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Antidepressant and Anticonvulsant Medication for Chronic Pain

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The evolution of contemporary clinical pain care dates back to the publication of Melzack and Wall's gate control theory in the journal *Science* in 1965 [1]. Around that time, most of the attention was given to the "gate" in this theory of pain, which referred to inhibitory interneurons within the substantia gelatinosa of the dorsal horn of the spinal cord. The gate closed when stimulation of large diameter fibers by touch or vibration activated these inhibitory interneurons, decreasing central neurotransmission from small diameter C fibers. At that time, little attention was paid to the role of descending control from the brain. Melzack and Wall did note this in their model, but little was known about descending pain modulation in 1965. Most of the pain research in the 40 years since that time has focused on the central control component of the gate control theory. Because central control is so important, antidepressants and anticonvulsants have a prominent role in the treatment of chronic pain problems.

Persons attending medical school in the 1970s and 1980s were still being taught that the neuroanatomy of pain essentially consisted of two ascending systems: the neospinothalamic and paleospinothalamic systems. It is now clear that this is only half of pain neuroanatomy. Equally important are the descending systems traveling from the central nervous system (CNS) to the periphery that continually modulate transmission in the ascending systems. The descending systems have opioid and nonopioid components. Activity in the opioid system can be blocked through use of the opioid

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antagonist naloxone. The nonopioid component of the system uses many different neurotransmitters. Two of the important neurotransmitters active within the system are serotonin and norepinephrine. These substances are the same neurotransmitters altered by commonly used antidepressants. Norepinephrine-containing cell bodies are found in the dorsolateral pontine tegmentum. Serotonin-containing cell bodies are generally contained in the rostroventral medulla [2]. Currently, antidepressant medication is the primary means of augmenting transmission in these systems.

The old thinking about pain bequeathed to us from Descartes taught that pain was primarily a function of peripheral tissue damage. Many studies have documented that clinical pain is only loosely related to the amount of tissue damage in the periphery. The severity of clinical pain is best understood as a function of the overall threat to the organism rather than the amount of tissue damage in the part that hurts. The organism is continually adjusting the sensitivity of its pain system given its overall life situation. In situations of great threat to survival, such as those explored by stress-induced analgesia experiments, the pain system is adjusted to low sensitivity. In other situations of less life-threatening distress, the sensitivity of the system can be adjusted upward [3].

Reasons for using antidepressants

There are three basic reasons for considering antidepressant medications for patients with chronic pain. First, psychiatric disorders are common in patients with severe or disabling chronic pain. Second, sleep disturbance is common, even in patients who do not meet criteria for psychiatric disorders. Third, there is evidence that certain classes of antidepressants produce pain relief separate from relief of depression or other psychiatric disorders.

Psychiatric disorders

The DSM-IV defines major depression as 2 weeks or more of depressed mood or loss of pleasure. Patients with chronic pain may deny depressed mood and may attribute their lack of pleasure to the pain itself; however, according to the DSM-IV decision rules, these patients still qualify as meeting the symptoms of anhedonia. In addition to these core symptoms, it is required that a patient have four of the following symptoms to quality for the diagnosis of major depression: weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, worthlessness or guilt, trouble concentrating or deciding, or thoughts of death or suicide. Two percent to 4% of the US general population meet the criteria for major depression at any time. Among ambulatory medical patients, this prevalence is doubled to 5% to 9% of patients. Among medical inpatients, the rate is doubled again to 15% to 20% who meet the criteria for major depression at any point in time. It has been difficult to obtain stable prevalence estimates

of major depression from pain clinic populations, largely because these are such select groups. Prevalence rates have varied from 10% to 100%, with most estimates being greater than 50%. Certainly, major depression is common in patients with chronic pain and is often underdiagnosed owing to the stigma associated with psychiatric disorders and an often adversarial medical/legal environment focused on responsibility for the initial injury.

One of the most frequently asked questions by clinicians about depression and chronic pain is whether the depression causes the pain or the pain causes the depression. The appropriate answer to this question is yes. There are now 13 studies of the prevalence of pain complaints in depressed patients. The range of reported rates is between 15% and 100%, with a mean of 65% of depressed patients complaining of pain. Most of these studies were done in psychiatric settings, but similar rates have been evident in primary care studies. There have also been 41 studies of the prevalence of depression in patients with chronic pain. Rates reported include 38% in pain clinics, 35% in psychiatry clinics, 52% in rheumatology clinics, 78% in dental clinics, 23% in obstetric-gynecology clinics, and 27% in primary care clinics [4].

These studies demonstrate that depression and pain strongly reinforce each other. Multiple studies have shown that patients with pain have a depression risk two to five times that of the general population [5]. This risk is especially true for patients who have multiple pain complaints, multiple episodes of chronic pain, or especially severe pain. Patients with pain and depression have more pain complaints, more pain intensity, and more pain chronicity than those without depression [6].

