Translating Evidence on Depression and Physical Symptoms Into Effective Clinical Practice

This ACADEMIC HIGHLIGHTS section of The Primary Care Companion to The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference "Translating Evidence on Depression and Physical Symptoms Into Effective Clinical Practice," which was held November 27, 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.*

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Physical symptoms that seem to have no physical cause may obscure a mood disorder. In a series of presentations chaired by David A. Fishbain, M.D., experts reviewed evidence and offered opinions regarding diagnosis and treatment for overlapping pain and depression in primary care patients.

Pain and Depression in Primary Care

Although a patient may be more concerned with physical symptoms than emotional ones, Bill H. McCarberg, M.D., stated that clinicians must remember that painful physical symptoms often have an emotional aspect.

Presentation and Diagnosis

In primary care, patients often have physical symptoms that health care providers are unable to explain. Kroenke and Mangelsdorff[1] reviewed 1000 patient records from an internal medicine clinic and found an organic etiology for patients' symptoms in only 16% of cases despite diagnostic testing in more than two thirds of the cases (Table 1). Ten percent of the symptoms were considered to have a psychological cause related to depression, stress, anxiety, or grief. A review[2] of European studies showed an association between depression and painful physical symptoms in 46 of the 70 studies reviewed, whether in the general population, in patients presenting to a primary care physician, or in patients presenting to pain clinics or psychiatric clinics.

Kroenke and Price[3] found that in patients with any of 14 physical symptoms common in primary care, the lifetime risk of common psychiatric disorders was at least twice as high as in those without the symptom. Further, Dr. McCarberg advised that the greater the number of unexplained physical symptoms a patient has, the less likely it is that the primary problem is an anatomical abnormality. Katon et al.[4] found that when the number of medically unexplained somatic symptoms rose above 5 in women or 3 in men, the rates of lifetime major depressive disorder (MDD) or panic disorder increased significantly.

Physical symptoms are often the chief complaint of patients with depression, particularly in a primary care setting. Simon et al.[5] showed that 69% of patients with depression reported only somatic symptoms. Dr. McCarberg commented that when patients focus on physical symptoms, psychiatric disorders are more difficult for physicians to recognize than when patients report psychological symptoms. One study showed a drop in physician recognition of depression from 77% when psychosocial symptoms were described by patients to 22% when only physical symptoms were mentioned.[6]

Relationship Between Pain and Depression

Neurochemical pathways provide a link between depressive symptoms and physical symptoms. Many of the ascending serotonin and norepinephrine pathways in the brain mediate mood, suicidal ideation, changes in appetite, sleep, and pleasure; descending serotonergic and noradrenergic pathways modulate pain, such as headache and vague joint, back, or abdominal pain.[7,8] If norepinephrine-serotonin pathways malfunction, many emotional areas of the brain as well as physical areas of the body may be affected, and patients

Table 1. Three-Year Incidence and Probable Etiology of 14 Common Symptoms in 1000 Internal Medicine Outpatients[a]

Symptoms	Symptoms, No.	Probable Etiology, %		
		Organic	Psychological	Unknown
Chest pain	96	11	6	83
Fatigue	82	13	21	66
Dizziness	55	18	2	80
Headache	52	10	15	75
Edema	45	36	0	64
Back pain	41	10	0	90
Dyspnea	37	24	3	73
Insomnia	34	3	50	47
Abdominal pain	30	10	0	90
Numbness	26	19	4	77
Impotence	24	21	4	75
Weight loss	18	5	28	67
Cough	15	40	0	60
Constipation	12	0	0	100
Total	567	16	10	74

[a]Reprinted with permission from Kroenke and Mangelsdorff.[1]

may experience physical complaints as well as depression.[8]

Significant associations have been found between pain conditions and mood and anxiety disorders. McWilliams et al.[9] found that people with arthritis, migraine, and low back pain were at greater risk (odds ratio [OR] = 1.48 to 3.86) of having MDD, panic disorder, and generalized anxiety disorder, than people without a pain condition. Dr. McCarberg remarked that conversely, people with emotional symptoms are at increased risk for physical health problems. For example, at a 13-year follow-up[10] of people free of heart trouble at baseline, those with a history of a major depressive episode were at a 4 times greater risk for myocardial infarction than those who did not experience a depressive episode (the risk was independent of major coronary risk factors).

