Chronic Sleep Disruption and the Reexperiencing Cluster of Posttraumatic Stress Disorder Symptoms Are Improved by Olanzapine: Brief Review of the Literature and a Case-Based Series

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Background: Posttraumatic stress disorder (PTSD) is one of the most prevalent psychiatric disorders in young adults. Early diagnosis and treatment of PTSD are essential to avoid possible long-term neuropsychiatric changes in brain physiology and function. A cardinal symptom of PTSD is chronic sleep disruption, often with recurring nightmares. If untreated, PTSD symptoms often contribute to substance abuse and the development of other comorbid psychiatric disorders. Once PTSD is diagnosed, drug treatment should begin with antidepressant therapy. If antidepressants do not correct the sleep disruption, adjunctive treatment with the atypical antipsychotic olanzapine or other agents should be considered.

Method: This case series reviews 7 cases of patients with PTSD (DSM-IV criteria) seen in primary care clinics who were successfully treated with olanzapine. In most cases, olanzapine therapy was adjunctive and followed failed treatment with antidepressant monotherapy for sleep disturbances.

Results: All patients reported improved sleep with decreased or absent nightmares, as well as improvements in other PTSD symptom clusters.

Conclusion: Further controlled studies are needed to better characterize and validate this therapeutic indication.

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Posttraumatic stress disorder (PTSD) is a serious anxiety disorder with a lifetime prevalence of 5.0% to 13.8%.[1] Most people will experience or be exposed to a traumatic event at some point in their life, with 15% to 24% developing PTSD. This connotes to about 1 in 12 adults being affected by PTSD during their lifespan and makes the disorder one of the most prevalent psychiatric disorders in young adults, after depression, phobia, and alcohol and substance abuse.[1] A cardinal symptom of PTSD that should alert the clinician is the complaint of chronic sleep disruption. On further questioning about the onset of this problem, some PTSD patients may provide vivid descriptions of recurring nightmares about a precipitating traumatic event. Others may not remember specific nightmares replaying the event, but will complain that they cannot remember the last time they experienced a restful night's sleep. If patients of this type can identify an abrupt onset of their sleep disturbance, then the clinician should try to identify a precipitating event and consider a more in-depth diagnostic workup for PTSD.

In light of the recent attacks on the World Trade Center, clinicians will need to be more aware of PTSD symptoms and treatment. A follow-up survey of Manhattan, N.Y., residents 5 to 8 weeks after Sept. 11, 2001, indicated a prevalence of symptoms consistent with the diagnoses of PTSD and depression that was more than twice the accepted baseline values for this population.[2]

DIAGNOSIS

PTSD is characterized by 3 core symptom clusters[3,4]:

1. Reexperiencing: unwanted recollections of the event in the form of intrusive and distressing images, nightmares, flashbacks, or emotional and physical distress at exposure to reminders (triggers) of the event. Reexperiencing the trauma in the form of chronic nightmares often leads to chronic sleep disruption, which may further predispose the patient to cognitive dysfunction.
2. Avoidance: attempts to avoid reminders associated with the experience, together with diminished

responsiveness to the external world (psychic numbing).
3. Hyperarousal: physiologic manifestations of the disorder that may occur persistently and that are manifested as insomnia, irritability, hypervigilance, increased startle response, and impaired concentration.

Diagnosis of PTSD is often complicated by a high degree of psychiatric comorbidity that may approach 80%.[5] Concurrent depression occurs in 30% to 50% of PTSD patients.[6] Other concomitant disorders commonly seen in PTSD include bipolar disorder, substance or alcohol abuse, and other anxiety disorders, notably, panic disorder and generalized anxiety disorder.[6]

PATHOGENESIS

If diagnosis and treatment are not initiated soon after the trauma, PTSD may persist for years with definite neuropsychiatric changes noted in brain physiology and function. Mid-adolescence is an age at which major structural changes occur naturally in the brain.[7] Trauma during this period of rapid brain change and growth may arrest development or produce a regression to an earlier stage of neural structure.[7] Adults diagnosed with PTSD typically demonstrate a reduction in the volume of the hippocampus as measured by magnetic resonance imaging, with associated memory deficits.[8,9] However, neuroimaging of children and adolescents with PTSD reported lower corpus callosum volume, greater cerebrospinal and ventricular fluid volumes, and lower overall cerebral volume, all results consistent with an underdeveloped or atrophied brain.[10]