Another psychiatric disorder with high prevalence in selected chronic pain populations is panic disorder. Panic disorder is defined as recurrent unexpected panic attacks in which at least one of the attacks has been followed by a month or more of persistent concern about additional attacks or worry about the implications of the attack or a significant change in behavior related to the attacks. Panic attacks themselves are defined as discrete periods of intense fear or discomfort in which four or more symptoms develop abruptly and reach a peak within 10 minutes. These symptoms include palpitations, sweating, trembling, shortness of breath, choking, chest pain, nausea, dizziness, derealization, paresthesias, and hot flashes, as well as fears of losing control, going crazy, or dying. In the general US population, 1% to 2% of adults meet the criteria for panic disorder at any given time. If patients presenting to an emergency room with chest pain are assessed for panic disorder, 16% to 25% will meet these criteria. If one goes a bit ''further down the career'' of a potential cardiac patient to patients who have had coronary angiography and are found to have normal coronary vessels, nearly half of these patients have panic disorder. Similarly, 28% of patients with irritable bowel syndrome have been found to have panic disorder, and 13% to 15% of patients with chronic headaches, particularly migraine headaches, have panic disorder [7].

A significantly underexplored problem among patients with chronic pain is posttraumatic stress disorder (PTSD). The prevalence of DSM-IV PTSD

in the US general population is estimated to be approximately 8%, with 6% of men and 12% of women meeting the criteria. If one examines particular subsets of patients with chronic pain, high rates of PTSD are evident [8]. Motor vehicle accident patients who have persistent pain show a 30% to 50% rate of PTSD [9]. Injured workers referred for rehabilitative treatment have a 35% rate of PTSD [10]. Fibromyalgia patients have been reported to have a 20% current rate of PTSD and a 42% lifetime rate of PTSD [11].

As is true for pain and depression, many possible relationships are possible between chronic pain and PTSD. PTSD can give rise to pain as suggested by the high rates of chronic pain in patients with a history of severe childhood maltreatment. The physical trauma that gave rise to the pain complaint also can give rise to PTSD. Some evidence suggests that dissociation during the injury increases the risk of subsequent PTSD. The pain from the injury itself can produce PTSD, especially if the pain induces dissociation.

Although it may seem implausible that traumatic events such as childhood abuse could produce chronic pain problems many years after the abuse has ceased, data from animals and humans provide plausible mechanisms for this. Heim and coworkers [12] reported on 49 women aged 18 to 45 years separated into four groups: (1) one group with no childhood abuse or psychiatric disorder, (2) one group with current major depression and childhood abuse, (3) one group with no depression but having suffered abuse, and (4) one group with current major depression and no childhood abuse. They were able to show that the abused women showed a greater corticotropin (ACTH) response to a standardized speaking stress. The abused women who also had current major depression showed a six times greater rise in ACTH than those without depression or childhood abuse. This observation is consistent with animal research among rodents and primates suggesting that there are critical periods during development when the sensitivity of the hypothalamic pituitary adrenal axis is set. Young animals deprived of certain nurturing or subjected to particular stress during these critical periods have been demonstrated to show increased stress hormones in response to other stressors throughout their lives.

Antidepressant medication has been shown to treat these psychiatric disorders effectively. Cognitive-behavioral therapy also has been shown to work. These disorders are often missed or dismissed by clinicians who conceptualize the disorders as secondary to the injury or chronic pain problems. It is more appropriate to think of the disorders as comorbid illnesses that can benefit from treatment. There is clear evidence that treatment of concurrent psychiatric disorders improves the outcomes for patients with chronic pain [13].

Sleep disturbance

The second reason to use antidepressant medications in patients with chronic pain concerns the treatment of sleep disturbance. Fifty percent to

80% of patients with chronic pain have significant sleep disturbances [14]. Experimental disruption of slow-wave sleep has been shown to increase pain sensitivity in most studies. Clinical studies show a reciprocal relationship between sleep disturbance and pain. It is well known from depression treatment studies that persistence of insomnia strongly predicts persistence or relapse of depression.

Chronic pain patients are often prescribed benzodiazepines to address their sleep disturbance [15]; however, chronic benzodiazepine therapy does not correct the disturbed sleep architecture typical of many patients with chronic pain but may, in fact, further decrease slow-wave sleep. It is unclear whether the new "Z-drug" sleep agents, which are partial benzodiazepine receptor agonists, are any better. The most popular among these agents, zolpidem (Ambien) and the new eszopiclone (Lunesta), do seem to have some advantages when compared with the traditional benzodiazepines in terms of rebound after discontinuation and cognitive impairment, but it is not clear whether they affect sleep architecture more favorably [16].

