

Reviews of Therapeutics

Antidepressants in the Management of Chronic Pain Syndromes

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Conditions in which antidepressants have been used include diabetic neuropathy, postherpetic neuralgia, headaches, arthritis, chronic back pain, cancer, thalamic pain, facial pain, and phantom limb pain. Although much of the available information is derived from inadequately controlled trials, it seems that antidepressants provide analgesia in many of these disorders. The analgesic effects tend to be independent of antidepressant effects, and doses of heterocyclic antidepressants used for analgesia seem to be lower than those considered effective in the treatment of depression. Doses should be started low and gradually increased until the patient reaches the highest tolerable dose. Onset of analgesia is variable, ranging from 1 day to 10 weeks. Common side effects include dry mouth, drowsiness, urinary retention, orthostatic hypotension, and constipation. Optimum dosages and schedules have not been established.

(Pharmacotherapy 1990;10(4):262-270)

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Antidepressant agents such as amitriptyline, nortriptyline, imipramine, desipramine, doxepin, trimipramine, and trazodone have been used in the treatment of various chronic pain conditions. These agents are known as heterocyclic antidepressant agents (HCAs). Although the biochemical mechanisms of analgesia appear theoretically sound, clinical evidence supporting the efficacy of HCAs as analgesics is mainly anecdotal. Few controlled studies provide data on appropriate indications, optimum

dosages, or the relative efficacy of available agents.

Pathways and Mechanisms of Pain Transmission

The transmission, modulation, and perception of pain involve several pathways. Afferent pathways carry sensory input of painful stimuli; efferent pathways modulate pain transmission.¹ Afferent pathways originate in peripheral pain receptors (nociceptors). Sensory neurons carry pain impulses from these nociceptors to the dorsal horn of the spinal cord, forming synapses with spinal neurons. Pain fibers then travel by way of ascending spinal tracts to the brain for perception. Pain impulses carried by the afferent fibers are modulated by three major mechanisms.¹⁻⁵

The first mechanism is known as gate control; pain transmission to the central nervous system is mediated by small myelinated and unmyelinated nerve fibers.^{3,4} Sensory input to these fibers is modulated by larger unmyelinated nerve fibers with the capacity for fast impulse transmission. The second mechanism involves the sympathetic nervous system, which modulates the transmission of pain in a manner that is poorly understood.

Descending or efferent pathways are the third and probably the major mechanism of pain modulation. Efferent pathways extend from the cerebral cortex to the dorsal horn of the spinal cord. Transmission of pain by afferent pathways is modulated through

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powerful inhibitory processes in the dorsal horn that are activated by the release of endogenous opiate substances (enkephalins and endorphins).¹⁻⁴ In addition, the neurons of the descending pathways release serotonin, dopamine, norepinephrine, and other neurotransmitters that cause the release of endorphins and enkephalins. This appears to be the site where antidepressant agents act to modulate pain.^{2,3} Stimulation of the nucleus raphe magnus, an area of the brain rich in serotonin, results in analgesia, whereas serotonin deficiency results in hyperalgesia.⁶⁻¹²

Types of Pain

Important differences exist between acute and chronic pain. Acute pain is typically associated with acute disease or injury.^{13, 14} Its biologic function is to warn one of tissue damage. It has a well-defined temporal onset and usually subsides as healing progresses. Chronic pain may appear when an acute pain episode does not resolve in the expected time, or when pain emerges with no definite precipitating factor. It may persist for months or years¹³⁻¹⁶ and, unlike acute pain, serves no biologic function.

A number of psychologic variables must be considered when treating patients with chronic pain. Many experts believe that there is a definite psychologic profile of individuals who are prone to the idiopathic pain syndrome or so-called psychogenic pain disorder.¹⁷ This theory suggests that chronic pain is a somatic symptom of an underlying depressive disorder and that treatment of the depression results in pain relief.^{17, 18} Chronic pain and depression are closely related; it is often difficult to identify which came first.¹⁹⁻²⁴ Evidence shows that the biochemical mechanisms of the two are linked.^{25, 26} Some investigators, however, believe that depression associated with chronic pain is the result of an adjustment disorder that is not biochemically mediated and therefore not likely to respond to treatment with HCAs.^{27, 28} Successful management of chronic pain must include evaluation and treatment of any accompanying psychologic disorders.²⁴

Mechanism of Action of Antidepressants

The HCAs inhibit reuptake of serotonin, norepinephrine, or both by the presynaptic neuron. This prolongs the availability of neurotransmitter within the synapse so that it can stimulate receptors on the postsynaptic neuron.²⁹⁻³² The mechanism by which HCAs relieve depression may be related to the increased availability of neurotransmitters; however, it is not completely understood.

