Letters to the Editor

A Relapse in Pedophilic Sex Offending and Subsequent Suicide Attempt During Luteinizing Hormone–Releasing Hormone Treatment

Sir: In 1998, Rösler and Witztum[1] published the first systematic study of antihormonal treatment of paraphilias with luteinizing hormone–releasing hormone (LHRH) agonists. Since the publication of their promising results, there has been an increasing interest in this new form of treatment.[2] Our recently published review[3] in the *Journal* revealed that 118 patients did not relapse if they remained on LHRH treatment. We now present the first case report of a patient who relapsed during LHRH treatment.

Case report. Mr. A, a 39-year-old unemployed, very isolated man, had DSM-IV diagnoses of cocaine and opiate dependence, alcohol abuse, and borderline intellectual functioning. He had a history of pedophilia since his early teens with a specific interest in pubescent males. He had been convicted of sexual child molestation 3 times. Since he suffered from hepatitis C, antihormonal treatment with cyproterone acetate seemed impossible.[3] He received the LHRH agonist depot leuprolide acetate, 11.25 mg every 3 months, in combination with supportive psychotherapy for a 1-year period. The patient's testosterone fell to castration levels, and he reported a reduced frequency of erections, ejaculations, and masturbation (decrease from more than once a day to twice a week).

At first, he also showed good control of his sexual behavior and started working again. Despite this, his only social contact was a family with a 14-year-old boy. Mr. A reported feeling sexually attracted to the boy; his interest in being near him and his fantasies about having sexual contact with him remained nearly unaffected by the treatment. However, he seemed to be able to control his sexual behavior.

After 1 year, he developed more problems. Our relapse prevention plan for the patient included never being alone with the boy and abstaining from alcohol and drugs. One day he drank alcohol, visited the family of the boy, and they drank together. While the other family members and the boy went to sleep, Mr. A stayed awake. After a while, he went to the sleeping boy and touched his penis. He reported later that he wished to be close to the boy. The patient himself had no penile erection but felt sexually aroused. The boy woke up, and Mr. A left.

The next day, Mr. A went to the police, where he reported this event. After that, he attempted suicide with 1 g of doxepin and alcohol. He called us by telephone, was sent to an intensive care unit, and survived. Three months later, during treatment, Mr. A reported 4 other pedophilic acts (without the influence of alcohol) against a 12-year-old boy, including mutual masturbation and oral intercourse. Subsequently, he was arrested.

We share the opinion of Rösler and Witztum[4] that LHRH agonists are currently among the most effective medications in the treatment of paraphilias. However, the effect on paraphilic fantasies remains uncertain[5] because careful double-blind research has not been conducted. The presented case shows that despite testosterone at castration levels and better control of sexual behavior, a risk of further offenses, and also of subsequent suicidal reactions, remains.

The authors have no financial relationships to disclose relevant to this letter.

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Peer Briken, M.D.
Andreas Hill, M.D.
Wolfgang Berner, M.D.
Institute of Sex Research and Forensic Psychiatry
University-Hospital Hamburg-Eppendorf
Hamburg, Germany

Cardiopulmonary Complications of Ergot-Derivative Dopamine Agonists

Sir: We read with interest the study by Cavallaro et al.[1] that evaluated the usefulness of cabergoline in treating risperidone-induced hyperprolactinemia. The authors of this small, 8-week study concluded that low-dose cabergoline is a safe and effective treatment for many patients with risperidone-induced hyperprolactinemia. We are concerned, however, about reports linking the ergot-derivative dopamine agonists with cardiopulmonary disease.

The ergoline dopamine agonists include cabergoline, bromocriptine, and pergolide. These medications can all cause pleuropulmonary fibrosis.[2–4] Pergolide at high doses has been associated with valvular cardiac disease; by the end of 2002, 15 cardiac valvulopathy cases had been reported to the U.S. Food and Drug Administration (FDA).[5] In the United States, the 2 dopamine agonists approved by the FDA to treat hyperprolactinemia are bromocriptine and cabergoline. Pergolide is also commonly used for this indication. A few small studies, recently

reviewed by Bankowski and Zacur,[6] suggest that the non-ergoline dopamine agonists pramipexole and ropinirole also lower prolactin levels.

