Pain & Depression:

Pathology, Prevalence, & Treatment

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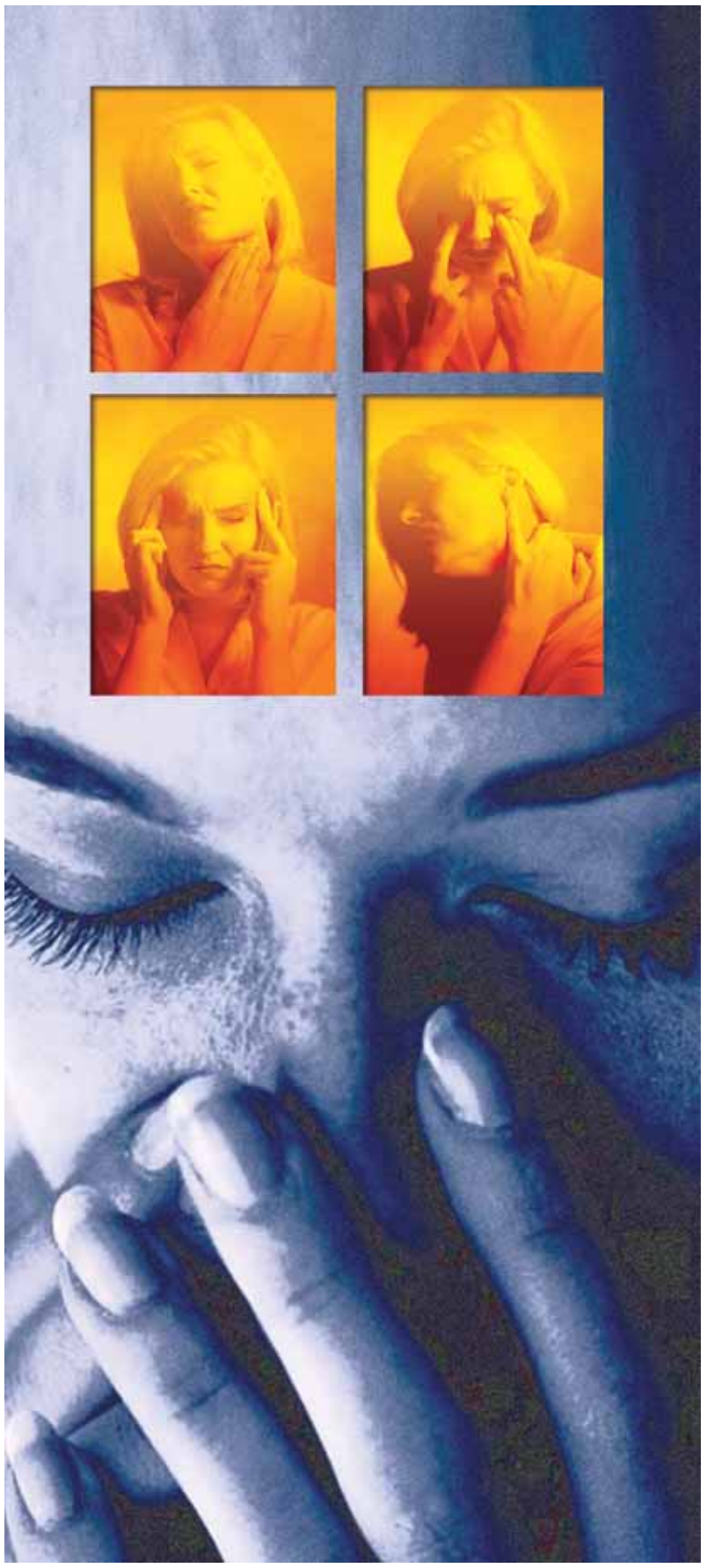

Chronic Pain and Depression

A strong association between chronic pain and depression has long been suggested.[1-5] Not surprisingly, serotonin and norepinephrine, the neurotransmitters most associated with depression, play key roles in the modulation of pain.[6] The reported prevalence of major depression in patients with chronic pain conditions varies from 5% to 87%.[7-9] This large discrepancy is due to a number of study criteria, including diagnostic criteria used, type of pain studied, selection bias, type of interview (structured vs nonstructured), and type of patients studied (clinically depressed patients vs patients with depressive symptoms). Somatic criteria for major depressive disorder may overlap with symptoms of chronic pain (Table 1). Response to more active treatments for chronic pain, such as physical therapy, may be limited by untreated depressive symptoms and patient personality traits.[10]

