

Depression and Pain

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The planning teleconference series was chaired by **John H. Greist, M.D.**, Department of Psychiatry, University of Wisconsin School of Medicine and Public Health; Healthcare Technology Systems, Inc.; and the Madison Institute of Medicine, Madison. The faculty were **John F. Greden, M.D.**, Depression Center and the Molecular and Behavioral Neuroscience Institute and Department of Psychiatry, University of Michigan Health System, Ann Arbor; **James W. Jefferson, M.D.**, Department of Psychiatry, University of Wisconsin School of Medicine and Public Health; Healthcare Technology Systems, Inc.; and the Madison Institute of Medicine, Madison; and **Madhukar H. Trivedi, M.D.**, Mood Disorders Research Program and Clinic, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas.

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Introduction

"... if there be a hell upon earth, it is to be found in a melancholy man's heart."

—Robert Burton

So wrote Robert Burton in *The Anatomy of Melancholy* in 1621, and today, observed John H. Greist, M.D., melancholy—or depression—still places an enormous burden on the individual and on society. In 2000, depressive disorders ranked fourth worldwide as a source of disability-adjusted life years (DALYs), accounting for 4.5% of DALYs and 12.1% of total years lived with disability.¹ Further, added Dr. Greist, in the Americas, depression is ranked first in total DALYs, responsible for a full 8% of the burden.¹

Major depressive disorder (MDD) has a lifetime prevalence rate of 16.2% in the United States and is associated with an increased risk for serious medi-

cal conditions, increased mortality in existing medical conditions, and a reduced life expectancy.²⁻⁴ Depression also increases the risk of suicide, one of the leading causes of death in the United States.⁵ Still, depression remains an underdiagnosed and undertreated disorder.⁶

One reason that depression is underdiagnosed may be that some patients present with pain or unexplained physical symptoms. In the following presentation, Dr. Greist addressed the adverse effect of pain on the course of depression, and then his colleagues presented information about the recognition of depression in patients who present with pain, the common neurologic pathways of depression and pain, and effective pharmacologic treatments for patients with both pain and depression.

The Effect of Comorbid Pain on Depression and Course of Illness

Depression, Dr. Greist emphasized, is a multifaceted disorder, with emotional symptoms such as sadness and apathy, physical symptoms that include changes in appetite or sleep, and other associated symptoms such as irritability or excessive worry (Figure 1).⁷ One of the most common associated symptoms of depression is pain.

Risk for Depression and Pain

A meta-analysis⁸ showed a mean prevalence of 65% for painful symptoms for patients with depression. Conversely, in people with pain, the risk of clinical depression increased in relation to the number of pain symptoms reported, with just 2 pain complaints

causing a 6-fold increase in the likelihood of clinical depression relative to no pain complaint.⁹ In fact, the presence of major depression was predicted not by severity or persistence of pain but by number of painful symptoms.

Course of Depression With Pain

Dr. Greist explained that pain has an additive effect on depressive episodes, both lengthening the duration and increasing the severity of episodes and also delaying patients from seeking psychiatric help.¹⁰⁻¹² Patients with both depression and painful physical symptoms also have nearly twice as many work loss days as patients with depression alone.¹²

FOR CLINICAL USE

- ◆ Although the diagnostic criteria for major depressive disorder emphasize emotional and vegetative symptoms, depression is also frequently associated with painful physical symptoms, and patients often report only somatic symptoms.
- ◆ Chronic painful conditions are associated with higher lifetime prevalence rates of depression than are found in the general population.
- ◆ The neurotransmitters serotonin and norepinephrine may regulate not only the emotional and vegetative symptoms of depression but also the painful physical symptoms of depression.
- ◆ A comprehensive treatment plan should treat pain and depression concurrently, and patients should receive long-term maintenance treatment to help prevent recurrence.