Antidepressants almost all suppress rapid eye movement (REM) sleep, whereas they have variable effects on sleep continuity and slow-wave sleep. In general, the tricyclic antidepressants have a more predictably positive effect on sleep continuity and slow-wave sleep than do the popular selective serotonin reuptake inhibitors (SSRIs). This factor may be one important reason why the tricyclics have shown better effects in some chronic pain conditions. In some illnesses such as fibromyalgia, controlled trials suggest that the optimum treatment is the combination of a tricyclic with an SSRI [17]. The authors' interpretation of these data is that fibromyalgia patients frequently require full-dose antidepressant treatment, which is difficult to achieve with the tricyclic antidepressants owing to side-effect problems. Addition of an SSRI allows full antidepressant dosing, and the tricyclic portion of the regimen addresses problems with sleep continuity and slow-wave sleep. This theory has not been specifically tested.

Pain

The third principal reason to prescribe antidepressants to patients with chronic pain is that there is evidence of antidepressant analgesia independent of their effects on depression. Antidepressant analgesia has been well investigated over the past two decades. A 1992 review article documented that antidepressant analgesia could be found in over half of previous studies, although, on average, the pain relief was only 50% [18]. At that time, it appeared that the most responsive pain syndromes were neuropathic pain syndromes such as diabetes and postherpetic neuralgia. The next most responsive were headache, facial, and central pain syndromes. These findings have been largely confirmed in subsequent studies. Whether depression was present or an antidepressant effect noted appeared to make no difference in analgesia. The meta-analysis was unable to confirm the then popular

presumption that serotonin was more important than norepinephrine. Instead, the investigators concluded that mixed agents affecting serotonin and norepinephrine were best.

The evidence suggesting that the tricyclics were better than the SSRIs for neuropathic pain began with the report by Max and coworkers [19] in 1992. His team at the National Institutes of Health performed two simultaneous crossover randomized controlled trials, with 38 subjects receiving amitriptyline or desipramine and 46 subjects receiving fluoxetine or placebo. Moderate or greater improvement in pain was noted by 74% of the amitriptyline group and 61% of the desipramine group. These differences were statistically equivalent. Moderate or greater improvement in pain was noted in 48% of the fluoxetine group and was not statistically significantly different from the 41% in the placebo group. Interestingly, it did not appear to make a difference in the response to tricyclics whether the patients were depressed; however, the SSRIs appeared to produce analgesia only if the patients were clinically depressed.

Subsequently, other mixed action antidepressants have been shown to be effective for neuropathic pain. Bupropion (Wellbutrin) has been shown in a trial of 41 patients with neuropathic pain to be superior to placebo over a period of 6 weeks [20]. Venlafaxine (Effexor) has also been shown to be superior to placebo for neuropathic pain. Rowbotham and coworkers [21] studied 244 patients with diabetic neuropathic pain and showed that the relief in the group receiving venlafaxine, 150 mg over a period of 6 weeks, was superior to that in the placebo group. An earlier study by Sindrup and coworkers [22] of 40 patients in a placebo-controlled crossover trial showed that venlafaxine, 225 mg, and imipramine, 150 mg, were superior to placebo for neuropathic pain [22].

Duloxetine (Cymbalta) is an antidepressant that has been approved by the Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain. Goldstein and coworkers [23] reported on a randomized trial of 457 patients treated for 12 weeks with 20, 60, or 120 mg a day of duloxetine. The 60 mg and 120 mg a day doses demonstrated greater improvement than placebo in the 24-hour average pain score beginning 1 week after randomization. Duloxetine has a similar pharmacology to venlafaxine in that it is a reuptake inhibitor for serotonin and norepinephrine. It differs from venlafaxine in that it is a norepinephrine reuptake inhibitor at lower doses. The clinical significance of this difference has yet to be demonstrated.

Mirtazapine is another atypical antidepressant with some norepinephrine reuptake action. It has been shown to be effective for chronic headache. Bendtsen and Jensen [24] showed that mirtazapine, 15 to 30 mg for 8 weeks, was superior to placebo for prophylaxis of chronic tension headache. An open label study by Samborski and coworkers [25] suggests its effectiveness in fibromyalgia. Mirtazapine is effective in improving sleep continuity. The same antihistaminic action that promotes sleep with mirtazapine

unfortunately promotes weight gain, prompting many patients to discontinue mirtazapine.

St. John's wort, a popular naturopathic remedy that has been shown to treat depression successfully in European studies, was tested by Sindrup and coworkers [26] in a population with neuropathic pain, but it did not produce greater analgesia than placebo.

Multiple meta-analyses of antidepressant analgesia have been reported over the past few years. Tomkins and coworkers [27] analyzed 38 trials of antidepressants for chronic headache. The relative risk of improvement was 2.0 on antidepressants when compared with placebo, with 31% more antidepressant-treated patients improving. The number needed to treat (NNT) was 3.2, and the effect size was large on average. There did not seem to be a difference in response rates by drug class or headache type. Depression was not well monitored in these trials. In general, chronic headache is one disorder in which the SSRI medications seem to function just as well as the tricyclic or mixed reuptake inhibitor medications. There is a good database demonstrating efficacy for SSRIs in prophylaxis in patients who have chronic tension and recurrent migraine headaches. Holroyd and coworkers [28] reported that stress management added significantly to an antidepressant regimen for chronic tension headache. Rates of achieving at least a 50% reduction in the headache index were 64% for a combination of stress management and amitriptyline or nortriptyline versus 38% for tricyclics alone and 34% for stress management alone. The response rate was 29% for placebo alone.

