antidepressant therapy.

While the SCL-90 is not designed to assess the presence of persistent pain syndromes, it does appear to discriminate between pain and general somatic complaints among depressed outpatients. The signal detected in this analysis—that self-reported pain slows antidepressant treatment response—supports the current revived interest among psychiatrists in the relationship between pain and depression. In conclusion, we feel that secondary analyses of archived data from the 1980s and 1990s, when pain was often an overlooked variable, may inform current and future intervention studies in the age of potent, and well-tolerated, dual-mechanism antidepressants.

Drug names: duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), venlafaxine (Effexor).

REFERENCES

1. Greden JF. Physical symptoms of depression: unmet needs. J Clin Psychiatry 2003;64(suppl 7):5–11
2. Bair MJ, Robinson RL, Katon W, et al. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433–2445
3. Kocher R. The use of psychotropic drugs in the treatment of chronic, severe pains. Eur Neurol 1976;14:458–464
4. Gringras M. A clinical trial of Tofranil in rheumatic pain in general practice. J Int Med Res 1976;4(suppl 2):41–49
5. Kvinesdal B, Molin J, Froland A, et al. Imipramine treatment of painful diabetic neuropathy. JAMA 1984;251:1727–1730
6. Bromm B, Meier W, Scharein E. Imipramine reduces experimental pain. Pain 1986;25:245–257
7. Poulsen L, Arendt-Nielsen L, Brosen K, et al. The hypoalgesic effect of imipramine in different human experimental pain models. Pain 1995;60:287–293
8. Enggaard TP, Poulsen L, Arendt-Nielsen L, et al. The analgesic effect of codeine as compared to imipramine in different human experimental pain models. Pain 2001;92:277–282
9. Sindrup SH, Bach FW, Madsen C, et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 2003;60:1284–1289
10. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. J Gen Intern Med 1997;12:384–389
11. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326: 1250–1256
12. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255–259
13. Sawynok J, Esser MJ, Reid AR. Peripheral antinociceptive actions of desipramine and fluoxetine in an inflammatory and neuropathic pain test in the rat. Pain 1999;82:149–158
14. Fishbain DA, Cutler R, Rosomoff HL, et al. Evidence-based data from animal and human experimental studies on pain relief with antidepressants: a structured review. Pain Med 2000;1:310–316
15. Merskey H, Bogduk N. Classification of Chronic Pain. Seattle, Wash: International Association for the Study of Pain Press; 1994:xi–xv
16. Byers MR, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:26–72
17. Fava M, Wohlreich MM, Mallinckrodt CH, et al. Does the alleviation of painful physical symptoms associated with depression lead to higher remission rates? In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif. NR 447:167
18. Lithner F. Venlafaxine in treatment of severe painful peripheral diabetic neuropathy [letter]. Diabetes Care 2000;23:1710–1711
19. Schreiber S, Bleich A, Pick CG. Venlafaxine and mirtazapine: different mechanisms of antidepressant action, common opioid-mediated antinociceptive effects: a possible opioid involvement in severe depression? J Mol Neurosci 2002;18:143–149
20. Songer DA, Schulte H. Venlafaxine for the treatment of chronic pain [letter]. Am J Psychiatry 1996;153:737
21. Taylor K, Rowbotham MC. Venlafaxine hydrochloride and chronic pain. West J Med 1996;165:147–148
22. Yilmaz ME, Kadiroglu AK, Kara IH, et al. Venlafaxine in the treatment of painful peripheral diabetic neuropathy in a uremic patient undergoing hemodialysis [letter]. MedGenMed 2002;4:23
23. Karp JF. Venlafaxine XR and chronic pelvic pain syndrome [letter]. J Clin Psychiatry 2004;65:880–881
24. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52:1166–1174
25. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
26. Fava M. The role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of depression. J Clin Psychiatry 2003;64(suppl 13):26–29
27. Frank, E, Kupfer DJ, Perel JM, et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093–1099
28. Frank E, Kupfer DJ. Maintenance treatment of recurrent unipolar depression: pharmacology and psychotherapy. In: Kemali D, Racagni G, eds. Chronic Treatments in Neuropsychiatry. New York, NY: Raven Press; 1985
29. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 1978;35:773–782
30. Raskin A, Schulterbrandt J, Reatig N, et al. Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. J Nerv Ment Dis 1969;148:87–98
31. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1978;35:837–844
32. Klerman GL, Weissman MM, Rounsaville BJ, et al. Interpersonal Psychotherapy of Depression. New York, NY: Academic Press, Basic Books Inc; 1984
33. Derogatis LR, Lazarus L. SCL-90-R, Brief Symptom Inventory, and matching clinical rating scales. In: Maruish M, ed. The Use of Psychological Testing for Treatment Planning and Outcome Assessment. Hillsdale, NJ: Erlbaum; 1994:217–248
34. Ghali WA, Quan H, Brant R, et al. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. JAMA 2001;286:1494–1497
35. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of a psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
36. Terre L, Poston WS, Foreyt J, et al. Do somatic complaints predict subsequent symptoms of depression? Psychother Psychosom 2003;72:261–267
37. Pancrazio JJ, Kamatchi GL, Roscoe AK, et al. Inhibition of neuronal Na+ channels by antidepressant drugs. J Pharmacol Exp Ther 1998;284: 208–214
38. McCleane G. Pharmacological management of neuropathic pain. CNS Drugs 2003;17:1031–1043
39. Dworkin SF, Von Korff M, LeResche L. Multiple pains and psychiatric disturbance: an epidemiologic investigation. Arch Gen Psychiatry 1990; 47:239–244
40. Lundeen TF, Sturdevant JR, George JM. Stress as a factor in muscle and temporomandibular joint pain. J Oral Rehabil 1987;14:447–456
41. Neumann L, Buskila D. Epidemiology of fibromyalgia. Curr Pain Headache Rep 2003;7:362–368
42. Hudson JI, Goldenberg DL, Pope HG Jr, et al. Comorbidity of fibromyalgia with medical and psychiatric disorders. Am J Med 1992;92:363–367
43. Triadafilopoulos G, Simms RW, Goldenberg DL. Bowel dysfunction in fibromyalgia syndrome. Dig Dis Sci 1991;36:59–64
44. Gur A, Karakoc M, Nas K, et al. Cytokines and depression in cases with fibromyalgia. J Rheumatol 2002;29:358–361
45. Dickens C, Creed F. The burden of depression in patients with rheumatoid arthritis. Rheumatology (Oxford) 2001;40:1327–1330
46. Katz PP, Yelin EH. The development of depressive symptoms among

