

Common Pathways of Depression and Pain

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Depressive disorders are chronic conditions that produce both emotional and physical symptoms. Increasing evidence suggests that in some patients with depressive disorders a neurodegenerative process may occur, highlighting the importance of early and aggressive intervention. Serotonin (5-HT) and norepinephrine (NE) neurotransmitter systems influence neuroplasticity in the brain, and both are involved in mediating the therapeutic effects of most currently available antidepressants. Some dual-action antidepressants have been shown to be effective in managing the pain symptoms associated with depression. These agents may have advantages over others by treating a wider array of physical symptoms. Additionally, these agents may also have a role in modulating neurogenesis and other neuroplastic changes, thereby leading to more complete recovery in patients suffering from the emotional and physical symptoms of chronic depression. (*J Clin Psychiatry* 2004;65[suppl 12]:16–19)

For many years, depression has been known as a condition that produces both emotional and physical symptoms. However, only recently have researchers begun to reconsider how physical symptoms are important to the presentation of depression and how treatment with different antidepressants may reduce these symptoms. Psychiatrists are very familiar with the common emotional symptoms of depression, such as depressed mood, anxiety, anhedonia, and feelings of guilt or worthlessness but are generally less familiar with some of the physical symptoms associated with it. For example, patients with depression frequently report body aches, pain, headaches, gastrointestinal disturbances, fatigue, and loss of energy.

Physical symptoms are common in a variety of psychiatric disorders. In 1973, Kellner and Sheffield¹ reported that a greater percentage of psychiatric patients than healthy subjects described feeling tired and lacking energy, complained of headaches or head pains, reported feeling dizzy or faint, described weakness in parts of their bodies, and complained of muscle pains and body aches (Table 1). A recent reanalysis of data² from the National Institute of Mental Health (NIMH) epidemiology study showed that the percentages of patients with depression or anxiety who complained of aches and pains were high, and actually higher in women than men. Women were twice as

likely as men (2.8% vs. 1.4%) to report somatic depression (exhibiting appetite and sleep disturbance and fatigue). Also, women with somatic depression were more likely to have had an anxiety disorder or chronic depression than women who did not exhibit these somatic symptoms. Physical symptoms are as important to recognize and treat as the mood symptoms that accompany them.

EFFECTS OF RECURRENCE

It is important to recognize that depression is a chronic disorder. Like many other chronic disorders in medicine, such as diabetes and hypertension, much of the burden of depression is linked to the recurrent nature of the condition. Increasing evidence suggests that preventing recurrence and the consequences of multiple episodes may be as important, if not more important, than treating an acute episode. For example, in diabetes, it is important to aggressively treat recurrences in order to prevent the occurrence of renal, eye, or cardiovascular complications. Similarly, some evidence^{3,4} suggests that in some patients, after each new episode of depression, the next episode tends to occur sooner and have a more severe, treatment-resistant course than the preceding episode. Further, depression interferes with daily activities, including work and social events,⁵ which over time leads to chronic problems holding jobs and maintaining relationships.

A data review³ of patients on long-term maintenance treatment for depression suggested that the recovery rate from depression begins to diminish over time in people who continue to have persistent symptoms. The 5-year prospective NIMH Collaborative Depression Study⁶ found that 50% of the subjects recovered within the first 6 months, and then the rate of recovery dropped markedly so that at the end of 5 years, the probability of recovery within the next month was only 1%. On the whole, the

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Table 1. Physical Symptoms Common in Psychiatric Patients^a

Symptom	Psychiatric Patients (%)	Healthy Subjects (%)
Tired, lack of energy	85	40
Headache, head pains	64	48
Dizzy or faint	60	14
Parts of body feel weak	57	23
Muscle pains, aches, rheumatism	53	27
Stomach pains	51	20
Chest pains	46	14

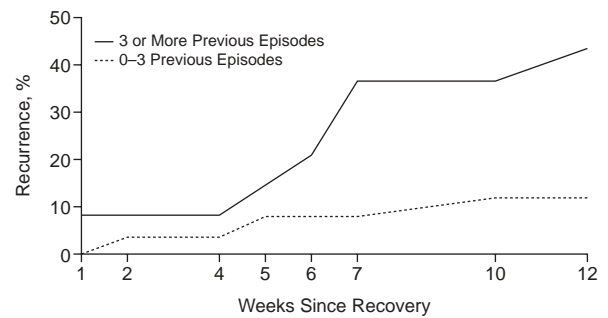
^aData from Kellner and Sheffield.¹

longer a patient is ill, the lower the chance of recovery; persistence of illness results in decreased recovery rates over time.

In addition, Judd and colleagues⁷ reported that longer major depressive episodes may lead to less likelihood of complete recovery and be a powerful predictor of time to episode recurrence. In patients who had a major depressive episode lasting up to 6 months from onset to recovery, only 6% (5/82) had residual symptoms. Conversely, 44% (36/82) of patients who had a major depressive episode lasting more than 2 years from onset to recovery continued to have residual symptoms. The longer the depressive episode, the less likelihood of complete recovery.

