Letters to the Editor

Restless Legs Syndrome Induced by Mirtazapine

Sir: Mirtazapine is a novel antidepressant, known as a noradrenergic and specific serotonergic antidepressant (NaSSA). It is an antagonist of presynaptic α_2-autoreceptors and α_2-heteroreceptors, resulting in an increased release of both norepinephrine and serotonin, and it also enhances noradrenergic and serotonergic neurotransmission. However, mirtazapine potently blocks 5-HT_2 and 5-HT_3 receptors. Although there are several studies in the literature that examine the effects of mirtazapine on sleep parameters, further study of larger groups of depressed patients is clearly needed.[1] In human volunteers, compared with placebo, a single dose of mirtazapine significantly shortened sleep latency, reduced stage 1 sleep, increased the amount of slow-wave sleep, increased the latency of rapid eye movement (REM) stage 2 sleep, and reduced nighttime waking.[2] In a recent study,[3] mirtazapine significantly reduced sleep latency and increased total sleep time and sleep efficiency in patients with major depression. It is thought that mirtazapine's ability to increase slow-wave sleep is also related to its 5-HT_2 receptor antagonism.[3] Thus, it may be suggested that mirtazapine is a useful treatment option for depressed patients with insomnia. We report a case of restless legs syndrome after mirtazapine administration.

Case report. Mr. A, a 45-year-old man with a DSM-IV diagnosis of major depressive episode, was admitted to the hospital. He reported severe insomnia and anxiety. He was hospitalized, and an overnight polysomnogram was performed on 2 consecutive nights. Sleep latency was 60 minutes and REM latency 51 minutes. He started on mirtazapine, 15 mg/day, in the evening. After the dosage was increased to 30 mg/day, Mr. A. developed restless legs. He reported deep paresthesias in the legs arising during postural rest in bed, especially when he was trying to fall asleep. He never reported restless legs in past history. A third polysomnogram was performed at the end of the first week of the mirtazapine treatment, and the diagnosis of restless legs syndrome was confirmed. The symptoms were observed when Mr. A got some sleep. He had a decreased sleep efficacy, an increased number of awakenings, increased stage 1 sleep, and decreased stage 3 and stage 4 sleep. He also had an index of 41 movements per hour. Mr. A's insomnia also worsened because of restless legs. In addition to mirtazapine treatment, clonazepam, 1 mg/day, was added in the evening at the second week of the therapy. Both restless legs and insomnia were improved with clonazepam therapy.

We describe a patient who had restless legs with mirtazapine and was treated successfully with clonazepam. The psychopathology of restless legs syndrome is unknown, although dopamine deficiency has been postulated.[4] Although other antidepressant drugs, as well as lithium[5] and venlafaxine,[6] have been reported to be able to produce restless legs, to our knowledge, mirtazapine has not been previously reported as an agent that may induce the syndrome. In any case, mirtazapine could be used as an explanation model for the etiopathogenesis of the disease, except where the dopaminergic hypothesis is concerned. The changes in noradrenergic and serotonergic neurotransmission may also be related to the physiopathology of restless legs syndrome.

The authors report no financial affiliation or other relationship relevant to the subject matter in this letter.

References

1. Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999;60(suppl 17):28–31
2. Ruigt GS, Kemp B, Groenhout CM, et al. Effect of the antidepressant Org 3770 on human sleep. Eur J Clin Pharmacol 1990;38:551–554
3. Winokur A, Sateia MJ, Hayes JB, et al. Effects of mirtazapine on sleep architecture in patients with major depression [abstract]. Biol Psychiatry1998;43:1065
4. Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic leg movements of sleep: response and complications of extended treatment in 49 cases. Sleep 1993;16: 713–716
5. Terao T, Terao M, Yoshimura R, et al. Restless legs induced by lithium. Biol Psychiatry 1991;30:167–170
6. Salín-Pascual RJ, Galicia-Polo L, Drucker-Colín R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry 1997;58:348–350

Mehmed Yucel Ağargün, M.D.
Hayrettin Kara, M.D.
Hanefi Özbek, M.D.
Temel Tombul, M.D.
Omer Akil Ozer, M.D.
Yüzüncü Yil University School of Medicine
Van, Turkey

Behavior Therapy Attenuates Clozapine-Induced Obsessions and Compulsions

Sir: There have been numerous accounts of obsessive-compulsive symptoms (OCS) emerging after treatment with clozapine[1–3] and other atypical antipsychotics.[4,5] We report the successful treatment of clozapine-induced OCS using behavior therapy.

Case report. Mr. A, now aged 50 years, was first admitted to hospital at age 17 years with depression. At 22, he developed paranoid delusions that colleagues and strangers could read his thoughts and laughed at him behind his back. He was hospitalized 4 times with similar delusions in his 20s and 30s but never had hallucinations of any kind. He gradually became socially withdrawn, with anhedonia and a flat affect, and was no longer able to work or live independently. He met DSM-IV criteria for schizophrenia. Although he was a meticulous and perfection-

© Copyright 2002 Physicians Postgraduate Press, Inc. One personal copy may be printed

istic man, he did not have a history of obsessions or compulsions.

