Depression in the Patient with Chronic Pain

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The management of patients with chronic pain is a challenging clinical problem that frequently requires a multidisciplinary approach. Depression is a common comorbidity associated with chronic pain, occurring in as many as 50% of chronic pain patients. Depression may develop secondarily or independently of the chronic pain syndrome, or it may occur as the primary cause of chronic pain. Regardless of their etiology, evidence exists to suggest that depression and chronic pain share common biologic pathways, namely, the serotonergic (5-HT) and noradrenergic systems. Chronic pain patients who are depressed require aggressive, full-dose treatment with antidepressants. Treatment should be selected based on a prior clinical response, the side-effect profile, the dosing schedule, and the potential for drug interactions. The newer antidepressants, including the selective serotonin reuptake inhibitors venlafaxine and nefazodone, are therapeutic options for the treatment of depression in the patient with chronic pain.

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Despite advances in pain management techniques, the patient with chronic pain continues to represent a clinical challenge. Chronic pain encompasses a broad spectrum of pathophysiologic etiology and psychological underpinnings. Chronic pain may originate from four potential sources: (1) an undiagnosed medical or surgical disease; (2) a psychiatric disorder; (3) a neurologic lesion; or (4) a somatic lesion (eg, metastatic tumor, chronic back pain, headaches, HIV-associated neurological problems). In some patients, chronic pain serves as a protective function associated with the disease state (eg, patients with arthritis or other joint disease). However, one frustrating element of managing the patient with chronic pain is that, in some cases, no identifiable underlying source of medical, psychiatric, or neurological disease can be determined.[1]

Chronic pain is a public health problem of some significance. In 1979, chronic pain was responsible for an estimated 7 million days lost from work and for associated costs of $40 billion in the United States.[2] When translated into current dollars, the economic burden of chronic pain has a huge impact.

The relationship between chronic pain and depression is complex and not entirely understood. Depression may occur secondarily as a complication of chronic pain. Alternatively, depression may be the primary disorder, with chronic pain occurring as a manifestation of an affective disorder. Depression and chronic pain may also occur independently, as in the patient with a family history of depression who suffers a traumatic injury with subsequent long-term pain. It has also been suggested that clinical depression does not alter the experience of pain but lowers the pain threshold.[3]

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DIFFERENTIATING ACUTE AND CHRONIC PAIN

Acute pain and chronic pain are distinguished by the temporal course, response to treatment, and associated psychological sequelae (Table 1). The purpose of acute pain is as a protective response or warning signal of injury or noxious stimulus. In general, acute pain is localized, is short-lived, and responds to analgesics. Acute pain frequently suggests a medical problem and is often one of the first clues to disease. Autonomic physiologic symptoms are present in patients with acute pain. In addition, patients experience fearfulness or anxiety in anticipation of the pain, and they are able to accurately describe the pain sensation as crushing, burning, stabbing, or throbbing.[1] Acute pain is associated with trauma, surgical procedures, or disease and generally subsides with healing.

The physical and psychological spectrum of

chronic pain is markedly different (Table 1) and much more difficult to manage. In contrast to acute pain, chronic pain tends to persist beyond the course of initial injury, or is out of proportion to the injury, and has minimal protective function. Chronic pain may be associated with specific disease states, such as diabetic neuropathy, migraine headaches, and arachnoiditis. Chronic pain is persistent and is of greater than 6 months' duration rather than being transient and self-limited. The severity of chronic pain ranges from mild to excruciating. Regardless of severity, the presence of chronic pain may have a profound impact on quality of life. Chronic pain often requires a multidisciplinary approach to treatment that can include pharmacotherapy, behavior modification, psychotherapy, and neurosurgery.[1]

