Valproate in Bipolar Disorder: Case Examples From a Family Practice

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Valproate, an antiepileptic drug, is useful in the management of various nonepileptic disorders. It is an effective and generally well-tolerated medication for the treatment of bipolar disorder and has been approved by the Food and Drug Administration for use in manic states. Studies also suggest that it is effective in other bipolar spectrum illnesses. This report describes 2 clinical cases of DSM-IV bipolar disorder where valproate provided robust, sustained relief of mood symptoms. In the first case, valproate was chosen for initial therapy in a bipolar patient suffering from a mixture of hypomanic and depressive symptoms. In the second case, valproate replaced lithium in the management of a patient with an incomplete response to lithium plus an antidepressant. This report addresses relevant clinical issues and includes a brief review of the clinical pharmacology of valproate.

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Valproate is an antiepileptic drug that has been used for years in the treatment of generalized tonic-clonic and absence seizures. Beginning with reports from Lambert et al.[1] in France during the 1960s, valproate has been noted for its thymoleptic (mood-stabilizing) properties.[2] In numerous studies, both open and controlled, it has proved effective and well tolerated. McElroy and colleagues[3,4] document its utility in those with rapid cycling bipolar states—a particularly difficult group to treat. Bowden et al.[5] published a placebo-controlled comparison of lithium and valproate in manic patients. In that study, valproate was particularly helpful in patients with dysphoric or mixed depressive and manic symptoms—patients in whom lithium proved less useful. The Food and Drug Administration has recently approved valproate for the treatment of acute mania.

The treatment of mania in bipolar disorder has been reviewed recently in family practice literature.[6] Rather than duplicate that material here, the objectives are to familiarize readers with the clinical usefulness of valproate through representative case examples and to highlight some practical aspects of valproate use in the treatment of bipolar disorder.

CASE 1

A 24-year-old woman presented with nervousness, headache, and insomnia. She experienced periods of sadness, often unexplained, as well as difficulty controlling her temper and dealing with stressful situations. Her sadness would occasionally last as long as a week and, when present, was intense, occurring all day every day, but she reported that she would then "bounce back" to her usual self. At times, her sadness would be accompanied by a restless energy and irritability that precipitated arguments with her husband and his ex-wife, among others. These periods of restless and boundless energy would then switch abruptly back to a state of intense, depressed mood. When depressed, she would sleep excessively and tended to overeat. She would isolate herself, let the housework go, and found it hard to get things done. She was also particularly sensitive to feelings of rejection by others, but her mood could be temporarily brightened, if she were occupied by activities she enjoyed.

The patient had a 9-month-old child (her first) and a 1-year marriage to a law enforcement officer (her first; his third). Her husband's second wife and a child from that marriage lived nearby. Her relationship with his ex-wife was problematic, but she had tried to be helpful and friendly in spite of the expected difficulties. She described her husband as a "control freak" who spent too much time with his buddies and helped little with parenting. A prenuptial agreement provided that their house stay in his possession if the marriage ended for any reason.

The patient smoked 2 or 3 packs of cigarettes per day, drank no alcohol, and never used marijuana, cocaine, or other illicit substances. She drank 4 caffeinated soft drinks per day. She took birth control pills and had been generally healthy except for migraine headaches without aura. She had been moderately successful at treating the headaches with ibuprofen and rest. Her pregnancy and delivery were uncomplicated, but her headaches had been increasing in frequency and duration since giving birth. Only since the delivery of the child had she been experiencing these brief, but intense, periods of depressed mood. She described herself before this time as cheerful and outgoing, and she had sought no prior treatment for mood or anxiety problems. By contrast, many of her relatives experienced anxiety and/or depression. Her paternal grandfather was diagnosed with manic depression and hospitalized in a state mental health facility on 1 occasion.

Several other male relatives abused alcohol or cocaine. Her father was an alcoholic. She described him as mercurial and impulsive, prone to outbursts and violent behaviors even during extended periods of sobriety.