The risks associated with the use of the ergot-derived dopamine agonists in the treatment of antipsychotic-induced hyperprolactinemia remain unclear. Additional research will be beneficial to determine if the non-ergot dopamine agonists are effective and safe treatments for antipsychotic-induced hyperprolactinemia.

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Michael J. Rack, M.D.
Alp Sinan Baran, M.D.
Allen C. Richert, M.D.
Howard P. Roffwarg, M.D.
Sleep Disorders Center
University of Mississippi Medical Center
Jackson, Mississippi

Dr. Cavallaro and Colleagues Reply

Sir: Rack et al. commented on our study of the treatment of risperidone-induced hyperprolactinemia with low doses of cabergoline with a warning about possible dangers of cardiopulmonary complications of ergot-derivative dopamine agonists. These adverse events are not yet completely understood, as only unconfirmed hypotheses (not driven by anatomicopathologic findings) about possible serotonergic mechanisms linking ergoline dopamine agonist drugs to cardiopulmonary (fibrotic) findings have been made.[1] Nevertheless, literature ranging from occasional reports to case series and incidence estimation, depending on the drug (mainly with bromocriptine and pergolide), is available for all compounds in this class.[1–3]

Although the underlying pathologic mechanism is unknown, all literature reporting and reviewing these adverse events shows a clear association of cardiopulmonary complications with the highest daily doses, used to treat Parkinson's disease, pointing then to a sort of "toxicologic threshold." In fact, doses are clearly critical in all reports of ergoline-related cardiopulmonary/pleuropulmonary inflammatory-fibrotic disorders. All of the disorders developed at the high doses: at least 20 mg/day of bromocriptine,[3] 1.5 to 8 mg/day of pergolide,[4] and 5 to 10 mg/day of cabergoline.[1,3] Other common features of the cases reported are concomitant use of antiparkinsonian drugs; previous treatment with another ergoline dopamine agonist at high doses, mainly bromocriptine[3,5]; and long-term treatment.

Doses of 5 to 10 mg/day of cabergoline are common or even low doses for Parkinson's disease,[1] but they are far higher than doses currently used in the treatment of primary and secondary hyperprolactinemia (0.5–1 mg once or twice per week). Our treatment protocol included even lower cabergoline doses: 0.125 to 0.250 mg/week for 8 weeks only, so that in each week of treatment our patients were exposed to a dose ranging from 1/280 to 1/560 of the doses given in case reports of cardiopulmonary syndromes during cabergoline treatment. Moreover, our treatment schedule took into consideration the long half-life of cabergoline, with once to twice per week administration to avoid drug accumulation, while in the reports in the literature of cardiopulmonary complications the schedule was always that of daily administration, with a possible additive "toxicologic" risk. With these facts in mind and considering that the common doses used to treat hyperprolactinemia (higher than in our study) have not been associated with pleuropulmonary fibrosis,[1,2] we think that the risk of cardiopulmonary/pleuropulmonary complications with the cabergoline dosage schedule we proposed is quite limited and dependent on uncommon idiosyncratic reactions that are possible with every drug in every patient, independent of doses, treatment schedules, and duration of treatment.

We now have data on 34 new patients treated with the same protocol and with the same efficacy results (R.C., F.C., E.S., et al., manuscript in preparation) with, again, no sign or suspicion of cardiopulmonary/pleuropulmonary disease. According to our measurements, prolactin lowering in these patients was still occurring 8 weeks after cabergoline withdrawal, as expected,[2] suggesting that in risperidone-treated patients with hyperprolactinemia, duration of low-dose cabergoline exposure may be limited to the 8-week protocol with long-term beneficial effects after withdrawal. This nonchronic treatment schedule should reduce further the low risk of cardiopulmonary consequences.

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

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Roberto Cavallaro, M.D.
Federica Cocchi, M.D.
Sara M. Angelone, M.D.
Enrico Lattuada, M.D.
Enrico Smeraldi, M.D.
Department of Neuropsychiatric Sciences
Vita Salute University Medical School
Milan, Italy

A Possible Case of Venlafaxine-Induced Stevens-Johnson Syndrome

Sir: We report a case of Stevens-Johnson syndrome (SJS) believed to be induced by venlafaxine in a woman with major depressive disorder who showed improvement in her rash when venlafaxine was discontinued. This report emphasizes that prescribers must aggressively follow up patients who have rashes while on treatment with any antidepressant, discontinuing the medication as soon as a serious skin reaction is suspected and watching closely for the emergence of potentially life-threatening dermatologic conditions.

