Key Words: serotonin, norepinephrine, venlafaxine, fibromyalgia, migraine, diabetic neuropathy, premenstrual dysphoric disorder, stroke, SSRI, SNRI

Coping With Somatic Comorbidities: Striving for Complete Recovery

By Christer Allgulander, MD, and Siegfried Kasper, MD

ABSTRACT *~ Depression is increasingly being recognized as a common comorbid disorder in patients with severe and chronic medical conditions. However, patients with depression and anxiety frequently present with somatic complaints such as aches and pains, headache, and chronic fatigue. This leads to underrecognition and undertreatment of the psychiatric disorder in an attempt to identify the medical cause of the somatic complaint. Reports are demonstrating the efficacy of antidepressants in treating disorders other than depression and anxiety. Tricyclic antidepressants have shown their usefulness in the treatment of diabetic neuropathy, fibromyalgia, and headache. Controlled studies of several selective serotonin reuptake inhibitors have been shown to be efficacious in relieving the symptoms of premenstrual dysphoric disorder and fibromyalgia. Pilot studies have also been conducted with the serotonin and norepinephrine reuptake inhibitor venlafaxine for the treatment of diabetic neuropathy, fibromyalgia, migraine, premenstrual dysphoric disorder, and stroke. The results encourage further controlled studies.*
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Introduction

Anxiety and depression are among the most common psychiatric illnesses in primary care.[1] Patients with severe and chronic medical conditions (eg, cancer, cardiovascular disease, and neurologic disorders) have been known to experience pain due to the illness; in these instances the pain may be associated with an organic cause. Patients with such illnesses are also prone to depression because of the severe, chronic, and fatal nature of the illness,[2] and the physician is faced with treating the illness, the depression, or both. However, patients do not always present with symptoms typical of depression and/or anxiety. The typical anxious or depressed patient in primary care is more likely to present with somatic com-

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plaints such as headache, difficulty sleeping, chronic fatigue, or vague aches and pains, rather than emotional complaints.[3-6] One study of 500 patients with anxiety and/or depression revealed that 84% presented with somatic complaints.[7]

Consequently, the physician spends significant time and resources trying to identify the medical cause of the somatic complaints,[5] while the depression and anxiety remain unrecognized by the physician. In a study of patients with somatic complaints, an accurate psychiatric disorder was correctly diagnosed in only 50% of cases.[7] As a result, anxiety and depression remain undertreated and the patient continues to suffer significant functional impairment.[3,4]

The efficacy of antidepressant agents in the treatment of depression and anxiety is well documented.[8-10] In addition, reports have begun to demonstrate the usefulness of antidepressants in treating a broad range of disorders (or somatic disorders), including fibromyalgia, diabetic neuropathy, premenstrual dysphoric disorder (PMDD), chronic headaches, functional gastrointestinal disorders, and postherpetic neuralgia.[11-13] (To date, only fluoxetine is indicated for the treatment of PMDD. Antidepressants mentioned in this article may be considered for the treatment of somatic comorbidities at the physician's discretion.) Although the analgesic efficacy of tricyclic antidepressants (TCAs) has been shown to be independent of their antidepressant effect,[14] their anticholinergic and cardiovascular effects limit their use as patients discontinue treatment prematurely because of adverse events. Selective serotonin reuptake inhibitors (SSRIs) have a favorable tolerability profile,[15] and a more rapid onset of action/response has been observed with SSRIs in PMDD compared with its onset of action in depressive disorders.[16] Attention is increasingly being given to other antidepressant agents, such as venlafaxine and nefazodone, with studies aiming to show their potential efficacy in treating a wide range of disorders.

Although some somatic symptoms may not be associated with an underlying organic cause, the symptoms alone may be debilitating enough to warrant treatment. Physicians should consider the possibility of an underlying depressive or anxiety disorder and weigh antidepressant therapy, even if a depressive disorder is not evident.[6] This article will review the available reports for the efficacy of antidepressants in the treatment of certain painful conditions, PMDD, and stroke.