O'Malley and coworkers [29] performed a meta-analysis of trials testing antidepressant treatment for fibromyalgia in 2000. They reviewed 13 adequate randomized trials and found that there was evidence for antidepressant treatment of fibromyalgia with an odds ratio for improvement of 4.2; the NNT was 4. They were able to show that antidepressants improved sleep, fatigue, pain, and well-being but not trigger points. Only one of these trials showed a significant correlation of analgesia with improvement in depression. There have been subsequent trials of antidepressants in fibromyalgia [30], including a recent trial with duloxetine demonstrating a superior efficacy to placebo [31]; however, it is important to remember that patients with fibromyalgia are heterogeneous psychiatrically. Some are relatively easy to treat and some are extremely difficult to treat, being resistant to psychopharmacologic regimens or intolerant of them. In general, the author (MDS) has found that fibromyalgia patients will improve if they can sleep and exercise.

Although the research literature concerning antidepressants and low back pain is large, many trials are poor in design. Two trials that are an exception to this rule were performed by Atkinson and coworkers. The first was a nortriptyline versus placebo trial reported in 1998 [32]. The second was a trial of maprotiline or paroxetine versus diphenhydramine reported in 1999 [33]. The 1998 trial was able to demonstrate clearly that among older males

with chronic low back pain nortriptyline produced greater pain relief than placebo. This difference was not related to pretreatment depression severity or depression response with treatment.

They followed this trial with a second trial to explore mechanisms. Maprotiline, an older tricyclic drug that was the most potent norepinephrine reuptake inhibitor at the time, was compared with paroxetine, a relatively pure serotonin reuptake inhibitor. These agents were compared with an active placebo (diphenhydramine), which is an antihistamine that produces a dry mouth and some sedation. An 8-week trial was performed randomizing 103 subjects. Seventy-nine of the patients completed the trial. Each subject had to have 6 months of back pain, and no one with a diagnosable mood disorder was entered into the trial. Pain relief by the highly sensitive descriptor differential scale was 45% in the group that received maprotiline (up to 150 mg), 27% for those receiving placebo (up to 37.5 mg of diphenhydramine), and 26% for those receiving paroxetine (up to 30 mg). Pain intensity diminished more markedly than pain unpleasantness. Although this group had prolonged pain (median pain duration of 10 years), it was not a failed back syndrome group, because only 12% had had previous back surgery. This finding was not simply a replication of neuropathic pain studies, because only 14% had radicular pain. There was no change in self-reported or observer-rated depression in the active treatment groups. In addition, there was no significant correlation between the change in mood symptoms and the change in pain intensity. On the basis of the Atkinson trials, the author believes that the noradrenergic antidepressants may be preferable not just for neuropathic pain syndromes but also for common musculoskeletal pain syndromes such as neck and back pain.

Not all pain syndromes show increased responsiveness to noradrenergic antidepressants. Headaches, particularly chronic daily headache, respond to SSRI antidepressants as well as tricyclic and serotonin norepinephrine reuptake inhibitor (SNRI) medications. Nonischemic chest pain may be another area in which SSRIs do well. Cannon and coworkers [34] originally reported in 1994 that imipramine, 50 mg, was able to produce a 52% reduction in chest pain episodes in a noncoronary chest pain group compared with a 39% reduction in a group treated with 0.1 mg twice daily of clonidine and a 1% reduction in a placebo group. Varia and coworkers [35] reported in 2000 on a cohort of 30 patients treated for 8 weeks with sertraline, 50 to 200 mg/day, or placebo. Sixty-six percent of the sertraline-treated group met a criterion of greater than 50% pain relief versus 8% of the placebo group [35]. Somewhat oddly, they were unable to show an effect of sertraline treatment on quality of life or depression measures. These trials await replication.

Psychiatric disorders are common in patients with chronic pain, especially if the pain is associated with significant activity impairment. Antidepressants with norepinephrine reuptake are probably the psychotropic agents of choice for pain relief. These agents include nortriptyline,

bupropion, venlafaxine, mirtazapine, and duloxetine. SSRI and SNRI antidepressants alone do not generally improve sleep continuity. This factor may be crucial in syndromes such as fibromyalgia and may mandate a combination of antidepressants with sedating agents such as the tricyclics trazodone or mirtazapine.

Anticonvulsants

Pain specialists typically discuss anticonvulsants primarily in relation to neuropathic pain, and the clearest evidence for their efficacy comes from studies of patients with this type of pain. As a first approximation, one could say that anticonvulsants should be used with enthusiasm in patients with neuropathic pain and with caution in patients with other types of pain; unfortunately, this simple rule is beguiling because the boundaries around neuropathic pain are far from clear.