Symptom provocation studies utilizing positron emission tomography scanning have demonstrated disrupted cerebral blood flow in brain areas associated with fear response.[4,8,11] Results to date point to increased reactivity of the amygdala and anterior paralimbic region to trauma-related stimuli, whereas activities of the anterior cingulate and orbitofrontal areas are decreased.[8] The amygdala and paralimbic areas are associated with processing negative emotions and the ensuing expression of autonomic arousal, whereas the anterior cingulate and associated medial frontal cortex are thought to play a role in the extinction of conditioned fear responses.[8] Thus, it appears that the brains of PTSD patients continue to overrespond to negative emotions with autonomic arousal, while lacking the stimulation of the medial prefrontal cortex to perform its compensatory role in the regulation of emotion.

Patients with PTSD have chronically low serum cortisol levels and high levels of corticotropin-releasing factor, indicative of major disruption of the hypothalamic-pituitary axis.[4,12] Current theory supports the hypothesis that the development of PTSD is facilitated by a failure to control the biological stress response at the time of the trauma, resulting in a cascade of alterations in brain functioning that lead to the core symptom complexes.[4] One consequence of these alterations appears to be higher circulating norepinephrine levels and an increased reactivity of adrenergic receptors.[4] These findings, plus the observation that thyroid levels may be increased in PTSD patients,[4] help to account for many of the somatic symptoms of PTSD.

MEDICATION TREATMENT OPTIONS

As our understanding of PTSD increases, it is apparent that early treatment and intervention are critical and that there is an urgent need for effective treatments that can control and reverse the potentially destructive pathophysiologic processes described above.[13] Treatment strategies to date have focused on the use of antidepressants combined with psychotherapy.[4,14] Antidepressants that have been shown in randomized trials to control at least some of the symptoms of PTSD include tricyclics, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs).[4] Antidepressants reported to control some PTSD symptoms in open-label trials include trazodone, nefazodone, venlafaxine, and mirtazapine.

Only sertraline and paroxetine have received U.S. Food and Drug Administration–approved indications for PTSD. The Expert Consensus Guidelines recommend switching to either nefazodone or venlafaxine if there is no response to an SSRI after an 8-week trial.[14] In addition, mood stabilizers have been shown in open-label trials to help control certain symptoms, to reduce irritability, and to improve impulse control. These drugs include lithium and valproate products, which demonstrate some efficacy against avoidance/numbing and arousal symptoms, and carbamazepine, which has been reported to reduce reexperiencing and arousal symptoms.[13] The Expert Consensus Guidelines also recommend adding divalproex to an SSRI if there is only partial response.[14] Preliminary reports with topiramate indicate rapid and effective reduction of reexperiencing symptoms associated with trauma-related nightmares or intrusive memories/flashbacks.[13] Similarly, the use of prazosin, a centrally acting α_1-antagonist, has been shown to reduce nightmares in up to 75% of combat veterans, usually the most unresponsive group of PTSD patients to most accepted treatments.[15]

CASE SERIES

In our practice, we have noted that not all patients have resolution of nightmares and sleep disruption when treated with SSRIs. In fact, sertraline actually failed to significantly separate from placebo on the reexperiencing

symptom cluster during pre-marketing trials.[16] On the basis of preliminary reports, its demonstrated efficacy for restoration of sleep architecture in bipolar and psychotic disorders, and its positive effects on cognition, olanzapine was tried as an adjunctive agent when SSRI treatments failed to reverse the reexperiencing symptom cluster or other symptom clusters.[17,18] To date, we have treated over 20 adolescent and adult outpatients meeting DSM-IV criteria for PTSD in this manner. Patients were between the ages of 17 and 46 years and were identified during visits with the primary author (J.H.S.) at 1 of 3 sites: a university counseling service, a rural health clinic, or a private practice, outpatient medical clinic. All psychiatric diagnoses were made according to DSM-IV criteria.

Patients were initially test-dosed with olanzapine, 1.25 mg p.o., given 12 hours before their usual awakening time. If tolerated, doses were titrated to a level that permitted 7 to 10 hours of sleep per night. Doses were decreased if daytime lethargy persisted. Patients were questioned at follow-up interview about nightmares, intrusive thoughts, and quality and duration of sleep. Final daily doses ranged from 2.5 to 15 mg, usually dosed 12 hours before the patient's usual awakening time.

