Clinical Note

The Use of Mirtazapine in a Patient with Chronic Pain

Guy E. Brannon, MD and Karen D. Stone, MD
Department of Psychiatry, Louisiana State University School of Medicine, Shreveport, Louisiana

Abstract
Antidepressant drugs that act on serotonin and noradrenergic systems may be analgesic. The newer antidepressant mirtazapine (Remeron) has activity on noradrenergic and serotonergic transmission and is approved for the treatment of a Major Depressive Disorder. This paper describes a case that suggests that mirtazapine may also be useful in the treatment of chronic pain. J Pain Symptom Manage 1999;18:382–385. *© U.S. Cancer Pain Relief Committee, 1999.*

Key Words:
Mirtazapine, chronic pain, treatment

Introduction

Pain is one of the most common problems addressed by physicians. Acute pain usually results from an obvious injury (e.g., a fracture or laceration) or infection, and by definition is self-limiting. Chronic pain is often characterized by functional loss, psychosocial problems, and economic stressors represents a more complex picture in terms of pathology and treatment.[1–3] The cost of chronic pain in terms of hospitalizations, evaluations, medications, laboratory tests, and lost productivity on the job is approximately forty billion dollars per year to the American population.[4]

Many medications are used in the treatment of chronic pain. Nontraditional analgesics, such as antidepressants play an important role.[5,6] As new antidepressants become available, their potential for beneficial analgesic effects must be addressed. Favorable anecdotal reports can be helpful in identifying those antidepressants deserving of addtional study. The following is a case study suggesting that mirtazapine may be useful in the treatment of chronic pain.

Case Summary

A 47- year- old African American man fell off an oil derrick in 1993 and sustained injuries to his neck and back. The following year, he underwent an anterior cervical discectomy with an iliac crest graft and fusion to relieve pain and weakness in his arms. The patient described his back pain as an "ache" which was exacerbated by walking and relieved by rest. He reported that his legs became "weak" as he walked and he used a cane to assist with ambulation. He denied any bowel or bladder incontinence and had no symptoms or signs consis-

Address reprint requests to: Guy E. Brannon, MD, Louisiana State University Medical Center, School of Medicine, 1501 Kings Highway Shreveport, Louisiana 71130, USA.

Accepted for publication: February 4, 1999

0885-3924/99/$–see front matter
PII S0885-3924(99)00098-6

tent with radiculopathy. The back pain initially was managed medically with amitriptyline 50 mg per day. Several years later, his primary care physician prescribed fluoxetine 20 mg per day to address symptoms of depression. The dose was increased to 40 mg per day without a noticeable improvement in mood.

After seven months, the primary care physician referred the patient to an outpatient psychiatric clinic for evaluation and treatment of continuing depression. A psychiatric evaluation confirmed the diagnosis of a major depressive disorder, single episode, severe. The patient reported that he was applying for disability because of the pain. Other problems included hypertension, which was treated with diet modification, and sexual dysfunction. Medications at this time included fluoxetine 60 mg daily, amitriptyline 100 mg daily, and yohimbine 10 mg daily for the sexual dysfunction. Psychological testing and laboratory tests, including a chemistry profile, complete blood count with differential and platelets, RPR, thyroid function test, urine drug screen, and EKG was ordered to complete the evaluation. No significant abnormalities were found.

After discussing treatment options with the patient, it was decided to taper and discontinue the fluoxetine and amitriptyline because the patient reported no change in his mood over the last seven months.The patient's complaints of low energy and sexual dysfunction led to the selection of bupropion as the next treatment choice. Over the next several months, the bupropion dose was titrated up to a maximum of 450 mg per day. The depression did not resolve and the drug promoted increased anxiety. Pain continued and the drug was subsequently discontinued.

The patient was then placed on mirtazapine 15 mg at bedtime. Mirtazapine was selected due to its lack of sexual side effects, once a day dosing, and reported anxiolytic properties. After one month of taking mirtazapine, it was noted that his mood had improved and other symptoms of depression decreased as well. He spontaneously reported that his back pain had also decreased from a 10 to a 3 on a 10-point scale. He was able to walk for greater lengths of time with less difficulty and without his legs becoming "weak." Along with an improvement in his back pain, the patient reported an improvement in sleep, appetite, and energy. There was no change in his weight. Currently, he continues to be followed in the outpatient clinic with good results in terms of his mood and back pain.