Depressive symptoms have been shown to predict the development of chronic musculoskeletal pain in some population studies. Magni et al[11] and Fishbain et al[12] reported higher levels of depression in chronic pain patients than in patients without chronic pain. Population studies have also examined possible predictors of depression in chronic pain (Table 2). In a study by Dworkin et al,[13] the number of coexisting pain conditions reported was a better predictor of major depression than measures of pain experience, including severity and persistence. Pain intensity and frequency, low self-efficacy, and lack of belief in one's ability to control pain may also contribute to the development of depression in chronic pain patients.[14-16] Studies also show that depressed patients are more likely to report a greater number and severity of physical symptoms.[17] In addition, chronic pain and depression show a significant clinical overlap with stress-related pain disorders, such as chronic low back pain, facial pain, fibromyalgia, irritable bowel syndrome, migraine, phantom limb pain, and temporomandibular disorders (Table 3).[18-25]

Table 1. Somatic Symptoms Of Major Depressive Disorder Common in Chronic Pain Patients

Change in appetite
Change in weight
Loss of energy
Motor retardation
Sleep disturbance

Table 2. Predictors of Depression In Chronic Pain Patients

Number of painful areas of the body[13]
Pain intensity[14]
Functional disability[14]
Psychosocial factors, including low self-efficacy and poor coping and problem solving[14]
Frequency that severe pain is experienced[15]

Table 3. Prevalence of Depression in Specific Pain Disorders

Disorder	Prevalence, %
Irritable bowel syndrome[18]	61
Fibromyalgia[19]	57
Temporomandibular disorders[20]	39 with clinical depression; 55 with moderate to severe somatization
Chronic low back pain[21,22]	30-45
Facial pain[23]	30-60
Migraine[24]	20-30
Phantom limb pain[25]	20

Prevailing theories of pain incorporate a link between sensory, cognitive, affective, and behavioral components.[26,27] Models describing the interaction between depression and pain have been proposed. The classic, somewhat outdated *dualistic* model describes pain in the absence of identified organic cause as a presentation of repressed depression.[28] Other models propose that elements of personal vulnerability (diathesis) interact with stresses, or threats, to well-being to create depression. A biopsychosocial model of chronic pain incorporates the physical, cognitive, affective, and behavioral components related to the ongoing pain experience. The dynamic interplay between these components may perpetuate chronic pain.[29] In this context, biologic factors may initiate a physical disturbance, but psychological factors appear to influence pain perception and ongoing pain experience.

Neuropathophysiology

Pain transmission occurs via ascending (excitatory) and descending (inhibitory) pathways involving norepinephrine and serotonin, or 5-HT. Serotoninergic neurons originate in the brain stem raphe region and project throughout the central nervous system (CNS), including descending projections to the spinal cord, which result in suppression of sensory input. They also project to areas of the brain including the frontal cortex (mediating mood), hypothalamus (mediating appetite and sleep), and amygdala (mediating anxiety and fear response).[30]

A reduction of presynaptic serotonin release and a compensatory upregulation of 5-HT_2, a postsynaptic serotonin neuron, have been found in depressed patients. Limited research has also suggested that pain may increase the turnover of serotonin.[31,32]

New Theories

Although a thorough understanding of peripheral mechanisms of pain and modulation at the spinal cord dorsal horn has emerged, more questions remain regarding the influence of the CNS. Understanding the CNS's supraspinal influences in processing and modulating pain may lead to new insight into the link between chronic pain conditions and affective disorders, including depression and anxiety.

The neuromatrix theory of pain proposes that a *neurosignatur*e of the pain experience is influenced by genetic and sensory factors. This pattern is modulated by sensory inputs from the environment and cognitive events, such as psychological stress. In turn, these many inputs contribute to the sensory, affective, and cognitive dimensions of the pain experience and subsequent behavior. Rome and Rome[33] recently suggested that neuroplasticity may explain how exposure to a noxious stimulus may, under certain conditions, lead to a sensitized corticolimbic state. Their proposal of a new condition, called limbically augmented pain syndrome, may describe a subset of chronic pain patients with treatment-refractory pain and affective distress.

Management

Medical management for pain and depression targets analgesia to improve mood. In addition, physical and occupational therapy, as well as psychological interventions, compose a comprehensive pain management treatment plan. Modulation of pain at the peripheral, spinal cord, and brain levels is an obvious target for medical management. Besides opioid receptor activation in the periphery, other factors modulate pain perception, including supraspinal effects in the midbrain, periaqueductal gray matter, and adjacent reticular formation in the spinal cord dorsal horn.