In this article, we review in detail the medical histories of 7 patients from this sample and their responses to olanzapine and other adjunctive therapies. These 7 patients were chosen because the other patients had serious comorbidities that required concomitant use of other medications.

Case 1

Ms. A is a 44-year-old white woman who presented with a past history of trauma, depression, anxiety, and PTSD. She had been treated previously with paroxetine, 20 mg/day. After 2 weeks, she discontinued paroxetine due to distress over an increase in nightmares in which she relived the trauma in a symbolic manner. The intrusive thoughts and nightmares were based on a childhood assault and left her with a sense of helplessness. Her primary symptoms at intake were severe early, middle, and late insomnia. She reported sleeping no more than 45 minutes at a time and waking up from "weird and terrifying" dreams. In each situation, Ms. A felt "helpless and vulnerable." Her childhood was also complicated by her mother's auditory and visual hallucinations and frequent paranoid thinking, leading to unprovoked attacks with knives and other weapons. Her sister was diagnosed with bipolar disorder.

Ms. A was treated initially with sertraline, 25 mg/day, but discontinued it after she felt like she was "in a cloud of confusion." She was then placed on treatment with olanzapine, 2.5 mg/day, combined with outpatient counseling. On day 7 of treatment, she reported that her sleep had improved, with no nightmares or night terrors. Her depressive symptoms were improved, and her mood had stabilized. She felt positive about the decreased nightmares and improved sleep, reporting that her concentration was better when she slept soundly. She indicated that she was experiencing her first uninterrupted sleep in over 20 years.

On day 11 after starting olanzapine, the patient reported that she had no nightmares and was sleeping through the night. She reported only "a little bit of intrusive thoughts." She was still experiencing recall of some the events surrounding the trauma, but without physiologic reactivation symptoms or anxiety. She indicated that the improved sleep and mood stabilization were helping her to experience psychotherapy more effectively, because her recall of adverse events was improved without triggering reactivation symptoms. After 3 weeks of treatment, Ms. A indicated that she was feeling less avoidance and had started to schedule recreational and social time with her peers.

Case 2

Ms. B is a 19-year-old white woman with a diagnosis of bipolar disorder not otherwise specified (NOS) and PTSD. Her past history included 3 episodes of rape and 1 hospitalization for suicidal ideation. Ms. B reported previous treatment trials with paroxetine, quetiapine, and nefazodone, with minimal improvement in her PTSD symptoms.

After 12 days of therapy with olanzapine, 5 mg/day, she reported a 75% improvement in sleep and nearly complete resolution of nightmares replaying her episodes of abuse, although she still experienced some daytime intrusive thoughts. The emergence of panic attacks with obsessive-compulsive features resulted in the addition of sertraline, 25 mg/day, to her regimen.

On day 24, Ms. B demonstrated no further mood cycling, panic attacks, or symptoms of diffuse anxiety and reported feeling less aggressive due to the decrease in nightmares and intrusive thoughts. She stated that she felt "a lot better" and was better able to finish her goals and tasks. Due to concerns over weight gain and to further optimize sleep patterns, topiramate, 25 mg/day for 7 days, followed by an increase to 50 mg/day, was initiated on day 24. Both the sertraline and topiramate doses were eventually increased over the next 2 months, with excellent resolution of the nightmares, intrusive thoughts, and symptoms of anxiety and depression.

Over 3 months later (day 124), the patient was receiving a regimen of olanzapine, 5 mg/day; sertraline, 150 mg/day; and topiramate, 200 mg/day. She discontinued olanzapine due to weight gain concerns. Rapid-cycling hypomanic symptoms, panic attacks, and nightmares returned 1 to 2 weeks post-discontinuation, leading to major sleep disturbance. On day 132, lithium, 300 mg t.i.d., was started and titrated to a serum level of 0.7 mg/dL. By day 139, the patient's hypomania had diminished and she

had stabilized on a regimen of sertraline, 25 mg/day; lithium, 300 mg t.i.d.; and topiramate, 100 mg b.i.d. Several weeks later, Ms. B began reexperiencing nightmares when she accidentally met the perpetrator of her abuse. At that point, she elected to reinitiate olanzapine, 2.5 mg q.h.s., in her drug regimen. The patient reported that her nightmares had decreased significantly by day 4 of her second course of olanzapine therapy.