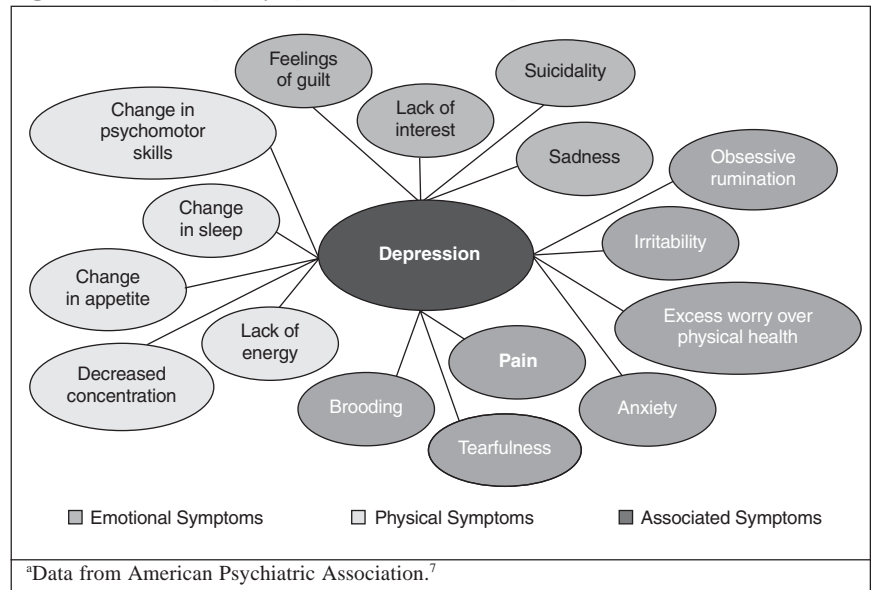
Importance of Asymptomatic Remission

Even after receiving a diagnosis of MDD, only about a third of patients who initially receive an antidepressant reach remission.¹³ Dr. Greist added that switching to another antidepressant after an adequate but unsuccessful course of treatment will yield an additional 20% to 25% remission rate,¹⁴ while augmenting the antidepressant with a second medication increases the remission rate by around 30%.¹⁵

Rapid remission is an important predictor that patients will achieve long-term remission of their depressive symptoms.¹⁶ However, the presence of residual symptoms after remission is a predictor of early relapse. In a study by Paykel et al.,¹⁷ 76% of patients with residual symptoms relapsed within 15 months of remission, while 25% of those without residual symptoms relapsed.

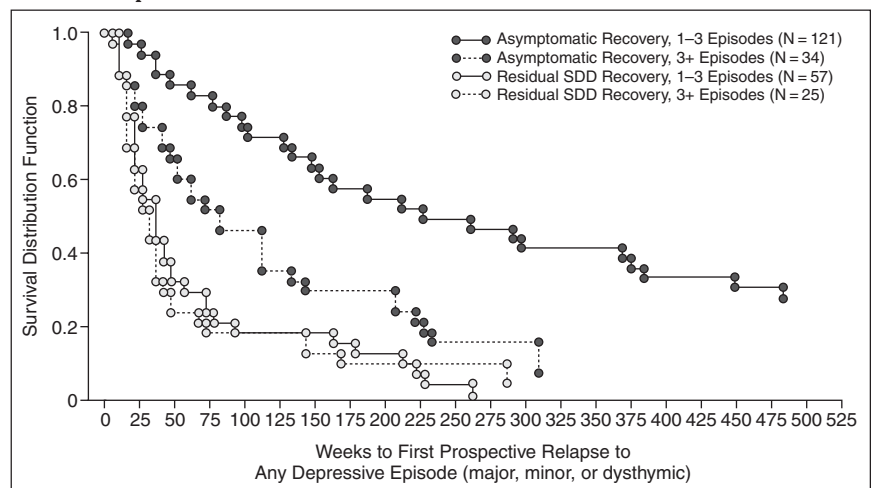
Not only do more patients who have residual symptoms after remission of depression relapse,¹⁷ but patients with

Figure 1. The Multiple Symptom Domains of Depression^a



^aData from American Psychiatric Association.⁷

Figure 2. Residual Symptoms in Patients With Major Depressive Disorder May Predict Relapse^a



^aReprinted from Judd et al.¹⁸

Abbreviation: SDD = subsyndromal depressive symptoms.

residual symptoms also relapse more quickly than asymptomatic patients. Judd et al.¹⁸ followed a group of patients for at least 10 years who had experienced a major depressive episode and found that patients with even 1 or more mild residual symptoms relapsed about 3 times faster than asymptomatic patients. The presence of residual symptoms had a stronger association with relapse than the number of previous episodes (Figure 2).