Case report. Ms. A, a 38-year-old woman, was admitted to the hospital in January 2004 for evaluation and treatment of anogenital ulcers. She had a history of major depressive disorder, migraine headaches, and pelvic inflammatory disease and a remote history of toxic shock syndrome. Seven days prior to admission, she began experiencing watery diarrhea. Four days later, she experienced the onset of fevers to 38.3°C (100.9°F) followed by 3 days of vaginal irritation, which persisted, and then 1 day of gum pain.

Twelve days prior to the onset of the above symptoms, she had begun taking venlafaxine 37.5 mg daily for recurrent depression. The depression was characterized by depressed mood, frequent tearfulness, anhedonia, poor sleep, poor concentration, poor appetite, and low energy, all of which had been developing over the previous 6 to 8 weeks. She had also applied miconazole topically for vaginal irritation for 3 days prior to admission. For at least 6 months, Ms. A had been taking topiramate 200 mg twice daily for migraine prophylaxis, alprazolam 0.5 mg as needed for anxiety symptoms, temazepam 15 mg at bedtime as needed for insomnia, and ethinyl estradiol/levonorgestrel daily for contraception. She had been prescribed sumatriptan 6 mg subcutaneously as needed for migraine, but had not taken any in several months. She denied recent use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), as well as the use of herbal or alternative medicines. She had no history of allergy or asthma. She denied engaging in sexual intercourse within the previous year, though she was in a heterosexual relationship and hoped that she would resume sexual activity soon.

Four years prior to this admission, Ms. A had received a 4-month course of paroxetine at a dose of 20 mg daily for depression (depressed mood, anhedonia, insomnia, decreased concentration, and decreased appetite) with no significant adverse effects. She had experienced some improvement in depressed mood, poor concentration, anhedonia, and sleep with this dose but had not experienced a full remission of depressive symptoms and had discontinued the medication against the recommendation of her primary care doctor, who had recommended increasing the dose.

On initial examination, Ms. A was found to have gingival erythema; tender, erythematous labia minora with multiple 3- to 5-mm white plaques; erythematous labia majora; and tender superficial ulcers on her rectum. She also showed significant anxiety and dysphoric affect with frequent crying, low energy, and psychomotor retardation. The patient's vital signs were normal except for a heart rate of 104 beats per minute. She was admitted to the hospital, where she developed a truncal rash of purpuric patches with central vesiculation and atypical macules with dusky centers. Nikolsky's sign (separation of the outer layer of the epidermis from the basal layer when lateral pressure is applied to the skin) was positive. Over the following 3 days, she developed oral ulcers, labial erosions involving the vermilion border, and painful vulvo-vaginal erosions. The patient's ophthalmologic examination results were unremarkable. Two days after admission, venlafaxine was discontinued.

A human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA), a hepatitis C virus antibody test, *Mycoplasma* antibody titers, herpes simplex virus (HSV)-1 and HSV-2 antibodies, and a heterophil antibody test were negative. Bacterial blood cultures were negative. Cultures for HSV, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* taken from genital swabs were also negative. A rapid plasma reagin test was nonreactive. Punch biopsy of a lesion from the patient's back showed vacuolar alteration of the dermoepidermal junction; a subepidermal vesicle, lymphocytes, and necrotic keratinocytes along the junction adjacent to the blister; and ballooning of keratinocytes in the roof of the blister and was interpreted as consistent with both erythema multiforme (EM) and SJS. Ms. A was seen by the dermatology consultation service, who reviewed her history, physical examination, and biopsy results and concluded that she had SJS, most likely due to an idiosyncratic reaction to venlafaxine.

All previous medications were discontinued, and the patient was placed on treatment with methylprednisolone 40 mg IV twice daily, topical lidocaine for pain, and clonazepam and lorazepam for anxiety. Over the next 3 days, the patient's skin lesions stabilized and then began to regress. At discharge, she was placed on treatment with paroxetine 5 mg daily for depression, with a plan to titrate very slowly up to a therapeutic dose and to discontinue the medication immediately if the rash worsened or failed to resolve.

