Depression is common in the United States and worldwide, and presents a significant burden to society. The results of a 30-year study authorized by the World Health Organization and undertaken by the Harvard School of Public Health estimate that depression will be the second most common cause of disability worldwide by the year 2020 (up from fourth in 1990 at the start of the study), trailing only heart disease. In the United States, depression is already estimated to be the second biggest cause of disability among women. Patients who do not respond to antidepressants are among the heaviest utilizers of healthcare resources. Patients who do not respond to antidepressants are among the heaviest utilizers of healthcare resources. Patients who do not respond to antidepressants are among the heaviest utilizers of healthcare resources.

Depression has always been associated in the minds of clinicians and patients with emotional symptoms, such as sadness, irritability, helplessness, guilt, and suicidal ideation. However, the spectrum of symptoms also includes anxiety symptoms, such as brooding, excessive worry, and somatic symptoms. The presentation of physical symptoms can range from body aches and pains, joint pain, and headaches to fatigue, lack of energy, and gastrointestinal (GI) disturbances. A U.S. study of subjects with MDD reported high rates of both anxiety disorder and gastrointestinal symptoms. These comorbidities were greater among women (35% anxiety disorder, 55% aches and pains) but were also common in men (28% anxiety disorder, 38% aches and pains).

Many patients first present to physicians with physical symptoms. A WHO study of 1,146 patients in a general medical practice who met the criteria for major depression reported that 69% presented with physical symptoms. Physical symptoms are common in patients with depression, and many patients first present to physicians with physical symptoms.

The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The University of Kentucky College of Medicine designates this activity for a maximum of 1.0 Category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit actually spent in the educational activity.
such as the Hamilton Depression Rating Scale (HAM-D). A partial response is characterized by significant residual symptoms and an overall symptom reduction of approximately 25% to 49%. Nonresponse characterizes a patient who shows little or no change in depressive symptoms (eg, less than a 25% reduction in symptom scores). Remission, the goal of treatment, is generally defined as no longer meeting the criteria for a major depressive episode and having no—or virtually no—symptoms. On the HAM-D, remission is often defined as a score of 7 or below. Even patients who respond to treatment, therefore, may remain significantly impaired, with HAM-D scores well in excess of the threshold for remission. Indeed, only approximately one third of patients achieve remission on existing single-drug therapies. The failure to achieve remission carries considerable risks, including increased risk of relapse, and increased healthcare costs. Paykel et al noted a 3-fold greater risk of relapse within 10 months in patients with residual depressive symptoms than in patients with no residual symptoms (76% vs 25% relapse rate). Ninety-four percent of the patients with continuing symptoms had physical symptoms.

The rate of relapse is also greater in patients with residual symptoms, as evidenced by the results of a study by Judd and colleagues. The rate of relapse was approximately 3-fold greater in patients with residual symptoms than in patients with no residual symptoms (an average of 23 weeks vs 68 weeks). The continuation of this relationship over time was demonstrated by a study comparing response to remission (Figure 1). In this study, patients who achieved remission showed little increase in the risk of relapse over 12 months, whereas those who did not achieve complete remission relapsed at a significant rate.

Patients who do not achieve remission are also at greater risk of developing treatment resistance, use more medical services, and do not function as well socially. Miller et al assessed treatment outcomes in terms of social adjustment and functional impairment. Patients who achieved complete symptom resolution scored similarly to normal subjects on the Social Adjustment Scale and significantly better than patients who showed no response to treatment, as well as those who showed response but not remission (P≤0.05).

Various factors may be predictive of the failure to achieve remission. Misdiagnosis influences the course of treatment and its success. Patients with MDD may be misdiagnosed because of the presentation of physical symptoms, for example, or may appear to have bipolar disorder, for which antidepressants are often avoided. Other predictors include psychiatric comorbidities, such as anxiety disorders, substance abuse issues, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder. Medical comorbidities can also influence outcomes, including conditions such as hypothyroidism. Psychotic features that go untreated may also prevent remission. Further, pharmacokinetic issues related to the antidepressant therapy may reduce the effectiveness of treatment.

