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Comorbidities in Chronic Neuropathic Pain

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ABSTRACT

Neuropathic pain arises from a lesion or dysfunction within the nervous system; the specific mechanisms that elicit neuropathic pain symptoms are the subject of ongoing research. It is generally acknowledged that neuropathic pain is extremely difficult to treat, and a major factor impacting outcomes is the presence of comorbidities such as poor sleep, depressed mood, and anxiety.

Patients who suffer from chronic pain experience difficulties in initiating and maintaining sleep. Sleep deprivation has been associated with a decreased pain threshold, muscle aches, and stiffness in normal volunteers. The interrelationship of these factors is complex: Many chronic pain patients are depressed and anxious; sleep deprivation can lead to anxiety; and depression can be both the cause and the result of sleep disturbances. Thus, physicians must evaluate all aspects of pain, sleep, and mood in chronic pain patients. Several instruments have been developed to aid physicians in gathering qualitative and quantitative information from chronic pain patients.

This triad of chronic pain, sleep disturbances, and depression/anxiety must be fully addressed if the patient is to be restored to optimal functionality. A multidisciplinary team approach allows for treatment of the whole patient. Nonpharmacologic interventions include relaxation therapy, sleep restriction therapy, and cognitive therapy. Strategies for pharmacologic interventions should attempt to maximize outcomes by employing, where possible, agents that address both the pain and the comorbidities. In this way, functionality may be restored and the patient's quality of life improved.

Key Words. Comorbidities; Chronic Pain; Neuropathic Pain; Sleep Disturbances; Depressed Mood; Anxiety

Introduction

Chronic neuropathic pain—pain sensation that arises from within the nervous system rather than from an external source—can be initiated by many different pathologies. Pain becomes intrinsic to the nervous system by perhaps only a few mechanisms; however, these mechanisms are the subject of active research and have yet to be fully elucidated. Regardless of the initiating condition, neuropathic pain is universally recognized as one of the most difficult to treat pain syndromes.

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The most significant aspect of this treatment dilemma is our current inability to identify specific neuropathic pain mechanisms in a given patient and to select the specific drug most likely to be effective for a particular mechanism. As a consequence, the choice among the many proposed pharmacologic treatments is most often determined by trial and error.

A less well-known issue is the failure to properly assess the real and significant psychological cofactors that make coping with chronic pain so difficult [1]. Among these comorbidities are inadequate sleep due to chronic pain and the anxiety and depression that stem from the stressful negative consequences of living with pain (e.g., interference with work, relationships, and hobbies), as well as knowing that one has a painful condition with no particular treatable cause and no apparent

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way to obtain relief. These comorbidities hinder a patient's enjoyment by negatively impacting functionality and quality of life (QOL) [2,3]. In addition to these psychological relationships, chronic sleep deprivation in normal individuals is associated with a decreased pain threshold, while acute deprivation of stage 4 sleep is associated with transient complaints of musculoskeletal and mood symptoms [4]. It is, therefore, reasonable to infer that lack of sleep in chronic pain patients can exacerbate their symptoms as well [5].

Fishbain reviewed studies of the prevalence of psychiatric comorbidities with pain disorders and discussed specifically the *Diagnostic and Statistical Manual* (DSM-IV) multiaxial classification for pain [6]. Comorbidities between chronic pain and Axis I disorders of the DSM-IV have been exhaustively studied and documented. Depression is the most common of these [7], with some studies finding a prevalence rate approaching 100% among clinical chronic pain samples [8].

Although most pain disorders begin with injury or disease, their courses, outcomes, and costs are affected by emotional, behavioral, social, and economic factors [9]. A patient's emotional reaction to and capacity to cope with the fluctuating course of a neuropathic pain disorder and complications such as physical impairment, disability, and loss of role functioning will also affect the outcome and cost. Therefore, it is important, when managing pain patients, to pay careful attention to conditions that may be comorbid with pain.

It has been proposed that neuropathic pain and its comorbid conditions represent negatively reinforcing pathologies [4,10,11]. Thus, it is usually necessary to treat the comorbid conditions as well as the pain itself if overall treatment is to be satisfactory [10]. Though hard clinical evidence is limited in the literature of several medical disciplines, a growing knowledge base supports a multifactorial approach to the treatment of neuropathic pain.

Chronic Pain and Sleep Disturbance

Several surveys of chronic pain of various etiologies have shown significant interference with sleep (Table 1). Most patients reported that their difficulties with sleep started after they began experiencing chronic pain [5,10]. Sleep difficulties pertain to both initiating sleep and remaining asleep, and most studies show a positive correlation between pain intensity and degree of sleep disturbance. In one of these studies, sleep latency, hours of sleep, number of awakenings, and time awake after sleep onset were all adversely affected in chronic pain patients who reported sleeping poorly [10]. However, the pattern of sleep disturbance in patients with chronic pain appears to be generally comparable with the profile evidenced by patients with primary insomnia [5]. In support of this, presleep cognitive arousal accounted for a larger portion of variance related to sleep difficulty than did somatic arousal, pain severity, or depression severity [5]. Interestingly, two studies reported a negative correlation between duration of pain (chronicity) and sleep difficulty [12,13]. This may indicate a gradual accommodation of sleep pattern to chronic pain or a survivor effect, that is, the patients with the most intractable sleep disturbances may have dropped out of the population from which samples were drawn.

Chronic Pain, Depressed Mood, and Anxiety

Many studies and reviews have documented the high degree of comorbidity between depression and chronic pain disorders [8,14,15], and some evidence shows that the incidence of depression among persons with chronic pain is higher than

Table 1 Incidence of sleep interference

	Widerström-Noga et al. [1]	Smith et al. [5]	Morin et al. [10]	Atkinson et al. [12]
Patient disorder	Spinal cord injury	Mixed etiology	Mixed etiology	Chronic back pain
N	217	51	105	51
Mean age (y)	39	44	41.5	54.7
Duration (y)	8.2	10.1	—	13.1
Male (%)	75	31	56	100
Female (%)	25	69	44	0
Overall interference (%)	38	88	65	51
Staying asleep (%)	40	37	74	26
Correlation with pain intensity	Yes	No	Yes	Yes
Correlation with depressed mood	—	—	No	Yes

for other chronic medical illnesses [16]. There is no indication that specific neuropathic pain conditions have different rates of depression or anxiety than the rates found in heterogeneous samples of patients with chronic pain.