At the initial interview, the patient was animated and dramatic. Her response to the first question—"What brings you here to see us today?"—lasted 7 minutes without interruption. She switched topics a number of times, and her speech was moderately pressured. She was affectively labile, alternately laughing and crying. Her mood contained elements of depression and hypomania. She related frenzied activity into the early morning hours that was often accompanied by talking with friends on the phone and planning social outings. She would then rest for 3 or 4 hours and awaken with the same pressured desire to "get things done." During the day, however, she was often tearful and irritable. Her judgment was not seriously impaired, and beyond arguments with her husband and his ex-wife, she was not involved in any self-damaging activities. There were no impairments in reality testing.

The patient was diagnosed with DSM-IV bipolar disorder not otherwise specified (hypomania without a history of major depressive disorder or a manic episode). She was placed on divalproex sodium, and the dosage was titrated to 750 mg/day in divided doses over 10 days. She noticed a normalization of her sleep pattern and cessation of her headaches after only 7 days. She felt much less irritable and more emotionally resilient. This improvement continued over the next 4 weeks, and her brief, depressed moods disappeared. Her serum valproate level was 53 µg/mL. After her mood stabilized, she focused attention on her problematic psychosocial situation with the help of a licensed clinical social worker.

Two months into treatment, the patient briefly discontinued the valproate complaining of a 12-lb (5.4-kg) weight gain. She had always lived in fear of becoming overweight, a condition that plagued many of her family members. Moodwise, she had been doing quite well. She felt that medication might no longer be needed. We discussed her concerns, focusing on the biopsychosocial nature of the illness. She considered the options of discontinuing the medication entirely or switching to lithium or carbamazepine. At this point, her marital stresses had lessened significantly, and she was resolute and confident that her planned divorce was the best option, since she was financially secure and had the support of her family. After weighing the risk of symptom reoccurrence and the effect that might have on her job and impending legal issues, she decided to make lifestyle changes (diet and exercise) and stay on valproate therapy.

CASE 2

A 30-year-old woman first presented with depression at age 26. She described more than 4 years of almost constant depressed mood, although she experienced her first episode of major depression at age 14. Her depression was characterized by sadness lasting most of the day, crying spells, severe irritability, hypersomnia with some periods of insomnia, anergia, severe inappropriate guilt feelings, and absent libido. She was referred by her mother, who had been treated recently with an antidepressant and was recovering from a similar condition. A maternal aunt had also suffered from depression. The patient's maternal grandmother was a diagnosed manic depressive who had committed suicide in the 1960s.

The patient described periods of high energy when her "mind ran away," and her mood was irritable with a decreased need for sleep. Initially, she stated that these times would last 1 or 2 days at the most. Her family would avoid confrontations with her during those periods of energy and activity.

The patient was initially diagnosed as suffering from dysthymic disorder with major depression (double depression). A bipolar illness was suspected based on family history and her 1- or 2-day bursts of energy and activity. Further history from family members confirmed that she had experienced expanded mood states lasting up to a week that met the DSM-IV criteria for hypomanic episodes. Her diagnosis was changed to bipolar II disorder. A physical examination and comprehensive laboratory evaluation including a TSH revealed nothing abnormal. She was placed on a regimen of bupropion, and the dose was increased to 300 mg/day. Her mood improved in a general way with less irritability, more energy, and less sadness. She continued to have rather pronounced premenstrual worsening of her mood, however, that did not respond to an increase in the dose of bupropion. In the meantime, her mother's physician added lithium to her medical regimen of fluoxetine with robust and stable augmentation. The patient also elected to begin lithium after a discussion of the rationale behind lithium augmentation focusing on the various uses of lithium, her family history, and her mother's response to the drug.

Lithium improved the quality of the patient's response to the bupropion by eliminating the premenstrual worsening of mood and fully normalizing her sleep pattern. Her serum lithium level was 0.5 mEq/L. For 4 years, this combination of bupropion and lithium provided robust and stable relief of her depressive illness. She then began to experience brief (2–3 day) depressions that worsened in intensity and duration. Lithium-induced hypothyroidism was considered as a cause of her reoccurrence. However, her TSH level was normal and unchanged over baseline. She had no signs or symptoms of other illnesses. An increase in the bupropion dose produced tremor, agitation, and no improvement in her depression symptoms. The lithium dose was then increased to achieve a serum level of 0.7 mEq/L. This improved her depression, but resulted in an unacceptable level of somnolence, tremor, and mild

ataxia. Lithium was then replaced with valproate with the dose titrated to 1000 mg/day. Her robust, stable antidepressant response returned without side effects beyond mild weight gain, for which regular exercise was prescribed. Her serum valproate level was 68 μg/mL.