Conclusion

Dr. McCarberg concluded that depression not only affects the brain but also has an effect on the body; therefore, treating the whole patient, not just the pain and not just the emotional symptoms, is important for achieving a successful outcome.

The Effect of Painful Physical Symptoms on Depression Remission

Response and Remission

Response and *remission* are not interchangeable terms, explained David A. Fishbain, M.D. *Response* refers to the level of change in symptoms since baseline, *nonresponse* is a less than 25% decrease in baseline rating scale scores, *partial response* is a 25% to 50% decrease in baseline scores, and *response* is a greater than 50% decrease in baseline scores.[11] *Remission* is the complete resolution of depressive symptoms and is defined as a score of less than 8 on the 17-item Hamilton Rating Scale for Depression (HAM-D) or a score of less than 11 on the Montgomery-Asberg Depression Rating Scale. Remission is the optimal outcome of treatment but is difficult to achieve. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[12] only 28% of patients achieved remission by 12 to 14 weeks.

Dr. Fishbain stated that patients who achieve remission have a better prognosis for their depression, function better, have a lower risk of relapse, and use fewer medical services compared with patients who merely respond to antidepressant treatment.[13] For patients who have demonstrated nonresponse, partial response, or response, treatment options for achieving remission include switching to an antidepressant in the same or another class as the first agent, augmenting with an antidepressant from a different class, or augmenting with an agent other than an antidepressant (Table 2).[14]

Prevalence and Consequences of Physical Symptoms and Depression

Pain is common in depression. Dr. Fishbain cited a large community survey[15] in Europe that found painful physical symptoms in 50% of respondents with depression. Further, another study[16] reported that primary care outpatients with 1 physical symptom had a 2% prevalence of mood disorders, whereas among outpatients with 9 or more physical symptoms, mood disorder prevalence was 60%.

Patients with physical symptoms associated with depression were more likely than depressed patients who did not have physical symptoms to[3,15–18]:

- be severely depressed
- have nonremitting depression
- be at risk for depression relapse
- have complex symptoms
- be difficult to treat
- have other psychiatric comorbidities
- have poor treatment outcomes
- lose work productivity
- require polypharmacy

Pain in patients with MDD is associated with increased health care costs[19] and increased severity of fatigue, insomnia, psychomotor retardation, weight gain, and impaired concentration.[20]

Dr. Fishbain further suggested that a bilateral relationship may exist between pain and depression. For ex-

Table 2. Treatment Options Adapted From STAR*D to Bring Patients With Depression Into Remission[a]

Switch from one antidepressant to another antidepressant within the same class
Switch to an antidepressant from a different class of antidepressants
Augment antidepressant therapy with an antidepressant from a different class
Augment an antidepressant with another agent, such as lithium or triiodothyronine (T_3)
[a]Adapted from Rush et al.[14]
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

ample, among neurology outpatients, the odds of having pain increased in patients with depression, and the odds of having depression increased in patients with pain.[21] A community survey[22] in Canada found that only 5.9% of respondents without back pain had major depression but in comparison, 19.8% of respondents with chronic back pain had major depression. As pain severity increased, the rate of major depression increased in a linear fashion. Greater severity of painful physical symptoms has also been associated with increased severity of depression.[23]

Response to antidepressants and remission of depression are affected by physical symptoms. One study[24] showed that a greater number of somatic symptoms present at baseline predicted delayed response to fluoxetine, and another study[25] found that more severe body pain at baseline predicted nonresponse to paroxetine among patients with late-life depression. Denninger et al.[18] reported that the degree of improvement in physical symptoms correlated with achievement of remission. Karp et al.[26] found that time to remission with imipramine was significantly longer in subjects with more pain at baseline.

Further, risk of relapse is greater in patients who have residual symptoms, including somatic symptoms, after depression treatment. Paykel et al.[17] reported that 76% of subjects with residual symptoms relapsed, whereas 25% of those without residual symptoms relapsed. Dr. Fishbain emphasized the importance of treating physical symptoms as well as psychological ones to prevent relapse after depression treatment.

Efficacy of Antidepressants for Pain and Achieving Remission

Managing somatic symptoms and pain are important considerations when selecting medications to treat comorbid depression. A meta-analysis by Fishbain and colleagues[27] of studies of patients diagnosed with psychogenic pain or somatoform pain disorder showed that antidepressants significantly decreased pain intensity ($z = 5.71$, $p < .0001$) compared with placebo.