A variety of medications have been reported to benefit patients suffering from pain and depression. Antidepressant medications, in particular, may be efficacious as analgesic agents. The use of tricyclic antidepressants (TCAs) for analgesia has been supported in numerous controlled trials and meta-analyses. Numerous analgesic mechanistic effects of TCAs are proposed (Table 4). Intrinsic analgesic effects of these compounds may be independent of their antidepressant effects. Data from controlled trials indicate that TCAs are as effective as analgesics in treating painful diabetic neuropathy, postherpetic neuralgia, central pain, tension-type headache, and migraine.[34,35] A meta-analysis of placebo-controlled studies found that chronic pain patients are more likely to benefit from antidepressant treatment than from placebo.[36] Their analgesic qualities in specific pain disorders have been found to be independent of any mood elevation effect.[37,38] TCAs have a range of side effects, including one or more of the following: anticholinergic effects, drowsiness, orthostatic hypotension, arrhythmias, and gastrointestinal distress (Table 5).

Table 4. Mechanism of Analgesic Effects of Tricyclic Antidepressants[34]

1. Central blockade of monoamine uptake (serotonin, norepinephrine)
2. Enhancement of descending inhibition
3. Adrenergic blockade of nerve sprouts
4. *N*-methyl-D-aspartate receptor antagonistic effects, opioid modification, and sodium channel blockade

Table 5. Antidepressants for Pain and Depression

Tricyclic Antidepressant (TCA)	Side Effects						Analgesic Dosage, mg	Dosages Supplied, mg	Drug Interaction
	Central Nervous System			Cardiovascular		Gastro-intestinal			
	Anticholinergic	Drowsiness	Insomnia/ Agitation	Orthostatic Hypotension	Arrhythmia	Distress			
Tertiary Amines									
Amitriptyline (Elavil, AstraZeneca; others)	++++	++++	0	++++	+++	0	75-150	10, 25, 50, 75, 100, 150	Should not be used with monoamine oxidase inhibitors (MAOIs) or epinephrine. Can aggravate paranoid symptoms in patients with schizophrenia and increase symptoms of mania in patients with manic–depressive disease.
Doxepin (Sinequan, Pfizer; others)	+++	++++	0	++	++	0	40-300	10, 25, 50, 75, 100, 150	Should not be used with MAOIs. Exaggerates the effects of other medications and drugs that slow the brain's processes, such as alcohol, barbiturates, and benzodiazepines.
Imipramine (Tofranil, Mallinckrodt; others)	+++	+++	+	++++	+++	+	25-350	10, 25, 50; sustained-release in 75, 100, 125, 150	Should not be used with MAOIs. Exaggerates the effects of other medications and drugs that slow the brain's processes, such as alcohol, barbiturates, and benzodiazepines.
Secondary Amines									
Desipramine (Norpramin, Sanofi-Aventis; others)	+	+	+	++	++	0	25-300	10, 25, 50, 75, 100	Should not be used with MAOIs. Exaggerates the effects of other medications and drugs that slow the brain's processes, such as alcohol, barbiturates, and benzodiazepines.
Nortriptyline (Aventyl, Lilly; Pamelor, Mallinckrodt; others)	0	0	0	0	0	0	0	10, 25, 50, 75	Should not be used with MAOIs. Exaggerates the effects of other medications and drugs that slow the brain's processes, such as alcohol, barbiturates, and benzodiazepines.
Trazodone (Desyrel, Apothecon; others)	0	0	0	0	0	0	0	50, 100, 150, 300	Should not be used with MAOIs.

0, none; +, minimal; ++, mild; +++, moderate; ++++, severe

Newer medications used to treat pain and depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). These medications affect single and multiple receptor types and may resemble TCAs, but are generally devoid of the anticholinergic and cardiovascular side effects related to their relative specificity (Table 6). Venlafaxine (Effexor, Wyeth), a novel SNRI that inhibits reuptake of serotonin and norepinephrine, is devoid of anticholinergic effects. It also shows no affinity for brain histamine-binding sites and no related clinical side effects, including dry mouth, hypotension, and sedation. At higher doses, dopaminergic and adrenergic effects may be exhibited.[39] In studies of nerve injury–induced hyperalgesia, animal models demonstrated analgesic effects of venlafaxine.[40] Duloxetine (Cymbalta, Lilly), another SNRI, has shown efficacy in treating depression in double-blind, placebo-controlled, fixed-dose studies. It has been established as an effective treatment for peripheral neuropathy-related pain in 2 randomized, 12-week double-blind, placebo-controlled, fixed-dose studies.[41]