The mechanism by which HCAs provide analgesia is also controversial. Some investigators postulate an antidepressant effect,^{33, 34} whereas others seem to suggest a direct analgesic action separate from the antidepressant effect.^{5, 35} Direct analgesic action is suggested by studies in which the onset of analgesia was more rapid than would be expected

for an antidepressant effect,^{36, 37} and by trials in which analgesia was reported in the absence of antidepressant effect.³⁷⁻³⁹ Experiments in laboratory animals showed that a prolonged availability of serotonin at the neuronal synapse increases the pain threshold.³⁵ The HCAs also have been shown to potentiate the effect of narcotic analgesics in animals and humans.⁴⁰⁻⁴⁶

Problems arise in evaluating literature describing the use of antidepressants as analgesics. Patients with chronic pain have a high rate of response to placebo⁴⁷; therefore, the results of studies lacking appropriate controls must be questioned. In addition, it is difficult to distinguish the reason for response to analgesics in patients with primary depressive disorders (with pain as an initial symptom) from that in patients who primarily have chronic pain (which results in situational or reactive depression).^{27, 28}

The HCAs have been used as analgesics in painful diabetic neuropathy, postherpetic neuralgia, tension and migraine headaches, arthritis pain, chronic back pain, cancer, and other painful disorders. They also have been employed against thalamic pain,^{48, 49} facial pain,⁵⁰ and phantom limb pain,^{51, 52} but insufficient data prevent critical evaluation of their efficacy for such uses.

Neurologic Pain

Pain resulting from peripheral nerve damage is particularly difficult to treat. In this condition, called deafferentation pain, the pain-conduction pathways are interrupted, making the usual methods of pain control unsuccessful.^{53, 54} The mechanism by which antidepressants act in this syndrome is unknown.

Diabetic Neuropathy

The pathophysiologic mechanisms involved in painful diabetic neuropathy (PDN) have yet to be elucidated. Postulated mechanisms include ischemia-induced damage to nerve fibers, nerve compression, and immunologic and biochemical derangements. Damaged efferent nerve fibers may generate abnormal impulses or alter the excitability of mechanoreceptors (receptors that respond to mechanical pressures), resulting in neuropathic pain.^{55, 56} The pain is often characterized as lancinating, burning, sharp, shooting, and biting. The HCAs have been widely used in the management of PDN.

Davis et al first reported beneficial results from antidepressants in the management of PDN.³⁶ In their series of uncontrolled case reports, a combination of amitriptyline 75 mg daily and fluphenazine 3 mg daily, or fluphenazine alone relieved pain within 5 days after initiation of therapy in three patients. A beneficial response also was reported in eight patients with the combination of an HCA and phenothiazine.⁵⁷

Investigators using a combination of HCA and neuroleptic were unable to document similar onset

of relief in two controlled studies.^{58, 59} In a crossover study, six patients who were treated with amitriptyline 75 mg daily and fluphenazine 3 mg daily had no improvement in pain compared to placebo after the 15-day trial.⁵⁸ A study of 24 patients comparing the combination of nortriptyline 10–20 mg three times daily and fluphenazine 0.5–1.0 mg three times daily to placebo⁵⁹ showed no decrease in pain or paresthesia after 15 days of therapy; significant decreases in pain ($p < 0.01$) and paresthesia ($p < 0.001$) were seen after 30 days.

The HCAs also have been used alone for the treatment of PDN. In a series of case reports, 58 of 80 patients had some relief of symptoms with imipramine 50–150 mg at bedtime ($n = 43$), mianserin (an investigational tetracyclic antidepressant) 30–90 mg at bedtime ($n = 6$), or amitriptyline 50–150 mg at bedtime ($n = 9$).⁵⁷ Dramatic relief of pain was documented with trazodone 100 mg daily in five of six patients.⁶⁰

Amitriptyline 100 mg at bedtime ($n = 19$), imipramine 100 mg at bedtime ($n = 20$), and diazepam 5 mg three times daily ($n = 20$) were compared in patients with PDN.³³ All 39 patients treated with HCAs experienced complete relief after a 3-month trial; no relief was reported with diazepam. The average onset of analgesia was 10 weeks, and pain relief correlated well with normalization of depression scores. The author concluded that HCAs relieve the pain of diabetic neuropathy by virtue of their antidepressant effect. In a double-blind, crossover study, imipramine 25–150 mg daily was compared to placebo in six patients with PDN who had previously responded to imipramine in an open trial.⁵⁷ All patients reported decreased pain with imipramine, with a mean onset of one day. No attempt was made to correlate analgesia with mood changes.