Mr. A was treated for most of his illness with fluphenazine decanoate depot injections. At age 44 years, due to persistent negative symptoms, he began clozapine in a dose titrated to 300 mg/day and subsequently reduced slowly after discharge to 125 mg. His negative symptoms gradually improved, but 1 year after he started clozapine, compulsive checking began: he scrutinized his used cigarettes for up to 5 minutes to ensure they were extinguished and checked up to 5 times that his taps, radio, and television were turned off. He knew that his checking was excessive, it distressed him, and it had no delusional basis. There were no cleaning or grooming rituals.

Mr. A's symptoms worsened over 5 years. He was unwilling to alter his drug treatment. A trainee psychiatrist guided him to carry out self-treatment by exposure and ritual prevention, over 4 months. For example, one task was to leave his taps trickling and then leave the house for 2 hours, allowing his anxiety to rise while resisting his urge to return home to check that he had not caused a flood. His score on the Yale-Brown Obsessive Compulsive Scale[6] was reduced from 12 to 4 (obsessions, 7 to 2; compulsions, 5 to 2) over 4 months. He maintained these gains at follow-up, 11 months later.

A MEDLINE search for 1966 to the present using the search terms *obsessive behavior*, *obsessive-compulsive disorder*, *clozapine*, and *antipsychotic agents* revealed 28 case reports describing the onset or exacerbation of OCS up to 100 weeks (mean = 22 weeks) after starting clozapine, and a retrospective case review has demonstrated that clozapine-treated patients have significantly more OCS than patients taking other antipsychotic drugs.[2]

Selective serotonin reuptake inhibitors (SSRIs) were used in 13 of the 28 case reports, but were unsuccessful in 4 of the 13 reports. Exposure plus ritual prevention is, if anything, even more effective than antidepressants in the treatment of obsessive-compulsive disorder, yields more lasting improvement,[7] and is particularly useful in patients who do not respond to SSRIs.[8] However, behavior therapy was not described in any of the published case reports, suggesting that clinicians are reluctant to use behavior therapy for clozapine-induced OCS. This reluctance may be because they assume that a drug side effect is best treated by medication. The present case report suggests that exposure with ritual prevention can improve OCS even when they appear to be drug induced. We therefore advocate that behavior therapy should be considered in apparently drug-induced OCS, particularly when drug treatment has been ineffective.

Asher Giora, M.R.C.Psych., was Mr. A's therapist at the start of treatment.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

References

1. Baker RW, Chengappa KN, Baird JW, et al. Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry 1992;53:439–442
2. de Haan L, Linszen DH, Gorsira R. Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. J Clin Psychiatry 1999;60:364–365
3. LaPorta LD. More on obsessive-compulsive symptoms and clozapine [letter with reply]. J Clin Psychiatry 1994;55:312
4. Mahendran R. Obsessive-compulsive symptoms with risperidone [letter with replies]. J Clin Psychiatry 1999;60:261
5. Andrade C. Risperidone may worsen fluoxetine-treated OCD [letter with reply]. J Clin Psychiatry 1998;59:255–256
6. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011
7. Marks I. Behaviour therapy for obsessive-compulsive disorder: a decade of progress. Can J Psychiatry 1997;42:1021–1027
8. Simpson HB, Gorfinkle KS, Liebowitz MR. Cognitive-behavioral therapy as an adjunct to serotonin reuptake inhibitors in obsessive-compulsive disorder: an open trial. J Clin Psychiatry 1999;60:584–590

James H. MacCabe, M.R.C.Psych.
Isaac M. Marks, M.D., F.R.C.Psych.
Robin M. Murray, F.R.C.Psych.
Institute of Psychiatry
London, United Kingdom

Olanzapine Treatment for Patients With Schizophrenia and Cocaine Abuse

Sir: Up to 50% of patients with schizophrenia are now recognized as having a comorbid substance abuse disorder.[1] Typical antipsychotics have been used to treat them, with limited effectiveness. Some authors have even suggested that using haloperidol might lead to cocaine relapse.[2] Atypical antipsychotic agents may be more effective for treating these patients.[3–6] This letter describes a pilot trial comparing olanzapine versus haloperidol for treatment of cocaine-abusing patients with schizophrenia.

We intended to study 30 outpatients at a Veterans Administration (VA) hospital for a 24-week double-blind medication trial. The study was approved by the VA institutional review board. However, for administrative reasons, the trial was suspended after entrance of only 4 subjects. We here present very preliminary findings from these 4 patients who met DSM-IV criteria for schizophrenia and cocaine abuse. Weekly measures included the Brief Psychiatric Rating Scale (BPRS), the Scale for Assessment of Negative Symptoms (SANS), a cocaine craving analogue scale (a 5-point scale with values anchored by "no cocaine craving" = 0 to "more than ever in craving" = 100), and a checklist of side effects. Urine toxicology was measured at baseline and twice per week during the study. All conditions were kept the same between the olanzapine and haloperidol subjects except for the medications. Informed consent was obtained from all subjects.

Both subjects 1 and 3 received olanzapine and completed the study. Subject 1 had reductions in BPRS score (36 to 31), SANS score (25 to 18), and number of side effects (8 to 5; baseline values vs. mean scores during the study). His cocaine craving scores decreased from 56 to 36. He used less cocaine, with the reduction of cocaine metabolite benzoylecgonine in his urine from a baseline mean of 59,000 ng/mL urine to 6-month study mean of 26,000 ng/mL. He took 20 mg of olanzapine per day. Subject 3 had reductions in BPRS score (51 to 27), SANS score (55 to 10), and number of side effects (9 to 3). He stopped using cocaine, and his cocaine craving scores decreased from 75 to 0 after 1 week of study. He took a mean of 15 mg of olanzapine per day.