Although significant literature supports the analgesic effects of traditional TCA medications in chronic pain, studies of the analgesic response to SSRIs have demonstrated conflicting results (Table 7).[42]

Patients failing to respond to initial conservative pain management measures may exhibit depressive symptoms, including associated sleep disturbance,

Table 6. SSRIs and SNRIs for Pain and Depression

Class	Adult Dosage, mg/d	Dosages Supplied, mg	Neurotransmitter Activity			Drug Interactions
			Serotonin	Norepinephrine	Dopamine	
SSRIs (single-receptor)						
Citalopram (Celexa, Forest)	20-40	10, 20, 40; oral solution (OS) 10/5 mL	++++	0	0	Should not be used with MAOIs.
Escitalopram (Lexapro, Forest)	10-20	5, 10, 20	++++	0	0	Should not be used with MAOIs.
Fluoxetine (Prozac/Prozac Weekly, Lilly; others)	20-80	10, 20; oral suspension (OSU) 20/5 mL	++++	0	0	Should not be used with MAOIs or tryptophan. Caution when taking this medication with the heart drug digoxin (Lanoxin, GlaxoSmithKline; others) and the anticoagulant warfarin (Coumadin, Bristol-Myers Squibb; others).
Paroxetine (Paxil/Paxil controlled release [CR], GlaxoSmithKline)	20-50	10, 20, 30, 40; CR 12.5, 25, 37.5	++++	0	0	Should not be used with MAOIs.
Sertraline (Zoloft, Pfizer)	50-200	25, 50, 100; OS 20/mL	++++	0	0	Should not be used with MAOIs.
SNRIs (multiple-receptor)						
Bupropion (Wellbutrin/ Wellbutrin sustained release [SR], GlaxoSmithKline; others)	150-400	75, 100; 100, 150	+	+	+ +	Use with caution in combination with antiseizure medications.
Duloxetine (Cymbalta, Lilly)	40-60	20, 30, 60	++++	+++	0/+	Should not be used with MAOIs.
Mirtazapine (Remeron/Remeron SolTab, Organon)	15-45	15, 30	+++	++	0	Should not be used with MAOIs. Adds to the sedative effects of benzodiazepines, narcotics, TCAs, some antihypertensive and antihistamine medications.
Trazodone (Desyrel, Apothecon; others)	200-600	50, 100, 150, 300	++	0	0	Should not be used with MAOIs.
Venlafaxine (Effexor/Effexor extended release [XR], Wyeth)	75-375	25, 37.5, 50, 75, 100; XR 37.5, 75, 150	++++	++	0/+	Should not be used with MAOIs.

MAOIs, monoamine oxidase inhibitors; **SNRIs**, serotonin–norepinephrine reuptake inhibitors; **SSRIs**, selective serotonin reuptake inhibitors; **TCAs**, tricylic antidepressants
0, none; +, low; ++, medium; +++, high; ++++, very high

Table 7. Placebo-Controlled Trials of SSRIs To Treat Chronic Pain[42]

Authors	Drug	Dose, mg/d	Pain Diagnosis	N	Outcome
Atkinson et al[43]	Paroxetine (Paxil/Paxil CR, GlaxoSmithKline)	10-30	Low back pain	74	–
Bendtsen et al[44]	Citalopram (Celexa, Forest)	20	Tension headache	40	–
Goldenberg et al[45]	Fluoxetine (Prozac/Prozac Weekly, Lilly; others)	20	Fibromyalgia	19	+
Max et al[46]	Fluoxetine	40	Diabetic neuropathy	46	–
Sindrup et al[47]	Citalopram	40	Diabetic neuropathy	18	+
Sindrup et al[48]	Paroxetine	40	Diabetic neuropathy	9	+
Wolf et al[49]	Fluoxetine	20	Fibromyalgia	42	–

CR, controlled release; **SSRIs**, selective serotonin reuptake inhibitors
+, effective; –, ineffective

Table 8. Hypnotics/Sedative Medications

Class	Medication	Adult dose, mg/d	Drug Interactions
Antihistamines	Diphenhydramine (Benadryl, Pfizer; others)	25-100	Adds to the sedative effects of benzodiazepines, narcotics, TCAs, some antihypertensive and anticholinergic medications.
	Doxylamine (Unisom, Pfizer; others)	25-100	None
Omega-1 Receptor Agonists	Zaleplon (Sonata, Wyeth)	5-10	No alcohol consumption allowed.
	Zolpidem (Ambien, Sanofi-Synthelabo)		
SNRIs	Mirtazapine (Remeron, Organon)	15-45	Should not be used with MAOIs. Adds to the sedative effects of benzodiazepines, narcotics, TCAs, some antihypertensive and antihistamine medications.
Triazolopyridines	Trazodone	25-200	Should not be used with MAOIs.