Even among patients who do achieve remission, some residual symptoms are common. One study indicated that more than 50% of those who achieve remission have 2 or more residual symptoms after 8 weeks of treatment. Approximately one quarter of patients in remission in this study had 1 residual symptom; less than 20% were considered completely symptom-free. Residual symptoms following remission may be psychological (eg, lack of interest/motivation, anxiety), behavioral (eg, reduced work productivity, social withdrawal), or somatic (eg, fatigue, aches/pains). Residual pain symptoms may be linked to depressive symptoms. A study of 86 patients compared the somatic symptom scores of subjects who responded to antidepressant treatment but did not achieve remission to those who went into remission. Patients who achieved remission in this study had significantly lower scores on a measure of somatic symptoms (P≤0.05). A second study reported similar results. Patients at the end point of antidepressant treatment were evaluated on the Clinical Global Improvement–Severity as well as the Visual Analogue Scale (VAS) for general pain severity. The results (Figure 2) demonstrate a clear relationship between severity of depressive symptoms and severity of pain. Patients who do not...
achieve remission, therefore, are likely to have residual somatic as well as psychological symptoms.

**Neurobiology of Depression**

Over the past several decades, researchers have focused on the roles that specific neurotransmitters play in depression. In particular, serotonin and norepinephrine—and, to a lesser degree, dopamine—have been implicated. An array of evidence from various sources supports the involvement of these neurotransmitters. For example, low levels of the metabolites of serotonin are found in the cerebrospinal fluid (CSF) of depressed and suicidal patients. The receptors for serotonin are also upregulated in postmortem tissues and platelets from depressed patients, suggesting a compensatory mechanism for low serotonin levels. Similar findings have been demonstrated with norepinephrine: decreased metabolites in the urine, plasma, and CSF of depressed subjects, and increased expression of norepinephrine receptors on lymphocytes.

The strongest evidence for the involvement of serotonin and norepinephrine in the mechanism of antidepressant drug action was provided by studies of specific neurotransmitter depletion. Tryptophan depletion, for example, blocks the synthesis of serotonin, while alpha-methyl-paratyrosine prevents the synthesis of norepinephrine and dopamine. Investigators employed these depletion mechanisms in 3 groups of patients: those who responded to selective serotonin reuptake inhibitors (SSRIs), those who responded to norepinephrine reuptake inhibitors (NRIs), and nondepressed patients. The results (Figure 3) illustrate the means by which these antidepressants function. Patients classified as SSRI responders were sensitive to serotonin depletion but not norepinephrine depletion; the opposite was true of NRI-responsive patients. Nondepressed patients were not sensitive to either test. Thus, serotonin and norepinephrine (and possibly dopamine) mediated the actions of the antidepressant drugs that were tested.

A large number of studies have been conducted comparing serotonin-acting antidepressants (ie, SSRIs) and the tricyclic antidepressants (TCAs); however, several of the TCAs are not selective for norepinephrine. In a meta-analysis of 15 studies comparing selective serotonin agents with selective NRIs, investigators found virtually no difference in response rates or percent of change in HAM-D scores between these classes of medications. It is possible, however, that serotonin and norepinephrine antidepressants treat different patients and/or symptoms. It has been suggested that serotonin and norepinephrine may affect slightly different symptom domains. Serotonin, for example, may have greater effects on impulsivity, while norepinephrine may have greater effects on vigilance. Both neurotransmitters affect anxiety, irritability, cognition, and mood.

To date, reviews of available data have not found consistent differences in the symptoms that respond to serotonin and norepinephrine agents. Initial studies of pharmacogenomics suggest that genetic differences may explain some of the variation in the response of individuals to drugs of different classes. It is possible that pharmacologic agents that affect both serotonin and norepinephrine may have greater efficacy than selective agents. This might be the result of drug action across a broader symptom domain because dual action drugs or drug combinations are less vulnerable to reduction in efficacy resulting from generic variability, or because there is sufficient “cross-talk” between systems that effects are amplified.

As a proof-of-principle study, investigators examined the use of the SSRI fluoxetine and the selective norepinephrine agent desipramine in subjects with nonpsychotic major depression. After 1 to 2 weeks in the hospital without medication, subjects were randomized to 6 weeks of double-blind treatment in 1 of 3 groups—monotherapy with either desipramine or fluoxetine, or combination treatment with both agents. The results clearly show a statistically superior rate of remission in the combination group compared to either monotherapy group (P=0.0005), suggesting that potentiating both serotonin and norepinephrine neurotransmission is more effective than affecting only one neurotransmitter.

**The Link Between Depression and Pain**

Both serotonin and norepinephrine appear to play a role in the perception of pain as well as in the regulation of mood. Peripheral pain sensations are relayed to the brain via the ascending pain pathway of the spinal cord; the descending pain pathway modulates these signals, inhibiting pain transmission and acting as an endogenous analgesic system. Serotonin and norepinephrine are key modulators in the descending pain pathway. Abnormalities in these neurotransmitters leading to depression could also affect the function of the descending fibers and thus the perception of pain. Patients with major depression, therefore, may experience physical symptoms such as bodily aches and pains for the same reason that they experience mood symptoms—a dysregulation in 2 key neurotransmitters. Agents that increase the availability of both norepinephrine and serotonin could influence not only mood symptoms but also physical symptoms through direct effects in the pathways that control the perception of pain.