Case 3

Ms. C is a 30-year-old Native American woman who presented with depression with mood swings and full diagnostic criteria for PTSD, as well as a history of asthma, physical abuse resulting in multiple head injuries with loss of consciousness, and substance dependence, including seizures secondary to amphetamine abuse. She had a positive family history for bipolar disorder.

Initial treatment consisted of continuing venlafaxine, 300 mg/day; discontinuing trazodone for sleep; and adding olanzapine, 5 mg q.h.s. One week after starting olanzapine treatment, she experienced a seizure. She discontinued olanzapine after 5 weeks due to weight concerns, but continued venlafaxine.

A later electroencephalogram revealed paroxysmal abnormalities, most likely epileptiform and mild focal seizures, resulting in a diagnosis of partial seizure disorder (both focal and generalized) secondary to multiple head injuries. Ms. C was started on treatment with divalproex sodium, which was titrated to 500 mg b.i.d. Due to concerns over increased nausea on day 55 after discontinuation of olanzapine, the patient discontinued venlafaxine. She was then started on treatment with sertraline, 25 mg/day, with the dose being slowly increased over the next 2 months to 100 mg/day.

Eight months after discontinuation of olanzapine, she reported a more stable mood with the divalproex-sertraline combination, but was concerned about increasing nightmares and other PTSD symptoms related to her incidents of abuse. Continuing problems with nightmares and severe sleep disruption led to her restarting olanzapine, 2.5 mg q.h.s. One month later, Ms. C reported that her nightmares had resolved. Her mood was stable, with some residual depressed symptoms.

Case 4

Ms. D is a 22-year-old white woman who presented with a history of chronic nightmares and depression stemming from multiple episodes of sexual abuse. Ms. D met full criteria for PTSD and had been on treatment with venlafaxine extended release (XR), 375 mg/day, for over 2 years. In addition, she was receiving trazodone, 150 mg, at bedtime for sleep and had escalated the dose to 300 mg previously. Her nightmares and sleep disturbance continued despite medication compliance with venlafaxine XR and trazodone.

She was started on treatment with olanzapine, 2.5 mg q.h.s., and was tapered off trazodone during the first week of treatment. The patient's nightmares rapidly resolved over a period of 2 weeks, but then slowly returned. The patient's olanzapine dose was then increased to 5 mg q.h.s. on day 14. Two weeks later (day 28), her venlafaxine XR dose was decreased to 300 mg/day in response to mild hypertension. On day 35, Ms. D reported that olanzapine, 5 mg q.h.s., had stopped the nightmares, stating, "It is totally under control; I don't wake up with a sense of doom or terror." The patient was sleeping well and reported remembering traumatic events, but without activation or anxiety about them.

Case 5

Ms. E is a 31-year-old white woman who was sexually molested at 10 years of age. She had experienced distressing symptoms since the trauma and met full diagnostic criteria for PTSD. In addition to PTSD, her presenting symptoms included depression and early and middle insomnia. She had had previous trials with paroxetine, fluoxetine, bupropion, nefazodone, and sertraline. Ms. E reported that fluoxetine caused manic symptoms, that sertraline and paroxetine increased her anxiety, that bupropion did not alleviate her depression, and that nefazodone made her forgetful. She was taking trazodone at bedtime for sleep; gabapentin, 900 mg/day; and venlafaxine, 75 mg/day, at the time of the first interview. The patient reported that trazodone was not helping her insomnia. Her initial diagnoses included PTSD, alcohol abuse, and bipolar disorder NOS.

During the first week of treatment, trazodone was discontinued and the patient was started on treatment with olanzapine, 2.5 mg q.h.s., which was increased incrementally until she achieved adequate sleep with 10 mg q.h.s. She initially remained on treatment with gabapentin, but was tapered off this medication by the end of week 3. Over the next several weeks, Ms. E required 10 to 15 mg of olanzapine q.h.s. to maintain normal sleep without nightmares. By week 8, her mood had stabilized and her nightmares had resolved completely with olanzapine, 15 mg q.h.s., and venlafaxine, 75 mg/day.

Case 6

Mr. F is a 36-year-old white man who reported a history of depressed and irritable mood that had been present since childhood. At the first interview, the patient met DSM-IV criteria for PTSD, bipolar disorder NOS with current episode depressed, and developmental learning disorder. The patient was diagnosed with a developmental reading disorder via psychological testing in 1995. Mr. F had experienced multiple family traumas, physical and emotional neglect, and sexual abuse from family members. Current stressors included recent loss of a relationship with a female friend and academic problems.