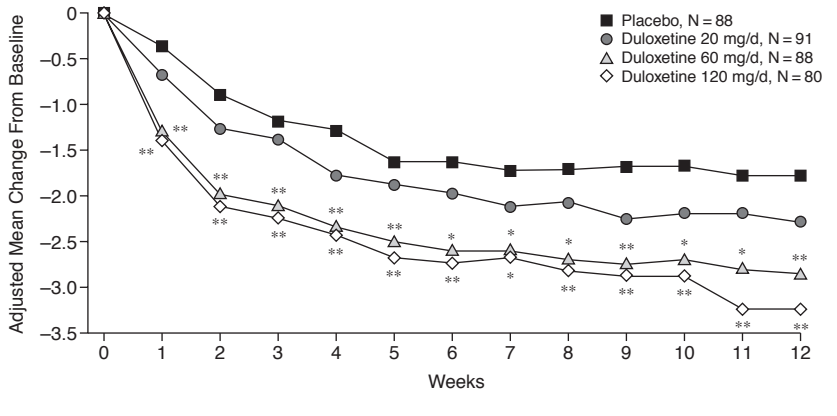
Further, dual-action antidepressants that block both serotonergic and noradrenergic reuptake have been found to be more effective than other antidepressants for the treatment of pain. In a review of animal and human studies by Fishbain et al.,[28] pain relief was demonstrated in 100% of trials of serotonergic-noradrenergic antidepressants, compared with 89% of studies using noradrenergic antidepressants, and 14% of studies using serotonergic antidepressants. Similarly, a meta-analysis by O'Malley et al.[29] found that tricyclic antidepressants (TCAs), which are all dual-action antidepressants but are serotonergic and noradrenergic in varying proportions, appeared to have a greater likelihood of analgesic effect than selective serotonin reuptake inhibitors (SSRIs) for headache, fibromyalgia, functional gastrointestinal syndromes, and idiopathic pain. Lynch[30] found that 80% of TCA studies showed a beneficial effect for pain compared with only about 36% of SSRI studies. Additionally, a calculation[31] of the number of patients needed to treat showed SSRIs to be less effective for various types of neuropathic pain than TCAs.

In reference to depression remission, dual action antidepressants appear to also offer an advantage over the SSRIs. Clomipramine, a dual-action antidepressant, demonstrated greater remission rates than the SSRI citalopram.[32] The SSRI fluoxetine combined with the noradrenergic antidepressant desipramine showed a superior rate of remission after 4 weeks compared with desipramine alone (71% vs. 14%).[33] Patients treated with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine also had a significantly higher remission rate (45%) than those treated with the SSRIs fluoxetine, paroxetine, or fluvoxamine (35%).[34] Finally, the SNRI duloxetine produced a greater remission rate (43%) than the SSRIs paroxetine, sertraline, or fluoxetine (38%).[35]

Interestingly, the SSRIs also appear to be less effective for the somatic symptoms of depression than for the emotional symptoms of depression. Greco et al.[36] studied depressed primary care patients during 9 months of SSRI treatment and found that, while depressive symptoms continued to gradually improve, somatic symptoms decreased most during the first month and then ceased to resolve. In the same population,[37] 69% of patients reported pain at baseline and 58% still reported pain after 3 months, and the odds ratio for poor treatment response was positively correlated with severity of pain.

One study[38] showed that venlafaxine, an SNRI, is effective for neuropathic pain, although it is not approved by the U.S. Food and Drug Administration (FDA) for this use. Patients with diabetic peripheral neuropathic pain treated with higher doses (> 150 mg/day) of extended-release venlafaxine had significantly greater mean Visual Analog Pain Relief scores than placebo by week 6 of the study, as well as significantly reduced mean Visual Analog Pain Intensity scores ($p < .001$).[38] Dr. Fishbain noted that when venlafaxine is used at lower doses, it acts like an SSRI, but at

Figure 1. Mean Change From Baseline in 24-Hour Average Pain Severity Score for Different Doses of Duloxetine for Diabetic Peripheral Neuropathic Pain[a]



[a]Reprinted with permission from Goldstein et al.[39]
*p ≤ .01 vs. placebo.
**p ≤ .001 vs. placebo.

higher doses, it has more dual-action activity.