Subject 2 was switched to haloperidol, 5 mg/day with increase to 10 mg/day during the second week. During week 2, the number of side effects increased from 0 to 30. He used cocaine, attributed it to the increased side effects, and requested to be discontinued from the study. Subject 4 never returned after starting on 5 mg/day of haloperidol.

This was a small pilot trial. However, both patients treated with olanzapine did better in terms of cocaine use than did the

haloperidol-treated patients. Possible mechanisms for this finding may include a reduction in side effects, psychopathology, or cocaine cravings. Larger studies are needed to confirm our findings.

This pilot trial was funded by Eli Lilly and Company.

References

1. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. JAMA 1990;264:2511–2518
2. LeDuc PA, Mittleman G. Schizophrenia and psychostimulant abuse: a review and re-analysis of clinical evidence. Psychopharmacology 1995;121:407–427
3. Littrell KH, Petty RG, Hilligoss NM, et al. Olanzapine treatment for patients with schizophrenia and substance abuse. J Subst Abuse Treat 2001;21:217–221
4. Green AI, Zimmet SV, Strous RD, et al. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry 1999;6:287–296
5. Drake RE, Xie H, McHugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull 2000;26:441–449
6. Newton TF, Ling W, Kalechstein AD, et al. Risperidone pre-treatment reduces the euphoric effects of experimentally administered cocaine. Psychiatry Res 2001;102:227–233

John Tsuang, M.D.
Harbor/UCLA Medical Center
Torrance, California
Stephen R. Marder, M.D.
West Los Angeles VA Medical Center
Los Angeles, California
Amanda Han, B.S.
Winnie Hsieh, B.S.
California School of Psychology
Los Angeles, California

Limbic Leucotomy in Self-Mutilation

Sir: The article by Price et al.[1] on improvement in self-mutilative behavior following limbic leucotomy is a valuable contribution to the literature on this disabling behavioral syndrome, especially in view of the chronicity and severity of the self-mutilative behaviors so graphically described in their series of 5 cases. However, it seems worthwhile to note that despite some improvement in 4 of the 5 cases, all patients required many months of continuing inpatient care, and in several it appears that hospitalization continues (cases C, D, E), with case D remaining in a locked unit and being allowed to bang her head for 5 minutes out of every hour after her rituals and head-banging returned within 6 months of surgery.

The economic burden of caring for these patients thus remains staggering (albeit perhaps less than prior to surgery). Indeed, the authors might have commented on the costs of the neurosurgical procedures, especially in view of the precarious financial situations of many institutions and clinics where such an undertaking might be considered.

In addition, the authors might have commented more fully on the legal issues involved in consent. They did mention that consent of the patients or guardians was obtained, but the case histories suggest considerable doubt about the competency of any patient to give informed consent. For example, patient A could not even complete a preoperative Beck Depression Inventory, patient B had been under constant home supervision by his father since age 5, and patient C had no use of language until age 5. While the authors mention changes in Wechsler Adult Intelligence Scale-Revised scores in several cases, no scores were reported, and the degree of educational attainment was not described, leaving serious questions about cognitive impairment. It seems likely that some jurisdictions would require a judge to give consent to an irreversible neurosurgical procedure under these circumstances.

Finally, while 3 patients had received electroconvulsive therapy (ECT) without benefit, none had received maintenance ECT, which was successful in our case of a 35-year-old man with a long history of severe self-mutilative behaviors.[2] These included pulling out his fingernails with his teeth, burning off tattoos with cigarettes, throwing himself down stairs, and on one occasion requiring plastic surgery after taking out a large area of his scalp by throwing himself head-first on a seclusion room floor. He had been hospitalized 27 times in 10 years, with 80 recorded instances of self-mutilation, leading to over 1500 days of hospitalization. Multiple medications, including a year-long trial of clozapine, had failed. One treatment course of bilateral ECT failed.

We then suggested leucotomy, but his parents opted for a second course of bilateral ECT followed by maintenance ECT. This resulted in early and sustained improvement. Over the past 3 years, he has had only one minor episode of self-injurious behavior, is living in the community, and is working part-time. As with limbic leucotomy, the ultimate value of this approach needs to be investigated in controlled trials.

The authors report no financial affiliation or other relationship relevant to the subject matter in this letter.

References

1. Price BH, Baral I, Cosgrove GR, et al. Improvement in severe self-mutilation following limbic leucotomy: a series of 5 consecutive cases. J Clin Psychiatry 2001;62:925–932
2. Dean CE. Severe self-injurious behavior associated with treatment-resistant schizophrenia: treatment with maintenance electroconvulsive therapy. J ECT 2000;16:302–308

Charles E. Dean, M.D.
Minneapolis VA Medical Center
Minneapolis, Minnesota

Dr. Price and Colleagues Reply

Sir: We appreciate Dr. Dean's careful review and thoughtful comments about our article.[1] Regarding the cost of the neurosurgical procedure we described, we do not believe that economic arguments should enter into our clinical decision making. Our primary concern is the patient's well-being. We have described elsewhere the rigorous process by which informed consent is obtained.[2] All of the patients described in this article were psychiatrically examined by one of us (E.H.C.), who then approached the patients and their legal guardians about the procedure. Four of the 5 patients were deemed capable of giving informed consent. One patient was approved only after 2 legal guardians gave informed consent and a court-mandated second psychiatric opinion was obtained. All patients were represented by their legal guardians, who included one patient's mother and another patient's physician sister.