Chronic Pain

Pain is a complex phenomenon, involving both the central and peripheral pathways,[17] and both the norepinephrine and serotonin systems have an important role to play in its modulation.[17]

The analgesic properties of TCAs have been recognized for over 30 years and are thought to be based on their effect on the reuptake of norepinephrine and serotonin.[11] Their actions on opioid and adenosine receptors, excitatory amino acids, and ion channels may also be implicated.[17] Until recently, central pain pathways were the main focus of attention. However, the effect of antidepressants on peripheral pathways is now also being investigated.[17]

There is a general belief among nonpsychiatrists that TCAs are more effective than SSRIs in the treatment of pain. This is supported by a critical review of the literature that highlights the lack of evidence for the use of SSRIs in pain management.[18] It is also not clear whether SSRIs are beneficial in the management of chronic pain.[11] The analgesic efficacy of TCAs appears to be independent of antidepressant efficacy, while that of SSRIs remains unresolved.[11] However, the poor tolerability profile of TCAs may preclude their use in patients with comorbid medical conditions, and limit their long-term use. The newer, more selective antidepressants, such as venlafaxine, mirtazapine, and the SSRIs, may therefore be suitable alternatives.

Diabetic Neuropathic Pain

Neuropathic pain is related to injury of the peripheral or central nervous systems and is classified according to causality.[19] It is refractory to conventional analgesics, but can successfully be managed by a number of other pharmacologic agents, including antidepressants, antiepileptics and non-narcotic analgesics.[19,20] The analgesic efficacy of antidepressants is now thought to be a specific property of TCAs, rather than related to their antidepressant efficacy.[19]

The use of TCAs in the management of chronic pain is based on clinical experience in patients without depression, rather than controlled studies. Data from a small number of placebo-controlled studies support the use of TCAs in the treatment of diabetic neuropathy.[19,21] Amitriptyline has demonstrated efficacy over placebo in relieving both steady and lancinating pain in patients with diabetic neuropathy in a randomized, double-blind, crossover trial of 6 weeks duration.[22] The degree of pain relief was proportional to the dose up to a maximum of 150 mg. The analgesic efficacy of amitriptyline was similar in both depressed and nondepressed patients (Figure 1).

The efficacy of an extended-release (XR) formulation of venlafaxine has been evaluated in a placebo-controlled multicenter study of 244 patients with diabetic neuropathic pain.[23] Venlafaxine XR (150–225 mg/day) provided significantly better pain relief (Visual Analog Scale) at weeks 2–4 ($P<.05$) and at weeks 5 and 6 ($P<.001$) compared with

placebo. Visual Analog Scale-Pain Intensity was significantly lower with higher doses of venlafaxine XR (150–225 mg/day) at weeks 3 and 6 compared with placebo, and at weeks 5 and 6 compared with the lower dose of venlafaxine XR (75 mg/day [Figure 2]).[23]

Fibromyalgia

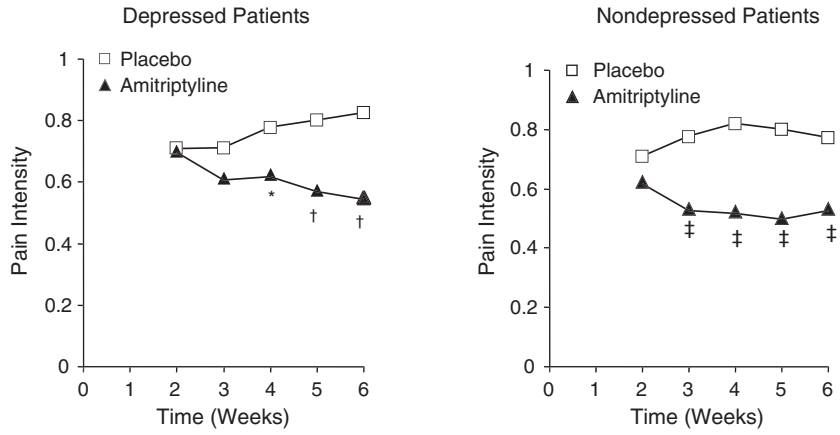
Fibromyalgia is a condition characterized by nonspecific joint pain at multiple locations and sleep disturbance. Comorbidity with depression is a common feature[24] and is thought to arise from disturbances in the neuroendocrine axis.[25] Treatment is empirically based, though there is some evidence to support the use of exercise and low-dose antidepressants.[24] Both TCAs and SSRIs have demonstrated beneficial effects on fibromyalgia symptoms,[6] and preliminary data from an open clinical study showed 8 of 15 fibromyalgia patients who received 8 weeks of treatment with venlafaxine (mean final dose, 167 mg/day) had a ≥50% reduction in symptoms; venlafaxine was also well tolerated.[26]

Headache/Migraine

The etiology of recurring headaches and migraine is not known, although both TCAs and SSRIs provide symptom relief.[6] In an open

FIGURE 1

Pain Intensity During 6 Weeks of Treatment With Amitriptyline and Placebo in Depressed and Nondepressed Patients With Diabetic Neuropathy[22]



* *P*<.05 versus placebo.
† *P*<.01 versus placebo.
‡ *P*<.001 versus placebo.