EPIDEMIOLOGY OF DEPRESSION IN CHRONIC PAIN STATES

Depression is a common finding in patients with chronic pain. Dworkin and Gitlin reviewed a number of studies that evaluated the incidence of depression (using DSM-III criteria for diagnosing depression) in patients with chronic pain (Table 2).[4] Although these studies do not give the actual prevalence of depression in chronic pain patients, they do provide an estimate. Between 1.5% and 57% of patients with chronic pain were found to have major depression. In addition, the lifetime prevalence of depression in these patients ranged from 20% to 70%. The proportion of patients who had suffered major depression at other times in their lives was at least 2-fold higher than the prevalence of depression observed during the clinical study. These findings are consistent with those of the NHANES-1 (National Health and Nutrition Examination Studies) Epidemiologic Follow-Up Study (NHEFS) of 2341 adults in which 16.4% of subjects with chronic musculoskeletal pain were clinically depressed. In contrast, only 5.7% of persons in the NHEFS sample without evidence of chronic pain were depressed.[5]

TABLE 1

Differentiation Between Acute and Chronic Pain

Feature of Pain	Acute Pain	Chronic Pain
Associated with trauma or disease	+++	++
Pain related to intensity of disease	++	+
Pain related to stage of healing	+	-
Pain subsides with healing	+	-
Psyche involved	+	+++
Lifestyle involved	+	+++
Family involved	+	+++
Social environment affects pain	+	+++

Minus - sign = not related; + = slightly related; ++ = moderately related; and +++ = strongly related.

Does depression increase the risk of developing a chronic pain syndrome? Longitudinal assessment of patients from a large health maintenance organization revealed that depressed patients were more likely to develop chest pain, headache, or temporomandibular disorder (TMD) pain over a 3-year period than were nondepressed controls.[6] Depression often manifests not as the typical symptoms of depressed mood or loss of interest in usual activities, but as somatic complaints, including pain.[7]

The relationship between medically unexplained pain and depression has been studied in one family medicine practice.[8] In this study of 101 depressed patients and 101 age- and gender-matched nondepressed controls, the incidence of pain was significantly greater in depressed patients before they were diagnosed with depression (Figure 1).[8] Medically unexplained pain was defined as pain that was not associated with a definite diagnosis or infection, such as headache, backache, or pelvic pain. Still, once the diagnosis of depression was made and antidepressant treatment or psychotherapy presumably started, the incidence of pain in the depressed group did not differ from that in the controls.[8]

EXPERIENCE OF PAIN IN COMORBID DEPRESSION

Clinical depression has a profound influence on a patient's perception of chronic pain. The relationship between pain behavior and depression was assessed in a study of 37 adults participating in an inpatient chronic pain management program.[3] Pain behavior was defined as verbal complaints, nonverbal complaints (eg, groaning), facial grimaces, standing posture, mobility, body language, reliance on supportive equipment, and medication use. Patients were categorized in terms of low depression (Beck Depression Inventory [BDI] score 0 to 5) or high depression (BDI 6 to 21).

When trained nurse observers rated patients for pain behavior, there was no significant difference between depressed and nondepressed patients

TABLE 2

Major Depression in Patients with Chronic Pain

Investigators	N	Setting	Population	Major Depression (%)	
				Current Episode	Lifetime
Benjamin et al, 1988	106	Outpatient pain clinic	Chronic pain	33.0	—
Bouckoms et al, 1985	62	Inpatient neurosurgery	Pain >6 months	24.2	—
Chaturvedi, 1987	203	Outpatient psychiatry	Pain >3 months	6.9	—
Fishbain et al, 1986, 1988	283	Pain clinic	Pain >2 years	4.6	—
France et al, 1984, 1985, 1987, 1988	15-80	Inpatient pain program	Low back pain >6 months	30.8-54.5	—
Goldenberg, 1986	82	Arthritis clinic	Fibrositis/fibromyalgia	13.4	59.8
Haley et al, 1985	63	Pain clinic	Chronic pain	49.2	—
Hudson et al, 1984, 1985	23-31	Arthritis clinic	Fibrositis/fibromyalgia	25.8-26.1	71.0
Katon et al, 1985	37	Inpatient pain program	Pain >1 year	32.4	56.8
Katon et al, 1985	49	Psychiatric consultation	Chronic pain	57.1	—
Kirmayer et al, 1988	20	Rheumatology practice	Fibromyalgia	—	20.0
Large, 1986	50	Psychiatric consultation	Pain >6 months	6.0	—
Love, 1987	68	Private practice clinics	Low back pain >6 months	25.0	—
Magni et al, 1984	29	—	Pelvic pain >6 months	17.2	—
Merskey et al, 1987	32	Psychiatric consultation	Chronic pain	28.1	—
Muse, 1985	64	Pain clinic	Pain >6 months	1.5	—
Reich et al, 1983	43	Pain board	Chronic pain	23.2	—
Remick et al, 1983	68	Psychiatric consultation	Atypical facial pain	13.2	—
Turner et al, 1984	40	Pain clinic	Pain >6 months	30.0	—
Harrop-Griffiths et al, 1988; Walker et al, 1988	25	Laparoscopy patients	Pelvic pain >3 months	28.0	64.0