As previously described, physical symptoms are common in depression. Studies have demonstrated, for example, a much higher prevalence of headaches, muscle pains, stomach pains, and chest pain in psychiatric patients than in healthy patients. Chronic pain was also found to be significantly more common in patients with major depression (43% vs 16%; P<0.001). In fact, the rate of chronic painful physical conditions increases in relation to depressive symptoms, rising from less than 30% of patients with 2 depressive symptoms to approximately 60% of patients with 8 depressive symptoms. Antidepressants and pain. Pharmacologic evidence supports the serotonin–norepinephrine hypothesis of the link between pain and depression. The SSRIs, which potentiate only serotonin, are generally ineffective in the treatment of pain, whereas agents with activity for both serotonin and norepinephrine have far greater efficacy for pain. A meta-analysis of neuropathic pain treatment trials compared the use of SSRIs, the antiepileptic drug gabapentin, and various tricyclic antidepressants (TCAs). The TCAs were subdivided according to their pharmacologic profiles—ffecting mostly norepinephrine or potentiating both serotonin and norepinephrine. The investigators calculated numbers needed—to treat (NNT) for each group (an NNT of 2, for example, indicates that 2 patients must be treated for 1 positive outcome to be seen). The NNT for SSRIs was 6.7—by far the highest—indicating poor efficacy for neuropathic pain. For gabapentin the NNT was 3.7; for norepinephrine-acting TCAs, it was 3.4. However, for optimally dosed, dual-acting TCAs, the NNT was 1.4, indicating that nearly every patient treated with dual-acting agents showed relief of neuropathic pain.

Other studies have reported similar findings. While SSRIs are very effective in treating the nonsomatic symptoms of depression, painful physical symptoms are largely unaffected by SSRIs use. Serotonin-norepinephrine reuptake inhibitors. While the introduction of SSRIs such as fluoxetine dramatically changed the treatment of depression and the antidepressant market, the main differentiating factor was not a drastic increase in efficacy. Rather, SSRIs provided a therapeutic option with a greatly improved side-effect profile and less risk for potentially dangerous adverse events associated with certain TCAs. While the SSRIs are significantly safer than TCAs, they have little, if any, effect on norepinephrine and only questionable efficacy in pain reduction. The limitations of these classes of agents spurred the development of new medications that affect both norepinephrine and serotonin: the serotonin–norepinephrine reuptake inhibitors (SNRIs). Three SNRIs have been extensively developed (milnacipran, duloxetine, and venlafaxine); currently, only venlafaxine is available in the United States, although duloxetine...
is in the final stages of the US Food and Drug Administration review process. Duloxetine is the most potent of these agents with respect to in vitro reuptake inhibition of both serotonin and norepinephrine. Venlafaxine is less potent in potentiating norepinephrine, and at low doses acts more like an SSRi; at higher doses, however, venlafaxine affects both neurotransmitters.

The SNRIs appear to be very effective in treating painful syndromes, both in the context of depression and outside of depression. Data from a clinical trial of duloxetine (60 mg once daily) in depressed patients demonstrated significant reduction in painful symptoms. Compared to placebo, duloxetine produced significantly greater overall reductions in pain scores (P<0.005); it produced statistically significant abatement in individual symptoms, including backache (P<0.001), shoulder pain (P<0.007), interference with daily activities (P<0.005), and pain while awake (P<0.034).

Looking specifically at back pain, investigators reported significant reduction in symptoms within the first week of treatment with duloxetine (P<0.05) — a difference that persisted throughout the study.

**Nondepressive Painful Conditions**

Of interest, the effects of SNRIs are not limited to patients with major depression. In patients with diabetic neuropathic pain, for example, the SNRI venlafaxine produced a significantly greater reduction in pain scores than placebo. This study also exploited a unique characteristic of venlafaxine. As previously noted, venlafaxine acts primarily as an SSRI at lower doses, affecting mostly serotonin reuptake. At higher doses, however, venlafaxine acts as an SNRI, potentiating both serotonin and norepinephrine. In this placebo-controlled study, the investigators tested both lower doses (75 mg per day) and higher doses (150 to 225 mg per day) of venlafaxine. The lower-dose group of venlafaxine (reflecting SSRi activity) was not significantly superior to placebo, while the higher-dose group (reflecting SNRI activity) showed significant improvement in pain scores. This unique internal control provides strong evidence that the potentiation of both serotonin and norepinephrine produces synergistic effects on pain.

