



How Do Neuropathic Pain, Depression, Anxiety and Quality Of Life Interconnect?

Chronic pain can be exacerbated by mood disorders, thwarting successful control of pain symptoms.

Barbara is a 53-year-old female with painful diabetic peripheral neuropathy who complains of feeling depressed all the time. She can recall having “some” depressed feelings during her 20s but after being diagnosed with diabetes mellitus and developing the neuropathy, she has become overtly depressed. These conditions are now interfering with her ability to function both at home and at work. Have you seen patients like this? How commonly does this occur?

For decades, there’s been great interest in understanding how psychiatric comorbidities may affect treatment of various disease states. For example, patients with neuropathic pain may experience a number of Axis I disorders, including affective disorders (depression-MDD), generalized anxiety disorders (GAD), substance-use-related disorders, and somatoform disorders or Axis II psychiatric (personality) disorders. For the purposes of this month’s column, discussion will be focused on comorbid anxiety and depression in patients with neuropathic pain. It is possible that the psychiatric disorder may have preceded the onset of neuropathic pain or it may have developed after the neuropathic pain diagnosis has been made.

Depression and Anxiety

The percentage of chronic pain patients (neuropathic and non-neuropathic) who suffer from depression ranges from 22 to 78 percent, with some studies reporting rates as high as 100 percent. This is in stark contrast to a range of two to 45 percent reported in patients with physical illnesses other than chronic pain.

The relationship between chronic pain and depression is not simple. The prevalence of depression is greater among patients with chronic pain, and multiple studies of depressed patients demonstrate they report more pain symptoms than those who aren’t depressed. This is not to suggest that a causal relationship exists. Although there is no clear information suggesting a direct causal relationship between depression and pain, the *DSM-IV* recognizes that psychological factors play a sizeable role in the onset, severity, exacerbation or maintenance of pain.

Anxiety disorders such as GAD, panic disorder, social phobia and post-traumatic stress disorder are often associated with chronic medical conditions. Chronic pain patients in general have a high prevalence of anxiety disorders associated with somatic complaints. In one study, chronic pain was reported by almost 40 percent of patients with panic disorder. To maximize treatment of the patient, it is vital to target both the psychiatric condition as well as the neuropathic pain state, and any other associated relevant medical conditions.

Psychiatric comorbidities frequently have a negative impact on the chronic pain patient, with the potential to negatively alter treatment and outcome significantly. Anxiety can reduce pain threshold, decrease pain tolerance and result in increased patient self-reported pain ratings. As already mentioned, for many chronic pain patients, the onset of MDD may occur prior to the development of the neuropathic pain condition. Furthermore, because both of these can coexist in the same patient, each may magnify the

symptoms of the other, demonstrating the clear interrelationship between psychiatric disorders and neuropathic pain.

Diagnosis of Comorbid Psychiatric Disorders

It has been clearly noted that there is a risk of increased morbidity and mortality in chronic pain patients who also suffer from one or more psychiatric disorders. Therefore, it is in the best interest of the patient for these interrelated comorbidities to be diagnosed and treated aggressively. Not infrequently, such patients will need to be managed in a collaborative fashion with a behavioral health specialist.

In-office screening tools can help to both identify and quantify mood disorders. Multiple scales have been developed for use as initial screening of psychological distress in patients with pain. The Pain Patient Profile, for instance, is a self-report instrument. It is a measure of anxiety, depression and somatization in patients presenting with pain. Furthermore, numerous scales are available to determine the severity of a psychiatric condition, such as the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A), each of which have been widely used in patients with a variety of affective and anxiety disorders.

Other commonly used rating scales include the Beck Depression Inventory and the Montgomery-Asberg Scale. The response to treatment of the mild-to-moderate depression often seen in patients with chronic pain can be assessed using the scales above or other self-rating scales. The list of self-rating scales is extensive (*e.g.*, Profile of Mood States, Hopkins

Symptom Checklist-HSCL and Zung Self-Rating Scale).

Treatment Options—and Challenges

As discussed in last month's column, antidepressants and anticonvulsants are frequently used to treat neuropathic pain. Since they are also used to treat a wide variety of psychiatric disorders, the neurologist can optimize treatment regimens and hopefully minimize patient exposure to drugs with undesirable side effects by prescribing agents that treat multiple components of the patient's conditions.