Adapted from Dworkin and Gitlin, 1991, with permission.[4]

(Figure 2).[3] However, patient self-rating scores of pain behavior in both categories were always higher than observer scores. Moreover, depressed patients rated themselves with significantly higher pain behavior scores ($P< .05$).[3] These findings suggest that depressed patients perceive their pain as more severe than do nondepressed patients.

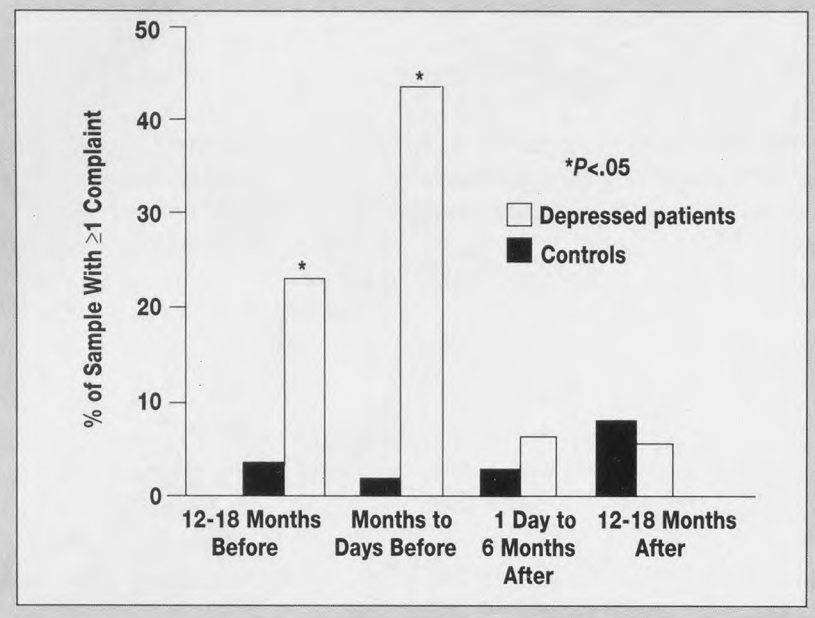
COMMON BIOLOGIC PATHWAYS FOR PAIN AND DEPRESSION

The neurotransmitters serotonin (5-HT) and norepinephrine have been implicated in both the perception of pain and the pathogenesis of depression. Support for the theory that depression and chronic pain share a common pathway comes from the observations that the neurotransmission of pain may be mediated, in part, through serotonergic mechanisms.[9] In addition, the tricyclic antidepressants (TCAs) and other antidepressants have been shown to be effective in the treatment of a variety of chronic pain syndromes, including peripheral neuropathic pain, headache, migraine, facial pain, fibrositis, and rheumatic pain.[10]

The TCAs amitriptyline (with both serotonergic and noradrenergic effects) and desipramine (with