A randomized, controlled trial in patients with migraine suggested analgesic effects with venlafaxine. Although this study did not report statistical analyses, 20 of 30 patients treated with venlafaxine reported at least moderate relief of migraine pain, compared to 12 of 30 treated with the SSRI fluoxetine. Venlafaxine has also been evaluated in premenstrual dysphoric disorder, showing a significantly greater reduction on a measure of pain than placebo.

Milnacipran, an SNRI that is available in Japan and some countries in Europe, appears to have some efficacy in the treatment of fibromyalgia. For example, one study showed that bid dosing of milnacipran produced significantly greater improvement in fibromyalgia than placebo, with 37% of patients versus 14% (P=0.04), classified as responders.

Duloxetine has also been examined for pain outside the context of depression. In patients with diabetic neuropathic pain, and without depression or anxiety, doses of 60 mgqd and 60 mg bid produced significantly greater reductions in pain severity than did placebo, beginning as early as the first week of treatment. Overall, these 2 doses of duloxetine resulted in approximately 50% reduction in pain severity at end point. Among the secondary outcomes of this study was reduction in concomitant acetaminophen use for pain; patients in the 60-mg qd and bid dose groups showed significantly less need for acetaminophen than the placebo group (P=0.011 and P=0.003, respectively). Through the use of a path analysis, the investigators estimated that 88.6% of this analgesia was a direct effect, with only 11.4% due to improvements in mood (P=0.001).

**The Spectrum of Serotonin- and Norepinephrine-Responsive Disorders**

In addition to depression and pain, a variety of other disorders may also be responsive to the effects of serotonin and/or norepinephrine potentiation. The norepinephrine-selective TCA desipramine, for example, has been examined for the treatment of attention-deficit/hyperactivity disorder (ADHD). In adults with ADHD, desipramine reduced scores on ADHD rating scales significantly compared to placebo (P=0.01 by week 2), suggesting that norepinephrine potentiation can relieve ADHD symptoms.

Bupropion has also been tested in adult ADHD. Over 6 weeks of treatment with bupropion 200 mg bid, nearly 50% of subjects showed improvement, compared to approximately 10% with placebo (P=0.02). Results also suggest that ADHD is responsive to norepinephrine-acting agents.

Bupropion has also been evaluated for use in smoking cessation. A study comparing the use of bupropion, placebo, and nicotine patches (both as monotherapy and in combination) suggested that bupropion alone is more effective in helping people quit smoking than nicotine patches alone. The 2 agents together were the most effective treatment.

Other disorders that are responsive to serotonin- or norepinephrine-acting agents include various anxiety disorders and OCD. Anxiety disorders are highly comorbid with major depression, and a variety of antidepressants, as well as other agents, have been used to treat the range of anxiety disorders. The SSRI sertraline, for example, has been shown to be significantly superior to placebo in relieving the symptoms of PTSD (P=0.001). The SNRI venlafaxine has also been examined for anxiety. In patients with generalized anxiety disorder, venlafaxine was superior to placebo at all time points in this 28-week study (P<0.05 at weeks 1, 4, and 20; P=0.001 for all other time points).

Together, these studies demonstrate that a wide range of disorders, from depression to anxiety to chronic pain, are responsive to serotonin- and/or norepinephrine-acting medications. Agents that act on both neurotransmitters, therefore, are likely to cover a broad spectrum of disorders and symptom domains.

**Strategies To Achieve Remission From Depressive Symptoms**

Residual symptoms following the treatment of a depressive episode increase the risk of relapse. Such residual symptoms may be mood symptoms, anxiety symptoms, or physical symptoms. Unfortunately, a very large proportion of patients never achieve remission with antidepressant therapy. For these reasons, clinicians may require additional new strategies to improve patients’ chances of achieving and maintaining remission.

Various tactics have been suggested. These strategies include psychoeducation, enhancing adherence to treatment, ensuring the adequacy of the dose and duration of treatment, tailoring antidepressant choice to specific subtypes or populations, and encompassing the full range of symptom domains, including physical symptoms.