Anxiety may represent an independent dimension of mood disturbance apart from poor sleep [1]. Nevertheless, when measured as an independent variable, as in the Profile of Mood States (POMS) questionnaire, patients with higher self-rated pain experience a greater degree of tension/anxiety [12]. Other factors besides pain or lack of sleep contribute to the risk for anxiety [1].

Manifestations of Comorbidity in Specific Chronic Pain Settings

Postherpetic Neuralgia

Few data specifically quantify the comorbidities associated with postherpetic neuralgia (PHN), but it may be generally agreed that patients with PHN can experience a variety of constitutional symptoms, including chronic fatigue, anorexia, weight loss, physical inactivity, and insomnia, as well as psychological problems, such as depression and difficulty concentrating [17]. Mauskopf et al. reported that PHN significantly interfered with the physical mobility, energy, sleep, social engagement, emotional reactions, and global QOL dimensions of the Nottingham Health Profile (NHP), and that the magnitude of interference increased with pain severity [18].

Diabetic Peripheral Neuropathy

Galer et al. surveyed 105 patients with painful diabetic peripheral neuropathy (DPN) using a modified Brief Pain Inventory (BPI) [19] (Table 2). The modified inventory contained additional items covering self-care, recreational activities, and social activities. On average, pain was expressed as 6/10 in severity and most often described as burning, electric, sharp, or dull/ache, which was worse at night and when tired or stressed. Pain also substantially interfered with sleep in 57% of the surveyed population and with mood in 43%. In another study of DPN employing two control groups [20], Benbow et al. showed a significantly greater interference from pain in five of six dimensions of the NHP in patients with longstanding DPN compared with either control group. The affected dimensions included emotional reactions, energy, pain, physical mobility, and sleep; social isolation was the one dimension that remained relatively unaffected by pain [20]. Similar to the performance of many self-rated health questionnaires, the specificity of the mood item on the BPI is low (i.e., the false-positive rate is relatively high, so that many patients who score high on the scale don't have major depression or have something else) and the sensitivity is high (i.e., the false-negative rate is relatively low, so that the scale doesn't miss many cases of depression). This indicates the need for further evaluation for a specific diagnosis (see below).

Table 2 Comorbidities in patients with diabetic neuropathy

Pain interferes with	Substantial interference (% with score ≥5)
Enjoyment of life	58
Mobility	57
Normal work	57
Sleep	57
Recreational activities	56
Social activities	51
General activity	48
Mood	43
Relations with other people	36
Self-care	35

Trigeminal Neuralgia

Trigeminal neuralgia (TGN), or tic douloureux, is a disorder of the fifth cranial nerve that causes episodes of intense, stabbing, electric-shock-like pain in the facial distribution of the nerve, including lips, eyes, nose, scalp, forehead, upper jaw, and lower jaw. The disorder most often affects one side of the face, and occurs most often after age 50. TGN is not fatal, but it is universally considered to be one of the most painful afflictions known to medical practice. Zakrzewska and Patsalos described a prospective longitudinal study of 15 such patients treated with oxcarbazepine, whose pretreatment pain, anxiety, and depression scores were elevated [21]. Eight of the 15 patients were evaluated for both anxiety and depression; seven patients with anxiety and all eight patients with depression showed improvement with treatment. Long-term pain relief was obtainable with oxcarbazepine; however, surgical intervention was sought in most cases.

Complex Regional Pain Syndrome II

Complex regional pain syndrome (CRPS) is divided into two subtypes: CRPS I and II. CRPS II occurs after a defined partial nerve injury and results in burning pain, allodynia, or hyperpathia in the associated area, whereas CRPS I lacks a

definitive nerve insult. Comorbidities associated with CRPS II include mood disturbances such as anxiety and depression, which may lead to an increased risk of suicide [22].

Spinal Cord Injury

Spinal cord injuries are universally associated with significant deterioration in QOL measures pertaining to work and self-sufficiency; however, transition to or relief from correlative pain conditions may be more important in regard to overall ability to cope [23]. In a sample of 270 patients with traumatic spinal cord injuries followed up for at least 2 years post injury, Putzke et al. showed that patients whose pain status did not change between year 1 and year 2 experienced little change in self-rated QOL. In comparison, those whose pain status worsened also generated worsening QOL scores (including mental status), while those whose pain status improved showed improved QOL scores. It is not possible to determine a causal direction from these data; therefore, separate treatments for pain and depression are in order for these patients, in addition to any rehabilitative strategy.

Clinical Evaluation of Sleep and Mood in the Context of Chronic Pain

The physician evaluating a chronic pain patient who is failing to respond to initial treatment should begin with a complete history and physical examination. When possible, an interview with the patient's spouse or other close relation may provide additional data and clarify the patient's history. General observations regarding behavior, particularly the patient's appearance, speech, mannerisms, and motor activity during the interview and examination, may provide additional insights. For example, the history may reveal medical problems suggesting a somatoform disorder or another psychiatric comorbidity. Such conditions, if present, require psychiatric evaluation and treatments that are usually beyond the scope of the pain clinic.

Several well-tested, documented instruments evaluate specific components of the pain-sleep-mood triad, including the Pittsburgh Sleep Quality Index (PSQI) [24], Hamilton Depression Rating Scale (HAM-D) [25], Beck Depression Inventory (BDI) [26], Short Form-36 Health Survey (SF-36) [27], NHP [28], and Treatment Outcome for Pain Survey (TOPS) [29], a version of the SF-36 specifically developed for pain clinics. For the purposes of evaluating pain patients for possible comorbidities, this review focuses on brief, well-documented instruments that expedite diagnosis and treatment in an office setting. Self-administered tests are preferred, not only because they are less expensive to administer, but also because they avoid two limitations of observer-based scales: A tendency to limit observations around the midpoint of a scale and a significant time delay in detecting changes in status relative to patient self-evaluations [30]. The following are three examples of screening tools that fit the above description and are sensitive enough to detect clinical changes in a patient's status. Routine use of these assessment tools should help the clinician better gauge the degree of pain-related sleep and mood disturbance, and establish a clinical marker by which to measure improvement.