FIGURE 1

Complaints of pain before and after the time that depression was diagnosed in depressed patients and nondepressed controls in a primary care practice. Modified from Wilson et al, 1983, with permission.[8]



predominantly noradrenergic effects) have shown efficacy in the treatment of diabetic neuropathy.[11] Clomipramine, a TCA with potent serotonergic properties, has shown clinical response in the treatment of diabetic neuropathy.[12] The selective serotonin reuptake inhibitors (SSRIs) have also been shown to elicit pain relief in patients with diabetic neuropathy in some,[13,14] but not all[11] studies. The SSRIs have also been used, with some success, in the treatment of chronic headache.[15-17] These observations suggest a common biologic pathway for both depression and chronic pain.

DIAGNOSIS OF DEPRESSION IN THE PATIENT WITH CHRONIC PAIN

Many patients with chronic pain will resist the possibility of a psychiatric diagnosis, such as depression, even if the depression is caused secondarily by the syndrome of chronic pain. These patients tend to mask their psychological distress and deny that they are depressed. In such cases, questions that sympathize with the patient (eg, "Your pain must be hard to handle. Do you ever feel low because of it?") or normalize their experience of pain (eg, "Many of my other patients with pain feel down. Has this ever happened to you?") may facilitate assessment. In addition, patients may be more responsive when asked about other symptoms of depression, such as loss of interest or pleasure in formerly pleasurable activities, sleep disturbances, fatigue, changes in weight, and poor concentration. Patients should also be questioned about suicidal tendencies.[4] Major depression is diagnosed when a patient fulfills the criteria published in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), published by the American Psychiatric Association (Table 3).[18]

TREATMENT APPROACHES

Regardless of whether depression is secondary to the pain syndrome or is the primary condition, the mood disorder should be thoroughly assessed and treated pharmacologically. Psychotherapy may also be a useful treatment approach in the depressed patient with chronic pain. The large number of clinically effective antidepressants available enables therapy to be tailored to individual patients based on a previous antidepressant response, the side-effect profile, the dosing schedule, and the potential for drug interactions. Because of the dysfunctional lives often led by patients with chronic pain, the impact of antidepressants on quality-of-life factors is an important consideration in the selection of antidepressant therapy.

Selective Serotonin Reuptake Inhibitors

The SSRIs, fluoxetine, sertraline, and paroxetine, are now considered the first-line treatment for depression because of their demonstrated efficacy and well-tolerated side-effect profile, particularly when compared with the TCAs or the monoamine oxidase inhibitors (MAOIs).[19] The side-effect profile of the SSRIs is directly related to their antidepressant mechanism of action, which is to selectively inhibit 5-HT uptake by the presynaptic neurotransmitter. The spectrum of side effects associated with SSRIs consists of nausea, headache, sleep disturbance, and sexual dysfunction.[19,20] The SSRI-related side effect of nausea typically occurs early in the course of treat-

ment and often resolves within 1 to 2 weeks of beginning therapy.[21]

Suicide and suicidal tendencies are among the most serious consequences of untreated or inadequately treated depression and can be a major risk factor in the patient with chronic pain. The SSRIs possess a significantly higher therapeutic index and are safer than the TCAs or MAOIs when taken in an overdose[19] situation and therefore represent a safer option for treating the depressed patient with suicidal tendencies.

Recognition of the individual differences between SSRIs can be exploited to clinical benefit in selected patients. For example, some patients have difficulty accepting their disease and exhibit extreme anxiety about the course and prognosis of their pain. Patients whose depression in the setting of chronic pain includes significant symptoms of anxiety may respond favorably to treatment with a nonactivating agent. In clinical studies, paroxetine is associated with a low incidence of exacerbating existing anxiety symptoms or of inducing the emergence of anxiety during treatment.[22,23] Of the SSRIs, fluoxetine is more likely to produce symptoms of anxiety, feelings of inner restlessness, and nervousness.[24,25] To minimize these symptoms, a short 2-week course of alprazolam (0.5 to 4.0 mg per day) therapy that is gradually tapered and discontinued may be prescribed during initiation of fluoxetine therapy.[26]

Patients' baseline bowel function may also be a factor in the selection of an SSRI, particularly in patients with opioid-related constipation or diarrhea due to chemotherapy or radiation therapy. For example, sertraline is associated with diarrhea or loose stools in some patients, whereas paroxetine is associated with mild constipation.[20,27] An awareness of these opposing gastrointestinal effects will allow antidepressant therapy to be tailored to individual patients.