Psychoeducation. A good first step is psychoeducation. Caregivers can explain to patients that depression is a medical illness and is associated with changes in brain function. Depression, therefore, necessitates medical treatment, and often responds favorably to adequate antidepressant therapy. Patients should be fully aware that complete symptom

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**Figure 4. Duloxetine vs. paroxetine: remission rates and relative benefit**

![Figure 4](image-url)
resolution (remission) is the ultimate goal of treatment, and that all therapies should be continued until remission is achieved. Communication and collaboration between patient and caregivers should be emphasized, building a strong therapeutic alliance. Psychosocial materials can assist in these endeavors. Enhancing adherence. No medical therapy is effective without adequate adherence to treatment. Treatment adherence can be improved through several means. Adequate follow-up is critical but often difficult to accomplish, particularly in the primary care setting. Long periods between appointments can increase the risk of treatment interruptions and discontinuation. Tolerability can also influence adherence, and clinicians should take care to choose the most tolerable medication that is appropriate for the patient. Since all drugs have side effects, extra time spent discussing the likelihood of adverse effects, and strategies to cope with these effects, can improve patients' willingness and ability to continue treatment. For example, some side effects pass after the initial stages of treatment, while others, such as insomnia or nausea, can be treated with simple add-on medications.

Adequate duration of treatment. Antidepressant medications should be used within the recommended therapeutic range, rather than in subtherapeutic doses. While some patients will respond to lower doses, most will; some will require doses well above the therapeutic range. Monitoring for therapeutic response in the first 6 to 12 weeks may help in evaluating the dose in patients who are not responding to treatment and not reporting side effects. Treatment should also be of adequate duration. Most patients require at least 6 to 12 weeks to achieve remission.64,65

However, minimal improvement by week 5 generally indicates a slim chance for an adequate response.48 Patients in one study who did not respond early in treatment to fluoxetine were unresponsive at week 4 responded by end point, Rating Scale (MADRS) than either treatment alone (P<0.05 for all other time points).47,48

Among the common symptoms of depression are physical symptoms, both in the context of depression and in persons who will not respond to antidepressant therapy, and failure to reach this goal has real consequences. Not only do patients continue to suffer with residual symptoms, they also have a very high risk of relapse.

A potential link between depression and pain is the involvement of serotonin and norepinephrine in the regulation of both mood and the perception of pain. Indeed, agents that potentiate both of these neurotransmitters appear to be superior in the treatment of painful symptomatology, both in the context of depression and in persons who will not respond to antidepressant therapy.47,48

A number of strategies may be employed to increase the chance of achieving remission. These tactics include augmentation and combination with antidepressants or other types of agents and switching from one antidepressant to another. Of particular note, recent data suggest that the SNRIs venlafaxine and duloxetine produce greater remission rates than SSRIs. These agents, therefore, not only relieve a broad range of symptoms—depressive, somatic, even anxiety—but also are associated with a greater chance of complete recovery.

References

CME Questions

1. Which of the following physical symptoms is common in depression?
   a. headache  
   b. joint pain  
   c. chest pain  
   d. all of the above

2. The most common definition of depression treatment response is:
   a. HAM-D score reductions of ≤75%  
   b. HAM-D score reductions of ≤50%  
   c. MADRS score reductions of ≤75%  
   d. VAS score reductions of ≤10%

3. Which neurotransmitter is involved in both depression and pain?
   a. serotonin  
   b. norepinephrine  
   c. dopamine  
   d. all of the above

4. Norepinephrine is believed to be associated with which of the following symptom domains?
   a. vigilance  
   b. irritability  
   c. anxiety  
   d. all of the above

5. Predictors of remission failure do NOT include:
   a. medical comorbidities  
   b. gender  
   c. anxious comorbidities  
   d. all of the above

6. In patients with 8 or more depressive symptoms, the incidence of pain is high as:
   a. 60%  
   b. 70%  
   c. 80%  
   d. none of the above

7. Selective serotonin reuptake inhibitors do not significantly treat which depressive symptom?
   a. irritability  
   b. painful symptoms  
   c. anxiety  
   d. sadness

8. Factors for improving treatment adherence include:
   a. avoiding interruption of treatment  
   b. selecting treatments that are well tolerated  
   c. providing adequate follow-up  
   d. all of the above

9. Research shows that minimal improvement by week _____ indicates a low probability of treatment response
   a. 2  
   b. 3  
   c. 4  
   d. 5

10. Switching antidepressant treatments is:
    a. highly discouraged  
    b. appropriate in some cases  
    c. highly encouraged  
    d. none of the above

Post-Test Answers:
1. a b c d  
2. a b c d  
3. a b c d  
4. a b c d  
5. a b c d

Evaluation:
1. Extent to which the objectives were achieved: 1 2 3 4 5
2. Potential effect on your practice: 1 2 3 4 5
3. Overall evaluation of this CE activity: 1 2 3 4 5
4. Suggestions for future CE topics:

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