Evaluation of Pain

The rapid evaluation of patients with neuropathic pain might be best accomplished with the administration of the BPI, one of the most extensively tested and frequently employed instruments for measuring pain and the efficacy of pain interventions (Figure 1) [31]. This inventory relies principally upon an 11-point, 0 to 10, Likert scale that produces essentially the same sensitivity of response as a visual analog scale, but is easier to administer and score [31]. It gives reliable and reproducible measurements without regard to disease state, clinical status of the patient, or a patient's educational or cultural background, and results are generally consistent across time when the test is readministered to the same patient [31]. The ninth item of the instrument explores the dynamic among pain, mood, sleep, and functionality, and is, therefore, ideal in making an initial assessment of the comorbid conditions of neuropathic pain. The presence of significant sleep and mood disturbance identified by the BPI serves as an indicator for further evaluation as well as a benchmark for the effectiveness of any treatment that may be implemented.

Evaluation of Sleep and Mood

Compared with sleep laboratory studies, self-reports of sleep problems are more convenient and less expensive to obtain, and they have the distinct advantage of greater clinical relevance because they directly measure the patient's sense of discomfort [13]. A sleep diary is considered a more reliable means to obtain a self-report of sleep difficulty than a patient interview, because the bias of recall is eliminated [13]. Indeed, patient diaries

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

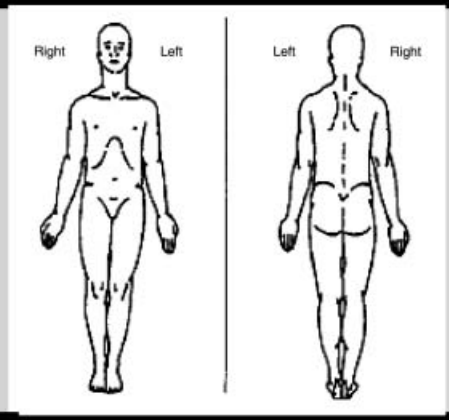
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Figure 1 Brief Pain Inventory.

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Figure 1 Continued.

have proven useful in the evaluation of chronic pain patients by demonstrating an acceptable stability of responses over time and good correlations with self-reports of activity level, medication use, and pain intensity [32,33].

Haythornthwaite et al. developed a sleep diary that should be especially useful in evaluating chronic pain patients [13]. This instrument was initially tested on an in-hospital sample of 46 patients with chronic pain of mixed etiology who were undergoing evaluation and rehabilitation. Those patients reported an average of 5.24 hours of sleep per night (compared with 6.5–7.8 hours for normal older adults who required 30–60 minutes to fall asleep initially) and reported awakening one to two times during the night [13]. Measured repeatedly on four consecutive nights, internight coefficients of variation were all significant, and none were found to change across the recording period. Each item in the diary showed reliability coefficients that were higher than the interitem correlations, supporting the discriminatory characteristic of each item for a different aspect of sleep. The results obtainable with this sleep diary are generally consistent with results in the sleep literature and suggest that it would be a simple, cost-effective adjunct in the evaluation of chronic pain patients.

Depression often follows chronic pain [16], even in those without apparent risk such as a personal or family history of depressive illness [34]. Phenomenologically, depression seems to play an important role in the experience of chronic pain, as patients with depression have been found to report higher levels of pain, be less active and report greater disability, report greater interference due to pain, and display more pain behavior [35–38].

A number of studies also suggest that depression can augment the impairment associated with pain, and functional impairment related to pain and depression persists in community populations despite access to excellent health care. One prospective study of 228 well-insured older adults, evaluated every 6 months over 24 months, demonstrated: that pain and depression symptoms were commonly comorbid, with greater symptoms of depression associated with greater pain-related impairment; that this comorbidity was sustained longitudinally [39,40]; and that even mild depression increased health care utilization in persons with pain [41].

The successful management of depression begins with a thorough initial patient assessment to establish diagnosis and to investigate potential biopsychosocial risks and strengths. Physicians initiating treatment have at their disposal a rapidly growing pharmacopeia. In addition, several psychotherapeutic techniques may help.

All patients with pain diseases and disorders must be screened for depression using simple screening instruments such as the BDI [26] or by imbedding screening questions into the review of systems, which has the advantage of reducing systematic response bias [42]. A quick preliminary assessment of whether a patient with chronic pain is depressed can be made by asking two questions: 1) During the past month, have you often been bothered by feeling down, depressed, or hopeless? and 2) During the past month, have you often been bothered by having little interest or pleasure in doing things?

The sensitivity of these questions in detecting depression is 96%; however, their specificity for depression is only 57%. If screening is positive, a more thorough evaluation is needed to make a definitive diagnosis of depression. Neuropathic pain is considered a chronic disease associated with considerable risk for the onset of complicating or recurrent depressive illness. Also, initial evaluation of pain may have a significant false-negative rate [43]. Even when not detected at first, clinicians should periodically screen for depression during treatment. Evaluation is particularly indicated when a change in pain symptoms, impairment, or disability is observed.

Evaluating the safety of a patient with depression is critical. Chronic neuropathic pain can be fatal because of its associations with suicide and with violence [6,44]. A careful assessment of suicidal risk has a direct bearing on whether the individual would be best treated in an inpatient or outpatient setting. The assessment of suicide risk should include the presence of suicidal ideation, plans made by the patient, the availability of means/methods, and the lethality of methods being contemplated. All suicidal patients should be evaluated by a professional with the proper training to assess suicidal risk and to arrange appropriate management. Pain clinicians should be aware that depression also increases the risk for anger attacks and violence. Persons with chronic pain who are in treatment have higher rates of violent ideation than do community controls, and the presence of depression increases this risk [44,45]. Other factors associated with an increased risk include job dissatisfaction, unemployment, workers' compensation, work rehabilitation pro-

grams, litigation, and a physician-made diagnosis of malingering [46]. The physician should be aware of these risks and should always ask patients at evaluation, or during the course of treatment when there is a setback, if they are bothered by anger outbursts or angry thoughts, and whether they can control these thoughts.

Creating a trusting and positive working relationship with the patient and, if possible, with the family or significant others, is crucial to ensuring reliable, safe, and effective treatment, particularly in the era of rational polypharmacy. Treatment starts with educating the patient and appropriate family members about pain and depression, the goals of treatment, the rationale for different treatment choices, and the clinician's expectations of the patient's responsibilities for recordkeeping, adherence, and follow-up. The trust in this relationship becomes critical when dealing with matters of safety—toxicity, suicide, and violence. Successful treatment of depression requires maintenance of antidepressant treatments for long (>4 months) or indefinite durations to assure full remission and to prevent relapse or recurrence [47]. However, often in the early stages of treatment, patients with pain and depression may be poorly motivated and unduly pessimistic about recovery. In addition, side effects of medications must be carefully explained, as they may be an important reason for noncompliance.