Neuropathic pain

Neuropathic pain has been defined as ''pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system'' [36]. Some experts have argued that the term should be limited to pain caused by abnormalities in the peripheral nervous system, or at least that neuropathic pain of peripheral origin should be distinguished from neuropathic pain of central origin [37].

A wide range of disorders of the peripheral nervous system can cause persistent pain, including peripheral polyneuropathies, entrapment neuropathies, radiculopathies, and traumatic injuries to nerves. Pain can also be associated with damage to the CNS. Examples include central poststroke pain and pain in spinal cord injury. The characteristic pain syndromes that occur in the context of these CNS lesions are sometimes called central pain syndromes. Some research supports the efficacy of treating central pain syndromes with anticonvulsants [38], although it is not as extensive or consistent as support for their use in painful disorders of the peripheral nervous system.

A much more difficult question is whether chronic pain syndromes associated with CNS hypersensitivity or dysfunction should be construed as neuropathic pain syndromes. To a large extent, the answer hinges on the interpretation given to the word ''dysfunction'' in the International Association of Pain definition of neuropathic pain [36]. As discussed in that text, nociception can lead to changes in the function of the CNS in the absence of any clear evidence of damage to the CNS. If pain associated with such functional changes is construed as neuropathic pain, the range of conditions falling under the rubric of neuropathic pain increases enormously. For example, complex regional pain syndrome [39,40] and fibromyalgia [41–43] have been construed by some as neuropathic pain disorders.

The issue of a narrow versus a broad conceptualization of neuropathic pain has been summarized by Rowbotham as follows [43], "An examination of how the term neuropathic pain is defined reveals a conceptual split into 2 partially overlapping groups of disorders: those with demonstrable pathology in the nervous system and those characterized primarily by enduring dysfunction of the nervous system. Requiring demonstrable pathology in the nervous system in the definition of neuropathic pain is the traditional approach. The expansion of the definition to require only enduring nervous system dysfunction is less palatable because it opens the classification to many disorders of uncertain etiology."

If fibromyalgia is construed as a neuropathic pain syndrome, only a short conceptual leap is needed to infer the presence of neuropathic pain in any chronic pain patient who demonstrates evidence of CNS hypersensitivity. It is beyond the scope of this article to discuss procedures for identifying CNS hypersensitivity in clinical populations, but one indicator of such hypersensitivity is widespread hyperalgesia in response to palpation over muscles. If this criterion is accepted, CNS hypersensitivity would probably be found to be the rule rather than the exception in chronic pain syndromes. For example, essentially all patients with myofascial pain would be construed as having CNS hypersensitivity [44].

Anticonvulsants in the treatment of neuropathic pain: research findings

Anticonvulsants are thought to inhibit seizures by multiple mechanisms, including functional blockade of voltage-gated sodium channels, functional blockade of voltage-gated calcium channels, direct or indirect enhancement of inhibitory GABAergic neurotransmission, and inhibition of glutamatergic neurotransmission [45,46]. The result is that they reduce the neuronal hyperexcitability that is fundamental to seizure disorders.

Because neuropathic pain is also characterized by neuronal hyperexcitability [47], clinicians and researchers have reasoned that anticonvulsants might alleviate it. This supposition is supported by a substantial amount of empirical data on the effectiveness of anticonvulsants in neuropathic pain. The multiple studies in this area have been the subject of recent systematic reviews and have been considered by expert panels devoted to developing guidelines for treating neuropathic pain. The discussion herein relies largely on guidelines developed by Dworkin and coworkers [48], three recent Cochrane systematic reviews [49–51], and a systematic review by Goodman and coworkers [52].

Goodman and coworkers searched for studies relevant to several anticonvulsants—phenytoin, valproic acid, carbamazepine, gabapentin, lamotrigine, oxcarbazepine, zonisamide, levetiracetam, tiagabine, and topiramate. The studies they included in their review dealt with the first five. As is typical of systematic reviews on therapies for chronic pain, Goodman and colleagues described significant methodologic flaws in the research on anticonvulsants

in neuropathic pain and ended up with cautious conclusions. In combination with the guidelines developed by Dworkin and coworkers [48], the review permits the following conclusions to be reached with reasonable confidence:

