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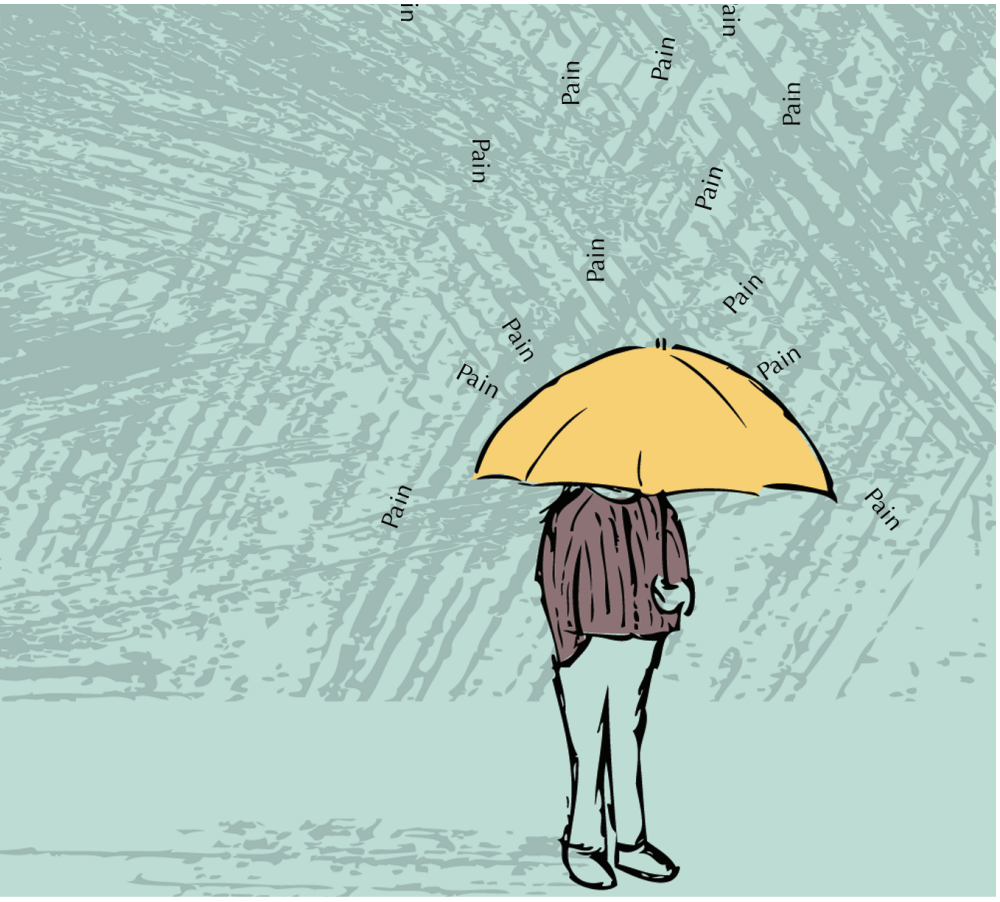

Pain, Pain, Go Away:
Antidepressants and Pain Management

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Pain, including neuropathic pain, is a relatively common complaint in various clinical settings. Several antidepressants have been efficacious in the management of chronic neuropathic pain, including the tricyclic antidepressants (particularly the tertiary-amine subtypes, such as amitriptyline, doxepin, and imipramine) as well as venlafaxine, bupropion, and duloxetine. The selective serotonin reuptake inhibitors have either been less robust (paroxetine, citalopram) or lacked any efficacy at all (fluoxetine). In this article, we review these various medications and offer an interpretive comparison, as there are few head-to-head comparison studies.

INTRODUCTION

Pain complaints, which emerge in both psychiatric and primary care settings, are a costly medical phenomenon. According to Jackson and St. Onge, the management of pain disorders in the US exceeds $100 billion annually, which includes medical care, workers compensation, and lost work productivity.[1] This estimate is echoed by the American Pain Society.[2] While lower back pain appears to be the most prevalent pain disorder,[2] pain encompasses a number of different syndromes, including neuropathic pain. In this overview article, we have elected to focus specifically on neuropathic pain syndromes and will summarize the recent review articles in this area with regard to the use of antidepressants.

THE WORKING DEFINITION OF NEUROPATHIC PAIN

Neuropathic pain is a subcategory of the larger group of pain syndromes and is characterized by (a) chronic pain, (b) various heterogeneous diagnoses (e.g., diabetic peripheral neuropathy, post-herpetic neuralgia, central post-stroke pain, phantom limb pain), and (c) differing etiologies.[3] In addition, within a specific diagnosis, there is notable variability in the presentation as well as the characteristics of the experienced pain.