Given their severe psychiatric disabilities, our patients' levels of formal education were low. Their IQ scores were within the normal range of intelligence. No significant decline in their postoperative Wechsler Adult Intelligence Scale-Revised scores were noted.

Unlike the case described in Dr. Dean's report, in which bilateral electroconvulsive therapy (ECT) eventually resulted in early improvement that provided the rationale for maintenance ECT, 2 of our patients did not have a diagnosis of major depression, and ECT was never used in their treatment. ECT was used in 3 patients. One patient showed no beneficial response. ECT was stopped because of cognitive impairment in a second patient, and it caused a dissociative state in the third patient, which severely intensified self-destructive behavior and led to subsequent discontinuation of ECT.

The authors report no financial affiliation or other relationship relevant to the subject matter in this letter.

References

1. Price BH, Baral I, Cosgrove GR, et al. Improvement in severe self-mutilation following limbic leucotomy: a series of 5 consecutive cases. J Clin Psychiatry 2001;62:925–932
2. Cosgrove CG, Rauch S. Psychosurgery. In: Gildenberg PL, ed. Neurosurgery Clinics of North America. Philadelphia, Pa: WB Saunders; 1995

Bruce H. Price, M.D.
McLean Hospital
Belmont, Massachusetts
G. Rees Cosgrove, M.D.
Scott L. Rauch, M.D.
Michael A. Jenike, M.D.
Edwin H. Cassem, M.D.
Massachusetts General Hospital and
Harvard Medical School
Boston, Massachusetts
Isin Baral, M.D.
University of Istanbul School of Medicine
Istanbul, Turkey

Fluvoxamine Treatment of a Japanese Patient With Koro

Sir: This letter reports a Japanese patient with koro who was treated with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. To the author's knowledge, SSRI treatment of koro has previously been reported in only 1 case, in which the use of citalopram, 10 mg/day, was described by Hallak et al.[1]

Case report. Mr. A, a 36-year-old Japanese man, first presented with hypochondriacal cardiac complaints. He was diagnosed with hypochondriasis according to DSM-IV and treated with the benzodiazepine bromazepam at a dose of 12 mg/day. About 5 months later, hypochondriacal symptoms remitted. Treatment continued for 2 years with bromazepam, 12 mg/day. Neither the patient nor his parents reported any familial history of mental disorder, although a hypochondriacal episode was untreated and lasted only 1 month when he was 16 years old.

When Mr. A was 40 years old, he suddenly experienced a sensation that his penis was shrinking and feared that it would recede into his abdomen (koro). At this stage, he presented to the author. The patient felt a continual compulsion to manually pull his penis in order to impede its disappearance into his abdomen, and when he was sleeping, cloth was wound around the base of his penis. He was unclear whether disappearance of the penis would result in death. Bromazepam (up to 15 mg/day) was administered. However, bromazepam treatment (15 mg/day) for 4 weeks was not effective. Risperidone treatment (2 mg/day) was initiated, but was discontinued 2 weeks later because, according to the patient, a dose of only 1 mg of risperidone produced severe fatigue. Treatment with fluvoxamine was initiated at 100 mg/day and increased to 150 mg/day over a 2-week period. Remission of symptoms was demonstrated 1 month later. After fluvoxamine treatment (150 mg/day) continued for 1 year with no symptoms of koro developing, Mr. A's fluvoxamine dose was reduced to 50 mg/day, and he subsequently felt that his penis was shrinking again. The fluvoxamine dose was increased to 150 mg/day again, and koro symptoms remitted 1 week later. Excluding this episode, fluvoxamine treatment (150 mg/day) continued for about $1^1/_2$ years with no symptoms of koro developing.

Koro was originally described as a psychogenic syndrome among the Chinese and comprises 3 essential beliefs: that the penis (or breasts and labia, in females) is shrinking, that it will disappear into the abdomen, and that this will result in death.[2–4] However, non-Chinese individuals demonstrate an incomplete form of this syndrome, characterized in most reported cases by the absence of the belief associated with death. The complete form of koro is considered the classic culture-bound form, while incomplete forms are considered noncultural.[5] Moreover, 2 types of koro have been described: epidemic and sporadic.[4] Epidemic koro spreads and involves numerous people by mental induction on the basis of a common sociocultural background.

The present case is considered to represent the sporadic form and lacked the belief associated with death. However, the patient firmly believed that penile shrinkage occurred. If this symptom is classifiable as a delusion, koro may be classified as a delusional disorder (297.1) or brief psychotic disorder (298.8). Moreover, shared psychotic disorder (297.3) may fit the epidemic form of koro. However, the symptoms may be considered a result of pathologic somatic sensations secondarily leading to the beliefs characterizing koro. Bernstein and Gaw[6] considered koro to fit in the category of somatoform disorders in DSM-IV, and Lipschitz[7] proposed that koro should be included in the class of body dysmorphic disorder (300.7). Interestingly, Chowdhury[8] found a perceptual abnormality of penis image in koro patients independent of koro episode, using a graphomotor projective test. According to Chowdhury, in comparison to normal controls, koro patients perceive less penis length and fail to accurately perceive the morphological change of penis state in terms of length increase. Chowdhury's findings seem to be consistent with the propositions of Lipschitz about the classification of koro.