Dosing guidelines for the SSRIs and other newer antidepressants are listed in Table 4. The most common initial and clinically effective dose of both fluoxetine and paroxetine is 20 mg per day. However, many patients require the initial 50-mg dose of sertraline to be titrated up to 100 to 150 mg per day.[28-32]

As clinical experience with the SSRIs has grown, so have reports of drug interactions with these agents. Patients with chronic pain are likely to be taking a large number of different drugs, and the addition of an SSRI or any other antidepressant for the treatment of depression should be undertaken with careful consideration of the potential for drug interactions.

Combined therapy with an SSRI and an MAOI has resulted in the serotonergic syndrome, a potentially fatal overstimulation of central 5-HT receptors.[33] Patients are also vulnerable to the serotonergic syndrome when discontinuing an SSRI and switching to an MAOI. Therefore, at least 2 weeks should lapse between stopping therapy with paroxetine or sertraline (ie, SSRIs with half-lives of approximately 24 hours) and beginning therapy with an MAOI. Longer washout periods of at least 5 weeks and as long as 8 to 10 weeks in the elderly should be followed when discontinuing the longer-acting fluoxetine.[27]

Drug interactions mediated through the inhibition of cytochrome P450 drug-metabolizing enzymes in the liver are now recognized as a potential consequence of therapy with the SSRIs or other newer antidepressants. In vitro studies have shown that each of the SSRIs inhibits cytochrome P450 3A4, an enzyme that is believed to be the predom-

Figure 2

Mean pain behavior ratings from patients (self-rating) and nurses (observer rating). Reproduced from Krause et al, 1994, with permission.[3]

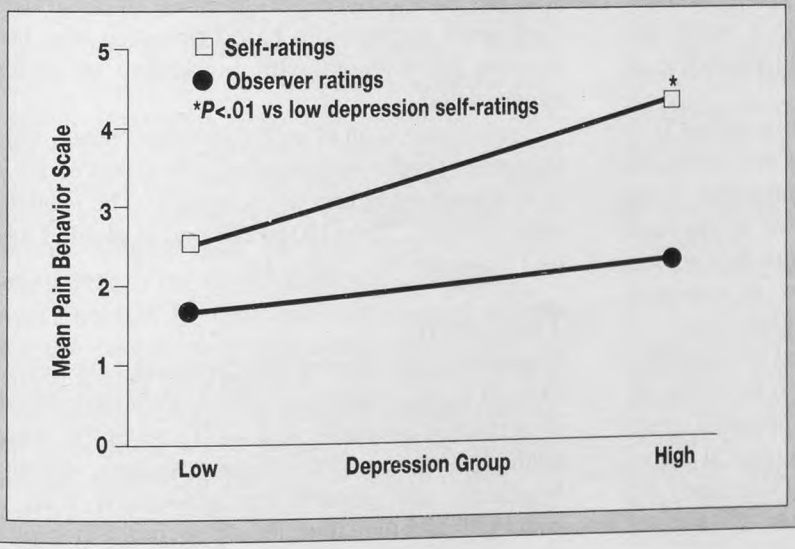


TABLE 3

***Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) Criteria for Major Depressive Episode**

At least 5 of the following symptoms are present during the same period. Either depressed mood or loss of interest or pleasure must be present. Symptoms are present most of the day, nearly daily, for at least 2 weeks:

- Depressed mood (sometimes irritability in children and adolescents) most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Significant weight loss/gain or decrease or increase in appetite
- Insomnia/hypersomnia
- Psychomotor agitation/retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive inappropriate guilt
- Impaired concentration or indecisiveness
- Recurrent thoughts of death, suicidal ideation with or without a specific plan, or suicide attempt