Outcome of Depression With Pain

Dr. Greist cited a 3-year study that examined recovery from depression in older adults. Geerlings et al.¹⁹ showed a poorer prognosis for patients with depression and pain as opposed to patients with depression and no pain (9% versus 47% recovery rate, respectively).

Dr. Greist emphasized that treating pain is therefore an important part of treating depression. Pooled results

from two 9-week randomized, double-blind clinical trials found that the depression remission rate doubled when patients with both MDD and painful physical symptoms responded to treatment for pain as opposed to not responding to pain treatment (36.2% versus 17.8%).²⁰

Conclusion

Depression with pain is common, recurrent, often debilitating, and potentially lethal through suicide, but treatable. Dr. Greist stressed that it is important to diagnose depression correctly, recognizing pain as both a symptom and predictor of depression.

Recognizing Depression in Patients Who Present With Pain

James W. Jefferson, M.D., agreed with Dr. Greist that pain affects the course of depression and stated that, conversely, depression complicates the course of pain. A patient with chronic pain and depression will have more pain complaints, greater pain severity, longer duration of pain, and less likelihood of fully recovering than a patient with chronic pain and no depression.⁸ These patients will also have greater utilization of health care resources, functional impairment, and unemployment.

Prevalence of Depression in Patients With Chronic Pain

Dr. Jefferson cited a Canadian epidemiologic study²¹ with a sample of more than 131,500 persons. The study showed that those with chronic pain conditions had an 11.3% rate of MDD, whereas individuals with no chronic pain had a prevalence of 5.3%. Similarly, a study²² of 5,808 primary care patients who responded to self-assessment questionnaires on mood disorders, chronic pain, and quality of life found that the prevalence of MDD in individuals without pain was 4.5%, but for individuals with chronic pain

it was 10.4%. Among the individuals with chronic pain, the prevalence of MDD differed depending on whether the pain was disabling; for those with chronic pain that was not disabling the rate of MDD was 5.4%, but for individuals with disabling pain it was 23.3%.²² The authors pointed out that cause and effect is unclear; people with chronic pain, especially if disabling, may be more susceptible to MDD, but those with MDD may be at risk for becoming disabled by pain.

According to Dr. Jefferson, different prevalence rates of MDD are found among different types of pain conditions. Among patients referred to headache specialists, Jelinski et al.²³ found a 27% prevalence of moderate-to-severe depression; a correlation between disability and depression was also noted. In a study²⁴ spanning 17 countries and comprised of 85,088 individuals with chronic back or neck pain, the pooled odds ratio for dysthymia and MDD was 2.3. A review²⁵ of 9 studies of patients with chronic low back pain found an average 21% prevalence rate of depression.

A positive association was also found for depression and diabetic

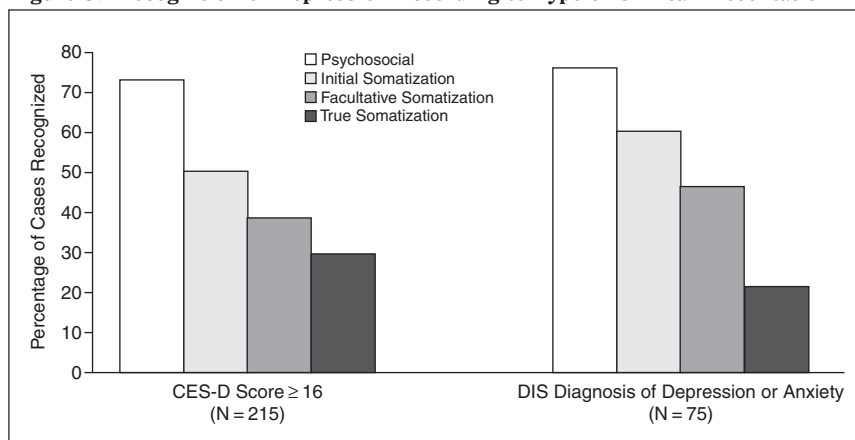
peripheral neuropathy; mediators of this relationship included the unpredictability of symptoms, lack of treatment control, and restrictions in activities of daily living.²⁶ Other chronic painful conditions also are associated with higher lifetime prevalence rates of depression than are found in the general population; in patients with fibromyalgia, the rate of MDD is estimated to be as high as 74%.^{27,28}

With the high correlation between chronic pain and depression, Dr. Jefferson advised that patients with chronic pain should be considered depressed until proven otherwise.

