Carbamazepine in Bipolar Disorder With Pain: Reviewing Treatment Guidelines

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ABSTRACT

Objective: To determine if any monotherapy drug treatment has robust efficacy to treat comorbid bipolar disorder and chronic pain.

Data Sources: The American Psychiatric Association (APA) treatment guidelines for bipolar mood disorder and the 2012 Cochrane database for pain disorders.

Study Selection: We relied on the treatment guides to determine if the drugs that are APA guideline–supported to treat bipolar disorder have supporting data from the Cochrane database for chronic pain.

Data Synthesis: No single drug was mentioned by either guideline to treat this comorbidity. However, carbamazepine was the only drug that has guideline-supported robust efficacy in the management of each condition separately.

Conclusions: Carbamazepine was found to have strong preclinical data for the treatment of comorbid bipolar mood disorder and chronic pain disorders. While requiring more studies in this population, we propose that this treatment modality may benefit patients.

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The prevalence of chronic pain in patients with bipolar disorder has been reported to be 51.2%.[1] Both conditions carry an increased risk of morbidity and mortality, as well as a substantial cost burden. Women and older patients have higher rates of this comorbidity.[1,2] Veterans with bipolar disorder are twice as likely to suffer from chronic pain relative to patients without bipolar disorder.[3] A primary care study (N = 740) found that almost half of the patients with bipolar disorder endorsed either current treatment for a pain condition or had regular pain interfering with daily function.[4] Although several antidepressants have an established role in the treatment of pain disorders, current guidelines discourage the use of antidepressant medications in the management of any phase of bipolar mood disorder.[5–7]

METHOD

The American Psychiatric Association (APA) treatment guidelines for bipolar mood disorder[8,9] and the 2012 Cochrane database for pain disorders were reviewed. We relied on the treatment guides to determine if the drugs that are APA guideline–supported to treat bipolar disorder have supporting data from the Cochrane database for chronic pain.

No single drug was mentioned by either guideline to treat this comorbidity. However, carbamazepine was the only drug that has guideline-supported robust efficacy in the management of each condition separately.

We begin the discussion by reviewing what is known about bipolar disorder and comorbid chronic pain, and then introduce carbamazepine's history and discuss some treatment options for chronic pain and bipolar disorder. Finally, we discuss issues of obesity and polypharmacy in this population and explain how carbamazepine has unique properties that bolster its place in the management of this comorbidity.

BIPOLAR DISORDER AND CHRONIC PAIN

Treating a bipolar patient with medications that are intended for the treatment of chronic pain with unipolar depression or anxiety may result in iatrogenic complications of manic switching. High doses of antidepressants are implicated in the development of mood cycle induction, manic switching, and worsening of future depressive episodes.[7,10] Serotonin reuptake inhibitors and bupropion may have lower rates of manic switch than tricyclic antidepressants and norepinephrine-serotonin reuptake inhibitors. The frequency and severity of antidepressant-associated mood elevations appear to be greater in bipolar I disorder than in bipolar II disorder. Hence, in bipolar I patients, antidepressants should be prescribed only as an adjunct to mood-stabilizing medications.[6,7] This recommendation may exclude the safe use of commonly prescribed medications such as duloxetine, venlafaxine, and amitriptyline in chronic pain patients. In addition, cyclobenzaprine, milnacipran, and tramadol have been reported as potentially problematic with regard to iatrogenic manic switching.[11–14] The efficacy and safety of these drugs in bipolar patients are currently not well established. If a patient under antidepressant treatment does develop manic switching, the *DSM-5* requires the clinician to assign the diagnosis of bipolar disorder.[15] In addition, bipolar mood

Clinical Points

- About 50% of patients with bipolar disorder also suffer from a pain disorder. This comorbidity has a high rate of morbidity and mortality.
- Many drugs used to treat pain disorders can cause manic switching and weight gain and may contribute to polypharmacy.
- Carbamazepine is the only American Psychiatric Association guideline–supported mood stabilizer with robust efficacy in chronic pain.

disorder is often misdiagnosed as unipolar depression or as an anxiety disorder.[10] The pharmacologic treatment of unipolar depression and neuropathic pain has more data and treatment choices, such as duloxetine and tricyclic antidepressants.[5,16] Such data and approved drugs do not currently exist for the treatment of chronic pain in bipolar patients.