EPIDEMIOLOGICAL ASPECTS OF NEUROPATHIC PAIN

According to Wolfe and Trivedi, about 1.5 percent of the US population is affected by neuropathic pain.[4] This prevalence rate is reflected in healthcare costs. For example, in a

2007 study, Barrett et al[5] found that the average annual cost of pain medication per diabetic patient with peripheral neuropathy was just over $1,000.

HOW ANTIDEPRESSANTS WORK IN PAIN MANAGEMENT

The explicit way in which antidepressants are effective in pain management remains unknown, but multiple mechanisms are likely to be involved.[6] Perhaps the most popular theory is that antidepressants exert their effects on serotonin and norepinephrine, particularly along the descending spinal pain pathways. Antidepressants may also exert adjunctive therapeutic influences through histamine receptors as well as modulation of sodium channels.[6]

NEUROPATHIC PAIN AND DEPRESSION

One common comorbid psychiatric diagnosis encountered in patients with neuropathic pain is depression, which affects the majority of individuals (i.e., 57%).[1] Studies indicate that patients with pain have a substantially increased risk for depression, anywhere from 2 to 5 times that of the general population.[7] Given that these syndromes are commonly comorbid, the assessment of depression in the presence of pain is typically complicated by the presence of shared features between the two syndromes (e.g., fatigue, sleep disturbance). In addition, the format for assessment may affect findings. Specifically, prevalence rates of depression among pain patients are seemingly higher when assessed through self-report measures compared with standardized diagnostic approaches.[2]

Investigators have also found that the prevalence rate of depression among pain patients may vary as a function of the clinical setting. In a review of the literature, Bair et al[8] found that the prevalence of depression among pain patients in psychiatry clinics was 35 percent, in pain clinics 38 percent, in rheumatology clinics 52 percent, and in dental clinics 78 percent. Surprisingly, despite the frequent comorbidity of pain and depression, Jackson and St. Onge indicate that both remain under-recognized and under-treated in this clinical population.[1]

While various relationships between pain and depression might be postulated, the most common hypotheses for their comorbidity are that (a) depression precedes pain; (b) pain precedes depression; (c) prior depression heightens the risk of subsequent depression in the presence of new-onset pain; and (d) the two phenomena occur independently of each other. Regardless of the relationships between the two syndromes, according to Sullivan and Robinson, the level of comorbidity between pain and depression is one of the basic rationales for considering antidepressant therapy as a treatment.[9] However, this is not an exclusive relationship as the doses of TCAs used to treat pain are often much lower than those used to treat depression and depression is not always present in those who experience pain relief.

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ANTIDEPRESSANTS AND NEUROPATHIC PAIN

Many antidepressants are effective in the treatment of pain, but not all and not to the same degree.

Tricyclic antidepressants. TCAs are the most studied antidepressants for the treatment of neuropathic pain and are a mainstay in the treatment armamentarium.[1] These antidepressants inhibit the reuptake of serotonin and norepinephrine at the synapse, but do so differentially according to chemical structure. The tertiary amines (e.g., amitriptyline, doxepin, imipramine) inhibit serotonin to a greater degree than norepinephrine. In contrast, the secondary amines (e.g., desipramine, nortriptyline) have more pronounced effects on norepinephrine. While some authors report approximately equal efficacy between these two subclasses of TCAs,[4] others advise that the tertiary amines are somewhat more effective than the secondary amines.[1,2,6] Interestingly, pain relief appears to be independent of the antidepressant effects of these drugs and may be achieved at doses lower than those used in the treatment of depression. While TCAs are reliable and effective, their use is potentially complicated by a host of beleaguering side effects (e.g., weight gain, anticholinergic effects, orthostatic hypotension, cardiovascular effects, lethality in overdose).

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRIs) exert their efficacy predominantly through the reuptake inhibition of serotonin. Compared with TCAs in the management of neuropathic pain, the data with regard to SSRIs is more inconsistent[3,6] and studies are considerably fewer in number. To date, paroxetine and citalopram have

TABLE 1. The authors' comparison of antidepressants for the treatment of neuropathic pain

ANTIDEPRESSANTS	EFFICACY	EVIDENCE -BASED SUPPORT	DOSE	SIDE EFFECT LOADING
Tertiary amine tricyclic antidepressants (amitriptyline, doxepin, imipramine)	Yes	+++	Low to Standard	+++
Venlafaxine	Yes	++	Standard	+
Duloxetine	Yes	++	Standard	+
Bupropion	Yes	+	Standard	+
Secondary amine tricyclic antidepressants (desipramine, nortriptyline)	Yes	++	Low to Standard	+++
Paroxetine, citalopram	Modest	+	Standard	+
Fluoxetine	No	--	Standard	+