Treatment Strategies for the Comorbidities of Chronic Pain

Treating the Whole Patient

Chronic pain affects many activities of daily living, both directly, by restricting or preventing normal movement, and indirectly, through disruption of mood and sleep. While it is essential to treat the underlying pain condition as effectively as possible, it is quite common that pain symptoms cannot be eliminated completely. In certain patients, surgery may be an effective measure; however, in a sample of 575 chronic pain patients treated solely by surgical intervention, only 30% were relatively pain free 4–17 years afterward [48]. In comparison, a multidisciplinary team approach—including nurses, pharmacists, and various physical, behavioral, and occupational therapists in cooperation with the physician—may be able to achieve equal or better results. A meta-analysis was performed, consisting of 65 studies that evaluated a multidisciplinary approach, which found that, 6 or more months after intervention, the pain reductions achieved with multidisciplinary measures were double those of control groups [49]. As a pragmatic indicator of success, whole-patient management can dramatically reduce the number of pain-related clinic visits [50].

Treating Sleep Disturbances

The association of neuropathic pain with sleep disturbances has been recognized for many years. Although the connection between chronic pain and impaired sleep might seem more obvious than the connection between lack of sleep and deterioration in mood, the directionality of the interactions of these three dimensions in the context of chronic neuropathic pain is far from clear. Disrupted sleep, anxiety, and depression often coexist in the same patient and have a superadditive effect upon day-to-day functioning. Sleep disturbance may not only be a result of chronic pain, it may also contribute to it. Cognitive-behavioral interventions targeting sleep disturbances may be useful in improving sleep and mood even when they are secondary to chronic pain [10].

Nonpharmacologic Interventions

Behavioral interventions are highly useful in improving sleep in patients with primary insomnia [51]. Such measures include: Relaxation therapy, wherein techniques are taught that reduce both cognitive and somatic arousal before bed; Sleep restriction therapy, wherein overall time in bed is restricted in order to increase the percentage of time asleep while in bed; Stimulus control therapy, wherein the bedroom is used only for regular nighttime sleep; and Cognitive therapy, in which dysfunctional attitudes and beliefs about sleep are confronted and replaced by more rational understandings [51]. Although virtually no large-scale studies examine the effects of behavioral interventions to promote sleep in neuropathic pain patients, Morin et al. showed that both stimulus control and sleep restriction techniques reduced sleep onset latency, wake time after sleep onset, and premature awakening, which was confirmed by objective sleep laboratory studies [52]. These changes were accompanied by improvements in measures of anxiety, depression, and fatigue [52]. Improvements in sleep satisfaction were maintained for at least 6 months from posttreatment evaluations [52].

Pharmacologic Interventions

Patients being evaluated for chronic neuropathic pain will, in most cases, be receiving drug treatments for their pain conditions, or they may have

tried one or more of the standard agents in the past, such as tricyclic antidepressants (TCAs) or antiepileptic drugs (AEDs). If a comorbid sleep condition is suspected, some form of sedative-hypnotic may ultimately provide the best relief; however, it is worth examining any current or proposed medication for pain relief, because some agents can be the cause of sleep pathology, whereas others promote more normal sleep (Table 3).

The TCAs have been a mainstay of the treatment for neuropathic pain for many years [53–56]; however, when selecting one of these agents (e.g., amitriptyline, clomipramine, desipramine, imipramine, or nortriptyline) in the context of sleep difficulties, it is worth noting that some activate the central nervous system, while others produce sedation. For example, desipramine alleviates pain in patients with DPN [53,57] but can also increase alpha-wave activity. The selective serotonin reuptake inhibitor (SSRI) paroxetine has also been shown to be effective in patients with DPN, but is associated with diminished sleep time and rapid eye movement (REM) sleep suppression [58,59].

Sedating antidepressants, such as amitriptyline, decrease normal alpha-wave activity and increase slow-wave activity (Table 3) [60]. With other TCAs, such as desipramine, REM sleep remains unchanged, while slow-wave sleep (SWS) and sleep maintenance increase [60]. For these reasons, a sedating TCA may be the better alternative in neuropathic pain patients complaining of insomnia. Though daytime sedation is a common complaint with amitriptyline, it may be avoided or diminished by giving a larger dose at bedtime and smaller, more widely spaced doses during the day. Daytime pain relief may not be complete, but a better-rested patient may be able to tolerate moderate levels of pain.

The AEDs are also effective in the treatment of neuropathic pain, but interestingly, may also improve the quality of sleep [61]. The two most frequently used AEDs in neuropathic pain stabilize sleep, an effect that seems to be a direct result of changes in sleep architecture as opposed to suppression of epileptic discharges. In the case of carbamazepine, SWS and sleep continuity are improved, while sleep latency and REM sleep are decreased [61]. Treatment with gabapentin improved REM sleep and SWS and decreased awakenings and arousals [60]. In a clinical setting, gabapentin was found to improve sleep quality and sleep consolidation and to reduce the number of nighttime awakenings in six patients with refractory CRPS I [62]. Gabapentin was also effective in restoring sleep architecture in neuropathic pain patients in a large-scale clinical trial [63,64]. Based on these observations, if a TCA is unacceptable in a particular patient, it would be reasonable to try carbamazepine or gabapentin before resorting to an opiate or other hypnotic-sedative.

The opiates are generally less effective in neuropathic pain than in nociceptive pain, with the exception of a subset of patients whose neuropathic pain is treatable by medications from this class. For those patients, an opioid may not be an advantageous choice to relieve both neuropathic pain and comorbid insomnia. Morphine, for example, decreases REM sleep and SWS, and increases awakenings or arousals (Table 3) [60]. If an opioid is chosen, it is important to observe such patients carefully, because opioids may produce excitation or even mania [65].

