

Antidepressants and Chronic Pain

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Successful treatment of pain syndromes is one of the most common and most difficult problems facing family physicians. Frequently analgesics provide inadequate treatment, and clinicians are forced to consider alternatives. This article reviews the neurophysiologic similarities between depression and the chronic pain syndromes and describes several well-designed double-blinded studies that give evidence for the efficacy of antidepressants in chronic pain syndromes. These studies conclude that antidepressants should be considered in chronic pain syndromes that do not respond to analgesics. For chronic pain, antidepressants should be started at a low dosage and increased in a stepwise manner until an improvement in the pain occurs or intolerable side effects intervene. Side effects are a bothersome aspect of antidepressant therapy but are more tolerable at the doses generally needed for pain relief than at antidepressive doses. At least three weeks of antidepressant therapy is generally needed to gain significant relief of symptoms.

Pain is the most common symptom that brings patients to see physicians, and chronic pain is one of the most difficult problems facing family physicians.¹ Despite the intense suffering pain causes, there is frequently minimal objective evidence of disease. Many of the chronic pain syndromes, such as low back pain, do not respond to the mild analgesics. Stronger agents, such as narcotics, have an abuse potential and are not advisable in chronic syndromes. It is in such a setting that many clinicians have been empirically using antidepressants. This article reviews the recent evidence for the use of antidepressants in chronic pain syndromes.

SIMILARITIES OF DEPRESSION AND PAIN

Depression and chronic pain frequently exist concurrently,² and it is difficult to determine whether the depressive syndrome developed before or after the pain syndrome.³ Hendler⁴ argues that chronic pain almost always leads to depression and that previously well-adjusted individuals who are exposed to chronic pain become de-

pressed in four stages. In the acute stage (lasting up to two months), the patient believes the pain to be transient and is not depressed. In the subacute stage (from two to six months), the patient is still experiencing pain, and the scores on such tests as the Minnesota Multiphasic Personality Inventory (MMPI) are elevated for hypochondriasis and hysteria, although there is a legitimate basis for these traits. In the chronic stage (which lasts from six months to eight years), the patient realizes the pain may be permanent. This stage is characterized by full-blown depression, often accompanied by sexual dysfunction, sleep disturbance, loss of self-esteem, and guilt. In the final stage, the patient becomes reconciled to the situation and the depressive symptoms decline significantly.

Patients in pain frequently suffer from insomnia⁵; similar symptoms are also found in depression. Lack of sleep appears to decrease the patient's pain threshold⁶ and ability to cope with stressful situations. Many antidepressants have sedative effects⁷ and are useful to break the cycle of insomnia and depression caused by chronic pain.

From a neurophysiologic basis there are also many similarities between the control of mood and the modulation of pain perception. The biogenic amines, including the catecholamines (such as norepinephrine) and serotonin, appear to be important in the control of mood and the perception of pain. For example, conditions that tend to elevate neurotransmitter levels may lessen depressive symptoms and decrease the perception of pain.⁴

The transmission of pain involves an extremely complex network of fibers, ganglia, synapses, interneurons,

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tracts, and brain centers. Many of the incoming pain messages can be modified by neurotransmitters at the level of the synapse.⁸ In general, neurotransmitters are synthesized and stored within nerve terminals, and their action can be altered by various enzymes or drugs that affect the distribution or breakdown of the neurotransmitter.⁸ Several of the tricyclic antidepressants are known to block serotonin reuptake at the presynaptic level.⁴ Blocking reuptake of serotonin increases the synaptic action of this neurotransmitter and may in part explain the beneficial aspects of antidepressants in chronic pain.

Enkephalins also play an important role in modulating incoming pain messages at the level of the dorsal horn.⁸ These endogenous opioids may also act by a presynaptic inhibitory response to modulate pain messages. The tricyclic antidepressants may inhibit the enzyme that breaks down enkephalin and may act through this mechanism to decrease the perception of pain.⁴

Nonetheless, the exact mechanisms of neurophysiology are still incompletely understood. It is known, however, that antidepressants can affect both the perception of pain and mood.