- The effectiveness of anticonvulsants in the treatment of neuropathic pain has been studied extensively. For example, the review by Goodman and coworkers considered 37 studies.
- The preponderance of evidence supports the conclusion that, as a group, anticonvulsants are effective in the amelioration of neuropathic pain in comparison with placebos.
- This conclusion must be tempered by the fact that studies on anticonvulsants have been concentrated heavily on a few neuropathic pain conditions, especially diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia. It is possible that some neuropathic pain conditions are responsive to anticonvulsants, whereas others are not. A related issue is that some observers have proposed that, for the purposes of treatment, neuropathic pain syndromes need to be classified according to the specific symptoms that patients experience (eg, spontaneous burning pain versus allodynia versus lancinating pain) or the pathophysiologic mechanisms underlying the neuropathic pain [37]. The general point is that research to date has not been broad enough to determine how robust anticonvulsants are in treating the broad scope of symptoms, pathophysiologic processes, and diagnostic entities that are subsumed under the broad definition of "neuropathic pain."
- There have been virtually no head-to-head comparisons between different anticonvulsants [52]. One indirect method for comparing the effectiveness of different drugs is to compare the NNT for them; however, comparisons with respect to NNTs must be interpreted cautiously (Table 1). The summary NNT data suggest that carbamazepine is more effective overall than gabapentin in the treatment of neuropathic pain, but the determination of NNT for carbamazepine was based primarily on studies of trigeminal neuralgia, whereas the NNT for gabapentin was based primarily on studies of diabetic neuropathy and postherpetic neuralgia. Given this difference, it may be meaningless to compare summary NNTs for the two drugs. Another problem is that data from some studies do not permit a reviewer to calculate the NNT. Summary NNTs are based on only a portion of the studies that have been done with a drug.
- Owing to the previously cited methodologic issues and several others, research to date does not permit any conclusive statements to be made about the relative efficacy of different anticonvulsants in the treatment of neuropathic pain. A few anticonvulsants (eg, carbamazepine, gabapentin, and lamotrigine) have been studied in several randomized controlled trials on neuropathic pain, whereas little or no systematic research has been done on the effectiveness of some of the newer anticonvulsants (eg, zonisamide, levetiracetam, tiagabine).

Table 1
NNT for CZP, gabapentin, and antidepressants in neuropathic pain: calculated from systemic reviews

	CZP	Gabapentin	Antidepressants
Trigeminal neuralgia	NNT = 1.9[a]	—	—
Postherpetic neuralgia	1 study – CZP group did better	NNT = 3.9[b]	NNT = 2.2[c]
Diabetic neuropathy	1 study – CZP group did better	NNT = 2.9[d]	NNT = 1.3[e]
Average for all neuropathic pain	NNT = 2.5[f]	NNT = 4.3[g]	NNT = 2.0[h]

The NNT is calculated by first dichotomizing subjects in a placebo controlled clinical trial into those who achieved a certain degree of pain relief (eg, moderate relief or more) and those who did not. The percentage of subjects who achieve moderate or better pain relief is calculated for those who received the drug under study and for those in the placebo control group. The difference between these two percentages is then determined, and this number is divided into 100 to determine the NNT for the drug. For example, if a study found that 60% of subjects receiving gabapentin achieved at least moderate pain relief versus 20% of subjects in the placebo control group, the NNT for gabapentin would be 100/40 = 2.5.

Abbreviations: CZP, carbamazepine; NNT, number needed to treat.

[a] Based on 2 studies, with total N = 47 [47].

[b] Based on 2 studies, with total N = 207. Dose ranged from 2400 to 3600 mg/d [48].

[c] Based on 4 studies, with total N = 77 [54].

[d] Based on 4 studies, with total N = 142. Dose ranged from 900 to 3600 mg/d [48].

[e] Based on 5 studies, with total N = 98 [54].

[f] Based on 4 studies, with total N = 91 [47].

[g] Based on 7 studies, with total N = 466 [48].

[h] For amitriptyline only; based on 7 studies, with total N = 112. Doses up to 150 mg/d [54].

- Assessing the relative effectiveness of different anticonvulsants is complicated by the fact that some of the newer ones have been investigated so recently that the relevant studies have not been considered in systematic reviews of anticonvulsants. For example, neither of the two most comprehensive reviews [51,52] considers several recent studies on topiramate [53–55].

Clinical use of anticonvulsants in neuropathic pain

A clinician who plans to use anticonvulsants in the treatment of neuropathic pain conditions will be heartened by evidence that as a class they are effective; however, he or she will immediately be confronted with a host of more specific questions that are not answered conclusively by research. This section discusses strategies for using anticonvulsants that are based on clinical experience rather than on research.

Diagnosis

The first step in using anticonvulsants to treat neuropathic pain is to establish that a patient has neuropathic pain. This step requires the identification of a disorder in the nervous system and reasonable clinical evidence that the patient's pain is a produced by the disorder. The latter determination is

based on information about the distribution of symptoms, the quality of pain, and the settings under which the patient experiences pain [48].

With regard to distribution, neuropathic pain is suggested when the patient reports symptoms in a pattern that is consistent with the suspected neuropathy. The precise distribution, of course, depends on the neuropathy, for example, an L5 dermatome for an individual with an L5 radiculopathy and symptoms primarily in the feet in a patient with a diabetic neuropathy. With regard to quality, a combination of numbness and pain is suggestive of neuropathic pain. Also, the pain is frequently described as burning or lancinating. With respect to settings in which pain occurs, neuropathic pain is often distinctive in that it is worse when a patient is inactive. A patient with a diabetic neuropathy will often experience more symptoms when trying to sleep at night than when walking during the day. Another distinctive feature is that a patient with neuropathic pain will often describe discomfort from the light pressure of clothing on the body area that is symptomatic.