Table 3 Effect of antidepressants on sleep architecture

	REM sleep	SWS	Awakenings/arousals*	Sleep maintenance*	Reference
Opioids					
Morphine	↓↓	↓↓	↑↑↑		[104]
Antiepileptic agents					
Carbamazepine†	↓	↑			
Gabapentin	↑	↑	↓	↑	[105]
Antidepressants					
Bupropion	↑	↓			[106]
MAOIs	↓	↔		↓	[58]
Nefazodone	↑	↔		↑	
SSRIs	↓	↓ or ↔		↓	[106]
TCAs					
Amitriptyline	↓↓	↑		↑	[58]
Desipramine	↔	↑		↑	[58]
Trazodone	↓	↑		↑	[55,58,106]

*No arrows indicates no data available.
†Sammaritano and Sherwin, 2000 [61].
↑ = increase; ↓ = decrease; ↓↓ = significantly decrease; ↔ = no change.

Hypnotics are, generally, a less-appealing choice in the treatment of neuropathic pain patients who may find themselves using sleep aids for an extended period of time. Benzodiazepines (temazepam, flurazepam, triazolam, and estazolam) may be tried in the short-term management of insomnia, although they may cause amnesia and rebound insomnia [66] and alter sleep architecture. Nonbenzodiazepine medications, such as zaleplon, zolpidem, or zopiclone [67], are preferable for longer term treatment because they have little or no effect upon sleep architecture and have fewer side effects than benzodiazepines. Currently, zopiclone is not available in the United States.

The foremost goal of pharmacologic intervention in the neuropathic pain patient is to treat the underlying disorder and alleviate pain. Treating pain may have an ameliorative effect on the comorbidity of sleep disturbances. It is crucial to choose an agent that will not disrupt sleep, and, when possible, to consider drug options and dosing regimens that may promote better sleep and minimize side effects.

Treating Depression and Anxiety

Expanding on the idea that neuropathic pain and its comorbid conditions represent a dynamic triad that will worsen outcome, it must be said that the psychological dimensions of depression and anxiety are poorly studied as isolated comorbidities of neuropathic pain. The prevalence of depression in neuropathic pain patients is very high, and may approach 100% [8]. Yet a determination regarding the relative importance of depression and anxiety as a predominant expression of the triad is very much a clinical judgment, the accuracy of which depends on physician training and experience, perhaps aided by the simple assessment instruments outlined previously and consultation with mental health specialists with training and experience in chronic pain. Treatment of neuropathic pain patients whose psychological disturbance is beyond the scope of these simple instruments may be better managed in a psychiatric setting.

Nonpharmacologic Interventions

Establishing a therapeutic alliance between the patient and the clinician is essential in securing an adequate trial of new drugs and adherence to dosing, given the long-term nature of the pain condition. Once efficacy is achieved, educating the patient regarding inevitable side effects may diminish the chances that a trial will result in failure [68]. As with comorbid sleep disturbance, it is likely that neuropathic pain patients presenting to the pain specialist with depressed mood will have tried or will currently be receiving one or more of the standard neuropathic pain therapeutics, namely an antidepressant or an anticonvulsant. The uppermost question is, "What adjustments or additions to the regimen might improve response in an neuropathic pain patient with comorbid depression and/or anxiety?"

Although psychopharmacological treatment of psychiatric comorbidities associated with chronic pain is helpful, psychotherapeutic techniques also help, because pain disorders also involve the conditioning of the neurophysiologic system, both by pain itself and its psychosocial contextual experience. Psychotherapeutic interventions form one of the cornerstones of managing not only the psychiatric comorbidities, but also the pain itself. Cognitive behavioral therapy [69] and interpersonal psychotherapy are effective for depression [70]. Behavior therapy, a form of psychotherapy, uses contingency management or operant conditioning not to treat pain, per se, but to help patients modify their pain-related behavior. These methods can also be used for rehabilitating pain patients by increasing their functional performance in daily life.

Pharmacologic Interventions

It is perhaps fortuitous that many agents employed in treating the pain component of neuropathic pain have mood-stabilizing effects as well, and in the case of the antidepressants, are employed principally for that purpose. In this regard, it is well established that the doses of antidepressants used in neuropathic pain are usually lower than those employed for depression, and several clinical studies have observed an analgesic benefit with no apparent effect on mood [71,72].

With the introduction of escitalopram, 22 compounds have been approved by the U.S. Food and Drug Administration (FDA) as antidepressants. Two additional drugs (clomipramine and fluvoxamine) are now being marketed outside the United States as antidepressants and have FDA approval for the treatment of obsessive compulsive disorder (OCD) [73]. Reboxetine and duloxetine may be the next antidepressants approved for marketing in the United States.

With the wide variety of antidepressants available, the clinician is forced to consider whether the medications differ in their efficacy and analgesia, before deciding on a treatment plan. Although antidepressants remain the first line of treatment

for depression, several important limitations exist. Thirty percent of patients do not respond to their antidepressant medication [74], and only approximately 30–40% of patients achieve full remission of symptoms in controlled antidepressant trials [74–77]. The mechanism by which antidepressant medications achieve their therapeutic benefit is not completely understood. To emphasize this point, no single drug has been proven to be more effective than any other for the relief of depressive symptoms [78], although some recent evidence suggests that dual-action antidepressants with both noradrenergic and serotonergic reuptake inhibition may have a greater efficacy in achieving depression remission [78]. Factors that may be considered in selecting a particular antidepressant include a previous response to that medication, a family history of a response to the same medication, and anticipated side effects [79]. Anxiety and insomnia do not necessarily predict a better response to more sedating medications [80–82]. Although SSRIs cost more than TCAs, the total costs of treatment are usually similar when comparing these two drug classes [83]. The side-effect profile of TCAs increases with the age of the patient, raising the chances of an adverse reaction.

Unlike TCAs, newer antidepressants with dual norepinephrine and serotonin reuptake inhibition have minimal activity at other receptor sites. Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) may prove to be advantageous clinically owing to their higher rates of depression remission, fewer side effects, and fewer drug-drug interactions. Many experienced clinicians consider SNRIs to be the drugs of first choice for patients with neuropathic pain and depression because of their effectiveness in neuropathic pain, their higher rates of depression remission, and their superior tolerability compared with TCAs.

All tricyclic and tetracyclic antidepressants are equally effective in treating depression, and most TCAs are efficacious in neuropathic pain disorders; thus, the choice of a particular antidepressant for comorbid depression is often influenced by the side-effect profile of the antidepressant and the potential for suicide or mania. Two factors that should always be kept in mind when prescribing TCAs are the potential for a lethal outcome in an overdose and the possibility of inducing a manic episode in patients with or without a history of mania. Other side effects include sedation and anticholinergic, autonomic, and cardiac effects.

The SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram) have become the most frequently prescribed antidepressant medications. Although not superior to other antidepressants in therapeutic response rates, their favorable side-effect profiles, compared with TCAs and monoamine oxidase inhibitors (MAOIs), and their safety with regard to overdoses make the SSRIs the drugs of choice in the treatment of depression.

Bupropion, a dopamine-norepinephrine reuptake inhibitor, is as effective as other antidepressants and has a unique side-effect profile, notably little psychosexual dysfunction. The adverse effects of bupropion are caused by its potentiating effects on the dopaminergic system. These are delusions, hallucinations, and the risk of seizures, which occur in approximately 5% of patients administered 450–600 mg/day. These side effects are thought to be lower with the sustained-released preparation, which is now widely used.

Venlafaxine, an SNRI, is an effective antidepressant that blocks the reuptake of norepinephrine and serotonin much like the TCAs, but without the undesirable side effects associated with them. The properties of an SNRI include a faster-than-usual onset of action and demonstrated efficacy in seriously depressed patients (e.g., patients with melancholic features). The norepinephrine reuptake inhibiting properties of venlafaxine, particularly at higher dose ranges, along with its structural similarity to tramadol, an analgesic with both opioid agonist and monoaminergic activity, make it a promising antidepressant for neuropathic pain [84].

Venlafaxine is generally well tolerated, although side effects include nausea (37%), somnolence (23%), dry mouth (22%), and dizziness (22%). The most potentially bothersome adverse effect associated with venlafaxine is an increase in blood pressure in patients treated with more than 300 mg/day. The other nontricyclic SNRIs with proven efficacy in depression, which will be available in the near future, include duloxetine and milnacipran [85].

Trazadone and nefazodone, which are both serotonin modulator antidepressants, are structurally related to each other, but unrelated to the TCAs, MAOIs, and SSRIs. Trazodone is distinctive in its sedating properties and is used to treat insomnia in both pain and depression. Nefazodone has a potentially fatal interaction with terfenadine and may cause liver failure.

The norepinephrine-serotonin modulator mirtazapine is an antidepressant with a novel mechanism of action. Antagonism of the central presynaptic α_2-adrenergic receptors results in a

potentiation of central noradrenergic and serotonergic transmission. An effective antidepressant, it lacks the anticholinergic effects of the TCAs and anxiolytic effects associated with some SSRIs. The adverse effects associated with mirtazapine include somnolence, comparable with that of amitriptyline and welcome in patients with sleep disturbances, increased appetite with weight gain, increased serum cholesterol, and rarely, agranulocytosis and neutropenia (0.3% of patients taking mirtazapine).

MAOIs act by increasing biogenic amine levels by inhibiting their degradation. The indications for MAOIs are similar to those of TCAs. MAOIs may be particularly effective in panic disorder with agoraphobia, posttraumatic stress disorder (PTSD), eating disorders, social phobia, and typical depression that is characterized by hypersomnia, hyperphagia, anxiety, and the absence of vegetative symptoms. The side effects of MAOIs and the potential for precipitating a toxic central serotonin syndrome, when combined with other medications and certain foods, limit their use to only treatment-resistant depression. Tyramine-induced hypertensive crisis in patients taking MAOIs can be life threatening. Other side effects include orthostatic hypertension, weight gain, edema, sexual dysfunction, and insomnia.

AEDs, such as carbamazepine and gabapentin, have an established role in the treatment of chronic neuropathic pain, especially when patients describe classic symptoms. AEDs may also have a role in neuropathic pain patients with depressed mood. Patients with neuropathic pain and concomitant depressed mood that were given AEDs showed an improvement versus those given placebo [86]. Anticonvulsants are generally safe and well tolerated.

Anxiety Disorders

Anxiety disorders are the most common form of mental illness in the United States, with one fourth of the population acknowledging current or past symptoms of anxiety disorders, compared with one fifth who report a lifetime history of a mood disorder [87]. Severe acute pain activates stress-related noradrenergic systems in the brain and is often accompanied by cognitive-emotional reactions such as fear and anxiety, which, to some degree, are contextually determined. The association of pain, anxiety, and depression may have a common neurochemical substrate in the serotonergic systems [88]. Patients with pain conditions commonly experience anxiety because of the stress of living with pain. Severe trauma incurred in battle may lead to PTSD, or a motor vehicle accident may lead to a driving phobia, which can be comorbid with injury-related pain. The presence of comorbid OCD with chronic pain can make both conditions harder to control. The patient undertakes compulsive motoric acts, such as cleaning rituals, that activate neuropathic pain.

Panic attacks occur in a variety of psychiatric disorders and, when recurrent or associated with significant apprehension and behavioral change, are the central manifestations of panic disorder. Panic attacks by definition are abrupt and intense, with symptoms referable to several bodily systems. These patients often present to the emergency department with the complaint of chest pain. In general, experience has shown the superiority of the SSRIs and clomipramine over benzodiazepines and other TCAs and MAOIs in the treatment of panic disorder. A recommended approach is to start treatment with an SSRI when managing patients with panic disorder. If a rapid control of anxiety symptoms is needed, then a short-acting benzodiazepine should be used until the SSRI takes effect, bearing in mind the abuse potential and other possible negative effects of prolonged use of benzodiazepines.

Social phobia is a persistent, disproportionate fear in a performance or a social setting. It may include intense anticipatory anxiety. Often it is associated with hypersensitivity to criticism and low self-esteem. It may be generalized to involve multiple, slightly similar situations, or be specific for a particular event. It is frequently a lifelong problem that usually is handled by avoidance, which limits opportunities. Paroxetine, fluvoxamine, and sertraline have been investigated in double-blind studies and found to be effective in treating social phobia. Only paroxetine has been approved by the FDA for this indication. New data indicate that social phobia responds well to medication and may benefit from specific behavioral treatments. SSRIs and high-potency benzodiazepines are currently the treatments of choice.

It is estimated that 2% of the general population suffers from OCD [89]. An obsession is a recurrent and an intrusive thought, feeling, idea, or sensation, whereas a compulsion is a conscious, standardized, recurring pattern of behavior. People with this disorder recognize that their acts are irrational and disproportionate. Fluoxetine, fluvoxamine, sertraline, and paroxetine have all been approved for the treatment of OCD. Higher doses may be necessary, such as 80 mg/day for fluoxetine. Of the TCAs, clomipramine is the most

selective for serotonin reuptake and was the first FDA-approved drug for OCD. It is limited by a side-effect profile that is shared with other TCAs. As with SSRIs in many psychiatric disorders, the best outcome in OCD is seen in patients receiving a combination of pharmacotherapy and behavior therapy.