Duloxetine, an SNRI balanced in noradrenergic and serotonergic activity, is FDA-approved for the treatment of diabetic peripheral neuropathic pain as well as MDD (Figure 1).[39] Duloxetine has been shown to separate from placebo at week 1 for its analgesic effect and this may be secondary to its balanced activity.[39] Duloxetine has also been shown to be effective for backache, shoulder pain, time in pain while awake, and interference with daily activities secondary to pain in patients with MDD.[40] Fava et al.[41] found that patients whose pain responded to duloxetine had better rates of depression remission than those whose pain did not respond (39% vs. 25%).

Table 3. Treatment Plan for Depression Associated With Pain and Other Somatic Symptoms

Treat pain aggressively to make treatment of somatic symptoms easier and consequently achieve depression remission
Target individual somatic symptoms to control them and help achieve remission of depression
Use antidepressants with demonstrated analgesic properties such as dual-action antidepressants that make treatment of somatic symptoms easier

Conclusion

Dr. Fishbain concluded that alleviating painful physical symptoms in depression can speed remission and improve overall remission rates. Further, dual-action antidepressants are more effective at achieving remission because they are more effective in treating the painful physical symptoms of depression than SSRIs. A treatment plan for depression associated with pain and other somatic symptoms should include 3 aspects: aggressive pain treatment, the targeting of individual somatic symptoms, and the use of antidepressants that have demonstrated analgesic properties (Table 3).

Managing Treatment-Resistant Depression With Painful Physical Symptoms in Primary Care

In primary care, patients may seek treatment for depression, or for pain, or for a combination of both pain and depression, but many may not respond to initial treatment approaches, according to Ronald M. Glick, M.D.

Treatment-Resistant Depression With Comorbid Pain

Treatment resistance is a major problem in depression treatment. About 40% of patients with depression do not respond fully to adequate treatment.[42] The STAR*D study[14] resulted in a protocol for patients with depression who do not respond to the first medication prescribed (see Table 2). At each step of the protocol, a few more patients responded until eventually most patients responded to and tolerated their medication.[43] No evidence-based protocol like the STAR*D exists for treatment-resistant depression with comorbid pain.

Comorbid pain may contribute to treatment resistance and may warrant specific treatment or consultation. It is uncertain whether the data on treatment-resistant depression can be generalized to patients with comorbid pain; however, the use of dual-action medications appears to be the best strategy. Dr. Glick emphasized the importance of asking patients with treatment-resistant depression whether they have pain. Because depression is the primary concern, many patients will not mention that they suffer from pain unless asked.

Pain With Comorbid Depression

Dr. Glick noted that some patients seeking traditional treatment for chronic pain may be reluctant to acknowledge psychological symptoms, but patients seeking more integrative approaches may recognize an association between their painful symptoms and depression.

Patients with chronic pain, particularly when they have comorbid depression, tend to become increasingly passive because activity increases their pain. Dr. Glick encourages patients to take a more active role in their pain management through exercise, diet, and stress management. Almost all patients with pain and/or depression could benefit from increased activity.

Thirty minutes of aerobic exercise per day, whether it is walking at a brisk pace or something more rigorous, has analgesic and antidepressant effects.[44–46] Physical therapy or a pain rehabilitation program can be helpful for patients with a chronic pain syndrome[47] or with a specific musculoskeletal cause for their pain.[48] Being overweight can contribute to pain. Counseling encourages patients to reduce portion size, increase intake of fruits and vegetables, shift away from red meat and saturated fats, and shift toward foods with more omega-3 fatty acids such as coldwater fish and plant sources of fat.

Treatments that alleviate stress also seem to reduce pain. Sometimes patients are resistant to the idea that their pain may have a psychological component because they think that the physician does not believe their pain is real, so the idea of stress management is more palatable to these patients. Dr. Glick suggested that activities such as yoga, meditation, and other mind-body approaches may have a role in pain management. However, a patient whose life has been taken over by pain may benefit most from working individually with a psychologist who is knowledgeable about treatment of pain.

Given the prevalence of chronic pain, primary care physicians are experienced in addressing a wide array of general health and musculoskeletal conditions that result in pain. However, it is important to recognize when to refer patients with pain and comorbid depression or with treatment-resistant depression with pain to a psychiatrist, a psychologist, or to a pain management program. Warning signs that a referral is appropriate include suicidality, bipolar features (especially if there is a strong family history of bipolar disorder or prominent mood lability), irritability, substance use issues, prominent interpersonal or Axis II personality disorder features, full chronic pain syndrome in which the pain takes over and functioning continually declines, and cases in which standard methods of care have not helped.