However, excluding patients with a chronic or recurrent course, koro is usually regarded as an acute episode and often exhibits components of acute anxiety and fear of death. Moreover, some cases display a positive response to reassurance. The author feels that the syndrome of koro may be primarily based on pathologic penile sensations, which secondarily lead to a belief of penile shrinkage, but that the unique presentation of the syndrome may not accurately fit any classifications in DSM-IV.

In the present case, in addition to the symptoms of koro, social phobic tendencies were present, but did not meet the criteria for social phobia in DSM-IV. No other comorbidity was found. Improvement of koro may not have been due to fluvoxamine treatment, but to the natural course of the episode. However, a reduction in fluvoxamine dosage after 1 year of treatment led to

the recurrence of koro, which remitted again once the dose of fluvoxamine was restored. These findings seem to provide further evidence of SSRI efficacy for koro, in accordance with the report of Hallak et al.[1]

Dr. Nakaya reports no financial affiliation or other relationship relevant to the subject matter of this letter.

The author thanks Kenichi Ohmori, M.D., Ph.D., for invaluable advice.

References

1. Hallak JEC, Crippa JAS, Zuardi AW. Treatment of koro with citalopram [letter]. J Clin Psychiatry 2000;61:951
2. Kovacs A, Osvath P. Genital retraction syndrome in a Korean woman. Psychopathology 1998;31:220–224
3. Yap PM. Koro: a culture-bound depersonalization syndrome. Br J Psychiatry 1965;111:43–50
4. Chowdhury AN. The definition and classification of koro. Cult Med Psychiatry 1996;20:41–65
5. Adeniran RA, Jones JR. Koro: culture-bound disorder or universal symptom? Br J Psychiatry 1994;164:559–561
6. Bernstein RL, Gaw AC. Koro: proposed classification for DSM-IV. Am J Psychiatry 1990;147:1670–1674
7. Lipschitz A. Mechanism and classification of koro [letter]. Am J Psychiatry 1991;148:959
8. Chowdhury AN. Dysmorphic penis image perception: the root of koro vulnerability. Acta Psychiatr Scand 1989;80:518–520

Makoto Nakaya, M.D., Ph.D.
Dokkyo University School of Medicine
Mibu, Japan

Sildenafil Advertising and the Realities of Sildenafil Treatment

Sir: I was happy to see the recent supplement to the *Journal* that reviewed the issue of sexual dysfunction and the use of sildenafil, and I was particularly impressed by Dr. Leiblum's article on the relational dynamics of sexual functioning.[1] I have long felt that the psychodynamic and interpersonal aspects of sexual dysfunction have been neglected in the dialogue among medical and mental health professionals regarding the proper use of the drug sildenafil. I have 2 points to make.

While Dr. Leiblum does an excellent job of describing the dynamic of couples encountering erectile dysfunction and low sexual desire and the appropriate methods of evaluation and intervention in couples therapy, it is not my impression that this degree of assessment and treatment is typically employed by physicians in the course of treatment with sildenafil. As a clinician in a center for sexual and marital health, Dr. Leiblum has the opportunity to employ the holistic and comprehensive assessment and therapeutic interventions she describes, but this clinical setting is not typical. More typically, family physicians and psychiatrists prescribe sildenafil in the context of a busy private practice, allowing little time for the assessment of the interpersonal dynamics of the marital relationship and even less time for appropriate follow-through to assess how the prescription has impacted the relationship. This brings me to my second comment.

There has been considerable direct-to-consumer television advertising for this medication. While I am sure I have not seen all of the advertisements, so far I have seen none that promote the use of the drug in the context of an intimate relationship. The first advertisement I saw depicted a young man living alone, obviously frustrated by his current solitary lifestyle, with only his adoring schnauzer for companionship. In the next advertisement I saw, the name of the drug Viagra was seen emblazoned on the side of a racecar speeding around a professional raceway. In the one I saw most recently, men are encouraged to "step up to the plate" while a baseball player cracks his bat against the ball. Many of these advertisements invite men to ask their doctor for a free sample of Viagra without suggesting any discussion of the matter with a partner.

All of these advertisements serve to promote the view that the prescription of sildenafil should occur outside the context of an existing intimate relationship with a partner. What use does a man living alone, without an intimate partner, have for sildenafil? And what do racecars and baseball have to do with a satisfying sexual relationship?

The pharmaceutical company responsible for these ads provided funding for the symposium out of which all of the articles in the supplement came, and a package insert for the drug Viagra was included with the supplement. This sort of collaboration between pharmaceutical companies and journals should invite dialogue between the pharmaceutical industry and the psychiatric profession regarding the use of direct-to-consumer advertising and any possible misperceptions that this advertising might promote. At this point, there is considerable disparity between how we as a profession view the appropriate use of this medication and how this drug is being presented to consumers, and we have the responsibility to address this issue with the pharmaceutical industry.

The impact of potentially misleading advertisements on consumers plus the realities of current clinical settings for the treatment of sexual dysfunction combine to make treating these disorders in an appropriate and comprehensive way a true challenge to our profession.