Amitriptyline 25–150 mg at bedtime was more effective than placebo in producing analgesia in 29 patients with PDN; there was no correlation between antidepressant effect and analgesia.³⁸ The analgesia described by nondepressed patients was similar to that in depressed patients, and it occurred in some depressed patients without associated changes in mood. The average onset of analgesia was 3 weeks. Similar results were achieved in a 5-week comparison of imipramine 100 mg daily to placebo in 12 nondepressed patients with PDN.⁶¹ Pain was relieved more often with imipramine than placebo, with average onset of 1 week.

The rapid onset of action of combination HCA-phenothiazine therapy reported in early anecdotes may have been due to a placebo effect. The HCAs may be more effective than placebo in providing analgesia in PDN, with onset of 1–10 weeks. In general, analgesic doses are lower than those necessary for antidepressant effect.⁶² Trials have reported efficacy with daily doses of imipramine ranging from 25–150 mg, amitriptyline 25–150 mg, and nortriptyline 20–60 mg. Adverse effects of HCAs such as dry mouth, drowsiness, and urinary retention are com-

mon and may be minimized with slow upward titration of the dose. Currently, no controlled trials support the addition of a phenothiazine to an HCA in the treatment of PDN.

Postherpetic Neuralgia

The gate control theory of pain perception seems to explain best the intractable nature of postherpetic neuralgia (PHN).⁶³ Acute herpes zoster infections cause damage of large, unmyelinated nerve fibers. The damaged fibers regenerate slowly to form small nerve fibers, but lose their previous pain-modulating effect in the process. The net result is indiscriminate firing of nerve impulses by the small nerve fibers. Postherpetic neuralgia is characterized by its twisting, lancinating, pressing, gripping pain. Relief is often found in sleep.

In a series of case reports, five patients who received amitriptyline 75–100 mg daily with either perphenazine 12–16 mg daily, fluphenazine 4 mg daily, or thioridazine 100 mg daily experienced a marked decrease of PHN 1–2 weeks after initiation of treatment.⁶⁴ Although three of these patients had had no relief from previous therapy with either amitriptyline or nortriptyline alone, the trials of single agents may not have been of sufficient duration.

In a randomized, double-blind, crossover study amitriptyline 25–137.5 mg daily was compared to placebo in 24 patients with PHN.³⁷ Pain was measured by visual analog scale (VAS) and by verbal descriptors (no change, poor, good, excellent). Sixteen patients reported greater pain relief during amitriptyline treatment than during placebo ($p < 0.001$). Fourteen of 23 patients evaluated were not depressed by Beck depression inventory; of these, 11 noted a good to excellent response. Of the nine depressed patients, one had good pain relief without an antidepressant response, six had good pain relief with an antidepressant response, and two noted no change in either condition. Onset of pain relief was not reported. As expected, the most common adverse effects included dry mouth, drowsiness, and constipation. Uncontrolled follow-up in 22 patients after 1–19 months (median 12 mo) was also reported. Amitriptyline was still being taken by 7 of 12 patients who reported continued response, but was being taken by only 1 of 10 without continued response. Thus, there appeared to be an association between continued amitriptyline use and prolonged pain relief. The authors concluded that amitriptyline is effective in PHN and that its analgesic effect is not related to its antidepressant activity.

Although few controlled studies have been conducted, reports indicate that HCAs may be useful for PHN. The analgesic effect appears to be independent of the antidepressant effect. The addition of a phenothiazine has been reported to be effective; however, no controlled trials have supported this combination.