A difference in pain analgesia ratings to unpleasant stimuli has also been reported among unipolar, bipolar depressed, and bipolar manic patients. Bipolar patients showed increased pain insensitivity compared to unipolar depressed patients, and the authors speculated that a different mechanism accounts for these differences.[17] Neuroimaging studies have found significant reductions in the bilateral thalamus, hippocampus, and amygdala in patients diagnosed with bipolar disorder. A decrease in subcortical volumes was found throughout the brain in patients with bipolar disorder.[18] Functional magnetic resonance imaging studies during painful stimulation in depressed versus control groups have found increased activation in the amygdala, as well as the prefrontal and right thalamic areas. Decreased activation in periaqueductal gray matter and the rostral anterior cingulate and prefrontal cortices was also found.[19,20] Although these studies examined each of these diagnoses separately, no studies have been done in patients with comorbid conditions. Therefore, no valid conclusions can be drawn from these studies at this time.

CARBAMAZEPINE: A PAIN-RELIEVING TRICYCLIC

Carbamazepine is an iminostilbene derivative that is related chemically to tricyclic antidepressants and is structurally similar to phenytoin. Carbamazepine differs only slightly from the antidepressants imipramine and amitriptyline, in which the azepine ring is replaced by a cycloheptanone ring.[21] This structure may explain the efficacy of carbamazepine in pain and seizure treatment, as well as reports of its possible antidepressant properties.[10,22] Tricyclic side effects such as atrioventricular heart block, including second- and third-degree block, have been reported following carbamazepine treatment. The drug is mildly anticholinergic. Overdoses of carbamazepine and tricyclic antidepressants are treated similarly.[21–23]

ANTICONVULSANTS IN PAIN MANAGEMENT

Chronic pain responds to varying degrees with traditional analgesics and anti-inflammatory agents. However, anticonvulsants, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors are established therapies for neuropathic pain.[24] Carbamazepine, oxcarbazepine, gabapentin, and pregabalin have shown efficacy in randomized, double-blind, placebo-controlled trials of neuropathic pain.[25,26] Lamotrigine has weak findings and requires slow titration.[25,26]

Originating with treatment for trigeminal neuralgia in 1962,[25] carbamazepine has consistently shown robust efficacy (multiple trials over the past 30 years) for management of various pain conditions. Multiple randomized, placebo-controlled clinical trials have shown efficacy of carbamazepine in neuropathic pain and in diabetic neuropathy.[25–27] A 2012 Cochrane review examining the evidence for carbamazepine in chronic pain concluded that it provides pain relief for chronic neuropathic pain conditions such as trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia, and central poststroke pain.[28] Table 1 compares the various treatment options and efficacy data. Only carbamazepine has robust efficacy data in the management of concurrent acute mania and chronic neuropathic pain.

There are numerous practical problems that discourage studies in the chronic pain population. Possible reasons for this may include cost, ethical risks, time required, and validation of the techniques used.[28] Other drugs such as oxcarbazepine (a keto analog of carbamazepine) and pregabalin may be useful adjuvants in bipolar disorder. Pregabalin is helpful in neuropathic pain.[8,24,26] Gabapentin may be helpful for neuropathic pain, but was not efficacious in any phase of bipolar disorder.[26,30,31] Topical drugs such as lidocaine patch or cream and other analgesics can also be useful.[27]

CARBAMAZEPINE AND BIPOLAR TREATMENT

Carbamazepine has almost 3 decades of accepted therapy either alone or in combination with other mood stabilizers. Carbamazepine has been studied in at least 20 controlled trials for the treatment of mania and has a pooled response rate of 52%.[29] Carbamazepine has been found to have comparable efficacy to lithium and also has significant data and APA guideline support for its use in maintenance therapy.[29,32] Although carbamazepine is not indicated for depression, a few small positive studies of carbamazepine have been conducted in depressed patients.[22]

Medications with the strongest evidence for efficacy for acute treatment of depression in patients with bipolar I disorder are olanzapine-fluoxetine combination, quetiapine, and lurasidone. Lithium and lamotrigine are also useful agents in the treatment of bipolar depression.[6,7,10] It is unknown whether the additional burden of chronic pain would support the use of any particular strategy as a first-line therapy.

Complex polypharmacy is commonly seen in patients treated for bipolar mood disorder. However, in 1 study,[33] polypharmacy was least often present in bipolar patients treated with lithium, valproate, or carbamazepine and most often associated with atypical antipsychotics or antidepressants.