Source: Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology.* 1987;37:589-596. Reprinted with permission from Lippincott Williams and Wilkins.

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and retrospective study of 170 patients resistant to conventional therapy, there was a significant reduction in the frequency of chronic tension-type headache and migraine with venlafaxine XR at 37.5–300 mg/day (median 150 mg, $P<.001$).[27]

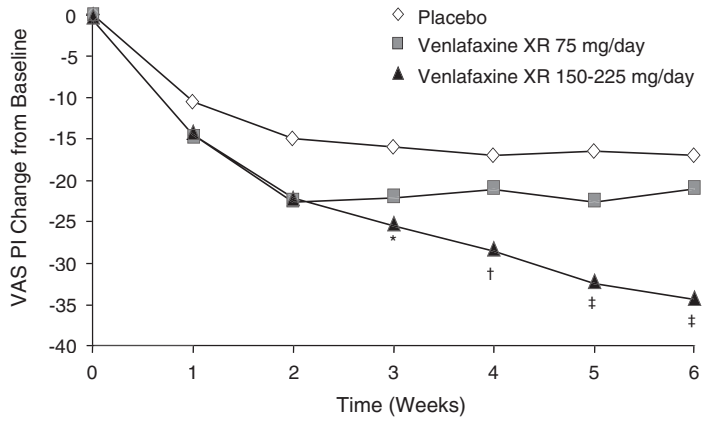
Premenstrual Dysphoric Disorder

PMDD affects 3% to 8% of women of reproductive age,[16] and is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[28] as a chronic disorder that impairs the functioning and quality of life of those affected. Symptoms occur in the luteal phase of the menstrual cycle, disappearing after the onset of menstruation.[29,30] An alteration in the transmission of serotonin in the brain, which has a close reciprocal relationship with the gonadal hormones, is thought to be associated with PMDD.[16] Thus, the serotonergic system is the main target of treatment.

Evidence showing the efficacy of SSRIs in the treatment of PMDD is substantial.[16,29,31] One example is fluoxetine, which is licensed in the United States and the United Kingdom for the treatment of PMDD. At doses of 20 and 60 mg/day, fluoxetine was

FIGURE 2

Pain Intensity During 6 Weeks of Treatment With Venlafaxine and Placebo in Patients With Diabetic Neuropathy



* $P<.05$ versus placebo.
†$P<.01$ versus placebo.
‡$P<.001$ versus placebo.
VAS PI=Visual Analog Scale-Pain Intensity.

Adapted from: Goli V, Kunz NR, Entsuah R, Rudolph R. Diabetic neuropathic pain management with venlafaxine extended release. *Int J Neuropsychopharmacol*. 2000;3(suppl 1):S225.

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significantly superior (P<.001) to placebo in reducing irritability, tension, and dysphoria.[30] In a double-blind, placebo-controlled study, the efficacy of fluoxetine, alprazolam, propranolol, and pyridoxine in the treatment of 120 women with severe PMDD was compared over a 3-month period.[32] There was a 65% mean reduction in symptoms with fluoxetine (Figure 3). Results from another more recent study also indicate that fluoxetine improved the physical discomfort of PMDD.[33] Citalopram has also shown efficacy in the treatment of PMDD, with intermittent administration during the luteal phase being significantly more effective than continuous administration throughout the menstrual cycle.[34]