Headache

There are three major types of headaches based on the etiology of pain: muscle contraction or tension, vascular or migraine, and traction-inflammatory secondary to organic disease in the skull.⁶⁵ Continuous contractions of external cranial muscles as well as muscles of the neck, head, and face cause the dull, bilateral pain of tension headaches.^{65, 66} Stress may be a precipitating factor. Migraine headaches, on the other hand, result from initial vasoconstriction in the craniocerebral circulation followed by excessive vasodilation. Secondary vasodilation may result from a sharp drop in serotonin levels, evidenced by an increase in monoamine metabolites in urine.^{65, 66} The HCAs may be beneficial in preventing this vasodilation by virtue of their ability to increase plasma levels of serotonin and monoamines, thereby preventing the vascular component of headache pain. Symptoms of migraine that differentiate it from other types of headache include nausea and vomiting, vision disturbances, and various neurologic signs (aura). Although migraines are generally thought to differ from tension headaches, some patients have features of both types; these headaches are labeled mixed tension-vascular. Because of this blurring between types, HCAs have been used in both conditions. Antidepressants have not been studied in the management of traction-inflammatory headaches.

A placebo-controlled, crossover trial of amitriptyline 10–25 mg three times daily was conducted in 27 patients with chronic headache.³⁹ Headaches were not associated with migrainelike features, but some were thought to have a vascular component; all headaches were present for at least a year and occurred more than 10 times monthly. Each treatment period was 1 month and pain was evaluated by patients as improved or unchanged at the end of the treatment period. Depression was assessed using the Hamilton rating scale for depression. Three patients responded to both placebo and active treatment, 12 had no improvement during either period, and 12 reported a response only to amitriptyline. These results were significantly in favor of amitriptyline (*p* value not reported); no association between response and antidepressant effect was noted.

A double-blind, randomized, crossover study compared the efficacy of doxepin starting with 25 mg at bedtime and increased gradually to 100 mg daily to that of placebo in 23 patients with mixed tension-vascular headaches.⁶⁷ Nine patients dropped out of the trial, four due to doxepin-related side effects. No significant differences were observed in the number of headache days during each 9-week period. During doxepin treatment, however, there was a significant reduction (*p* < 0.05) in headache index, defined as the product of headache days times severity. In addition, the consumption of additional analgesics and ergotamine preparations was reduced in 8 of the 10 patients who recorded

this information (*p* < 0.01). The authors concluded that doxepin should be considered as an alternative in the treatment of mixed tension-vascular headaches.

In a single case report, trazodone 100 mg daily was effective in the treatment of chronic, intractable, mixed tension-vascular headache.⁶⁸ The patient was not initially depressed and had been refractory to other treatment for 7 years. Headaches completely disappeared within 2 weeks of beginning treatment.

After initial positive results were seen with the use of amitriptyline for headaches,³⁹ a double-blind, crossover, placebo-controlled trial was conducted in 20 patients with migraine.⁶⁹ The drug was initiated at a dose of 30 mg daily and titrated to a final daily dose of 10–60 mg usually taken at bedtime. The average, final dose of 30–40 mg was established by the fourth week and continued for the remainder of the 27-week study period. The frequency of migraine attacks was reduced more during drug treatment than during the placebo period in 16 of 20 patients (*p* < 0.01). The total number of attacks recorded by the study group was 207 during amitriptyline treatment compared to 356 during placebo treatment, a decrease of 42% (*p* < 0.001).

In an uncontrolled study, 110 patients with migraine headaches were treated with daily doses of amitriptyline ranging from 25–175 mg; 90% of the patients received daily doses between 50 and 75 mg.⁷⁰ The frequency, duration, and severity of headaches were assessed between 4 and 12 weeks of therapy (average 5.4 wks). Patients were also evaluated for depression before and after treatment using the Zung depression scale. The frequency (55%) and duration (60%) of headaches compared to baseline decreased significantly (*p* < 0.01). Response was most striking in patients with disabling and severe headaches. The average onset of relief was 8.8 days; 66% of patients responded within 7 days, although some did not report a response until 42 days after initiation of therapy. Improvement of migraine correlated weakly with improvement of depression (*r* = 0.25; *p* < 0.01). The authors concluded that amitriptyline is effective in the prophylaxis of migraine, but that its efficacy is probably not due to antidepressant properties.