EVIDENCE FOR THE USE OF ANTIDEPRESSANTS IN CHRONIC PAIN

Antidepressants have been used empirically in chronic pain syndromes of many causes over the past 25 years. Because of the subjective nature of pain, it has been difficult to prove conclusively a therapeutic benefit; however, there are now adequate double-blinded studies that provide evidence for the efficacy of antidepressants in pain syndromes.

In a notable laboratory study, Spiegel et al⁹ demonstrated that antidepressants are effective analgesics in mice. By a standardized assay, they found amitriptyline to be 70 times as potent as aspirin in the analgesia of mild to moderate pain.

Arthritis

In a double-blinded, crossover study, MacDonald-Scott¹⁰ used imipramine (75 mg/d) in 24 patients with forms of arthritis (rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis) and found that pain and function were significantly improved in 33 percent of patients.

In a similar, larger study using 50 to 70 mg/d of imipramine, Gringas¹¹ confirmed the efficacy of imipramine in arthritis. Pain was lessened 48 percent more in the treatment group when compared with the placebo group. Function was also improved in 60 percent of the treatment group.

Cervical and Low Back Pain

In a double-blinded study using doxepin in 30 clinically depressed patients with chronic low back pain or cervical pain, Hameroff et al¹² found a significant decrease in incidence of pain. They also found maximal relief of pain after six weeks of treatment. In addition, they quantitated plasma opioid levels and found that nonspecific enkephalin-like activity was increased in the treatment group.

In a larger controlled study by Hameroff et al,¹³ doxepin was used in 60 clinically depressed patients with chronic cervical or lumbar spine pain. They found significant improvement of both depression and pain at a dosage of about 200 mg/d of doxepin.

In a similar study of chronic back pain and depression, Ward et al¹⁴ compared the effects of desipramine and doxepin. Both groups had significant improvements in depression and pain, although pain severity was reduced more in the group treated with doxepin.

Diabetic Neuropathy

In a small study of 15 patients, Kvinesdal et al¹⁵ used imipramine in a fixed-dose (100 mg/d), double-blinded crossover study in diabetics with severe, painful neuropathy of the lower extremities. A beneficial effect on pain, paresthesia, and dysesthesia was seen in seven of the 12 patients who completed the trial. Furthermore, the patients with the most improvement also had the highest plasma levels of imipramine and its breakdown product, desipramine.

Facial Pain

In a two-part study, Lascelles¹⁶ studied a total of 93 patients with prolonged facial pain. The first part of the study was not controlled and involved 53 patients with depression and prolonged facial pain. He used combinations of phenelzine, chlordiazepoxide, imipramine, and electroconvulsive therapy to control the depression, and found that 29 of 53 patients lost the facial pain completely and were symptom free. He went on to perform a double-blinded study using phenelzine (an inhibitor of monoamine oxidase) in depressed patients with prolonged facial pain, and found that both depression and facial pain were significantly improved.

Headache

In an early pilot study on chronic tension headache involving 280 patients, Lance and Curran¹⁷ compared the effects of 11 groups of medications to placebo and found that amitriptyline was clearly superior to many other drugs in the treatment of headache. They then performed a

double-blinded, crossover study of 27 patients with chronic tension headache. Forty-four percent of patients were improved on amitriptyline, while only 11 percent of patients were improved by placebo.

In a double-blinded study of 90 patients, Diamond and Baltes¹⁸ compared the effects of several doses of amitriptyline with placebo in chronic tension headache and found that low-dose amitriptyline (approximately 10 mg/d) had the most improvement in headache. The group using higher doses of amitriptyline was plagued with a higher dropout rate generally attributed to side effects (especially dry mouth and drowsiness). Both groups had significant improvement of depression.

In a double-blinded study of headaches, Okasha et al¹⁹ compared doxepin, amitriptyline, diazepam, and placebo. They found doxepin to be superior to the other trial groups in relief of headache and improving anxiety or depression. Amitriptyline was also shown to provide a moderate improvement of headache and a significant improvement of anxiety or depression as assessed on Hamilton rating scales.

Postherpetic Neuralgia

In a double-blinded, crossover study of 24 patients with postherpetic neuralgia, Watson et al²⁰ used amitriptyline (median dose 75 mg/d) and found that 16 of 24 patients had good to excellent relief of pain. Fourteen patients were not depressed (according to Beck scores), and 11 of these patients had good to excellent relief of pain. They also noticed a therapeutic window in three patients where higher levels of drug resulted in more pain and the pain was relieved after the dosage was reduced to previously effective dosages.