Table 4. Steps for Managing Primary Pain With Comorbid Depression

1. Identify and treat specific pain syndromes such as diabetic neuropathy, fibromyalgia, or headache
2. Encourage active patient self-management through exercise, dietary change, and stress management
3. Prescribe SNRIs that can help both pain and depression and choose appropriately energizing or sedating medications
4. Treat sleep problems including sleep apnea
5. Seek psychiatric, psychological, or pain management consultation if appropriate

Abbreviation: SNRI = serotonin-norepinephrine reuptake inhibitor.

Medication Choices

In patients primarily concerned with depression, addressing pain may help manage treatment-resistant depression. Dr. Glick supported the use of agents that boost both serotonin and norepinephrine such as venlafaxine and duloxetine.[49] Higher doses of duloxetine (120 mg/day) may produce a better analgesic effect than lower doses.[39,50,51] In Dr. Glick's clinical experience, at least 150 mg/day of venlafaxine are needed to achieve an analgesic effect. Dr. Glick recommended the TCA nortriptyline for pain and depression, dosed in an antidepressant range of 50 to 75 mg/day, but also cautioned that the dose should be reduced in older patients because of the risks of sedation, falls, and heart arrhythmia.[52]

Duloxetine carries a specific indication for use in neuropathic pain conditions such as diabetic neuropathy, but can be helpful for patients with fibromyalgia and other chronic pain states.[39,50,51] Dr. Glick stated that specifically for fibromyalgia or neuropathic pain, a higher dose (120 mg/day or 60 mg p.o. b.i.d.) may provide a greater benefit than the reduced dose of 60 mg/day most commonly used for depression. Similarly, the anticonvulsant pregabalin produces a better analgesic effect at a dose of 600 mg/day t.i.d.[53] Pregabalin does not have a specific antidepressant effect but can be used in patients primarily presenting with pain,[54] either alone or in concert with an antidepressant.

As with the primary management of depression, when treating depression with comorbid pain the choice of medication can be influenced by the desire for an energizing effect or for a sedating effect. Some patients with pain and depression have prominent lethargy, but others have prominent insomnia. Dr. Glick explained that in his clinical experience, venlafaxine has had energizing effects at higher doses, similar to bupropion; whereas trazodone, nortriptyline, mirtazapine, and amitriptyline have had sedating effects. Mirtazapine and amitriptyline are also associated with weight gain and sluggishness. Because of the risk of metabolic syndrome, atypical antipsychotics should be avoided unless the patient has comorbid bipolar disorder or psychotic illness.[55] However, physicians should note that atypicals may have analgesic properties.[56]

To combat insomnia, Dr. Glick recommended that patients avoid caffeine after the middle of the day, avoid exercise late in the day, and practice stress management approaches. Patients may also take 3 to 9 mg of melatonin at bedtime to promote sleepiness. For patients with sleep difficulties associated with myofascial pain or fibromyalgia, Dr. Glick recommended 2 to 4 mg of the muscle relaxant tizanidine at bedtime, although liver function should be monitored. If insomnia does not improve with behavioral approaches and monotherapy, particularly in the presence of obesity, Dr. Glick suggested screening for sleep apnea. Often, once sleep is improved, patients report both better mood and less pain.

Dr. Glick advised caution with combined serotonergic agents, such as the SSRI escitalopram and the pain medication tramadol, because of potential serotonin syndrome. Serotonin syndrome can cause hyperarousal

symptoms such as tachycardia, irritability, anxiety, tremor or shakiness, and seizures.[57] Medication should be stopped if even mild symptoms of serotonin syndrome occur.

Conclusion

Dr. Glick summarized steps for treating patients with primary pain and comorbid depression (Table 4). First, identify specific syndromes to treat, e.g., prophylactic agents for recurrent migraine. Next, help the patient shift to an active self-management strategy. Prescribe medications that treat both pain and depression, and select appropriately energizing or sedating medications. Polypharmacy will probably be necessary for adequate control of pain combined with depression. Then, if needed, use whatever consultation is available in the community.