Most patients who have had one episode of depression will experience another episode of depression. In fact, 75% to 90% of people with depression will have multiple episodes,^{8,9} and the time to recurrence decreases with each episode.³ During the first 3 months following recovery from a depressive episode, about 10% of patients who have had 0 to 3 prior depressive episodes will experience recurrence, compared with 45% of patients who have had more prior episodes within the 12 weeks since recovery (Figure 1).³ Several studies support these findings⁴ and suggest that patients who have had depressive episodes are more likely to have further depressive episodes.^{7,10}

The importance of recognizing depression as a chronic, recurring disorder and understanding that multiple episodes negatively affect recovery rates is underscored by the effect depression has on the brain itself. Prolonged depression may result in progressive and possibly cumulative damage to the brain. Several studies^{11–16} have shown that recurrent depressive episodes appear to increase the likelihood of neurochemical changes in the brain, including loss of hippocampal volume in people with depression who have had multiple episodes. Some of these volume changes may not be completely reversible. Additionally, Frodl et al.¹⁶ have shown that brain injury may predate depressive illness or originate with chronic illness. These findings suggest the importance of addressing depression not just at a phenomenological or symptom level but also to understand that underlying depressive symptoms may be associated with changes in brain structure and function that may be increasingly difficult to reverse over time. The

Figure 1. Cumulative Probability of Recurrence of a Depressive Episode^a

^aReprinted with permission from Keller and Boland.³

changes in brain structure may be associated with the observed differences in likelihood of recurrence and the lack of complete response in people with chronic depression.

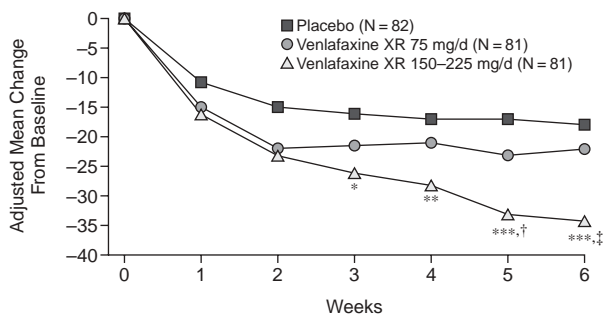
NEUROBIOLOGICAL PATHWAYS OF DEPRESSION

The emotional and painful physical symptoms of depression may be regulated by specific pathways for serotonin (5-HT) and norepinephrine (NE) in the brain and spinal cord.¹⁷ Serotonergic and noradrenergic neurotransmitters from the brain stem ascend into the brain and mediate numerous emotional and physical functions and descend down the spinal cord where they suppress painful input from the body. These neurotransmitters are the key modulatory transmitters and seem to be part of the body's endogenous analgesic system. Thus, antidepressants may exert their therapeutic action not only in depression but also in some pain conditions via the 5-HT system.¹⁸

While serotonergic and noradrenergic pathways overlap, and many symptoms of depression seem to be affected by both serotonergic and noradrenergic pathways—for example, mood, sleep, coping with stress, and possibly physical symptoms—there are certain areas in which each of these transmitter systems has a slightly divergent set of effects.¹⁹ The noradrenergic system may be involved in motivation—modulating energy, interest, and concentration—while the serotonergic system may be more involved in aspects of behavior—modulating sexual function, appetite, and impulsiveness. At both the brain level and the spinal cord level, these neurotransmitter systems are involved in the etiology of some physical and emotional symptoms of depression, and, therefore, in how medications work to treat depression.

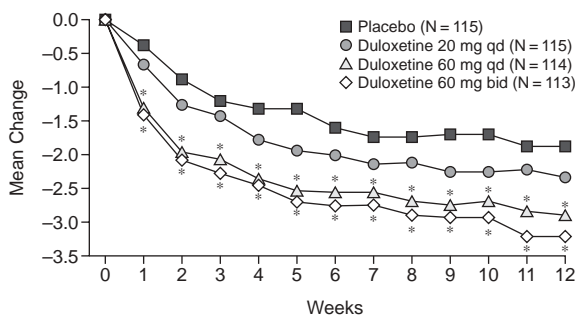
Along with the acute effects of antidepressants on serotonergic and noradrenergic function, some antidepressants induce neurogenesis, or growth of neurons, in the brain. Neurogenesis is currently being investigated as one of the potential mechanisms underlying antidepressant effects

Figure 2. Venlafaxine for Diabetic Neuropathic Pain^a



^aData from Kunz et al.²⁹ Venlafaxine has not been approved by the U.S. Food and Drug Administration for use in diabetic neuropathic pain.
 *For Visual Analog Scale-Pain Intensity scores: $p < .05$ vs. placebo.
 ** $p < .01$ vs. placebo. *** $p < .001$ vs. placebo. † $p < .05$ vs. venlafaxine XR 75 mg/day. ‡ $p < .01$ vs. venlafaxine XR 75 mg/day.