REVIEW OF VALPROATE PHARMACOLOGY

Valproate is best tolerated in the divalproex sodium form. Dosages required vary from patient to patient, but in adults, the usual range is 750–2000 mg (10–20 mg/kg of body weight) per day in divided doses. In acute mania, loading doses of 20 mg/kg can be used, and clinical experience supports the use of valproate beginning at or near the expected dose based on weight or rapid upward titration if valproate is begun at lower doses. Valproate seems to be effective at serum levels comparable to those needed in the treatment of epilepsy (45–100 or 125 μg/mL). Serum levels of valproate can be measured every several days, if needed, owing to its 8- to 17-hour half-life.

Side effects of valproate are principally gastrointestinal in nature and dose-related. Nausea, vomiting, diarrhea, bloating, and cramping may be seen. These symptoms may be minimized by administration with food. Reversible elevations in hepatic transaminases may occur. Valproate may cause tremor, sedation, and ataxia. Weight gain may be seen. Hair loss or change in hair texture may occur, and dietary supplementation with zinc and/or selenium has been suggested to minimize these hair changes. However, reports of the efficacy of zinc and selenium must be considered anecdotal.

More serious, but uncommon, side effects of valproate include reversible thrombocytopenia, platelet dysfunction, and coagulopathy. In addition, pancreatitis may occur in 0.5% to 1.0% of patients.[3] Valproate administration in children on multiple antiepileptic drugs has been associated with hepatic failure and death. No adults have suffered from hepatic failure associated with valproate as a single agent antiepileptic agent.

In clinical comparisons, valproate was found to be similar to lithium in its ability to treat mania, but valproate was superior to lithium when manic states also contained significant depression, even in mild degrees.[7] Mania coexisting with depression defines a mixed state, present in 30% to 50% of manic episodes. The use of valproate in hypomanic states is less well studied. Open investigations and clinical reports suggest it is useful in these conditions as well.[8]

CASE DISCUSSION

In the first case, valproate was chosen over lithium owing to the mixed features of the patient's hypomania. Although the symptoms did not meet formal criteria for a mixed episode, the presence of clear-cut depression symptoms mingled with hypomania was felt to be clinically significant and suggested that valproate was an appropriate first choice. The weight gain experienced by the patient is not uncommon. Once stable in her mood, the patient began to address her problematic marriage in assertive ways.

In the second case, the decision to use valproate was more pragmatic. Once historical investigation identified more prolonged periods of expanded mood, the patient could be formally diagnosed with bipolar II disorder. The etiology of her clinical deterioration was not clear, but the diagnosis and clinical course of the illness itself mandated that a thymoleptic medication be used. Valproate was 1 of 3 medications indicated for the condition. It was chosen over carbamazepine to avoid tricyclic-like side effects and the clinical difficulties entailed by the autoinduction of hepatic metabolism by carbamazepine.[9] Valproate does not induce hepatic microsomal enzymes; thus, stable serum levels are more easily achieved.

In both cases, valproate was an appropriate choice based on clinical presentation, family pedigree, treatment response, and longitudinal course of illness. Both patients achieved robust, sustained relief of their symptoms.

SUMMARY

Valproate is an effective medication for the treatment of mood disorders. It has been approved recently for use in acute mania. The scientific literature supports its use in manic and nonmanic subtypes of bipolar illness. Family physicians can use valproate effectively in selected patients suffering from these conditions. Consultation is appropriate for diagnostic dilemmas and refractory illness and when a patient is deemed a danger to self or others.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), divalproex sodium (Depakote), fluoxetine (Prozac), ibuprofen (Motrin and others), lithium (Eskalith and others).

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