Two weeks later, Ms. A was seen by her primary care physician, who found near-resolution of her rash and some reduction in her depressed mood. Her poor sleep, anhedonia, poor appetite, and poor concentration persisted, so the primary care physician recommended increasing the dose of paroxetine from 5 to 10 mg daily. The patient had resumed her previous regimens of topiramate, alprazolam, and ethinyl estradiol/levonorgestrel in the interim.

Stevens-Johnson syndrome is a rare, life-threatening, bullous intolerance reaction of the skin. It occurs at a rate of approximately 1.2 to 6 cases per million per year, with a female predominance. It is thought to exist on a spectrum with toxic epidermal necrolysis (TEN), a more serious condition that by definition involves 30% of the body surface and may require treatment in a burn care unit. It is also similar in presentation to EM, a less severe condition that may stem from a different disease process. The majority of SJS cases are thought to be drug-induced, with sulfonamide antibiotics, aminopenicillins, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, valproic acid, lamotrigine, oxicam NSAIDs, and allopurinol believed to carry particularly high risk. A minority of cases appear to be linked to infection, vaccination, or graft-versus-host disease, with *Mycoplasma pneumoniae*, hepatitis A, histoplasmosis, infectious mononucleosis, and herpes all implicated.[1] Drug-induced SJS typically begins 1 to 3 weeks after the initiation of therapy and is commonly preceded by a prodrome of fever and influenza-like symptoms. Persons with human leukocyte antigen phenotype B12, systemic lupus erythematosus, and HIV have an increased incidence of both SJS and TEN.

Clinically, both SJS and TEN are characterized by a macular exanthema ("atypical targets") that focuses on the face, neck, and central trunk. Lesions show confluence and a positive Nikolsky's sign and can result in widespread detachment of the epidermis and erosions. Mucosal, conjunctival, and anogenital mucous membranes are prominently involved. In addition to skin and mucosal lesions, ophthalmic, pulmonary, hepatic, and gastrointestinal complications may occur. Histopathology

shows satellite cell necrosis in the early stages that progresses to prominent necrosis of the epidermis, contrasting with rather inconspicuous inflammatory infiltrates of the dermis.[2] Stevens-Johnson syndrome is thought to be a result of cytotoxic immunologic attack on keratinocytes expressing nonself antigens. Damage to the skin is mediated by cytotoxic T lymphocytes and mononuclear cells that induce apoptosis in keratinocytes expressing drug-derived antigens at their surfaces.[2] Apoptotic epidermal cell death results in separation of the skin at the dermoepidermal junction with blister formation and loss of sheets of epidermis. The exact mechanism of injury remains unclear.

The mortality rate of SJS is estimated at 5% to 15% and of TEN at 30% to 35%, with death most often due to hemodynamic shock or sepsis from superinfection. There is no reliable laboratory test to determine the offending agent; diagnosis rests on the patient's history, the ruling out of infectious causes, and the known risk of drugs to which the patient has been exposed. Treatment remains controversial, as there have been no controlled clinical trials, and there are differing opinions as to the benefits of corticosteroids, intravenous immunoglobulins, cyclophosphamide, plasmapheresis, and hemodialysis.[3] Supportive treatment, withdrawal of any possible offending agents, monitoring of vital signs, use of ocular lubricants if there is ophthalmic involvement, and use of antibiotics in the case of superinfection are of utmost importance in the disease. Avoidance of the responsible drug and chemically related compounds is essential for the patient and for first-degree relatives.[2]

In this case, the diagnosis of SJS had a strong clinical and histologic basis. The clinical presentation and histopathologic findings described above are most consistent with a self-limited, exanthematous mucocutaneous disorder from the family of dermatologic conditions composed of EM, SJS, and TEN.[4,5] The presence of fever, significant multisite mucosal involvement, and a positive Nikolsky's sign is not typical of EM, the least severe of the 3 conditions. Toxic epidermal necrolysis, on the other hand, is a more severe illness than was present in this patient, one characterized by epidermal detachment of at least 30% of the body surface area along with acute systemic illness. Although generalized bullous fixed drug eruptions can present similarly, and show similar histology, mucosal sites are usually spared. Further, the negative workup for common infectious causes of SJS, the temporal connection with the initiation of venlafaxine, and the absence of other new drugs make this drug the most likely cause. The patient's rash improved with discontinuation of venlafaxine, though other chronically utilized drugs were also discontinued and the patient was simultaneously given corticosteroids.