Figure 3. Duloxetine for Diabetic Neuropathic Pain: 24-Hour Average Pain Severity^a



^aData from Goldstein et al.³⁰ Duloxetine has not been approved by the U.S. Food and Drug Administration for use in diabetic neuropathic pain.
 * $p \leq .01$ vs. placebo.

and as a possible reason it takes several weeks for antidepressant action to emerge. A recent study by Santarelli et al.²⁰ demonstrated that the selective serotonin reuptake inhibitor (SSRI) fluoxetine given for 10 to 28 days increased the formation of new neurons in the hippocampus of mice, an area that has been shown to be diminished in depressed patients. The growth in hippocampal neurons began at about 11 days and then continued throughout the 28-day course of treatment. No changes in neurons were seen at 8 days, suggesting that neurogenesis is a time-dependent process.

In this same investigation, Santarelli et al.²⁰ also compared the role of the dual-action antidepressant imipramine with fluoxetine. In genetically modified knockout mice that did not express 5-HT_{1A} receptors, fluoxetine was unable to induce neurogenesis, but imipramine was still capable of inducing neurogenesis in these mice. Arguing

that serotonergically selective antidepressants and dual-action antidepressants have potentially final common pathways that are affected but different mechanisms of action,²¹ one could speculate that the ability of imipramine to induce neurogenesis even in mice without 5-HT_{1A} receptors suggests that the effects of imipramine on neurogenesis may involve both serotonergic and nonserotonergic pathways.

Data from neurotransmitter depletion studies²¹⁻²⁷ support this view. These studies showed that the therapeutic effects of SSRIs in patients whose depression had responded to treatment could be transiently reversed by rapid depletion of 5-HT but not by depletion of NE. Conversely, the therapeutic effects of a NE reuptake inhibitor (e.g., desipramine) could be transiently reversed by depletion of NE but not by depletion of 5-HT.

MANAGING PAIN WITH ANTIDEPRESSANTS

Both the mood effects shown in depressed patients and neurogenesis effects shown in laboratory animals suggest that 5-HT and NE pathways may act independently of each other but potentially converge on common mechanisms. A study in animals,²⁸ for example, has shown that the serotonergic antidepressant paroxetine was associated with reduction in pain, as was the selective NE reuptake inhibiting drug thionisoxetine. Interestingly, the combination of the 2 drugs had a much more potent effect than either drug alone on reducing pain. This finding supports some of the clinical evidence that suggests that medications with dual action not only appear to have a more robust antidepressant effect that more frequently leads to remission of depressive symptoms compared with selective agents but also have advantages for analgesia.

Venlafaxine and duloxetine, both dual-action antidepressants, have demonstrated efficacy in reducing pain in patients with diabetic neuropathy. Kunz et al.²⁹ found that high doses of venlafaxine (150–225 mg/day) were more effective than low doses or placebo at reducing pain in this population (Figure 2). In another study with duloxetine,³⁰ patients with diabetic neuropathy were randomly assigned to treatment with duloxetine 60 mg b.i.d., 60 mg q.d., 20 mg q.d., or placebo. Patients receiving duloxetine at the 2 manufacturer-prescribed therapeutic doses (data on file, Eli Lilly and Company, Indianapolis, Ind.), 60 mg b.i.d. and 60 mg q.d., reported improvement as early as 1 week after randomization. Throughout the study, these doses continued to decrease pain sensitivity in patients with diabetic neuropathy more than the 20 mg q.d. dose (considered nontherapeutic by manufacturer) and placebo (Figure 3). Findings from both of these studies suggest that venlafaxine and duloxetine share a predilection for reducing pain and confirm the animal data that medications with dual action have a unique and powerful effect on pain sensitivity.

SUMMARY

The emotional and physical symptoms of depression appear to be modulated by very similar neurotransmitter systems. A growing body of evidence suggests that antidepressants that inhibit the reuptake of both 5-HT and NE have the best chance to reduce all of the symptoms of depression by targeting the multiple pathways that mediate them in the brain and spinal cord. Compared with selective agents, dual-action antidepressants that block both 5-HT and NE reuptake have shown evidence of treating a wider array of symptoms, including relieving painful physical symptoms. Additionally, these systems appear to be involved both in the therapeutic effects of antidepressants on somatic and psychiatric symptoms of depression and in the mechanisms that could potentially impact neurodegeneration and neuroplasticity in the brain.

Physical symptoms have been associated with depression, diminishing function in patients already experiencing emotional problems. Long major depressive episodes may lead to less likelihood of complete recovery; the recovery rate from an episode begins to diminish over time in people who continue to have persistent symptoms. Prolonged depression may result in progressive and possibly cumulative damage to the brain. The chronic nature of depression and the toll it takes on quality of life, as well as the injury it can cause to the brain, highlight the importance of early and aggressive intervention.

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

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, venlafaxine and duloxetine are not approved by the U.S. Food and Drug Administration for the treatment of neuropathic pain.

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