MAOIs, monoamine oxidase inhibitors; **SNRIs**, serotonin–norepinephrine reuptake inhibitors; **TCAs**, tricylic antidepressants

Table 9. Pain Treatment Levels of Care

Primary care—0-12 Weeks

- ➔ Control of pain symptoms with NSAIDs, COX-2 inhibitors, and low-dose opioid treatment, including combination medications with NSAIDs and acetaminophen
- ➔ Passive modalities, including ultrasound
- ➔ Physical/occupational therapy
- ➔ Manipulation

Secondary care—pain, sleep disturbance, and depressive symptoms

- ➔ Participation in medication trials
- ➔ Initiation of antidepressant medication
- ➔ Treatment of insomnia with low-dose TCAs or other sedating medications
- ➔ Referrals for individual psychological evaluation and treatment
- ➔ Physical therapy, including biofeedback training

Tertiary care—comprehensive multidisciplinary pain treatment program

- ➔ Treatment of depression and pain with medication titration
- ➔ Physical/occupational therapy, including aerobic conditioning and pool therapy
- ➔ Psychological treatment with cognitive behavioral therapy
- ➔ Vocational counseling
- ➔ Therapeutic recreation

COX-2, cyclooxygenase-2; **NSAIDs**, nonsteroidal anti-inflammatory drugs; **TCAs**, tricyclic antidepressants

Table 10. Staff Composition of an Interdisciplinary Pain Management Team[19]

Medical Director/Physician

- ➔ Plays leadership role
- ➔ Diagnoses/treats anatomic, pathologic, psychological, and physiologic processes associated with pain
- ➔ Encourages compliance across other disciplines. Monitors progress

Nurse

- ➔ Acts as physician aide
- ➔ Monitors progress/coordinates patient schedule and activities
- ➔ Educates patients regarding medication side effects, pain physiology, nutrition, and exercise

Pain Psychologist

- ➔ Assesses, treats, and monitors patient psychosocial functioning, personality characteristics, motivational state, beliefs, attitudes, and coping abilities

Physical Therapist

- ➔ Assesses and treats postural abnormalities and problems with range of motion and strength
- ➔ Tailors therapeutic program while encouraging long-term self-management techniques and exercise

Occupational Therapist

- ➔ Focuses treatment on body mechanics, energy conservation, activities of daily living, work, and leisure
- ➔ Supervises progressive increases in performance and improves tolerance and function at home and work
- ➔ May serve as liaison between employer and injured worker and aid in developing modifications for accommodations to be made in the workplace

Vocational Counselor

- ➔ Assesses and educates patients regarding job modification, retraining, and/or reentry into the workplace

Biofeedback Therapist

- ➔ Instructs patients to use electronic or electromechanical instruments that measure, process, and provide feedback on normal and abnormal neuromuscular and autonomic actions in the body
- ➔ Teaches patients relaxation training, deep breathing, and temperature regulation with the goal of helping patients develop greater awareness and voluntary control over their physiologic state as a means of decreasing muscle tension and pain

loss of appetite, weight loss, and affective distress. Early interventions should include the use of antidepressant medications for mood and sleep. For these patients, low-dose TCAs and tricyclic-like antidepressants may help augment serotonin levels in the brain and improve the quality of sleep. These dual mechanisms of action may be more efficacious than short-acting sleep medications, including over-the-counter preparations (Table 8).

Patients who fail to respond to medication and individual physical therapy may be candidates for multidisciplinary rehabilitation pain treatment (Table 9). Multidisciplinary programs typically utilize a number of healthcare providers, including rehabilitation specialists; physical, occupational, and therapeutic recreational therapists; pain psychologists; biofeedback specialists; and nursing and vocational counselors.[43] This interdisciplinary approach relies heavily on a coordination of services between healthcare provider team members with the goals of improving patient function at home and/or in the workplace, fostering independence, and improving psychosocial functioning (Table 10).

The treatment of chronic pain and related depression is a challenging healthcare problem. Targeting medications from various classes may be necessary to decrease pain, improve mood, and restore normal sleep. TCAs and newer, more selective agents may be useful, given their possible dual analgesic and antidepressant effects. Patients with ongoing chronic pain and affective distress for whom traditional conservative treatments have failed may be candidates for multidisciplinary treatment.

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