Discussion

Many patients with chronic pain are best managed by a multidisiplinary team. This patient was treated by specialists in orthopedics, family practice, and psychiatry. The optimal treatment of chronic back pain is often unclear, and the use of some treatments, such as opioid therapy, is controversial.[7] The pathophysiology of chronic pain may involve the serotonin and noradrenergic systems,[8,9] and this potential supports the treatment with antidepressants that work on serotonin, norepinephrine, or both. Tricyclic antidepressants (TCAs) such as amitriptyline have long been recognized to be beneficial in the treatment of chronic pain disorders.[10–12] Recently, there have been reports that selective serotonin reuptake inhibitors (SSRIs) also may be helpful.

Tricyclic antidepressants are employed in 25% of patients with chronic pain in low to intermediate doses. For example, amitriptyline is often used in dosages of 12.5 to 25 mg per day, a dose that may not yield an optimal clinical response.[10] Side effects, including cardiovascular toxicity, constipation, cognitive dulling, and dry mouth, may limit the usefulness of these drugs, particularly in elderly patients. The response to amitriptyline for chronic pain has been shown to be unrelated to its mood-elevating properties, and a good analgesic response can occur at a dose that is significantly lower than that used in the treatment of depression.[11] Selective serotonin reuptake inhibitors and newer atypical antidepressants, including fluoxetine, nefazadone venlafaxine, paroxetine and others, may be used effectively in the treatment of chronic pain.[7,13,14] The supporting data are limited but the potential for efficacy, combined with a better side effect profile than the TCAs may suggest the value of a therapeutic trial.

If depression were the predominating cause of the patient's pain, it could be assumed that his improvement resulted from the effect of

mirtazapine on his mood. However, the depression started after his back injury. Depression is commonly associated with chronic pain in 50% of patients. It is important to distinguish depression that is secondary to the pain (comorbid with the pain) from a primary depression which may be complicated by pain.[15,16] Pain may increase vulnerability to the development of depression, supporting the idea that depression can be a consequence of pain.[16] Interestingly, people with depression and pain have more serotonin transporters than people who are depressed without pain or controls (no depression or pain).[17]

The patient's back pain seemed to have responded to mirtazapine and not to amitriptyline. One explanation for this is that the amitriptyline could have been at a subtherapeutic dose. In some patients, this medication becomes effective when therapeutic levels needed to treat major depressive disorders such as (e.g., doses of 200–300 mg per day) are reached.

Another reason that the amitriptyline may not have been as effective in this patient is that mirtazapine could have a more beneficial effect on sleep than amitriptyline. In particular, mirtazapine may have a more specific effect on serotonin, increased activity of which causes a deepening of sleep, shortening of sleep latency, a reduction in night time awakenings and an increase in the latency between sleep onset and the first REM epoch (a decrease in stage one sleep with a increase in stage three sleep is also noted). This effect may be beneficial in patients with chronic pain.[18]

The newer antidepressant mirtazapine has activity on both noradrenergic and serotonergic transmission. In particular, mirtazapine has 5HT1A agonistic properties and blocks 5HT2 and 5HT3.[19] This reduces the likelihood of side effects related to nonselective serotonin activation.[19] Mirtazapine does have some histaminergic activity and blocks presynaptic alpha adrenergic receptors. However, it has virtually no anticholinergic, adrenergic, or typical serotonin reuptake inhibitor side effects.[20] Mirtazapine has low protein binding and high bioavailability, and does not induce or inhibit the cytochrome P450 system.[21] Adverse effects associated with mirtazapine include drowsiness, sedation, dry mouth, increased appetite, and increased weight, all of which are usually mild, and decrease over time despite an increase in the dose. The side effect profile changes with the dosage. At low dosages, this medication has a predominant effect on the histamine (H1) receptor, which is responsible for the increase in appetite, weight, and sedation. As one increases the dose, more noradrenergic and serotonin effects are noted. This in turn counteracts the effect on the histamine receptor and reduces sedation, often normalizing the appetite and reducing the possibility of weight gain associated with lower doses of mirtazapine. Therefore, based on the pharmacology of this medication, one can adjust the dose of mirtazapine to increase or decrease the likelihood of side effects in a manner that might optimize benefit for the patient.[22] The lack of cardiotoxicity makes this medication safer in overdose and in elderly patients. Several case reports have noted that an overdose with mirtazapine alone or in combination has led to excessive but transient sedation which resolved in a few hours.[23]

Because of its effect on sleep, mirtazapine potentially could be helpful in patients with insomnia associated with varied medical or psychiatric disorders. One double-blind, placebo- controlled study found that mirtazapine helped relieve expected insomnia and anxiety when administered before an elective gynecological surgery.[24]

There has even been a case report that suggested the use of mirtazapine as a treatment for serotonin syndrome, which can be caused from other medications, such as the monoamine oxidase inhibitors (MAOIs). This may be due to specific blockades of 5HT2 and 5HT3 receptors. Further investigation is warranted to evaluate the utility of mirtazapine for this indication.[25] Because mirtazapine blocks 5HT3, it also may be useful in treating drug-induced nausea, including nausea caused by the SSRIs.[26]

Mirtazapine may be a good option for patients with pain associated with low weight, agitation, anxiety, insomnia, nausea and drug-induced sexual dysfunction. It may not be the best choice in a patient with hypersomulence, psychomotor retardation, cognitive slowing, HIV infection in which close monitoring for neutropenia is needed, overweight patients or a patient to whom weight gain may be detrimental.[27] Controlled clinical trials are needed

to confirm the analgesic effects suggested in this case report.