The same authors then conducted a placebo-controlled, randomized, double-blind study of amitriptyline in 100 patients with migraine.⁷¹ Twelve of the 53 patients in the placebo group were depressed by Hamilton and Zung scales, compared to 8 of 47 patients in the amitriptyline group. The daily dose of amitriptyline was initiated at 50 mg and gradually increased to 100 mg over 3 weeks. Headache was evaluated as in these authors' earlier study.⁷⁰ Improvements in frequency, duration, and severity of 50% or more were noted in 55.3% of amitriptyline-treated patients and 34.7% of placebo-treated patients (*p* < 0.05) after 4 weeks of therapy. The authors showed a very weak (*r* = 0.32) but

significant ($p < 0.01$) correlation between improvement in depression and improvement in migraine. More nondepressed patients (51.9%) than depressed patients (37.5%) had improvement in migraine scores; however, suggesting a stronger antimigraine effect in nondepressed patients.

These studies demonstrate that antidepressants may be beneficial for the prophylaxis of tension and migraine headaches. Correlation between relief of headache and alleviation of depression was not strong. Pain relief occurred between 1 and 6 weeks of therapy in most studies, but not until after 8 weeks of therapy in some patients. Amitriptyline is the most commonly studied HCA for headache, reported to be effective in doses ranging from 25–200 mg daily. Doxepin⁶⁷ and trazodone⁶⁸ also may be effective, although additional studies are necessary. Doses should be started low and increased gradually to minimize or avoid adverse effects. The most frequently reported adverse effects of HCAs in these studies were drowsiness, dry mouth, tremor, and weight gain. Currently, no controlled trials suggest that the addition of a phenothiazine to HCA therapy is helpful.

Arthritic Pain

The primary cause of pain in patients with arthritis is inflammation of joints and surrounding structures, but adequate control of inflammation does not always result in control of pain.⁶⁶ Arthritic pain has features of both acute and chronic pain; release of chemical mediators during the inflammatory process represents acute pain, and mechanical destruction of tissues may cause chronic pain. The mechanism of action of antidepressants in this multifaceted disorder has yet to be elucidated. Although imipramine 150 mg daily reduced the rheumatoid factor titer in schizophrenic patients,⁷² this effect was not confirmed by another study.⁷³ Antidepressants generally are used as adjuvants to antirheumatic drugs in the study of arthritic pain management.

In a 6-week, double-blind study imipramine 75 mg daily in divided doses as compared to placebo in 20 patients with rheumatoid arthritis.⁷³ Rheumatoid factor titers, pain, joint tenderness, and depression (Beck depression inventory) were evaluated. Although there was no effect on rheumatoid factor, joint tenderness and depression improved more in patients receiving active treatment than in those receiving placebo. The lack of effect on rheumatoid factor may have been due to the dose, which was lower than that used by Haydu et al.⁷² The authors noted that it was difficult to separate improvement of arthritis from that of depression using the Beck depression inventory, and therefore, no conclusive statements regarding the efficacy of imipramine in rheumatic pain or its association with antidepressant effect were made.

In a multicenter, double-blind, crossover study, imipramine 50–75 mg daily or placebo was as-

signed to 65 patients already using analgesics for pain due to rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis.⁷⁴ Depressed patients were excluded from the study. Patients received 1 month of each treatment. Pain and stiffness were evaluated using a 4-point scale and a VAS. Ten patients did not complete the 8-week trial due to adverse effects ($n = 5$), hospitalization ($n = 3$), and noncompliance with the regimen ($n = 2$). In the 55 patients who completed the study, significant improvements in pain ($p < 0.01$), stiffness ($p = 0.05$), and grip strength ($p < 0.05$) were noted with imipramine compared to placebo. Subjective patient preference favored imipramine ($p < 0.005$). Adverse effects were common and included dry mouth, drowsiness, and constipation.

Clomipramine 10 mg and 25 mg daily was assessed in 46 patients suffering from rheumatic pain in an uncontrolled trial.⁷⁵ Pain and morning stiffness, evaluated by VAS, improved in both groups, with maximum response at 7 weeks. Additional analgesic requirements also decreased during treatment. Thirty-seven patients were asked their assessment of response; 21 (57%) said that pain was better, 4 (11%) that it was the same, and 12 (32%) that it had worsened. Physicians noted improvement in 68% of the subjects, with no difference in response between the two doses. Statistical significance of these results was not reported. Although the authors concluded that clomipramine is effective as an adjunctive analgesic in rheumatic pain, the lack of placebo control raises doubt about the validity of the results.