Dr. Sigmund has no financial affiliation or other relationship relevant to the subject matter of this letter.

Reference

1. Leiblum SR. After sildenafil: bridging the gap between pharmacologic treatment and satisfying sexual relationships. J Clin Psychiatry 2002;63(suppl 5):17–22

Judith A. Sigmund, M.D.
University of Cincinnati College of Medicine
Cincinnati, Ohio

Hypnotic Medication in the Aftermath of Trauma

Sir: Treatment guidelines published in the *Journal*[1] as well as a recent review in a prestigious medical journal[2] make recommendations for short-term use of hypnotic medication for early intervention following trauma. We have advocated this approach and recently followed up a pilot case series[3] with a small randomized, placebo-controlled trial.

Method. Twenty-two subjects (14 men; 18 Hispanic, 2 white, and 2 black subjects; mean ± SD age = 36.1 ± 11.4 years) who had been admitted to a level I trauma center following life-threatening incidents that included motor vehicle accidents (N = 15), industrial accidents (N = 2), and impersonal assaults (N = 5) and who were manifesting early posttraumatic stress disorder (PTSD) symptoms were included in the trial. They were recruited from a much larger pool of injured patients on the basis of having recall of the incident and endorsing at least moderate impairment of sleep initiation or maintenance

Table 1. Subjective Sleep and PTSD Severity Measures During Temazepam/Placebo Trial[a]

	Baseline		1st Night		1 Week Posttreatment[b]		Final Evaluation[c]	
Value	Temazepam (N = 11)	Placebo (N = 11)	Temazepam (N = 11)	Placebo (N = 11)	Temazepam (N = 10)	Placebo (N = 10)	Temazepam (N = 11)	Placebo (N = 11)
Total sleep, h	3.0 ± 2.5	4.0 ± 2.4	7.2 ± 2.7	5.4 ± 2.4	5.3 ± 1.4	5.5 ± 1.8	…	…
No. of awakenings	3.9 ± 4.7	5.4 ± 5.7	1.1 ± 0.7	2.5 ± 2.6	1.9 ± 1.0	2.2 ± 2.1	…	…
PTSD (CAPS score)	62.7 ± 24.1	56.7 ± 17.8	…	…	56.2 ± 21.0	40.9 ± 24.6	53.3 ± 19.1	44.1 ± 26.1

[a]Values shown as mean ± SD. Abbreviations: CAPS = Clinician Administered PTSD Scale, PTSD = posttraumatic stress disorder.
[b]Data missing for 1 patient in each group at this timepoint.
[c]Sleep data were not collected at the final evaluation, since the main study question was whether early improvement in sleep presages subsequent improvement in PTSD.

and meeting full criteria for at least 2 PTSD symptom clusters (DSM-IV criteria) during a structured interview assessment. Seven of the subjects met the full criteria for acute stress disorder. Inclusion further required not having been intoxicated at the time of the incident, absence of brain injury and preexisting active psychiatric disorders, and ability and willingness to provide written informed consent.

Study medication was initiated when medical/surgical stabilization was achieved, a mean of 14.3 ± 10.0 days after the traumatic incident. Subjects were randomly assigned to placebo taken at bedtime for 7 nights or 30 mg of temazepam at bedtime for 5 nights followed by 15 mg for 2 nights. Subjective measures of sleep were obtained from a morning diary for the first night of receiving medication and 1 week after its discontinuation. PTSD was assessed at the initial evaluation, 1 week after medication was discontinued, and at final assessment with the Clinician Administered PTSD Scale.[4] The final assessment for the trial was 6 weeks after the initial assessment or, in one half of cases, just prior to initiating nonstudy medication, which was initiated on the basis of the clinical judgment of the investigators when insomnia and/or other PTSD-related symptoms that were distressing to the subject did not diminish during or shortly after the trial (intent-to-treat analysis).

Results. Study measures are presented in Table 1. The number of cases not requiring further medication after 6 weeks (temazepam, N = 5; placebo, N = 6) and the mean number of days from the end of study medication to the final assessment (temazepam, 36.0; placebo, 37.9) were similar for the 2 groups. Six (55%) of the 11 subjects who received temazepam and 3 (27%) of the 11 subjects who received placebo met criteria for PTSD at the final assessment. PTSD severity was significantly reduced from the initial to the final assessment in the total study population ($F = 4.9$, $p < .04$); however, there was no interaction of repeated measures of PTSD severity with treatment group ($p = .5$). Improvement in sleep over the course of the trial was reflected in increased sleep duration ($F = 10.3$, $p < .001$) and a trend toward reduced awakenings ($F = 2.7$, $p < .09$). There was a significant ($p < .04$) interaction of increased sleep duration and having received temazepam for the first night of treatment; however, sleep parameters were similar between treatment groups when assessed 1 week after medication was discontinued. In the total group, reduction in awakenings from baseline to 1 week posttreatment was correlated with improvement in PTSD ($r = 0.55$, $p < .01$).