Recognition of Depression in Patients With Chronic Pain

Physicians are much less likely to recognize depression when patients present with somatic symptoms as opposed to mood symptoms. Kirmayer et al.²⁹ found that 80% of primary care patients scoring ≥ 16 on the Center for Epidemiologic Studies Depression Scale (CES-D) made somatized presentations, as did 76% of patients diagnosed with depression by the Diagnostic Interview Schedule (DIS). In patients diagnosed with depression

Figure 3. Recognition of Depression According to Type of Clinical Presentation^a



^aAdapted with permission from Kirmayer et al.²⁹ Psychosocial presenters presented with at least one psychosocial symptom or problem. Initial somatizers presented with only somatic symptoms, but when asked what caused their somatic symptoms spontaneously identified a psychosocial or psychiatric contributor. Facultative somatizers presented with only somatic symptoms and made only somatic attributions, but when prompted with a direct question accepted the possibility of such a psychosocial explanation. True somatizers presented with only somatic symptoms and somatic attributions and even when prompted did not accept "worries" or "personal problems" as a possible cause of their symptoms. Abbreviations: CES-D = Center for Epidemiologic Studies-Depression scale, DIS = Diagnostic Interview Schedule.

Table 1. Patient Health Questionnaire-9 (PHQ-9) Symptom Checklist^a

Over the <i>last 2 weeks</i> , how often have you been bothered by the following problems?	Not at All (0)	Several Days (1)	More Than Half the Days (2)	Nearly Every Day (3)
1. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Trouble falling asleep, staying asleep, or sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feeling bad about yourself, or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble concentrating in things, such as reading the newspaper or watching television	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety that you have been moving around a lot more than usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Thoughts that you would be better off dead or of hurting yourself in some way	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

^aAdapted with permission from Pfizer Inc.³¹ The scores relating to depression are: 1 to 4 = very low likelihood or remission, 5 to 9 = possible subthreshold, 10 to 14 = moderate, 15 to 19 = moderately severe, and 20 to 27 = severe.

according to either the CES-D or the DIS, somatic presentation reduced physician recognition of depression from about three fourths of patients to about one fourth (Figure 3).²⁹

Tools for Diagnosing Depression in Patients Who Present With Pain

Dr. Jefferson recommended that all patients with chronic pain be evaluated for depression. He asked that clinicians remember that unexplained pain symptoms or the presence of multiple physical symptoms have a particularly strong association with mood disorders.³⁰ Although pain is not one of the diagnostic criteria for a major depressive episode, it is an associated descriptive feature.⁷ Depression and chronic pain do have some symptom overlap, but symptoms such as anhedonia, agitation, or a sense of worthlessness are not shared by the 2 conditions and provide a means of separating the diagnoses of depression and chronic pain when evaluating a patient.

Tools used to diagnose depression include structured interviews, such as the DIS and others. Dr. Jefferson remarked, however, that these interviews are time-consuming and impractical in a busy clinician's office. Clinician-administered scales such as the Hamilton Rating Scale for Depression also take too much time for an office-based clinician.

Self-administered scales, such as the Beck Depression Inventory, Zung Self-Rating Depression Scale, and the CES-D, are practical to use in screening for depression, according to Dr. Jefferson. One self-rated scale, the Patient Health Questionnaire-9 (PHQ-9), evaluates the 9 items in the DSM-IV criteria for a major depressive episode (Table 1).³¹ The PHQ-9 has proven to be a useful tool for not only diagnosing depression but also measuring depression severity, and its brevity makes it useful in the clinical setting. The Hospital Anxiety and Depression Scale (HADS), used in medical outpatient clinics, has been found reliable for detecting depression and was designed to be used by patients with coexisting medical illnesses.³²

To take even less time screening for depression, Whooley et al.³³ tested a 2-question instrument. The 2 questions are, "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?" Dr. Jefferson offered that this instrument is appropriate if time with the patient is running short. The question of whether or not diagnostic criteria for depression that are different from those in the DSM-IV should be used in patients with medical illness was addressed by Simon and Von Korff.³⁴ Their findings indicated