+++ = High; ++ = Moderate; + = Low

Note: This summary reflects the authors' interpretation of the available data.

demonstrated modest efficacy in the management of neuropathic pain, whereas fluoxetine has not demonstrated any efficacy at all.[1] The overall impression is that SSRIs are less effective than other antidepressant options in the treatment of neuropathic pain.[2,4,9–11] Indeed, from a conservative perspective, it appears that SSRIs are not superior to the other types of antidepressants used in the treatment of neuropathic pain, such as the TCAs.[12] While SSRI side effects are generally mild, there is the risk of weight gain with the long-term use of some (e.g., paroxetine) as well as sexual dysfunction and discontinuation symptoms with abrupt cessation.

Venlafaxine. Venlafaxine is an unusual, mixed-action antidepressant that predominantly inhibits serotonin reuptake at low doses and norepinephrine reuptake at higher doses. Therefore, unlike SSRIs and like TCAs, venlafaxine affects both of the key neurotransmitters that are hypothesized to be involved in the modulation of neuropathic pain. In support of this theoretical observation, case reports[1,13] and empirical studies[9,14] indicate that venlafaxine is effective for the management of neuropathic pain at doses of 150mg per day or higher (i.e., typical antidepressant doses). Venlafaxine has also demonstrated efficacy with pain management in a study in which it was added to gabapentin.[4] In the treatment of neuropathic pain, venlafaxine is comparable to imipramine,[2,10,13] suggesting that it may be comparable to other TCAs as well. Despite a milder side effect profile than the TCAs, venlafaxine may elevate blood pressure and has a discontinuation syndrome with abrupt cessation.

Bupropion. Bupropion inhibits the reuptake of norepinephrine and dopamine. In a double-blind crossover study of patients with various forms of neuropathic pain, at doses of 300mg per day, bupropion SR was similar in efficacy to TCAs.[4] According to the proposed theory of how antidepressants work in pain syndromes (i.e., dual effects on serotonin and norepinephrine), bupropion clearly "breaks the rules." This observation indicates that other types of antidepressants also warrant investigation as potential medications in the treatment of pain. Bupropion has two absolute clinical contraindications (i.e., current or past history of seizures or eating disorder) and may be excessively activating for some patients.[15]

Duloxetine. Duloxetine is the only antidepressant approved by the US Food and Drug Administration for the treatment of neuropathic pain. It is purportedly a dual-action drug (i.e., it inhibits both serotonin and norepinephrine). Duloxetine has been confirmed in several studies as an effective agent in the treatment of neuropathic pain.[13] Doses for the treatment of neuropathic pain as well as depression are between 60mg and 120mg per day. Interestingly, in a study of healthy volunteers who were taking doses of 60mg per day of duloxetine, the drug exhibited a notable effect on serotonin reuptake inhibition, but not on norepinephrine reuptake inhibition.[16] If these data can be generalized to clinical populations, they indicate that the neurotransmitter effects of duloxetine may be dose-dependent. If so, then like bupropion, duloxetine may be an unexpected exception to the hypothesized requirement for dual

serotonin/norepinephrine reuptake inhibition in the treatment of neuropathic pain. We are not aware of any comparative studies between duloxetine and TCAs. As for side effects, duloxetine may cause nausea, somnolence, dizziness, and fatigue.

Comparisons of antidepressants. Based upon the presented data, we have developed a comparison table of these various antidepressants (Table 1). As a caveat, please note that there have been few head-to-head comparisons between TCAs and other types of antidepressants; hence, we have had to rely on some interpretation of these data. The most efficacious antidepressants for the treatment of neuropathic pain appear to be the tertiary-amine TCAs (amitriptyline, doxepin, imipramine), venlafaxine, bupropion, and duloxetine. These appear to be closely followed in efficacy by the secondary-amine TCAs (desipramine, nortriptyline). Modestly effective antidepressants may include the SSRIs paroxetine and citalopram. Ineffective antidepressants include fluoxetine.

CONCLUSIONS

Neuropathic pain is a relatively common clinical entity. Given the current diversity of available antidepressant options, many different types appear to be efficacious in the treatment of pain, with the exception of SSRIs. Hopefully, future studies will clarify the genuine role of neurotransmitters in pain modulation as well as the explicit comparative efficacies of the available antidepressants. In addition to their effects on pain, future studies may also take into consideration the effect of antidepressants on the overall quality of life and functioning. It seems clear that antidepressants have an important role in the treatment of neuropathic pain—an observation that is highly relevant for both psychiatrists and primary care clinicians.

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