Anticonvulsants versus antidepressants

Antidepressants and anticonvulsants have demonstrable efficacy in the treatment of neuropathic pain [51,56], and both classes of medication have been recommended as first-line therapy for neuropathic pain [57].

Indirect comparisons based on NNTs suggest that antidepressants (especially amitriptyline) are more effective than anticonvulsants; however, this conclusion is challenged by three head-to-head comparisons between anticonvulsants and amitriptyline [58–60]. These studies failed to demonstrate any difference in effectiveness; therefore, the currently available research data do not provide a clear basis for choosing between an antidepressant and an anticonvulsant for initial therapy of neuropathic pain. The authors recommend that if a patient demonstrates significant depression, anxiety, or sleep disturbance, initial therapy should be with an antidepressant that affects the reuptake of norepinephrine and serotonin (eg, nortriptyline, duloxetine, or venlafaxine) at a dose that is effective for treating depression. In patients without significant emotional distress, anticonvulsants and antidepressants are equally appropriate as choices for initial therapy.

One recent consensus article [48] identified not only anticonvulsants (specifically gabapentin) and tricyclic antidepressants as first-line pharmacologic therapies for neuropathic pain but also three other agents: opiates, tramadol, and a 5% lidocaine patch (specifically for postherpetic neuralgia). No research permits a clinician to choose where to start in this list.

Which anticonvulsant

In the absence of head-to-head comparisons between different anticonvulsants, it is reasonable to start with the ones that have been studied the most—gabapentin and carbamazepine. In particular, gabapentin is attractive because it does not interact significantly with other drugs, and because its characteristic adverse effects are reversible with termination of the drug.

The authors recommend it for initial anticonvulsant therapy in most neuropathic pain. One exception to this general principle might be trigeminal neuralgia or any neuropathic pain condition in which lancinating pain dominates. The presence of significant lancinating pain should make one strongly consider carbamazepine. One might consider an anticonvulsant other than Gabapentin in a patient with cognitive impairment. In that setting, the authors have found lamotrigine to be a good choice, because it seems to cause less cognitive impairment than gabapentin.

Options for the patient who fails initial therapy with an anticonvulsant

If a patient fails to benefit from a maximally tolerated dose of gabapentin, one option would be to switch to another anticonvulsant. Although there are no scientific data to guide the clinician in choosing an alternative anticonvulsant, it seems logical to choose one (eg, carbamazepine or lamotrigine) that influences Na+ ion channels, because gabapentin is thought to stabilize neurons primarily by its effects on Ca++ ion channels or enhancement of GABAergic neurotransmission [45,61]. It would also be reasonable to consider valproate [62] or one of the less studied second-generation anticonvulsants, such as oxcarbazepine [63,64], topiramate [53–55], zonisamide [65], or levetiracetam [66]. Another possibility is pregabalin, which was released during the latter part of 2005. It has the disadvantage of being new but the advantage of having FDA approval for use in postherpetic neuralgia and painful diabetic neuropathy [67–71]. Although the effectiveness of phenytoin for neuropathic pain has been studied, the results have been equivocal [72,73], and the authors do not recommend its use [74].

An alternative strategy in the patient with a failed trial on gabapentin would be to switch an antidepressant, or to prescribe an opiate, tramadol, or a 5% lidocaine patch.

Combination therapy

Although monotherapy for neuropathic pain has been reported to produce significant benefit for approximately 70% of patients [57], the responses are often partial [48]. As a practical matter, one will commonly encounter patients who continue to complain of significant pain despite trials on anticonvulsants, antidepressants, and other first-line agents. In this setting, combination therapy is a reasonable strategy.

Unfortunately, combination therapy involving anticonvulsants has received only minimal attention in research. Simpson [75] found that among diabetic neuropathy patients who failed to respond to gabapentin, patients who subsequently received a combination of gabapentin and venlafaxine reported more pain relief than did controls who received gabapentin and a placebo. Gilron and coworkers [76] recently studied the effects of morphine, gabapentin, and a combination of morphine plus gabapentin in a crossover trial of patients with diabetic neuropathy and postherpetic neuralgia. Although both morphine and gabapentin led to pain reduction,

the combination of the two agents was the most effective regimen. These studies suggest that combination therapy involving anticonvulsants may be effective, but more research is needed to determine what combinations are optimal.

The most logical drugs to combine would be an antidepressant and an anticonvulsant, because these two classes of drugs are thought to affect neuropathic pain by different mechanisms. The authors frequently see neuropathic pain patients who are receiving this type of combination therapy from their primary care providers. Typically, the anticonvulsant is prescribed for pain control, and the antidepressant is prescribed because of the patient's emotional dysfunction.