References

1. Russo CM, Brose WG. Chronic pain. Annu Rev Med 1998;49:123–133.

2. Barkin RL, Lubenow TR, Bruehl S, Husfeldt B, Ivankovich O, and Barkin SJ. Management of chronic pain part I. Dis Mon 1996;42(7):389–454.

3. Barkin RL, Lubenow TR, Bruehl S, Husfeldt B, Ivankovich O, Barkin SJ. Management of chronic pain part II. Dis Mon 1996;42(8):457–507.

4. Sheehan J, McKay J, Ryan M, Walsh N, O'Keeffe D. What cost chronic pain? Ir Med J 1996;89(6): 218–219.

5. Philipp M, Fickinger M. Psychotropic Drugs in the Management of chronic pain syndromes. Pharmacopsychiatry 1993;26(6):221–234.

6. Helme RD, Katz B. Management of chronic pain. Med J Aust 1993;158(7):478–481.

7. Deyo RA. Drug therapy for back pain, which drugs help which patients? Spine 1996;21(24): 2840–2849.

8. Ruoff GE. Depression in patients with chronic pain. J Fam Pract 1996;43(Suppl 6):525–533.

9. Von Knorring L, Ekselius L. Idiopathic pain and depression. Qual Life Res 1994;(Suppl 1):557–568.

10. Richeimer SH, Bajwa ZH, Kahraman SS, Ransil BJ, Warfield CA. Utilization patterns of tricyclic antidepressants in a multidisciplinary pain clinic: a survey. Clin J Pain 1997;13(4):324–329.

11. McQuay HJ, Carroll Glynn CJ. Dose-response for analgesic effects of amitriptyline in chronic pain. Anaethesia 1993;48(4):281–285.

12. Bryson HM, Wilde MI. Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states. Drugs Aging 1996;8(6): 459–476.

13. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the treatment of chronic pain. J Gen Intern Med 1997; 12(6):384–389.

14. Songer DA, Schulte H. Venlafaxine for the treatment of chronic pain. Am J Psychiatry 1996; 153(5):737.

15. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? a review. Clin L Pain 1997;13(2):116–137.

16. Jensen NH, Lauritzenl L, Lunde M., Eriksen, J, Plenge P, Mellerup ET. Platelet paroxetine binding in depressed and nondepressed chronic pain patients. Acta Psychiatr Scand 1994;90(2):141–144.

17. De Wester JN. Recognizing and treating the patient with somatic manifestations of depression. J.Fam Pract 1996;43(Suppl 6):S5–S15.

18. Ruigt GS, Kemp B, Groenhout CM, Kamphuisen HA. Effect of the antidepressant org 3770 on human sleep. Eur J Clin Pharmacol 1990;38:551–554.

19. DeBoer T. The pharmacological profile of mirtazapine. J Clin Psychiatry 1996;57(Suppl 4):19–25.

20. Puzantian T. Mirtazapine, an antidepressant. Am J Health Syst Pharm 1996;55(1):44–49.

21. Delbressine LP, Vos RM. The clinical relevance of preclinical data: mirtazapine, a model compound. J Clin Psychopharmacol 1997;17(2):295–335.

22. de Boer T. The pharmacogic profile of mirtazapine. J Clin Psychiatry 1996; S7(Suppl 4):19–26.

23. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10(Suppl 4):37–45.

24. Sorensen M, Jorgenso J, Viby-Mogensen J, Bettum V, Dunbar GC, Steffensen R. A double-blind group comparative study using the new anti-depresant org 3770, placebo and diazapam in patients with expected insomnia and anxiety before elective gynecological surgery. Acta Psychiatr Scand 1985; 71:339–346.

25. Hoes MJ, Zeijpveld JH. Mirtazapine as treatment for serotonin syndrome. Pharmacopsychiat. 1996;29:81.

26. Pedersen L, Klysner R. Antagonism of selected serotonin reuptake inhibitor-induced nausea by mirtazapine. Int Clin Psychopharmacol 1997;12:59–60.

27. Stahl SM. Psychopharmacology of Antidepressants. London: Martin Dunitz, LTD, 1998:70–79.