Modified from DSM-IV, 1994, with permission.[18]

inant drug-metabolizing enzyme in the liver.[34] Of the SSRIs, fluvoxamine (an SSRI that is indicated for obsessive-compulsive disorder in the United States but that is widely used as an antidepressant in Europe) and, to a lesser extent, fluoxetine are the most potent inhibitors of cytochrome P450 3A4 and are the most likely SSRIs to be involved in drug interactions mediated by this enzyme. Drugs that are metabolized by cytochrome P450 3A4 include carbamazepine, alprazolam, triazolam, midazolam, terfenadine, and astemizole.[35] Interactions between terfenadine and drugs that inhibit cytochrome P450 3A4 (eg, erythromycin and ketoconazole) have resulted in fatal ventricular arrhythmias.[36,37] As a result, the concomitant use of fluvoxamine and terfenadine or astemizole is contraindicated.[38]

Fluoxetine, sertraline, and paroxetine inhibit TCA metabolism by cytochrome P450 2D6, and instances of markedly elevated TCA concentrations have occurred. Interactions between these SSRIs and TCAs are uncommon in the family practice setting because such combination therapy is generally reserved for treatment-refractory patients seen by psychiatrists. If a TCA is administered for purposes of pain management to a patient also receiving an SSRI for treatment of depression, the potential exists for elevated TCA concentrations and clinical sequelae. However, the lower doses of TCAs used for adjunctive pain management (eg, 10 to 100 mg per day) may reduce the clinical consequences of this drug interaction. Nonetheless, the initial dose of the TCA may need to be reduced, blood levels of the TCA should be followed, and clinical response should be monitored.

Clinical observation of interactions between fluoxetine, sertraline, and fluvoxamine and drugs metabolized by cytochrome P450 2C (eg, phenytoin, diazepam, warfarin, and tolbutamide) also suggests the potential for interactions mediated by inhibition of cytochrome P450 2C.[35] Fluvoxamine is unique among the SSRIs because it is a potent inhibitor of cytochrome P450 1A2, and concomitant therapy has resulted in clinically important increases in plasma concentrations of theophylline, caffeine, and clozapine.[35]

VENLAFAXINE

The antidepressant properties of venlafaxine are due to the selective inhibition of norepinephrine and serotonin uptake.[39] Venlafaxine therapy is associated with side effects that include nausea, vomiting, blood pressure increases, sexual dysfunction, sweating, and somnolence. The side-effect profile of venlafaxine is clearly dose-related. For example, treatment-emergent nausea, which can be severe with higher doses, is minimized by beginning treatment with low doses (eg, 25 mg per day) that are gradually increased. When venlafaxine has been administered in doses of 375 mg or more, systolic blood pressure has been observed to increase by 7.5 mm Hg. Such small increases in blood pressure may be of concern for patients with borderline or existing hypertension.

Venlafaxine is an effective antidepressant, but its side-effect profile suggests that it be reserved for use in treatment-refractory depression.[40-43] The total daily dose of venlafaxine (150 to 225 mg) is divided into 2 or 3 doses per day (Table 4).

TRAZODONE

Trazodone, an effective antidepressant, is believed to exert its antidepressant effects through inhibition of serotonin reuptake and 5-HT_2 receptor antagonism.[44,45] Sedation, orthostasis, priapism, dizziness, headache, and nausea are associated with trazodone[46,47] and may limit its use as monotherapy for

depression. However, the sedating properties of trazodone are often used to clinical advantage by administering this drug as a nighttime adjunct to patients with sleep disturbances in doses of 50 to 100 mg. Antidepressant doses of trazodone range from 200 to 600 mg per day in divided doses.

