The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Tryptophan for refractory bipolar spectrum disorder and sleep-phase delay

A 45-year-old woman who worked in an office was first seen in our clinic in 2000 at the age of 36. She received a diagnosis of major depressive disorder with atypical features and had one suspected prior hypomanic episode. Subsequent trials of nefazodone and later venlafaxine were moderately effective in controlling her depressive symptoms. However, at age 40, she had another hypomanic or manic episode, during which she made 2 impulsive trips to gamble and accrued at least $10 000 in debt through impulsive spending, excessive drinking and online gambling at night. She did not report an increase in socialization or sexual activity during these episodes.

Divalproex was added as a mood stabilizer, and venlafaxine was replaced with risperidone; however, the latter drug was poorly tolerated. Owing to a recurrence of her depressive symptoms, venlafaxine (75 mg daily) was added for about 6 months. At that time, it became more apparent that a longstanding sleep-phase delay of several hours was a major concern. Although her employer tolerated her pattern of arriving after 11:00 am each day, this caused ongoing stress and conflict with her direct supervisor and fellow workers. Because the sleep disturbance was initially viewed as a residual symptom of bipolar depression, venlafaxine was stopped, and a trial of lamotrigine was undertaken but had no clear benefit.

The patient noticed a dramatic improvement in her sleep-phase delay during a 2-week work assignment in Mexico, but this ended with her return home. A sleep study obtained in February 2006 confirmed the phase-delay in her sleep. Over the next 15 months trials of zopiclone and light therapy were ineffective in altering her sleep–wake cycle or improving her mood. Divalproex was discontinued because of concern about alopecia and lack of efficacy.

A trial of L-tryptophan, starting at a dose of 1 g in the evening was begun in June 2007, and withing 3 weeks she began to report an improvement in her ability to get to sleep and wake on time in the morning. Over a few more weeks, the dosage was increased to 3.5 g daily combined with over-the-counter pyridoxine to limit the build-up of potentially toxic metabolites of tryptophan. After about 10 weeks of treatment, she began to consistently arrive at work at 9 am, and her depressive symptoms cleared.

Two years after L-tryptophan was initiated, she continued to show a normal sleep–wake pattern and remained free of depressive and hypomanic symptoms. She was taking no prescribed medications except L-tryptophan and pyridoxine.

This case illustrates how sleep disturbances can be important and underappreciated contributors to the burden of illness for patients with mood disorders. In this patient, a sleep-phase delay was the most disabling feature, and treatment of this symptom was associated with a major improvement in her overall functioning and well-being.

Animal studies have demonstrated that tryptophan is able to shift circadian rhythms in various contexts.[1,2] In humans, tryptophan has been shown to reduce sleep-onset latency while increasing subjective sleepiness.[3,4] Tryptophan has also shown success in the treatment of seasonal affective disorder,[5] which is characterized by hypersomnia and a delayed circadian phase in many cases. These studies suggest that a chronobiological mechanism is most likely to explain the marked improvement in overall functioning experienced by this patient. Whereas there is not yet systematic evidence for the efficacy of tryptophan and other phase-shifting strategies, they deserve consideration in patients with otherwise refractory bipolar disorder.

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