Other Considerations

There are also several double-blinded studies supporting the efficacy of tricyclic antidepressants in the pain of chronic peptic ulcers.²¹⁻²³ Some antidepressants, however, have been shown to be potent histamine H₂ receptor antagonists, which may explain their beneficial effect in the pain of ulcers.²⁴

Antidepressants have also been administered to relieve the chronic pain of cancer.²⁵ The pain associated with various types of cancer, however, may act as a type of longstanding acute pain with a continuous nociceptive input.²⁶ This type of pain is often more amenable to traditional analgesics than to the antidepressants. At present, it appears that antidepressants have a limited role in the control of pain associated with cancer.

Several studies have failed to demonstrate a therapeutic response to antidepressants in chronic pain syn-

dromes.²⁷⁻²⁹ Some of the possible explanations include bothersome side effects, poor patient compliance, inadequate doses of antidepressant, failure to account for a significant placebo response, and an inadequate study design.^{30,31}

THERAPEUTIC APPROACHES TO THE USE OF ANTIDEPRESSANTS IN CHRONIC PAIN

Although many studies on antidepressants and chronic pain have involved patients who were clinically depressed, there is also evidence that patients who are not clinically depressed may benefit from antidepressant therapy.²⁰

Of the antidepressants, the tricyclic agents have been used most widely in the treatment of chronic pain syndromes. There are some good studies that compare the effectiveness of the individual antidepressants. Lindsay and Wycoff³² found nearly identical analgesia among the four most widely used antidepressants (doxepin, imipramine, amitriptyline, and desipramine). Ward et al¹⁴ found doxepin to have a statistical advantage over desipramine in the control of pain. Because side effects are common reasons preventing the extended use of antidepressants, it may be necessary to choose these agents on the basis of their side effects. Cardiovascular side effects most frequently seen with amitriptyline and imipramine include tachycardia, postural hypotension, and quinidine-like effects on conduction.⁷ Amitriptyline, imipramine, and trimipramine are known to have significant anticholinergic side effects and should be used with caution in patients with organic brain syndrome, glaucoma, neurogenic bladder, prostatism, and erectile dysfunction.⁷ Pain relief has been reported at lower doses of antidepressant than is generally required for antidepressive effects, an important point, as most of the side effects are dose related and are minimized at low doses.³³

It is important to be aware that the wide variation in drug metabolism necessitates individualization of the drug dosage. For example, elderly patients may require only one half the dosage needed to achieve clinical improvement in a young adult patient.⁷ Disease states, such as impaired renal function and liver disease, can affect the plasma levels of these drugs.³⁴ Some drugs, such as the barbiturates, can lower plasma drug levels.³⁴ Furthermore, because antidepressants are highly bound to plasma proteins, hypoproteinemic states can increase the effective levels of the antidepressant.³⁴

At present it is advisable to start chronic pain patients on low doses of antidepressant (approximately one fourth the recommended antidepressive dose) and gradually increase the dosage in a stepwise manner while monitoring clinical indicators until there is relief of pain or the development of intolerable side effects. If there is no im-

provement in pain despite three weeks of adequate dosage, another antidepressant should be considered because, for reasons that are unclear, some patients respond to one but not to another of the antidepressants.³⁵

Patient compliance may be improved if expected side effects are explained early in the course of therapy and the patient is given an active role in titrating the dosage to maximize pain relief while minimizing side effects. It is also important for the patient to be aware that three weeks of therapy may be required before maximal therapeutic benefits are realized. In general, many of the antidepressants have long half-lives and can frequently be given as a single daily dose.⁷ Many of these drugs have significant sedative effects,⁷ which may be best tolerated if given as a single bedtime dose.

Antidepressants are generally not addictive, although a rebound in the pain syndrome may occur if they are suddenly discontinued.³³ Antidepressants do have a serious overdose potential,³⁴ and physicians should exercise caution when prescribing these medications.

In conclusion, there is now sufficient evidence to warrant the routine use of antidepressants in chronic pain syndromes that have not responded to traditional analgesics. This therapy has been proven to be relatively safe, and it is a valuable addition to the treatment of chronic pain syndromes.

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