women with rheumatoid arthritis: the role of function. Arthritis Rheum 1995;38:49–56
47. Breslau N, Lipton RB, Steward WF, et al. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology 2003;60:1308–1312
48. Marcus DA. Identification of patients with headache at risk of psychological distress. Headache 2000;40:373–376
49. Carroll LJ, Cassidy JD, Cote P. Factors associated with the onset of an episode of depressive symptoms in the general population. J Clin Epidemiol 2003;56:651–658
50. Venable VL, Carlson CR, Wilson J. The role of anger and depression in recurrent headache. Headache 2001;41:21–30
51. Materazzo F, Cathcart S, Pritchard D. Anger, depression, and coping interactions in headache activity and adjustment: a controlled study. J Psychosom Res 2000;49:69–75
52. Tomkins GE, Jackson JL, O'Malley PG, et al. Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 2001;111: 54–63
53. Plesh O, Curtis D, Levine J, et al. Amitriptyline treatment of chronic pain in patients with temporomandibular disorders. J Oral Rehabil 2000;27: 834–841
54. Mitsikostas DD, Gatzonis S, Thomas A, et al. Buspirone vs amitriptyline in the treatment of chronic tension-type headache. Acta Neurol Scand 1997;96:247–251
55. Szanto K, Mulsant BH, Houck P, et al. Occurrence and course of suicidality during short-term treatment of late-life depression. Arch Gen Psychiatry 2003;60:610–617
56. Fishbain DA. The association of chronic pain and suicide. Semin Clin Neuropsychiatry 1999;4:221–227
57. Chesterton LS, Barlas P, Foster NE, et al. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259–266
58. Fillingim RB, Doleys DM, Edwards RR, et al. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. Spine 2003; 28:143–150
59. Holtzman J, Saleh K, Kane R. Gender differences in functional status and pain in a Medicare population undergoing elective total hip arthroplasty. Med Care 2002;40:461–470
60. Keefe FJ, Lefebvre JC, Egert JR, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 2000;87:325–334
61. Unruh AM, Ritchie J, Merskey H. Does gender affect appraisal of pain and pain coping strategies? Clin J Pain 1999;15:31–40
62. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62