A double-blind, placebo-controlled study of clomipramine as adjunctive treatment of rheumatic pain⁷⁶ failed to confirm the drug's suggested efficacy.⁷⁵ Forty-nine patients with arthralgia from a variety of causes were assigned to either clomipramine 25 mg or placebo. Pain was evaluated by the patients using a VAS; joint tenderness was evaluated by the physician. These values as well as additional analgesic requirements were recorded at baseline and after 2, 4, and 8 weeks of treatment, with marked improvements in all groups. Thus, clomipramine was no better than placebo as an adjuvant analgesic in arthritic pain.

Amitriptyline 50–75 mg daily was compared to placebo in 36 patients with uncontrolled rheumatoid arthritis pain in a 12-week, double-blind study.⁷⁷ Pain was evaluated at weeks 0, 4, 8, and 12 using a 5-point scale. The number of inflamed joints and their relative size were recorded at the same time points. As in the study above,⁷⁶ subjects in both the placebo and active treatment groups showed marked improvement. Amitriptyline was no better than placebo for the treatment of arthritic pain.

Trimipramine was evaluated in a similar study of 36 patients with rheumatoid arthritis.⁷⁸ Inclusion criteria required the presence of at least minimal to mild depression (by the Zung scale). Trimipramine 50–75 mg daily was given for 12 weeks, and pain and articular indexes were assessed as in the study

above.⁷⁷ In contrast to the findings of others,^{76,77} improvement in pain ($p < 0.05$) and articular index ($p < 0.02$) were greater with trimipramine group than with placebo; no changes were noted in depression scores. Positive results were noted by the fourth week of therapy.

The efficacy of adding HCAs to existing analgesic therapy in the management of rheumatic disease is still in question. Two of the three controlled trials to date showed no benefit of HCAs due to marked placebo response. To help define the benefits of these drugs in arthritic conditions, additional studies emphasizing patient and dosage selection must be conducted. If a trial of HCAs is desired in an arthritic patient, imipramine or trimipramine may be effective in doses of 50–75 mg daily, with onset of action of about 4 weeks.

Chronic Back Pain

Chronic back pain has many etiologic factors. The origin of pain that persists after treatment of acute musculoskeletal and neurologic dysfunctions is not well understood.^{66,79} In a large percentage of patients with chronic back pain, degenerated disks appear to be the precipitating factor; however, many have no evidence of a pathologic disorder. Therefore, investigators studying the management of the condition have begun to focus on psychological as well as physical treatment.⁶⁶ Although the mechanism of action of antidepressants is difficult to delineate, since these patients have a well-documented psychological profile,^{17,18} several studies have evaluated the efficacy of HCAs in chronic low back pain.^{80–85}

In a 6-week, randomized, double-blind study, 60 clinically depressed patients (as assessed by the Hamilton scale) with chronic back pain were assigned to receive either doxepin or placebo.⁸⁰ Doxepin was initiated with a dose of 50 mg at bedtime and then increased to 300 mg at bedtime unless marked improvement or adverse effects were noted. The mean final dose was 200 mg. Patients were evaluated at weeks 1, 2, 4, and 6. Measurement tools included VAS for evaluating pain, Hamilton scale, and a clinical global assessment scale for evaluating mood improvement. Significant decreases in frequency of pain ($p = 0.05$), effect of pain on activity ($p = 0.04$), and effect of pain on sleep ($p = 0.02$) were observed in the doxepin-treated group compared to the placebo group after 4 weeks of therapy. The severity of pain was significantly decreased ($p = 0.01$) after 6 weeks. In addition, depression was significantly decreased in the doxepin-treated group ($p = 0.001$), and these subjects experienced a significant improvement in mood ($p = 0.005$).

Fifty patients with chronic low back pain were treated with placebo or imipramine 75 mg/day initially and increased to 150 mg/day after 3 days.⁸¹ Seven of the 48 evaluable patients were clinically depressed (Beck depression inventory). Significant

differences in the frequency of pain ($p < 0.002$) and effect of pain on activity ($p < 0.004$) were noted at the end of 8 weeks; however, baseline and post-treatment Beck scores did not differ.