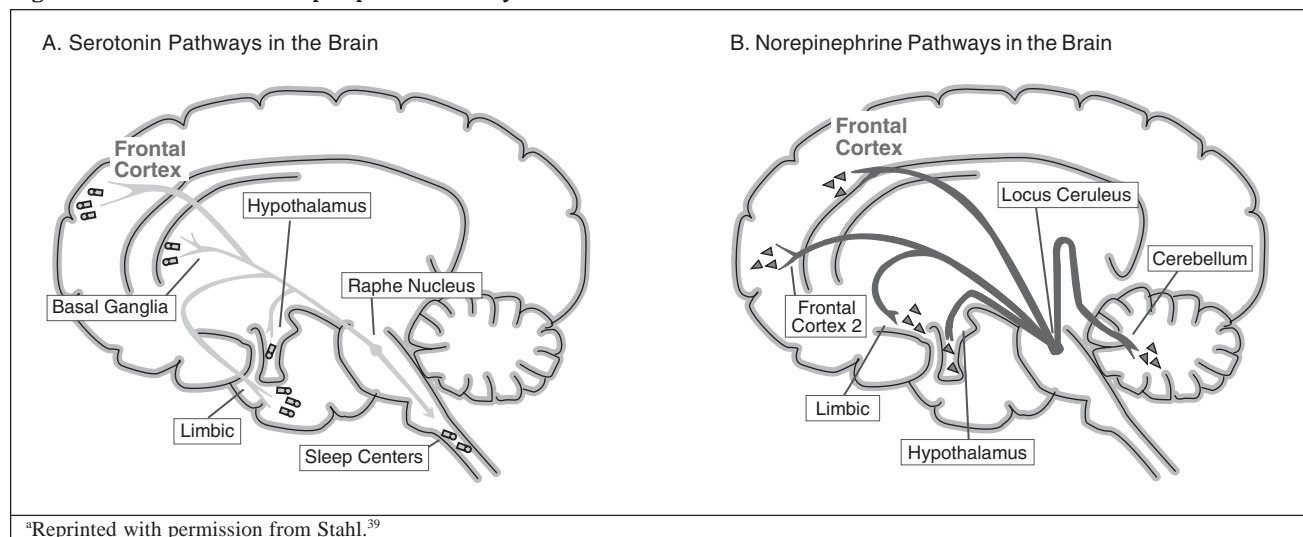
that somatic symptoms (fatigue, weight or appetite change, sleep disturbances, and psychomotor agitation or retardation) are valid indicators of depression in patients with or without chronic illness.

Conclusion

In the presence of chronic pain, a higher incidence of depression is found than in patients without pain conditions. If patients with chronic pain have depression, negative health consequences can result. Depression is under-recognized in patients with chronic pain conditions, partly because these patients frequently present somatically. Dr. Jefferson concluded that screening patients with chronic pain for depression is essential, and self-administered tests such as the PHQ-9 or the HADS have proven value in the clinical setting.

Common Pathways of Depression and Pain

Madhukar H. Trivedi, M.D., advised clinicians to consider both the mind and the body when assessing and treating patients. Neglecting the painful symptoms associated with depression while conducting clinical assessments, diagnosis, and follow-up has hampered clinicians' ability to help

Figure 4. Serotonin and Norepinephrine Pathways in the Brain^a

patients with depression achieve full remission. Similarly, not considering a psychiatric diagnosis in a patient who presents with unexplained or multiple physical symptoms may lead the clinician to perceive the patient as difficult, and the missed diagnosis can lead to the patient's greater use of health care services but less satisfaction with care.³⁵

Characteristics and Consequences of Pain Comorbidity

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial enrolled patients with MDD from both primary care and specialty care settings to evaluate treatment principles in real-world practice.³⁶ To study whether patients with MDD and pain complaints differed from those without pain complaints, Husain et al.³⁷ analyzed baseline data from a representative outpatient sample (N = 3745) from the STAR*D study. Patients with and without pain were compared in terms of sociodemographic, clinical, and presenting symptom features. Patients who had painful symptoms were more likely to be younger, African-American or Hispanic, and less educated than those without pain symptoms. Complaints of pain were correlated with other symptoms such

as anxious features with irritable mood, sympathetic nervous arousal, gastrointestinal problems, and a poorer quality of life.