Antidepressants have not only been used for affective and anxiety disorders, but certainly there are numerous reports which have confirmed their usefulness in reducing neuropathic pain symptoms. Thus, their potential utility in this setting is possibly significant. Since antidepressants have been used successfully to treat both neuropathic pain and depression, some investigators have suggested there may be similarities in the underlying mechanisms of these conditions.

The effect of treatment with the SNRI duloxetine on depression and pain has been investigated in an eight-week study. Depressed patients treated with duloxetine demonstrated significantly greater improvement from baseline in HAM-D scores than patients treated with 20mg per day of the SSRI agent paroxetine. Compared with placebo, patients treated with duloxetine also experienced a significantly greater improvement in overall pain severity related to somatic symptoms as measured on the 100-mm Visual Analog Scale; the difference in pain reduction was not significant for paroxetine versus placebo. As noted last month, certain antidepressants may disrupt sleep, so you must remember this when planning treatment for the patient with both sleep and psychiatric comorbidities and chronic pain.

Of those anticonvulsants with demonstrated efficacy in the treatment of neuropathic pain, carbamazepine, gabapentin and pregabalin have been studied in psy-

chiatric indications. Carbamazepine, an agent chemically related to the TCAs, is also occasionally used to treat depression. However, it is associated with the potential for rare blood dyscrasias and altered liver function tests and patients need to be monitored for such. Gabapentin has been reported to be effective in treating anxiety, and pregabalin has demonstrated efficacy in the treatment of GAD in two double-blind, placebo-controlled studies. In a study of 276 patients diagnosed with GAD, pregabalin 600mg per day significantly improved HAM-A scores compared with placebo and was as effective as the active comparator, lorazepam 6mg per day. Similar results were reported in a four-week study involving 271 patients with GAD: pregabalin 600mg per day achieved significantly greater reductions in HAM-A scores compared with placebo and similar reductions to active comparator lorazepam.

The effect of pregabalin on mood has also been noted in patients suffering from neuropathic pain. In a study involving 146 patients with DPN, patients treated with pregabalin tended to have more favorable changes in their Profile of Mood State scores than patients who received placebo, with significantly better changes in score for Tension-Anxiety and Total Mood Disturbance. Similarly, patients with PHN treated with pregabalin (n=157) in another study had greater improvement than placebo (n=81) on the Zung Self-Rating Depression Scale.

What may be the role of combination therapy? Many patients with neuropathic pain continue to suffer despite several monotherapy trials with different agents. In these instances, combination therapy may be beneficial. However, because there has been a dearth of studies investigating combination therapy in neuropathic pain, decisions about which agents to combine are usually based on the theoretical belief that there may be synergy between agents with differing mechanisms of action. Of course, the possibility of increased side

effects and drug-drug interactions must also be taken into consideration. The results of a recently published and widely cited study have provided some guidance in this area. The combination of gabapentin and morphine in 57 patients with DPN or PHN achieved a better reduction in pain score than either agent used as monotherapy.

Conclusions

Neuropathic pain is often associated with sleep disturbances and anxiety/depressive disorders that can greatly affect quality of life, negatively impact treatment outcome, and increase morbidity and mortality. A thorough assessment to identify the pain condition *and* all comorbidities will enable a treatment strategy that addresses all aspects of the patient's condition. This can be done using both clinician-led structured interviews and self-rated psychometric instruments. Currently available treatment options include a variety of antidepressants (*e.g.*, TCAs, SNRIs) and anticonvulsants (*e.g.*, carbamazepine, gabapentin and pregabalin) that have demonstrated efficacy in alleviating neuropathic pain and, in some cases, improving sleep and/or mood disturbances.

Treatment should be customized for each individual based on patient-related factors as well as drug-related factors such as efficacy in relieving pain, activity in sleep and mood disturbances, and safety profile. Treatment can be optimized and potential adverse events minimized by the use of agents that treat the neuropathic pain state as well as one or more comorbid conditions. Further research is needed to fully elucidate the dynamic interrelationships among neuropathic pain, sleep disturbance and psychiatric disorders and to further identify safe and effective combination therapies. **PN**



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