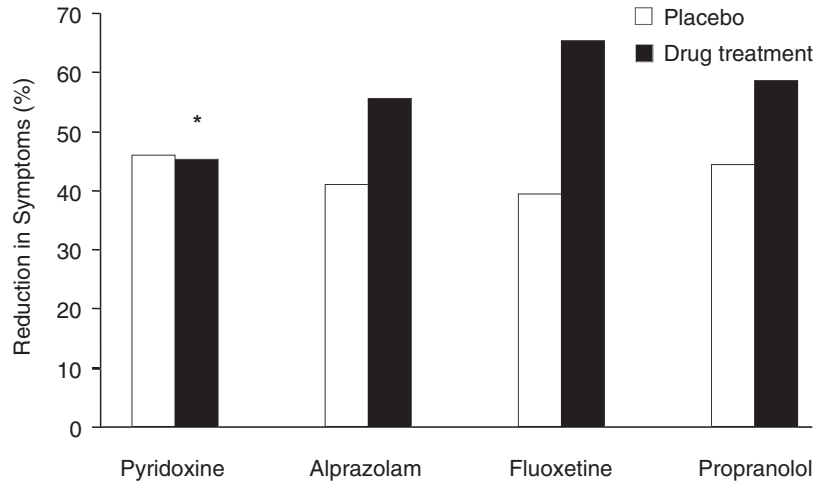
In one placebo-controlled study of nefazodone and venlafaxine, the majority of women with PMDD responded.[35,36] Nefazodone significantly improved premenstrual symptoms from pretreatment baseline values at the end of the first treatment cycle (4 weeks), and was maintained. Similarly, venlafaxine was significantly better than placebo after one treatment cycle, as assessed by the premenstrual total Daily Symptom Report score (P<.001).[36] Improvements with venlafaxine increased in the second cycle and were maintained until the fourth.

Stroke

Depression and anxiety are common following a stroke and can substantially impair physical recovery. There is limited placebo-

FIGURE 3

Reduction in Symptoms of Severe Premenstrual Syndrome



* P<.05 in pyridoxine versus other drug treatments.

Adapted from: Diegoli MS, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. *Int J Gynecol Obstet.* 1998;62:63-67.

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controlled data on the antidepressant efficacy of nortriptyline, trazodone, and citalopram in both of these disorders when associated with stroke.[37] In addition, there is evidence showing that recovery from the physical and cognitive impairments of brain injury can be promoted by agents that activate norephinephrine, serotonin, dopamine and acetylcholinergic systems.[38,39] A preliminary study with fluoxetine in 52 poststroke patients suggested that it might be associated with a better functional outcome than physical therapy alone.[39]

Venlafaxine was also associated with an improvement in both depression and neurological rehabilitation in an open uncontrolled study of 12 poststroke patients without psychiatric disorders, who were treated for 5 weeks with 75–150 mg/day (Figure 4).[40]

Conclusion

Data are emerging to support the efficacy of antidepressant therapy in the treatment of certain painful conditions, PMDD, and stroke. The beneficial effects of agents with a broader mechanism of action, such as selective norepinephrine reuptake inhibitors, on somatic comorbidities warrant further investigation in controlled studies. ✤

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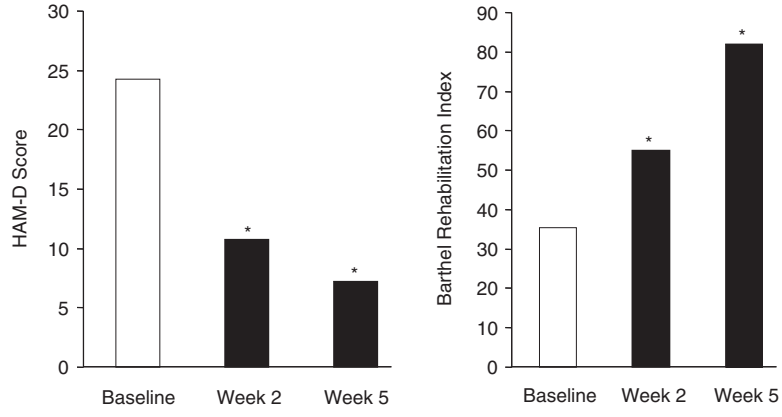
FIGURE 4

Poststroke Depressive Syndromes and Neurological Rehabilitation During Treatment With Venlafaxine



* *P*<.05 versus baseline
HAM-D=Hamilton Rating Scale for Depression.
Source: Dahmen N, Marx J, Hopf HC, Tettenborn B, Röder R. Therapy of early poststroke depression with venlafaxine: safety, tolerability, and efficacy as determined in an open, uncontrolled clinical trial. *Stroke.* 1999;30:691-692. Reprinted with permission from Lippincott Williams and Wilkins.

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