A double-blind study was conducted in 30 patients with chronic back pain who were at least mildly depressed by the Hamilton scale.⁸² Patients were randomized to receive either placebo or doxepin at an initial dose of 50 mg at bedtime; the dose was increased to 300 mg at bedtime unless marked improvement or adverse effects occurred. The final average dosage was 2.5 mg/kg/day. Patients were evaluated at weeks 1, 2, 4, and 6 using the Hamilton scale, a clinical global assessment scale, profile of mood states (POMS), and a VAS to evaluate seven aspects of pain. Significant improvement in depression scores was seen in doxepin-treated patients compared to placebo-treated patients at 1 week ($p = 0.008$); improvement continued throughout the 6 weeks. A marked decrease in the frequency of pain ($p = 0.05$), pain-associated muscle tension ($p = 0.03$), and effect of pain on sleep ($p = 0.003$) were noted by week 6 in the doxepin group but not the placebo group. No change was seen in the consumption of additional analgesics. The authors concluded that doxepin was useful in the treatment of patients with chronic low back pain and depression.

The success achieved in these trials^{80–82} was not substantiated by one group.⁸³ In a double-blind study, 44 patients with chronic low back pain (15 were depressed by Beck depression inventory and the Middlesex Hospital questionnaire) were assigned to receive either imipramine 25 mg three times daily or placebo for 1 month. Significant improvement was not documented by VAS in any of the back pain measurements. This may have been due in part to a marked placebo response. No effect was noted on depression scores.

Another study compared doxepin to desipramine in patients with chronic back pain and depressive disorders evaluated by Hamilton scale.⁸⁴ In an attempt to exclude placebo responders, patients who reported a response during the initial 2-week placebo phase were dropped from the study. The 35 patients entering the second phase of the trial were treated with either doxepin or desipramine at an initial daily dose of 50 mg. This was increased gradually to a target dosage of 3 mg/kg/day to complete a 4-week trial; average final doses of doxepin and desipramine were 188 mg and 173 mg, respectively. Weekly evaluation criteria included Hamilton scale, POMS, McGill inventory, clinical global inventory, Spielberger anxiety scale, a 10-point pain severity scale, and percentage of time pain was felt. Both HCAs resulted in significant improvement ($p < 0.05$) in depression and pain severity by the end of the first week; pain frequency decreased by the end of the second week. A full clinical response, defined by the author as a pain rating of less than 4, a 40% decrease in pain severity and/or frequency, and a Hamilton score of 10 or below, was not seen in a

majority of responders until the third week of treatment. Side effects were not reported. An association was found between improvement in depression and decrease in pain severity ($r = 0.61$; $p < 0.001$) and between improvement in depression and decrease in pain frequency ($r = 0.47$; $p < 0.003$). Although these associations were statistically significant, the correlation coefficients were relatively low, signifying that the changes in severity of depression were a relatively minor influence on the severity and frequency of pain. This, together with the fact that 8 of 30 patients reported a dissociation between pain and depression, led the author to conclude that the analgesic activity of HCAs is separate from the antidepressant effect. Since other investigators⁵⁸ reported a placebo response as late as 4 weeks, a 2-week washout may not have been adequate to exclude placebo responders.

In a similar study, this author treated 32 patients with chronic back pain and depressive disorders (by Hamilton scale).⁸⁵ Again, a placebo washout was used to exclude placebo responders. Dosing of doxepin and desipramine was identical to the earlier study.⁸⁴ Six patients dropped out secondary to perceived adverse drug effects. There was a significant reduction in pain frequency ($p = 0.01$) and depression severity ($p = 0.03$), but no correlation was found between them.

Antidepressants have been demonstrated to be effective in the management of chronic back pain. The most consistent responses are seen with doxepin and desipramine at doses above 150 mg daily; other HCAs have been less consistent in their ability to produce analgesia. This may be due in part to the use of ineffective doses in some studies. The onset of pain improvement was between 1 and 3 weeks in the studies reviewed; however, placebo response may occur as late as 4 weeks after initiation of therapy. The association between antidepressant effect and pain relief is still unclear.

Cancer Pain

Advanced cancer causes pain in up to 85% of patients.²⁰ Etiologic factors include tumor infiltration or compression of surrounding organs, anticancer therapy (surgery, drugs, radiation), and factors unrelated to neoplastic disease.^{19, 20} Despite the use of large doses of narcotic analgesics, in up to 25% of patients pain is inadequately managed.⁸⁶ Animal studies demonstrated enhanced analgesia with narcotic agents when HCAs are coadministered.⁶⁻¹² Theoretically, the addition of HCAs should result in decreased doses of narcotics, fewer adverse effects, and ultimately, better pain control.