Recognition and appropriate treatment of this disease are frequently delayed. Like generalized anxiety disorder (GAD), this is a closet disorder, and there is often a great delay between onset of illness and time of treatment.

PTSD occurs when a traumatic experience or exposure to a traumatic event is reexperienced persistently, resulting in avoidance of stimuli associated with the event and continual symptoms of increased arousal. In the context of pain, the presence of PTSD has implications for rehabilitation, which needs to be individualized [90].

Treatment of PTSD requires that physicians give patients adequate time to disclose their stories. Brief treatment does not mean rushed treatment. Clinicians should explain the nature of PTSD to survivors and families and encourage patients to speak about their traumatic experience with family or friends, in a nonpressured environment. Pharmacotherapy of PTSD includes a number of antidepressants. Amitriptyline, imipramine, fluoxetine, and sertraline have demonstrated efficacy [91–95].

GAD is characterized by excessive worrying that is difficult to control and is associated with somatic symptoms such as muscle tension, irritability, difficulty sleeping, and restlessness. The FDA-approved agents for the treatment of anxiety include benzodiazepines and buspirone, although long-term benzodiazepine use for the treatment of GAD may be associated with the risks of tolerance, abuse, and dependence [96]. Buspirone is effective in the treatment of GAD and avoids the disadvantages associated with benzodiazepines; however, it has a slower onset of action—typically 1–3 weeks. Among the newer antidepressants, only extended-release venlafaxine has been shown to possess unequivocal efficacy in GAD [97,98]. Phase III trials of pregabalin (an $\alpha_2\delta$ ligand with analgesic, anxiolytic, and anticonvulsant activity) in GAD have shown this novel compound to be effective, rapidly acting, and safe [99,100].

The principles of psychotherapy for patients with anxiety disorders are similar to those for depression, but with greater emphasis on behavioral methods. Treatment must focus on helping the patient learn specific cognitive and behavioral coping skills to prevent, abort, or ameliorate symptoms of anxiety.

Restored Functionality: Combined Outcomes in Clinical Trials

The best measure of the successful management of comorbid conditions in neuropathic pain is an improvement in patient QOL. Although this has rarely been the principal outcome measure in a clinical trial, numerous studies directed at the treatment of neuropathic pain have included measures of QOL because improved functionality is increasingly recognized as the most attainable goal of treatment. Improved functionality can be demonstrated for several agents for which clinical studies included effects on patient QOL, such as sleep, mental health, and activity level. Our own patients have obtained similar relief when measured in this way.

Bupropion

Semenchuk et al. studied 41 nondepressed outpatients with neuropathic pain in a randomized, double-blind, placebo-controlled, crossover study [101]. Patients received 1–2 tablets of 150-mg bupropion sustained-release (SR) or a placebo [101]. The primary outcome measure was mean average pain intensity, which was measured by patients in a daily diary on a visual analog scale ranging from 0 (no pain) to 10 (worst pain imaginable) [101]. Pain relief with bupropion SR was superior to placebo ($P < 0.001$), beginning at week 2 ($P < 0.05$), with steady improvement during the remaining 4 weeks of treatment [101]. More importantly, items on the BPI, including pain interference with general activity, ability to walk or move, mood, normal work, relations with people, sleep, and life enjoyment were all greater than with placebo treatment (Figure 2) [101].

Fentanyl Versus Morphine

Allan et al. studied 256 patients with chronic noncancer pain (approximately 25% of patients had neuropathic pain and 25% had combined neuropathic and nociceptive pain) in a randomized, multicenter, open-label crossover study [102]. The main outcome measure was preference for transdermal fentanyl or sustained-release oral morphine based on pain control and QOL after 4 weeks of treatment [102]. Most patients (65%, 138/212) preferred transdermal fentanyl over sustained-release oral morphine (28%, 59/212) [102], and more patients considered pain relief to be

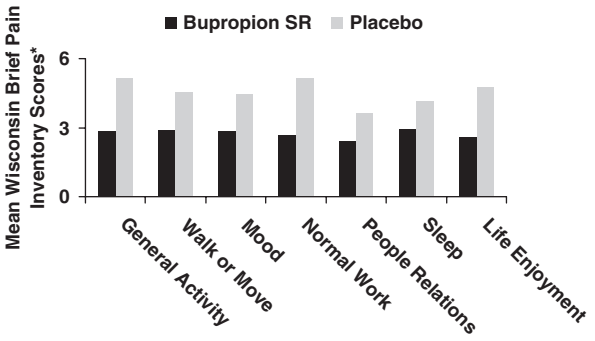


Figure 2 Results of the BPI following treatment of neuropathic pain patients with bupropion SR [101].
* Lower scores indicate less interference from pain. *P* values range between 0.05 and 0.001.

better with fentanyl as well (35% vs 23%) [102]. In addition, patients receiving transdermal fentanyl had higher overall QOL scores than patients receiving sustained-release oral morphine (Figure 3).

Gabapentin

Backonja et al. conducted a randomized, placebo-controlled, double-blind, 8-week trial in 165 patients with DPN [63]. Patients received gabapentin, 900–3,600 mg/day as tolerated (N = 84), or matching placebo (N = 81) [63]. The mean daily pain score at the end of treatment, measured on an 11-point Likert scale, was significantly lower in patients receiving gabapentin (3.9, from a baseline score of 6.4) than in those receiving placebo (5.1, from a baseline score of 6.5) ($P < 0.001$). Compared with those receiving placebo, patients receiving gabapentin demonstrated significantly better sleep scores [63] and better QOL, as measured by three items on the SF-36 QOL questionnaire: Bodily pain ($P = 0.01$), mental health ($P = 0.03$), and vitality ($P = 0.001$) [63].