Discussion. Results, while preliminary, do not support that early, brief treatment with hypnotic medication facilitated reduction of PTSD symptoms or improved sleep beyond the duration of its use. Limitations of the study include small sample size and use of subjective sleep assessments as outcomes. Studies of chronic PTSD have noted discrepancies between subjective and objective sleep assessments.[1] We did obtain polysomnographic assessments of an overlapping group of subjects, however, and in this acutely traumatized group with PTSD symptoms, the study sleep-diary measures were highly correlated with corresponding polysomnographic measures.[5]

While prescribing a benzodiazepine short term is unlikely to be harmful and may transiently alleviate distress, our findings and others[6] suggest that it is insufficient for preventing PTSD. The finding relating reduced awakening to improvement in PTSD, however, suggests the possibility of a role for other interventions for reducing sleep disruption.

Supported by grant MH54006 from the National Institute of Mental Health, Bethesda, Md. (Dr. Mellman).

References

1. Expert Consensus Guideline Series: Treatment of Posttraumatic Stress Disorder. J Clin Psychiatry 1999;60(suppl 16):1–76
2. Lavie P. Sleep disturbance in the wake of traumatic events. N Engl J Med 2001;345:1825–1832
3. Mellman TA, Byers PM, Augenstein JS. Pilot evaluation of hypnotic medication during acute traumatic stress response. J Trauma Stress 1998;11:563–569
4. Blake DD, Weathers FW, Nagy LM, et al. A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1. Behav Ther 1990;13:187–188
5. Fins AI, Mellman TA, Bustamante V, et al. The relationship between subjective and objective sleep in recently traumatized patients [abstract]. Sleep 1999;22:S248
6. Gelpin E, Bonne O, Peri T, et al. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry 1996;57:390–394

Thomas A. Mellman, M.D.
Dartmouth Medical School
Hanover, New Hampshire
Victoria Bustamante, Psy.D.
Daniella David, M.D.
University of Miami School of Medicine
Miami, Florida
Ana I. Fins, Ph.D.
Nova Southeastern University
Fort Lauderdale, Florida

A Case Report of Quetiapine-Related Tic-Like Symptoms

Sir: Antipsychotic agents are the most effective pharmacologic treatment for tic disorders. However, tic-like symptoms, including motor and vocal variants, have been reported for patients treated with clozapine.[1] We present a case in which a simple motor tic-like symptom emerged during quetiapine treatment.

Case report. Mr. A, a 24 -year-old man with DSM-IV schizophrenia, had a psychotic episode characterized by auditory hallucinations and delusions of persecution several months prior to this presentation. An olanzapine regimen (10 mg/day) was commenced when the patient visited our clinic due to the psychotic relapse. The psychotic symptoms soon subsided; however, quetiapine, 100 mg/day, was substituted 9 months after initiation of treatment in an attempt to control severe weight gain.

After 1 month of the new treatment, frequent eye blinking developed. The patient's eye blinking was rapid, arrhythmic, nonspasmodic movement of the eyelids. Treatment with risperidone, 1 mg/day, and then with haloperidol, 1 mg/day, alleviated the psychotic symptoms without producing the side effect of eye blinking. Mr. A insisted on using quetiapine exclusively, however, because he felt that it made him more socially active. A reduction of quetiapine dosage to 50 mg/day did not improve the eye blinking and resulted in recurrence of the psychotic symptoms. After treatment with quetiapine, 100 mg/day, and sulpiride, 200 mg/day, was initiated, the psychotic symptoms and eye blinking disappeared. Following 3 months of treatment with this combination, Mr. A could take sulpiride, 200 mg/day, alone without recurrence of either symptom. Both this patient and his elder brother had a history of transient tic-like eye blinking in childhood.

Compelling evidence suggests that increased central dopaminergic activity tends to exacerbate tics, while typical antipsychotics that block dopamine receptors suppress tics. This case and previous reports of clozapine-induced tic-like symptoms suggest a significant relationship between these 2 atypical antipsychotics and tic-like symptoms. Quetiapine, which is similar to clozapine, has potent serotonin 5-HT_2 blocking effects,[2] which may enhance the release of dopamine.[3] Further, both clozapine and quetiapine have relatively low dopamine D_2-receptor blocking and rapid dissociation from the dopamine D_2 receptor.[4] It is possible that the enhancement of dopamine release and the low dopamine D_2-receptor occupancy may increase dopaminergic function and promote tic-like symptoms.

In this case, transient tic-like eye blinking had been noted during childhood. Although it was reported recently that quetiapine improved symptoms of Tourette's syndrome for 2 patients,[5] our experience suggests that quetiapine may induce or exacerbate tic-like symptoms.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

References

1. Lindenmayer J-P, Da Silva D, Buendia A, et al. Tic-like syndrome after treatment with clozapine [letter]. Am J Psychiatry 1995;152:649
2. Goren JL, Levin GM. Quetiapine, an atypical antipsychotic. Pharmacotherapy 1998;18:1183–1194
3. Kinon BJ, Lieberman JA. Mechanism of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology (Berl) 1996;124:2–34
4. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? a new hypothesis. Am J Psychiatry 2001;158:360–369
5. Parraga HC, Woodward RL. Quetiapine for Tourette's syndrome [letter]. J Am Acad Child Adolesc Psychiatry 2001;40:389–391

Shu-Chi Huang, M.D.
Te-Jen Lai, M.D.
Chung Shan Medical University Hospital
Taichung, Taiwan
Shih-Jen Tsai, M.D.
Veterans General Hospital-Taipei
Taipei, Taiwan

A Case of Ziprasidone-Induced Mania and the Role of 5-HT_{2A} in Mood Changes Induced by Atypical Antipsychotics

Sir: There have been documented cases of mania/hypomania induced by various atypical antipsychotics.[1,2] However, on the basis of MEDLINE and PubMed searches using the keywords *mania, hypomania, atypical antipsychotics, risperidone, olanzapine, clozapine, ziprasidone,* and *quetiapine,* mania triggered by ziprasidone has not been reported in the literature, which may be due to the relatively novel status of ziprasidone as an atypical antipsychotic. Here, we report a case of ziprasidone-induced mania. We also briefly discuss potential mechanisms of the mood-altering effects of atypical antipsychotics. Interestingly, these hypotheses predict that the risk of ziprasidone-induced mania is higher than that for other atypical antipsychotics.