Neurobiologic Link Between Depression and Pain

Serotonin (5-HT) and norepinephrine (NE) are neurotransmitters that have both ascending pathways to the cerebral cortex and limbic areas, where they mediate many emotional and physical functions, and descending pathways to the spinal cord, where they are involved in pain suppression (Figure 4).^{38,39} Most of the 5-HT systems originate in the raphe nuclei, and the NE systems originate in the locus ceruleus, but their projections into the fore-brain have a number of overlapping tracts.

Evidence implicating the 5-HT and NE systems in the etiology of MDD has been found through studies in which selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), or a combination of the two, serotonin-norepinephrine reuptake inhibitors (SNRIs), have been shown to lead to improvement in depressive symptoms.⁴⁰ Further, neurotransmitter depletion studies have shown that patients successfully treated for MDD with an SSRI whose serotonin is rap-

idly depleted have a return of symptoms; depletion of NE in these patients does not cause symptoms to return.⁴¹ Conversely, NRI responders did not have a return of symptoms with the depletion of 5-HT but did with the depletion of NE. Depleting 5-HT or NE in healthy subjects did not induce depression, and depletion did not worsen depression in unmedicated symptomatic patients. Additional evidence for 5-HT and NE abnormalities in patients with MDD is the blunted neuroendocrine response to serotonin or α_2 -adrenergic agonists found in these patients, along with reduced cerebrospinal fluid levels of 5-HT metabolite.⁴²

Not only depression but also pain is associated with 5-HT and NE pathways. For example, neuropathic pain is associated with increased excitation and decreased inhibition of ascending pain pathways; the descending pathways modulate ascending signals, and 5-HT and NE are key neurotransmitters in descending inhibitory pain pathways.⁴³ Therefore, increasing the availability of 5-HT and NE may promote pain inhibition centrally.

Conclusion

Dr. Trivedi concluded by saying that depression and pain are highly comorbid conditions with overlapping

symptom domains. Painful physical symptoms not only increase the burden of illness for patients with MDD, but also delay remission in these individuals.⁴⁴ Depression and pain share neurobiologic pathways, as evidenced by studies showing analgesic effect for tricyclic antidepressants (TCAs)⁴⁵ and SNRIs.²⁰ Systematic measurement of symptoms that includes painful physical symptoms is necessary to help patients with MDD achieve and sustain remission.

Depression and Pain: A Pharmacologic Road Map for Psychiatrists

The traditional understanding of pain and depression as separate conditions with overlapping symptoms has evolved into an understanding that pain and depression share pathophysiology, with shared origins, mechanisms, and neurotransmitters, and, as a result, shared treatments. John F. Greden, M.D., stressed that depression and pain must be treated concurrently.

Patients may feel both pain and depression, but they often talk only about the pain, possibly due to the stigma attached to depression or because of perceived physician expectations. Psychiatrists should realize that when a patient whose chief complaint is pain is referred to them, the referral is often driven by frustration with inadequate treatment progress elsewhere.

Neuroscience Pain Profiles

An understanding of 3 models of pain and the role the brain plays in each type is helpful in understanding why certain treatments are essential and why others are to be avoided when treating individuals with pain and depression, explained Dr. Greden. The 3 types of pain are peripheral (nociceptive), neuropathic, and central (non-nociceptive) (Table 2).⁴⁶ Peripheral pain is caused by inflammation or mechanical damage. Examples would be sports injuries and arthritis. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) are characteristically used to treat peripheral pain; sometimes surgery is needed. Psychotropic medications show little evidence of resolving this type of pain.