Among psychotropic drugs, several antiepileptic agents have been commonly associated with EM, SJS, and TEN—lamotrigine, barbiturates, carbamazepine, valproic acid, and phenytoin—but antidepressants have been only very rarely implicated. Cutaneous drug reactions associated with selective serotonin reuptake inhibitor (SSRI) antidepressants have been well documented, but they are they are usually mild, and for some agents, rashes are no more common than with placebo. There is some evidence of cross-reactivity between SSRIs in spite of significant structural dissimilarities between agents in this class.[6] Despite widespread use of antidepressant agents, severe cutaneous adverse reactions with newer antidepressants have been only rarely described: 1 case of SJS with sertraline[7]; 1 case of SJS, 1 case of TEN, and 2 cases of serum sickness and photosensitivity with fluoxetine[8,9]; and 1 case of SJS and 1 case of TEN with fluvoxamine.[10] Bupropion has been associated with rashes with serum sickness–like reactions as well as drug rash with eosinophilia and systemic symptoms syndrome, but has not been found to cause SJS.[11,12] With first-generation antidepressants, rashes have occurred in 2% to 8% of patients, but severe reactions have only very rarely occurred. Tricyclic antidepressants, for example, have been associated with urticaria, exanthematous eruptions, and photosensitivity, but never with SJS or TEN.[13]

Venlafaxine hydrochloride is a selective serotonin-norepinephrine reuptake inhibitor introduced into the U.S. market in 1993.[14] It is a tertiary amine with a chemical structure that is distinct from those of all other antidepressant medications, including all SSRIs.[15] Common adverse effects that have occurred with an incidence at least twice the rate in placebo-treated controls include asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, abnormal ejaculation or orgasm, impotence, and hypertension.[15,16] In early clinical trials, rash was reported in 4% of patients who received venlafaxine, but also occurred in 3% of those treated with placebo.[17] A review of MEDLINE articles (January 1966 to February 2004; keywords were *SSRI, venlafaxine, antidepressants, Stevens-Johnson, erythema multiforme, dermatologic, rash, allergic,* and *hypersensitivity*) was conducted to identify allergic, hypersensitivity, dermatologic, or other serious reaction reports associated with the use of venlafaxine. This review revealed 1 case of severe TEN in the setting of recent venlafaxine initiation, but the patient had been simultaneously started on treatment with carbamazepine, a well-recognized cause of SJS and TEN and thus the far more likely cause of the reaction.[18] Other severe treatment-emergent reactions have included serotonin syndrome, which may occur at higher rates than with SSRIs, and hypertensive crisis.

We herein describe the first reported case to our knowledge of venlafaxine-induced severe drug rash of the Stevens-Johnson type. We report this case to notify clinicians of this potentially serious, but apparently very rare and idiosyncratic, dermatologic complication that can occur with venlafaxine, a widely prescribed antidepressant medication. Though venlafaxine at doses similar to that used in this patient has a pharmacodynamic profile that is similar to that of SSRIs, it is chemically distinct from all other antidepressants, and since the patient had previously tolerated paroxetine without significant adverse effects, it was felt to be appropriate to begin paroxetine treatment at discharge. The resolution of the rash and the preliminary evidence that paroxetine was again tolerated in this patient suggest that this was a sound choice. In general, clinicians starting any psychopharmaceutical agent should carefully evaluate new rashes in their patients during the first several weeks of treatment. Particular attention should be paid to mucosal involvement, lesions with vesiculation or central duskiness, significant desquamation, fevers, gastrointestinal symptoms, and malaise, all of which are signs of a more severe reaction and should lead the clinician to consider discontinuing the medication until a definitive diagnosis has been made.

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

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Nicholas Tsvi Weiss, M.D.
Lee Jones, M.D.
John C. Chamberlain, M.D.
Department of Psychiatry
University of California
San Francisco, California

A Case of Prolonged Peyote-Induced Psychosis Resolved by Sleep

Sir: Psychosis due to sleep deprivation has been frequently reported.[1] In hallucinogen use, however, the duration of sleep deprivation is usually limited to a few days, and psychosis is attributed to the direct effects of the hallucinogens on the central nervous system. As a source of hallucinogen, the peyote cactus has been used both as a psychedelic drug and, among many Native Americans in the southwestern United States and Mexico, as a spiritual sacrament. The active ingredient is believed to be mescaline, an alkaloid known to cause visual hallucinations and decreased sleep. These effects subside in a few days, with an average duration of 10 to 12 hours.[2] Here, we report a case of prolonged peyote-triggered psychosis and sleep deprivation that was resolved by sleep initiation.