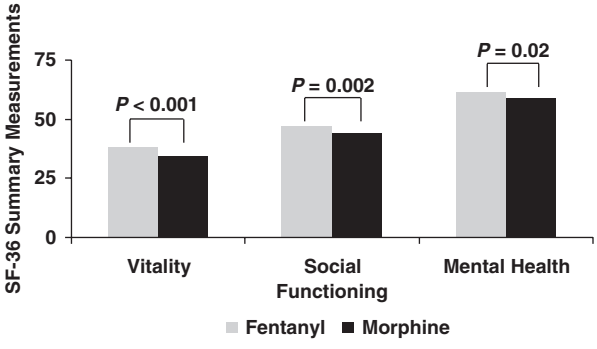


Figure 3 Effects of transdermal fentanyl in chronic noncancer pain patients. Improved daily living was seen following treatment with transdermal fentanyl as measured on the SF-36 health survey.

Rowbotham et al. assessed the analgesic effects of gabapentin in a placebo-controlled, double-blind, randomized, parallel-group, 8-week study involving 229 patients with PHN [86]. The reduction in average daily pain score was significantly greater in the gabapentin cohort compared with the placebo cohort (33.3% vs 7.7%, respectively) ($P < 0.05$) [86]. Similarly, gabapentin-treated patients showed significantly greater improvements than did placebo-treated patients on the POMS assessments of depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment, and total mood disturbance ($P \leq 0.01$) [86]. Similar results were obtained in another large study of gabapentin in patients with PHN [64].

Pregabalin

Pregabalin is an emerging treatment for neuropathic pain that has also demonstrated a beneficial effect on comorbid conditions. Dworkin et al. reported the effects of pregabalin, 600 mg/day (300 mg/day in patients with renal insufficiency; creatinine clearance 30–60 mL/minute), versus placebo on pain and sleep in a randomized, double-blind, parallel-group, 8-week study involving 173 patients with PHN [103]. The mean pain score, as measured on an 11-point Likert scale, was significantly lower at the study end point for pregabalin-treated patients than for patients who received placebo (3.60 vs 5.29; $P = 0.0001$) [103]. A daily sleep interference score demonstrated a significant improvement in pregabalin-treated patients at the study end point ($P < 0.0001$). Sleep was significantly better within the first week of pregabalin treatment and remained significantly better during the course of the study, compared with patients who received placebo (Figure 4).

Case Studies

A few case studies drawn from our clinical practice serve to illustrate the interrelatedness of and treatment strategies for comorbid conditions in neuropathic pain, as well as the degree of improvement that can sometimes be obtained:

Case #1: A 38-year-old female, with a history of disc herniation between the fourth and fifth lumbar vertebrae, developed chronic leg pain after a second surgery for laminectomy and disc decompression. Her symptoms were consistent with chronic radiculopathy with delayed onset of sleep secondary to pain. Treatment with gabapentin was initiated at 300 mg four times a day, but because of

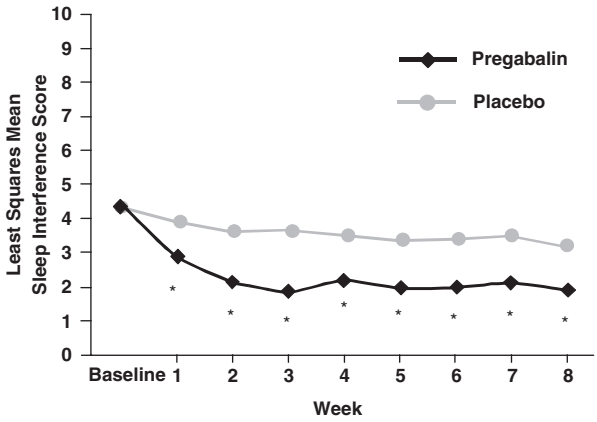


Figure 4 Improved sleep seen following treatment with pregabalin in PHN patients. *$P < 0.01$.

daytime sedation, the regimen was changed to 900 mg every night at bedtime (QHS). At follow-up, it was clear that the nighttime dosing regimen was serving as both an analgesic and a sleep aid, because her sleep onset had improved along with her overall sleep pattern.

Case #2: A 75-year-old female with a 2-year history of chronic progressive lower-extremity pain complicated by severe peripheral vascular disease complained, at the time of evaluation, of bilateral leg pain that was burning and throbbing in character, was particularly severe with ambulation, and improved somewhat at rest. Trials of antidepressants, anticonvulsants, and opiates were initiated for the peripheral neuropathic pain. Unfortunately, she responded poorly to medication trials because of multiple medication side effects at low doses. Other findings during evaluation included notable difficulty with sleep, anxiety, and spontaneous episodes of crying. Treatment with various SSRIs was attempted without improvement in depression or sleep. A trial of mirtazapine, initiated at 15 mg QHS and titrated to 30 mg QHS over 2 weeks, resulted in marked improvements in depression and anxiety, demonstrating the importance of trying several antidepressants of different classes until a response is obtained. The patient was offered a trial of spinal cord stimulation that was successful in relieving her peripheral neuropathic and vascular claudication pain. After 2 years, she continues to report a marked improvement in her pain.

These cases illustrate that, while it is desirable, and sometimes possible, to successfully implement single-agent therapy, it is important to take prompt action if pain relief proves unsatisfactory or if symptoms of insomnia appear, with or without anxiety or depression. These may be the manifestations of a comorbid condition and, depending upon the nature of the secondary symptoms, a reasonable trial of an antidepressant or an AED should be attempted.

Conclusions

Neuropathic pain is widely recognized as one of the most difficult to treat pain syndromes. A common cause of poor outcome is the failure to properly assess, and effectively treat, real and significant psychological cofactors and psychiatric comorbidities that make coping with chronic pain so difficult, such as poor sleep, depression, mood, and anxiety. These cofactors and comorbid conditions represent a dynamic triad of negatively reinforcing pathologies that must be adequately assessed in each patient to optimize treatment outcome. Assessment of an individual patient can be carried out expeditiously if the clinician relies mostly on patient self-evaluation using relatively simple screening questionnaires, such as the BPI, BDI, and sleep diaries. These assessment tools can identify those patients with psychological distress and psychiatric comorbidities who will require further evaluation to determine a diagnosis and begin treatment, choosing from a wide range of effective pharmacologic therapies and psychotherapies. Effective treatment of comorbidities will enhance outcomes of pain treatment. Single-agent therapy is possible in many situations, especially when drugs are selected to address both the pain and the most significant comorbidities. Though it is relatively rare for a patient to obtain complete pain relief, improvements in functionality and QOL are clearly obtainable goals in the treatment of neuropathic pain patients and, indeed, represent the most practical measures of effectiveness at this time.

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