NEFAZODONE

Nefazodone, which is a better-tolerated analogue of trazodone, is a 5-HT_2-receptor antagonist with modest inhibition of 5-HT uptake. Unlike trazodone, nefazodone does not negatively impact sleep architecture or cause orthostasis or priapism.[27,42] Nefazodone is a potent inhibitor of cytochrome P450 3A4 and is contraindicated for combined use with terfenadine or astemizole. Concurrent use of nefazodone with alprazolam, triazolam, or midazolam requires that the dose of the benzodiazepine be reduced[48] in order to prevent enhanced sedation, impaired cognition, and hangover effects. The relatively short elimination half-lives of nefazodone and its pharmacologically active metabolites require that the total daily dose of 300 to 600 mg per day be administered in divided doses (Table 4).

BUPROPION

The mechanism of action of bupropion is not known but may possibly be related to relatively weak effects on noradrenergic, dopaminergic, and serotonergic systems.[45] Bupropion is not associated with the anticholinergic, antihistaminergic, or cardiac effects of the TCAs or venlafaxine. In addition, sexual dysfunction and lethality in an overdose situation are not problems generally associated with bupropion treatment. However, the dopaminergic properties of bupropion are responsible for activation, appetite suppression, insomnia, psychotic symptoms and, rarely, seizures.[49] Depressed chronic pain patients who exhibit symptoms of psychomotor retardation (eg, slowed down) or who have gained considerable weight may do well with bupropion therapy. Still, if the depression is characterized by loss of interest in food and subsequent weight loss, the appetite-suppressing properties of bupropion may be a disadvantage. Activation and the extremely low risk of seizures associated with bupropion therapy may be minimized by administering no more than 450 mg per day in doses that do not exceed 150 mg and in dosing intervals of at least 6 hours (Table 4).

TRICYCLIC ANTIDEPRESSANTS

Despite their proven efficacy in the treatment of depression, the TCAs are now considered second- or third-line therapy when compared with the newer antidepressants that are significantly better tolerated. Low doses of TCAs have been shown to have an analgesic effect in chronic pain (eg, 25 to 150 mg of amitriptyline).[10] The analgesic efficacy of the TCAs in the absence of depression suggests that these drugs have intrinsic analgesic activity independent of their antidepressive effects. The broad-spectrum pharmacology of these agents includes interactions with cholinergic, histaminergic, serotonergic, and dopaminergic receptors. This nonspecific mechanism of action is also responsible for the variety of side effects associated with TCA therapy, including dry mouth, constipation, blurred vision (anticholinergic effects), sedation, weight gain (antihistaminergic effects), and sexual dysfunction (serotonergic effects).[45,50] The TCAs are also extremely lethal in an overdose situation and are associated with orthostatic hypotension (with subsequent falls and fractures), cognitive dysfunction, and cardiac effects causing bundle branch or complete heart block and sudden death.[27] TCA therapy should be initiated with conservative low doses and plasma-concentration monitoring. It is particularly important that TCA levels remain within the therapeutic range (eg, 50 to 150 ng/mL for nortriptyline; 125 to 300 ng/mL for desipramine) in elderly or cardiac patients. Plasma-concentration monitoring is not necessary for imipramine and doxepin. If a TCA is to be used, nortriptyline and desipramine are the best-tolerated agents in the class. Once tolerance to side effects has been established, doses should be titrated periodically to achieve the maximal therapeutic effect.

MONOAMINE OXIDASE INHIBITORS (MAOIS)

The potential for fatal food (eg, cheeses, wine, and other tyramine-containing foods) and drug interactions (eg, SSRIs, TCAs, and sympathomimetics) and intolerable side effects limit the use of the MAOIs phenelzine and tranylcypromine. Chronic pain patients also being treated with meperidine or high doses (or overdoses) of a TCA may develop severe hyperpyrexia during concomitant administration of an MAOI.[51,52]

TABLE 4

Dosing Guidelines for the Newer Antidepressants: SSRIs, Venlafaxine, Nefazodone, and Bupropion