Psychologic syndromes also accompany cancer pain, largely because increased pain frequency and intensity often signal progression of the disease. Although these patients have a high frequency of depression, it is estimated only that 6% have biochemically mediated (endogenous) depression.²² Some experts believe that only biochemically medi-

ated depression is responsive to treatment with HCAs and that reactive depression is more responsive to psychotherapy.²² Others believe that all patients with cancer who exhibit depression should be given a trial of HCAs.⁸⁷

Few clinical studies have been conducted to evaluate analgesic efficacy of antidepressants in cancer pain. Despite the lack of controlled studies, antidepressants are widely used in the oncologic setting because of the numerous anecdotal reports that suggest efficacy.^{89, 90} The majority of these reports, however, are published in foreign languages. A survey of oncology centers in Italy documented that 43% of patients with cancer pain receive antidepressants for analgesia; 98% of surveyed physicians documented worthwhile to good benefits.⁹¹

An open trial of a combination of doxepin 25–225 mg daily and piroxicam 60–120 mg daily documented improvement in pain and general feeling of well-being in 24 of 30 patients with severe cancer pain uncontrolled by analgesics containing codeine or oxycodone.⁹² The six patients dropped out due to complications of treatment. The 24 who completed the study continued with the therapy until death; however, 17 patients required daily administration of narcotic analgesics (daily dose not reported) in addition to the study treatment. Onset of symptom improvement was not reported. Although the authors concluded that this regimen was safe and efficacious, serious adverse effects such as piroxicam-induced gastric perforation and gastrointestinal bleeding occurred in three patients despite the prophylactic use of sucralfate.

A comparative trial of trazodone 75–225 mg daily and amitriptyline 25–75 mg daily as adjuvant analgesics was conducted in 45 patients, 33 with cancer pain and 12 with other neuropathic pain.⁹³ Pain was evaluated using verbal descriptors (slight, moderate, exhausting, terrible, killing). Hours of sleep, rest, and activity, and a variety of medication-related adverse effects were recorded. After 15 days of therapy, a marked decrease in pain scores was noted for amitriptyline and trazodone. Analgesic properties of the two drugs were similar. Although the authors concluded that the antidepressants were effective, the lack of placebo control raises doubts about the validity of the results.

At present, too little information is available from which to draw conclusions regarding the usefulness of HCAs in the treatment of cancer pain. To document the clinical efficacy of antidepressants as adjuvant analgesics in this setting, placebo-controlled clinical trials must be conducted.

Conclusion

Antidepressants are efficacious in certain chronic pain syndromes such as painful diabetic neuropathy, migraine headache, mixed tension-vascular headache, and chronic back pain. Postherpetic neuralgia, tension headache, and arthritis pain control may benefit by HCA treatment, but additional

controlled studies are necessary to confirm such use. No controlled trials have demonstrated the analgesic efficacy of HCAs in cancer pain, but some patients may be benefited by their use.

When HCAs are indicated, doses should be started low and increased gradually until relief is noted or adverse effects are intolerable. In the studies described, doses were usually given 2–3 times daily; however, single doses at bedtime are commonly used in clinical practice and may be advantageous for patients who experience sedation as an adverse effect. Onset of analgesic efficacy may occur as early as 1 day, but is more likely to be noted after 2–10 weeks. Although the addition of a phenothiazine to the regimen is advocated by some, no controlled studies support this theory.

Some investigators measured serum antidepressant levels in the patients studied.^{38, 39, 61, 80–82} Of these, a statistically significant correlation between serum antidepressant level and pain relief was found in only one.⁶¹ A trend toward a higher antidepressant level in responders was noted in two studies,^{37, 38} while no correlation was observed in one⁶¹ and no attempt at correlation was made in two.^{80, 82} At this time data are insufficient to suggest that analgesia is in any way related to a specific serum level of a given antidepressant medication. This is consistent with current recommendations of psychiatric experts,⁹⁴ who suggest that such values are of limited use in selected patients being treated for depression.

Because of the uncomfortable side effects associated with HCAs, such as dry mouth, drowsiness, constipation, urinary retention, and orthostatic hypotension, these agents should be used only when there is a clear therapeutic indication. While it appears that the analgesic effect of HCAs is not mediated entirely through the antidepressant action, it is possible that patients with an underlying depressive disorder may experience more profound responses. It is important to differentiate the indication for treatment, since the dosage range for analgesia may be lower than that for the antidepressant effect.

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