Successfully Managing Depressed Patients With Pain

Louis Kuritzky, M.D., remarked that most clinicians can readily anticipate that patients with chronic pain disorders often subsequently develop comorbid depression; however, it may come as a surprise that patients with depression can have painful symptoms that result from the depression itself. The impact of pain on treatment outcomes of depression deserves more attention, according to Dr. Kuritzky. Pain as a symptom of depression has been overlooked in diagnostic criteria[58] but is now being recognized as an important component with serious implications.[59] When patients have multiple unexplained physical symptoms, depression should be high on the list of possible diagnoses.[1,60,61]

"Depressalgia" and Treatment Outcomes

Dr. Kuritzky referred to the pain of depression as "depressalgia" because it does not necessarily fit into any specific pain category (e.g., migraine or osteoarthritis) but rather appears to be part of depression itself. One study[6] showed that 76% of patients who received a diagnosis of depression had initially reported somatic symptoms. Dr. Kuritzky noted that unexplained musculoskeletal pain and back pain in particular should alert clinicians to suspect depression. In a study[62] of primary care patients with depression, 43% had nonspecific musculoskeletal complaints and 39% had back pain.

Depression is likely to persist if pain is present and vice versa. Patients who were referred to a neurology outpatient clinic were more likely to still have depression at 3 months and at 12 months if pain symptoms were persistent than were patients without persistent pain symptoms, and similarly, patients were more likely to have continued pain if depression was present than they were if depression was not present.[63]

The presence of unresolved pain in patients with depression has 3 predictable consequences: (1) delay in time to depression remission,[26] (2) decreased likelihood of depression remission, and (3) increased likelihood of relapse.[41] The consequences of failing to achieve full remission in depression are decreased quality of life, social disability, increased use of medical resources, greater risk of suicide, and increased risk of relapse.[64–66]

Treating Depression With Pain

Dr. Kuritzky stressed the importance of recognizing that not all agents that are effective for depression have an impact on pain in depression. A meaningful connection between serotonin and norepinephrine has been recognized in modulation of pain.[67] Dr. Kuritzky explained that combined serotonin and norepinephrine modulation may be the endogenous pain-damping system from the central nervous system: serotonin modulation alone is typically not enough to treat depression and pain.

In a study[36] of primary care patients taking SSRIs, the treatment effect sizes on depression symptom clusters were measured; painful physical symptoms had the lowest effect size, while nonsomatic depressive symptoms had the greatest effect size. As Dr. Kuritzky elaborated, the SSRIs were effective for affective symptoms, but much less so for pain. In another study,[68] severity of pain at baseline predicted treatment response to SSRI therapy for depression; patients with the least pain had the best remission rate, supporting the concept that SSRIs are most efficacious in patients without comorbid pain.

Agents that modulate both norepinephrine and serotonin have been shown to have a favorable impact on pain in patients with or without depression. The TCAs amitriptyline and desipramine and the SSRI fluoxetine were tested in patients with painful diabetic neuropathy. Moderate or greater relief of pain was found in 74%, 61%, and 48% of the treatment groups, respectively. The TCAs were found to be as effective in patients with depression as without, but the SSRI was effective only in patients with depression, suggesting an affective component to the measured pain reduction, rather than a direct pain relief effect independent of depression.[69] The SNRI venlafaxine, which modulates both norepinephrine and serotonin, was also shown to produce a statistically significant reduction in painful diabetic neuropathy versus placebo.[38]

Nemeroff et al.[41,70] reviewed 6 double-blind, controlled trials of the SNRI duloxetine for MDD and found that in 4 studies, duloxetine was significantly superior to placebo in reducing mean HAM-D total scores. As part of these trials,[41,70] pain scores were obtained, and duloxetine was also significantly superior to placebo on pain measures; in accordance with the commentary above, these duloxetine trials[41] demonstrated that patients who

had a greater than 50% decrease in painful symptoms had a rate of remission from depression twice that observed for pain nonresponders.

Conclusion

Dr. Kuritzky concluded that unexplained physical symptoms, particularly pain, are commonplace in depressed patients and may delay an appropriate diagnosis and adequate treatment. The goal for treatment of depression is remission, which is correlated with a reduction in painful symptoms. When pain fails to remit, resolution of depressive symptoms, likelihood of attaining complete remission, time to remission, and likelihood of relapse are all altered unfavorably. Because of the interrelatedness of depression and pain, clinicians would do well to recognize which agents among the therapeutic choices for depression may also favorably impact pain.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), sertraline (Zoloft and others), tizanidine (Zanaflex and others), tramadol (Ultram and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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