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Table 1. Comparison of Various Treatment Modalities in Chronic Pain and Bipolar Disorder

Drug	Efficacy Supported by APA Bipolar Disorder Guidelines	Efficacy in Neuropathic Chronic Pain (Cochrane Database)	Weight Gain Potential	Other Potential Issues
Lithium	Yes	None	Moderate	May interact with NSAIDS
Valproate	Yes	Low to none	Moderate	Approved for migraine headache use
Carbamazepine	Yes	Robust	Low	High drug interaction potential
Lamotrigine	Yes	Low to none	Low	Slow titration
Second-generation antipsychotics	Yes	Low to none	Low to high	Metabolic issues
SNRI and tricyclic antidepressants	Avoidance advised	Robust	Low	Destabilizing effects in bipolar disorder
Gabapentin and pregabalin	Weak to none, adjunctive use only	Robust	Low	Low side effect profile

Abbreviations: APA = American Psychiatric Association, NSAID = nonsteroidal anti-inflammatory drug, SNRI = serotonin-norepinephrine reuptake inhibitor.

OBESITY: A PROBLEMATIC CONFOUNDING DISEASE

Patients with bipolar disorder are at greater risk than the general population for being overweight and obese. Correlations have been found with the number of depressive episodes; treatment with medications associated with weight gain, alone or in combination; and low rates of exercise.[34]

Obesity is associated with increased pain and reduced benefit from pain treatments. Obesity causes mechanical joint compression and body alignment changes that can lead to worsening pain. Obesity is also associated with an increased risk of many complications including heart disease, cancer, depression, sleep apnea, and spine, neck, and upper extremity pain, as well as fibromyalgia, migraine, and headaches. The rates of early retirement and disability and risks of requiring surgical treatment are several times higher among people who are overweight or obese.[34,35] Table 1 helps analyze the benefits and risks of pharmacotherapy in bipolar disorder patients with chronic pain.[10,26,29,30,32,36] Carbamazepine has one of the least propensities to cause weight gain.

CARBAMAZEPINE RISKS AND MONITORING

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported with carbamazepine treatment.[37] The risk in some Asian populations with the *HLA-B*1502* gene is estimated to be about 10 times higher.[37] Appropriate genetic testing should be done prior to treatment in such populations. Carbamazepine should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. Known sensitivity to one anticonvulsant may increase the risk of serious rash with another anticonvulsant. Diplopia and ataxia are the most common side effects.

Carbamazepine is a known teratogen, and women of childbearing potential should be advised of this. Hormonal contraceptives and other drugs can become less effective due to accelerated hepatic metabolism, requiring alternatives. Carbamazepine and its metabolite are also present in breast milk. Since older women with bipolar disorder and comorbid chronic pain were more prevalent in the epidemiologic studies, this issue may be less relevant in this population.[1,2]

Hematologic, electrocardiographic, and other laboratory monitoring is recommended to identify potential side effects such as agranulocytosis, hyponatremia, and hepatic or renal issues.[8,37] The generally accepted therapeutic range of total carbamazepine is 4–12 μg/mL.

CONCLUSION

The assessment of chronic pain patients with mood disorders requires a careful and comprehensive approach. Remarkably, few pain-related themes are currently included in psychiatric training programs.[38] Appropriate screening tools and collateral information provide valuable clues regarding a patient's physical illness, mood symptoms, maladaptive behaviors, life encounters, and personality dimensions. Psychotherapy is also an essential part of treating bipolar illness, with a focus on close monitoring of symptoms and involving family in care.[39]

Chronic neuropathic pain with bipolar disorder is a frequently encountered complex comorbidity with no established treatment guidelines. The risks of drug-induced manic switching, prescription drug dependence, polypharmacy, and weight gain complicate the treatment choices for this population. Although further studies are needed, we propose that robust preclinical guideline-supported data and beneficence make carbamazepine an important drug in the treatment of this population.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetro, and others), cyclobenzaprine (Amrix), duloxetine (Cymbalta), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lidocaine (Xylocaine and others), lithium (Lithobid and others), lurasidone (Latuda), milnacipran (Savella), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), phenytoin (Dilantin, Phenytek, and others), pregabalin (Lyrica), quetiapine (Seroquel), tramadol (Ultram, Ryzolt, and others), venlafaxine (Effexor and others).

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