Other symptoms noted at intake included early and middle insomnia that had lasted 2 years and was not responding to trazodone taken at bedtime, fatigue not relieved by rest, and nightmares and intrusive thoughts associated with childhood abuse and neglect. He complained of intermittent mood irritability with rapid and pressured speech and grandiose plans lasting a few hours. The irritability alternated with depression lasting 2 to 3 days. Mr. F reported no 2-month reprieve in symptoms during the last 2 years. He also complained of anhedonia and impaired concentration. He had been taking citalopram, 40 mg b.i.d., for 2 to 3 months and reported that it seemed to help his depression but not his nightmares or intrusive thoughts.

In the past, Mr. F had been treated unsuccessfully with thiothixene, diazepam, sertraline, paroxetine, and fluoxetine. Fluoxetine worsened his insomnia and made the patient "super-irritable." Sertraline at a dose of 200 mg/day for 1 year was judged "OK," helping with the patient's depression, but not nightmares.

Olanzapine was added to citalopram at an initial dose of 5 mg/day. This addition was associated with a 50% reduction in nightmares and intrusive thoughts during the first week of treatment. A further dose increase to 7.5 mg/day by week 5 of treatment led to resolution of nightmares and intrusive thoughts.

Case 7

Ms. G is a 29-year-old African American woman with a history of repeated rape and abuse that occurred in her own home, beginning at 5 years of age. She met full criteria for PTSD, presenting with complaints of recurrent nightmares, intrusive thoughts, and disrupted sleep that averaged 4 hours or less per night. She indicated that even returning to her current residence after school precipitated her PTSD symptoms. The case was further complicated by the death of a surrogate parent the day of her initial interview. She was receiving no medications at the time of intake.

Ms. G was started on treatment with olanzapine, 2.5 mg 12 hours before awakening, and reported complete resolution of nightmares at follow-up on day 7. Her sleep that week improved to 8.5 hours per night. During her third visit (day 24), she indicated that her nightmares had not returned. Because of a family history of diabetes and concerns over carbohydrate craving and recent weight gain, topiramate, 25 mg p.o. t.i.d., 1 to 2 hours before meals was added to the patient's regimen on day 24. At the next clinic visit (day 81), Ms. G indicated that she had lost 5 lb (2 kg) and was feeling very much improved. Her intrusive thoughts, nightmares, and sleep disturbance had resolved, with an "even mood" and good concentration until around 9:00 p.m. She still displayed avoidance of bathrooms (a site of early abuse) and significant psychic numbing.

SUMMARY

All 7 patients demonstrated rapid and significant reduction in PTSD-related insomnia and nightmares with olanzapine in the range of 2.5 to 15 mg/day, typically dosed 12 hours before the person's normal "alert" time after awakening. Six of 7 patients demonstrated improvement of these symptoms after failing to adequately respond to standard SSRI monotherapy. Other beneficial olanzapine actions included rapid mood stabilization, especially in the 3 patients with diagnosed bipolar disorder. Olanzapine was generally well tolerated, with 2 patients initially discontinuing therapy due to concerns about weight gain. Both elected to restart treatment due to recurrence of nightmares. A third patient concerned about weight gain was successfully treated with adjunctive topiramate. Olanzapine appears to be an effective and rational adjunctive agent for treating the reexperiencing cluster of PTSD symptoms, especially sleep disturbance secondary to nightmares. Future controlled studies are needed to better characterize and quantify this therapeutic indication.

The importance of recognizing and treating chronic sleep disruption in potential PTSD patients cannot be overemphasized. This symptom may be the only symptom patients will volunteer, and it should trigger a more in-depth PTSD workup on the part of the clinician. If PTSD is identified, treatment with SSRI antidepressants is warranted as baseline treatment, with or without psychotherapy. If antidepressant therapy does not adequately improve sleep or stop nightmares, then adjunctive treatment with olanzapine, topiramate, or prazosin should be considered.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), citalopram (Celexa), diazepam (Valium and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), gabapentin (Neurontin), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), prazosin (Minipress and others), quetiapine (Seroquel), sertraline (Zoloft), thiothixene (Navane and others), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor).

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