Dose	Fluoxetine	Sertraline	Paroxetine	Venlafaxine	Nefazodone	Bupropion
Adult patients						
Usual starting dose (mg/day)	20	50	20	75	200	200 (100 mg BID)
Usual clinically effective antidepressant dose (mg/day)	20	100-150	20	150-225	300-600	300-450 (≤150 mg TID)
Elderly patients						
Usual starting dose (mg/day)	5-10	25	10	37.5	100	75
Usual clinically effective antidepressant dose (mg/day)	10-20	25-200	10-40	75-225	100-600	75-300

BID denotes twice a day; SSRIs, selective serotonin reuptake inhibitors; TID, three times a day.

The spectrum of side effects associated with MAOI therapy includes nonaccommodating orthostatic hypotension, dizziness, headache, dry mouth, insomnia, sedation, memory impairment, fainting, constipation, blurred vision, nausea, peripheral edema, urinary hesitation, weakness, myoclonal jerks, weight gain, and sexual dysfunction.[53] These significant limitations to therapy underlie the use of MAOIs as third-line treatment options for depression.

CONCLUSIONS

Chronic pain patients may be particularly resistant to a diagnosis of depression because, in their minds, it implies that their pain is all in their heads. Also, despite inroads in the awareness and understanding of psychiatric disorders, a diagnosis of depression still carries with it an element of social stigma for many patients. Educational efforts directed at both the patient and family members will assist in convincing them of the biological nature of depression—it is not just a weakness of character—and its response to antidepressant treatment. Patients should be counseled about side effects and the expected time to onset of antidepressant response.

Clinicians must carefully assess patients prior to initiating antidepressant therapy. However, once depression is diagnosed, treatment in the patient with chronic pain is no different than in patients without pain. Antidepressant therapy should be started early and in full doses.[47] Patients with chronic pain should be screened proactively for symptoms of depression, and a family history should be taken. Family members or other caregivers may provide invaluable information about changes in the patient's mood and functioning. Clinical depression that is treated appropriately and early in its course is more likely to respond to antidepressant therapy. Effective treatment of depression is a critical element to breaking the pain cycle and to improving quality of life in patients with chronic pain.

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DISCUSSION

Dr De Wester: Is there a particular population with chronic pain that is more likely to develop depression?

Dr Ruoff: In general, the longer patients have pain, the greater the risk of depression. In my experience, chronic pain involving the neck and lower back appears to be a trigger point for depression. It seems that the functional limitations associated with pain in these areas are more pronounced, including decreased range of motion, tenderness, and inability to perform, which perpetuates feelings of dependency and inadequacy and therefore increases the incidence of depression observed in this population.

Dr Richardson: You mentioned that there is a high incidence of depression in chronic pain patients, but is there a problem with underdiagnosis of the depressive component? It seems that many of the symptoms associated with depression can also be attributed to chronic pain.

Dr Ruoff: It is true that symptoms of chronic pain can "mask" depression, which contributes to the underdiagnosis of depression in the general population. For example, difficulty sleeping or early-morning awakening may be a sign of depression or it may result from the severe pain the patient is experiencing. Similarly, fatigue, which is another common manifestation of depression, may actually be due to the debilitating nature of the patient's disease. Patients with chronic pain treated in specialized settings, such as pain clinics and hospitals, are more likely to be diagnosed with depression because practitioners in these areas are aware of the high incidence of comorbidity. I think there is a need for more educational efforts in the primary care setting concerning the prevalence and treatment of depression in the chronic pain patient.

Dr Susman: What about the concept of receptor fatigue? Many patients with chronic pain are being treated with centrally acting analgesics that have activity at the serotonin receptor. Is there a decreased antidepressant response when you try to treat these patients with antidepressants?

Dr Ruoff: Especially for patients who are dependent on narcotics or who are receiving multiple pain medications, antidepressants will not have a stimulatory response on the serotonin receptor until we withdraw the narcotic or decrease the dose. Once the patient has a narcotic-free period, we will see an improved response to antidepressant therapy.