Neuropathic pain is caused by peripheral nerve damage, such as that which occurs with diabetic peripheral neuropathy. Besides opioids, psychiatric medications such as SNRIs, TCAs, and anticonvulsants have been shown to be effective for treating neuropathic pain.⁴⁷⁻⁴⁹

Central pain is primarily due to brain disturbances in pain processing. Examples of central pain include illnesses such as fibromyalgia, irritable bowel syndrome, and chronic tension headaches. Depression is often linked with these illnesses, and behavioral factors are more prominent than in the previously mentioned pain conditions. Antidepressants may be effective for patients with various types of central pain.⁵⁰⁻⁵²

Sensory amplification, explained Dr. Greden, is a variable in central pain.⁵³ Dr. Greden calls sensory amplification *brain sensitization* to help his patients and their families understand. He explains to patients that the brain, spinal cord, or both, are possibly amplifying sensory signals, making patients' brains more sensitive to pain signals than other people's brains. Dr. Greden uses the analogy of television commercials to illustrate amplification, explaining that they often are much louder than the show they interrupt. When sensory perceptions are processed in those who have underlying brain abnormalities, the sensitization sometimes is registered as pain. Dr. Greden commented that when depression and pain are intertwined in patients with central pain disorders, clinicians need to address the depression and pain together because making a distinction between depression and pain is not helpful to ongoing treatment.

Road Map for Treatment

Dr. Greden described a comprehensive treatment road map for patients with depression and central or neuropathic pain (Table 3). To identify these patients, clinicians can use the PHQ-9 and a brief pain scale, since time is a key variable for clinicians. Patients should be educated before treatment starts. Physicians should describe the 3 types of pain and sensory amplification, the concurrence of depression and pain, the treatments that are used to target the mechanisms of pain and

Table 2. Neuroscience Pain Profiles^a

Types of Pain	Causes	Examples	Treatments
Peripheral (nociceptive)	Inflammation or mechanical damage in periphery (behavioral factors minor)	Osteoarthritis Rheumatoid arthritis Cancer pain Sports injuries	NSAIDs, opioids, surgical procedures
Neuropathic	Peripheral nerve damage or entrapment	Diabetic peripheral neuropathy	Both peripheral and central pharmacologic therapy: SNRIs, TCAs, other CNS medications are the most effective
Central (non-nociceptive)	Primarily due to a brain disturbance in pain processing (behavioral factors more prominent)	Fibromyalgia Irritable bowel syndrome Tension headache Idiopathic low back pain Depression often linked	SNRIs, TCAs, other CNS medications are the most effective

^aBased on Clauw.⁴⁶

Abbreviations: CNS = central nervous system, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Road Map for Treating Comorbid Depression and Pain

Step 1. Screen and monitor patients using PHQ-9 and a pain scale Identify peripheral pain and refer for proper treatment
Step 2. Educate patients before treatment starts regarding the following points: Duration of treatment Healthy sleep Avoidance of alcohol and over-the-counter medications Exercise Proper nutrition
Step 3. Start CBT Prescribe SNRIs or TCAs at a low dose and increase slowly Begin exercise program after 1 week; start low, go slow
Step 4. After 6–8 weeks, if necessary, augment with pregabalin or gabapentin (higher dose at night) or low-dose pain medications (avoid tramadol) Prescribe zolpidem or trazodone for sleep if needed (avoid benzodiazepines) Discontinue some medications before adding fourth and fifth medicines Consider cytochrome P450 genetic polymorphism assessment if patient unable to tolerate multiple medications
Step 5. Be persistent; long treatment periods are indicated (several months) Promote continuation of CBT, exercise, healthy sleep, and proper nutrition
Step 6. Implement long-term maintenance treatment (≥ 2 years) once improved
Abbreviations: CBT = cognitive-behavioral therapy, PHQ-9 = Patient Health Questionnaire-9, SNRI = serotonin-norepinephrine reuptake inhibitors, TCAs = tricyclic antidepressants.

depression, and the duration of treatment. Dr. Greden recommended that clinicians also highlight the importance of getting healthy sleep and proper nutrition, avoiding alcohol (which worsens depression and can also interfere with medications) and over-the-counter medications, and getting regular exercise.

Cognitive-behavioral therapy (CBT) should be started early. Stress worsens brain sensitization, said Dr. Greden, and CBT can focus upon stress-coping strategies and techniques for avoiding factors that worsen symptoms. The goal is for patients to return to their regular routines as soon as feasible.

Dual-action antidepressants such as SNRIs or TCAs should be started at low doses and increased slowly. Exercise should also be started at week 1 and gradually increased; family members should be involved in helping patients to sustain adherence.