Case report. Mr. A, a 54-year-old Native American man with no prior history of psychosis, was admitted in November 2003 for a 2-week history of psychotic symptoms. These began within a few hours after the patient drank peyote juice during a healing ceremony. He became convinced that he was hunted by animal spirits, which prevented him from getting any sleep for the next 2 weeks. A few days later, he developed visual and auditory hallucinations of these spirits. As the degree of his hallucinations and sleep deprivation worsened, Mr. A became increasingly depressed and began to coerce children to participate in various religious rituals.

He was finally persuaded by his fellow tribal members to seek care in an urban hospital. Mr. A had a history of alcohol abuse and combat-related posttraumatic stress disorder (PTSD), both in remission for 20 years. According to interviews of his family and friends who had extensive daily contact with him, Mr. A had been taking no prescription medications or other medicinal supplements and was the only person developing bizarre symptoms after the healing ceremony. They were certain that there was no alcohol in the peyote juice but were unsure whether other substances were added. Results of Mr. A's admission physical examination, complete blood count, Chem-7, liver function tests, thyrotropin measurement, and urine toxicology, which tested for common illicit substances such as cocaine, amphetamines, cannabinoids, and opioids, were unremarkable.

Once Mr. A was admitted, antipsychotic treatment was withheld pending further evaluation by the treatment team since the patient was in no immediate danger. Having difficulty falling asleep, he was given 50 mg of trazodone; this resulted in uninterrupted sleep lasting 15 hours, followed by complete resolution of his psychotic symptoms. At this time, further workup was deferred, as Mr. A asked to return home promptly. He was discharged without medications, and subsequent follow-up contacts showed that he remained asymptomatic.

Reports of prolonged peyote-induced psychosis are rare and often associated with sleep disturbances.[3] In the case described, the immediate resolution of psychosis with trazodone-initiated sleep offers 2 intriguing clinical implications. Because psychedelic hallucinogens such as mescaline are believed to exert some of their effects via 5-HT_{2A} receptor stimulation,[4] one can thus speculate that trazodone, a 5-HT_{2A} antagonist, may lessen mescaline-related symptoms. This scenario, however, would necessitate an unusually slow metabolism of peyote in the patient described. An alternative but not mutually exclusive explanation for his protracted psychosis implicates sleep deprivation, which is consistent with the correlation between the patient's progressively worsening psychosis and the duration of his sleep loss. Psychosis from sleep deprivation appears to affect only individuals with a predisposition for psychotic outbreaks, such as those with a previous psychiatric history or stress, those in the postpartum period, and those in acute medical settings.[5–8] With a history of PTSD and alcohol use placing him at such risk, the patient not only exhibited the depressed mood and irritability characteristic of a sleep-deprived state but also displayed predominantly positive symptoms of psychosis consistent with other previously observed cases of psychosis from sleep disruption.[5,9]

Both psychosis and mania have been reported as sequelae of sleep loss, leading to the notion that sleep disruption often underlies the evolution of these 2 states.[5,8,10] In fact, a majority of patients reported sleep disturbances prior to a psychotic relapse or psychiatric hospitalization.[5,11] Within such inpatient populations, one can thus argue that sleep restoration itself may achieve significant resolution of psychotic symptoms, and it then becomes unsurprising that most antipsychotics and mood

stabilizers confer sleep-promoting properties. Studies have also suggested that the particular sleep disturbance associated with psychosis appears to be REM deprivation.[5,12–14] These findings warrant further studies to examine whether sleep induction and/or pharmacologic modulation of the sleep architecture can be viewed as independent treatment modalities in the acute management of psychosis and mania.

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Brett Y. Lu, M.D., Ph.D.
Chad Woofter, M.D.
Rodrigo Escalona, M.D.
Department of Psychiatry
University of New Mexico Health Sciences Center
Albuquerque, New Mexico