Anticonvulsants in other painful conditions

A considerable amount of research has been done on the efficacy of anticonvulsants in central pain syndromes, especially poststroke pain and pain in spinal cord injury [38]. Although the evidence for efficacy of anticonvulsants in these disorders is less impressive than it is in neuropathic pain from disorders of the peripheral nervous system, it is reasonable to give patients with any central pain syndrome a trial of anticonvulsants.

The role of anticonvulsants in migraine headache has been studied extensively, and the results are generally favorable, especially for valproate [63].

As discussed previously, some experts have proposed that fibromyalgia is a neuropathic pain syndrome. Regardless of the utility of this hypothesis, it is clear that fibromyalgia involves CNS hypersensitivity [42]. To the extent that this hypersensitivity is a reflection of hyperresponsiveness of neurons in nociceptive pathways, the use of anticonvulsants in patients with fibromyalgia could be rationalized in the same way that it is rationalized for the treatment of pain that is unequivocally neuropathic. Moreover, as discussed by Curatolo and colleagues elsewhere in this issue, CNS hypersensitivity is by no means restricted to fibromyalgia; in fact, it probably occurs in most chronic pain disorders. There is a conceptual rationale for considering anticonvulsants in the treatment of many patients with chronic pain.

Obviously, such an expansive use of anticonvulsants needs empirical support rather than just theoretical plausibility. Some data support the efficacy of anticonvulsants in musculoskeletal pain syndromes with CNS hypersensitivity. In particular, pregabalin, a new anticonvulsant, has been shown to reduce pain in fibromyalgia in a dose-dependent manner [77].

In contrast, studies of anticonvulsants in musculoskeletal conditions such as chronic low back pain have yielded inconsistent results [78,79]. These studies are difficult to evaluate in relation to the hypothesis that anticonvulsants are effective for disorders characterized by CNS hypersensitivity, because participants in the studies were not systematically assessed for the presence of indicators of CNS hypersensitivity. In an ideal study, patients with a common musculoskeletal condition such as axial low back pain

would be divided into groups who did and did not show clinical evidence of CNS hypersensitivity, and both groups would be treated with an anticonvulsant. The expectation would be that only the patients demonstrating CNS hypersensitivity would benefit from the anticonvulsant therapy.

Clinicians in the authors' community frequently prescribe anticonvulsants (especially gabapentin) for patients with refractory musculoskeletal pain. In the absence of definitive research data, the authors' clinical experience suggests that a trial on an anticonvulsant is worth performing for a patient with chronic musculoskeletal pain and evidence of evidence of CNS hypersensitivity; however, these patients are often refractory to essentially all therapies, including anticonvulsants. If an anticonvulsant is prescribed, it is incumbent on the physician to monitor the patient's response carefully, and to discontinue the drug if it does not produce clear clinical improvement.

Prototypical cases

Case 1

The clinical information available on the patient in Case 1 in the introductory article suggests that his right lower extremity pain reflects a central pain syndrome. Although central pain syndromes represent a heterogeneous group of disorders with respect to the underlying CNS dysfunction, there is evidence that at least some of them respond to tricyclic antidepressants [80,81], lamotrigine [82], and possibly gabapentin [83]. It should be assumed that a patient with a history of prolonged coma from a traumatic brain injury would be sensitive to cognitive adverse effects from any centrally acting drug. This consideration implies that tricyclic antidepressants and gabapentin should be used with caution. Among the anticonvulsants, lamotrigine would probably be the best choice for this patient.

Case 2

Anticonvulsants and several antidepressants, including tricyclics, SSRIs, and dual reuptake inhibitors, have been shown to be effective in reducing pain associated with diabetic neuropathy; therefore, the patient in Case 2 provides the clinician with a plethora of pharmacologic options involving antidepressants or anticonvulsants. There is no obvious starting point for trials on these drugs, except that tricyclic antidepressants should be used with caution in an older individual with cardiovascular disease.

Case 3

Tricyclic antidepressants have repeatedly demonstrated effectiveness in the treatment of fibromyalgia, and one study has shown duloxetine to be effective. SSRIs and venlafaxine have demonstrated benefit in some studies. Among the anticonvulsants, only pregabalin has been shown to benefit

patients with fibromyalgia [77]. Based on research to date, it would be reasonable for the clinician to have the patient in Case 2 undergo trials with several different sedating antidepressants and pregabalin.

Case 4

It is not obvious that antidepressants or anticonvulsants are likely to help the patient in Case 4 with persistent spinal pain in the absence of any evidence of radiculopathy; however, if this patient demonstrated widespread hyperalgesia, the clinician might conclude that CNS sensitization was contributing to his pain, and perhaps that the patient had a fibromyalgia-like condition. In that situation, it would be reasonable to consider medications that have been shown to help fibromyalgia (see Case 3), as long as the clinician is aware that there are no well-controlled studies validating the effectiveness of such medications for the type of patient described in Case 4.

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