Case report. Mr. A, a 41-year-old man with schizoaffective disorder, bipolar type (DSM-IV), was admitted for exacerbation of psychotic symptoms. Entirely noncompliant with olanzapine and divalproex treatment for the past 4 months, Mr. A presented with disorganized speech patterns and worsening of auditory hallucinations. However, he did not exhibit features consistent with a manic or depressive episode (DSM-IV). Because of extrapyramidal side effects while on past treatment with haloperidol, risperidone, and olanzapine, he was started on ziprasidone, which was titrated to 120 mg/day by day 10 of hospitalization. He also received 1500 mg of divalproex extended release daily, achieving a valproate level of 86 μg/mL on day 6. On day 10, Mr. A began to show features suggestive of mania, including grandiosity, reduced sleep, and physical aggression. By day 14, his Young Mania Rating Scale (YMRS)[3] score had risen to 35, from 15 on day 1, while his Brief Psychiatric Rating Scale (BPRS)[4] score had also increased, from 43 to 52. Ziprasidone treatment was then discontinued, and Mr. A's divalproex dose was increased to 2000 mg/day. On day 15, Mr. A began receiving quetiapine. By day 30, at 600 mg/day of quetiapine, his manic symptoms improved substantially. He had a YMRS score of 14, a BPRS score of 38, and a serum valproate level of 105 μg/mL.

While the resolution of Mr. A's mania may have been due to the increased divalproex dose, the addition of quetiapine, or both, the onset of his mania coincided closely with the introduction of ziprasidone. Although it is also possible that the patient's manic episode was already in evolution prior to the administration of ziprasidone, we feel that this is unlikely, since his mood symptoms and YMRS score of 15 at admission were consistent with his baseline status, and there were few signs, if any, suggesting the beginning of a manic episode. Finally, there were also no apparent medical causes of his mania; his complete blood count, serum metabolic panel, thyroid panel, electrocardiogram, and urinalysis all had been within normal range. A review of Mr. A's past records also revealed no manic episodes attributed to antipsychotic use.

There are several reports of risperidone- and olanzapine-induced mania[1] in the literature, as well as at least one case of quetiapine-associated hypomania.[2] It has been proposed that the mood-altering effects of these drugs derive from their high 5-HT_{2A} receptor affinity, particularly as a function of the 5-HT_{2A}/D_2 occupancy ratio.[1,5] The high 5-HT_{2A}/D_2 ratio was invoked to explain risperidone-induced mania at lower doses, where the ratio is believed to be greatest, given the increased D_2 binding at higher doses.[5] Other studies also suggest that atypical

antipsychotics (olanzapine, risperidone, and clozapine) can increase norepinephrine and dopamine levels in the forebrain,[6] possibly mediated by antagonism of 5-HT_{2A}.[1,7] In estimating the risk of ziprasidone-induced mania, studies have shown that ziprasidone has the highest 5-HT_{2A} affinity among the atypical antipsychotics.[8] In addition, ziprasidone apparently has the highest 5-HT_{2A}/D_2 binding ratio among these drugs. An in vivo study using rat and pig brains demonstrated that, of all the atypical antipsychotics, only ziprasidone binds 5-HT_{2A} exclusively (with little D_2 affinity) at all concentrations tested.[7] These findings interestingly predict a much higher probability of mood changes with ziprasidone than with other atypicals. In contrast, quetiapine has the lowest 5-HT_{2A} affinity,[8] as well as the lowest 5-HT_{2A}/D_2 ratio.[7] As the use of newer atypical antipsychotic agents (ziprasidone and quetiapine) increases, it will be intriguing to see whether their mood-altering properties differ significantly, allowing further elucidation of the role of 5-HT_{2A} receptors in neuroleptic-related mood changes.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

References

1. Aubry JM, Simon AE, Bertschy G. Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. J Clin Psychiatry 2000;61:649–655
2. Benazzi F. Quetiapine-associated hypomania in a woman with schizoaffective disorder [letter]. Can J Psychiatry 2001;46:182–183
3. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978;133:429–435
4. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
5. Lane H-Y, Lin Y-C, Chang W-H. Mania induced by risperidone: dose related? [letter] J Clin Psychiatry 1998;59:85–86
6. Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? J Clin Psychiatry 2002;63:95–103
7. Schotte A, Janssen PFM, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996;124:57–73
8. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60(suppl 10):5–14

Brett Y. Lu, M.D., Ph.D.
Rachel Lundgren, B.S.
P. Rodrigo Escalona, M.D.
Brian B. Roberts, M.D.
University of New Mexico/Veterans Affairs Hospital
Albuquerque, New Mexico