If patients are still not doing well after 6 to 8 weeks, augmentation may be necessary. Pregabalin and gabapentin are anticonvulsants that have an analgesic effect. Additional pain medications can be added with care if necessary. The NSAIDs may be added, if taken with food, but if the patient is taking SNRIs or TCAs, avoid tramadol

because of the possibility of serotonergic syndrome, advised Dr. Greden.

If patients have evidence of sleep disturbances, clinicians should emphasize sleep hygiene procedures such as dark rooms, cooler temperatures, and avoidance of background noise. Pharmacologic interventions to aid sleep, such as zolpidem or trazodone, can be added cautiously. Clinicians should avoid overuse or routine use of benzodiazepines, as some of the other recommended medications produce drowsiness.

Before adding fourth, fifth, and even more analgesic medications, clinicians should ideally discontinue some medications while reminding patients and families that the core treatments take time. Carefully consider which medications should be discontinued; for example, do not discontinue an SNRI or TCA if progress has been made. If a patient is unable to tolerate different medications, Dr. Greden advised reviewing metabolic pathways or even considering a cytochrome P450 pharmacogenetic assessment to be sure that the patient can metabolize medications correctly.

Clinicians must be persistent, emphasized Dr. Greden. Long-term maintenance treatment (≥ 2 years) should be recommended at the beginning of

treatment, especially for those who have had prior depressive episodes. The clinician should continue to promote CBT, exercise, healthy sleep, and proper nutrition. Maintenance treatment should be continued once the patient has improved with the same medication during maintenance treatment that helped the patient recover during acute treatment.

Evidence for Treatment Efficacy

Evidence supports the use of CBT, aerobic exercise, and patient education in the treatment of chronic pain syndromes such as fibromyalgia.⁵⁰ A possible mechanism is that exercise has been shown to increase brain-derived neurotrophic factor (BDNF) in the hippocampus, both alone and in combination with antidepressants, which can counteract the reductions in BDNF that occur with stress, pain, and loss of sleep.⁵⁴

Other nonpharmacologic therapies, such as acupuncture, biofeedback, orthopedic manipulation, massage, or ultrasound therapy, have only modest to weak evidence of efficacy and, if tried, should not replace the framework of the road map. No evidence exists for the efficacy of trigger point injections.⁵⁰

Medications that inhibit both 5-HT and NE appear to have efficacy for neuropathic and central pain.^{49,55} TCAs, such as amitriptyline and imipramine, have efficacy in chronic pain, as do SNRIs, such as duloxetine, venlafaxine, and milnacipran. Anticonvulsants such as pregabalin and gabapentin also have efficacy, and, because they are predominantly excreted renally instead of hepatically, can be used together.⁵⁰

Minimal evidence exists for SSRIs or over-the-counter herbal medications or dietary supplements such as SAME for alleviating neuropathic and central pain. Benzodiazepines are not effective as analgesics, and other strategies are preferable for the symptoms they do treat. Ketamine, a research strategy, has been shown to attenuate pain and alter the pain threshold, but further study is required.⁵⁶

Glutamate shows tremendous research potential for future pharmacologic treatment. Other neurotransmitters and key neuromodulators hypothetically involved in depression and pain, such as substance P, neurotensin, adenosine, and γ -aminobutyric acid, need further research.

Conclusion

Dr. Greden concluded that patients must understand that depression and pain have overlapping mechanisms and that the 3 types of pain require different treatment strategies. The treatment road map for neuropathic and central pain includes CBT for stress reduction, exercise for neurotrophin enhancement, patient education regarding treatment, and appropriate pharmacotherapy to target serotonergic and noradrenergic neurotransmitters. The combination of these elements, sustained over time, promotes the most favorable outcome, said Dr. Greden, and the patient should receive long-term maintenance treatment to help prevent recurrence.

Drug names: duloxetine (Cymbalta), gabapentin (Neurontin and others), imipramine (Tofranil and others), ketamine (Ketalar and others), pregabalin (Lyrica), tramadol (Ultram and others), venlafaxine (Effexor and others), zolpidem (Ambien and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, gabapentin, ketamine, amitriptyline, and milnacipran are not approved by the U.S. Food and Drug Administration for the treatment of pain; and pregabalin is not approved for the treatment of pain other than diabetic neuropathic pain or herpes zoster.

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For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 2004–2006.
