

Olanzapine and Blepharoclonus

Sir: Olanzapine is an atypical neuroleptic associated with low risk of extrapyramidal symptoms (EPS).¹ However, recent case reports²⁻⁴ suggest that some patients developed abnormal movements while taking olanzapine. Incidence of motor eyelid complications associated with atypical antipsychotics is uncommon, and only a few case reports of blepharospasm or Meige's syndrome have been reported with risperidone and olanzapine.⁴ To our knowledge, no case of olanzapine-induced blepharoclonus has been reported. We report a case of an adolescent who presented with blepharoclonus while he was treated with olanzapine. Blepharoclonus is defined by bilateral, repetitive, 2 to 3 cycles per second large amplitude contractions of the orbicularis oculi muscles.⁵

Case report. A 17-year-old boy with a history of childhood onset schizophrenia (*International Classification of Diseases, Tenth Revision* criteria) was treated since age 7. In June 2002, when he was 14 years old, his first hospitalization occurred as a result of severe aggressive behavior over a period of 2 weeks. In March 2003, at the age of 15, despite antipsychotic treatment with risperidone, further aggressive episodes resulted in a second hospitalization for 2 weeks. At this period, the patient received quetiapine during 1 month. Due to lack of therapeutic benefit, this treatment was replaced by olanzapine (up to 15 mg daily), which was administered with levomepromazine (10 mg 3 times daily) during 3 months.

In August 2003, the persistent lack of efficacy on delusional ideas and aggressive behavior resulted in a third hospitalization for 3 months and led to the introduction of haloperidol (15 mg daily) with the concomitant medications levomepromazine (75 mg daily) and biperiden. One month after this treatment initiation, given the lack of compliance, haloperidol and levomepromazine were gradually stopped. Depot risperidone (50 mg via intramuscular injection every 15 days) was initiated with the concomitant medication sertraline (100 mg daily) in order to diminish the comorbid obsessional-compulsive symptoms. Sertraline had to be reduced to 50 mg daily due to the hypomanic agitation the treatment induced. Depot risperidone was replaced by oral administration. The combination proved to be unsuitable for the patient, as he complained about internal tension, cramps, tremor, awkwardness, and restlessness evoking akathisia. The blood level of risperidone (3 mg daily) was not increased by sertraline, as the plasma level indicated the following dose range: risperidone = 1 ng/mL; 9-OH-risperidone = 17 ng/mL. Consequently, an anticholinergic treatment was prescribed (biperiden).

In November 2004, a fourth hospitalization occurred for 2 weeks with a similar medication (risperidone 3 mg daily, sertraline 100 mg daily). Despite a relatively good stabilization of psychotic symptoms, the persistence of extrapyramidal side effects led to risperidone discontinuation in December 2004 switching to olanzapine without cross-titration. The patient became progressively provocative, and a sudden aggressive and violent episode occurred against a member of the medical staff 5 months after treatment initiation. There were no factors of stress or any circumstances at this period to account for this behavior deterioration. He was receiving at this time a 10 mg daily dosage of olanzapine and 100 mg of sertraline. A plasma olanzapine level of 18.2 ng/mL was measured. The patient was found to be below the therapeutic plasmatic level recommended with olanzapine, which should be ranged between 20 ng/mL and 80 ng/mL.⁶ Moreover, this level was relatively weak regarding

posology considering the comedication of sertraline, and, taking into account that this patient did not smoke, a partial and/or irregular compliance could have been suspected. As a result of the aggression, olanzapine dosage was then titrated to 15 mg daily for 1 week and then to 20 mg the following week. The dosage was increased for a sedation effect and the treatment of persecutory delusions.

Nine days after the aggressive raptus, a plasma level of olanzapine (dosage: 20 mg daily) was measured at 39.4 ng/mL, which ranged him in the therapeutic zone. However, 1 day after reaching the 20 mg daily dosage, the patient experienced extremely distressing compulsive blinking of the eyelids (up to 100 times per minute), which was videotaped. It occurred 5 months after risperidone discontinuation. Neurologic examination failed to elicit classical extrapyramidal symptoms (akinesia, rigidity, tremor, salivation, akathisia). The patient received artificial tears for ocular dryness without improvement. A secondary conjunctivitis was diagnosed by the ophthalmologist 2 weeks after the beginning of the blepharoclonus. The patient received antibiotic eyedrops for treatment of the secondary conjunctivitis. The adverse effects (blepharoclonus, ocular dryness, and secondary conjunctivitis) were still ongoing 1 week later, and a change of medication was planned. The blepharoclonus was continuous throughout the 3 weeks during the ocular treatments. A cross-titration switch between olanzapine and clozapine resulted in a rapid cessation (48 hours) of the blepharoclonus without recurrence.

The diversity of psychotropic medication the patient received during these years of treatment would certainly have increased the risk of tardive dyskinesia. Despite the multiplicity of treatment, he never experienced these kinds of side effects before.

Extrapyramidal symptoms are well-known side effects of first generation antipsychotics and, to a lesser degree, of atypical antipsychotics. Olanzapine is associated with a low risk of residual EPS estimated between 1.6% and 2.3%.⁷ However, blepharoclonus was observed upon reaching an olanzapine dosage of 20 mg and never occurred below 20 mg daily, suggesting a dose-related side effect.

The time sequence and the positive effect of discontinuation led us to consider this severe side effect to be more likely related to olanzapine. However, tardive dyskinesia following any of his previous antipsychotic treatments cannot be definitely ruled out, as it is not possible to distinguish effects between lowering olanzapine dosage and the introduction of clozapine, which can improve neuroleptic-induced dyskinesia.⁸ Comedication by sertraline could also play a possible role, as EPS related to sertraline treatment have been described.⁹ Selective serotonin reuptake inhibitors (SSRIs) may lead to EPS through an interaction between serotonergic and dopaminergic pathways.⁹ However such side effects are described as rare,¹⁰ and our patient did not experience SSRI side effects other than digestive complaints when he received sertraline up to 100 mg daily. Maintenance of sertraline treatment did not influence the quick relief of blepharoclonus.

The plausible explanation of the EPS that occurred in this situation with olanzapine and risperidone but not with clozapine could be that olanzapine has a D₂ receptor occupancy higher than that of clozapine and similar to that of risperidone,¹¹ which may have accounted for the development of the EPS side effects. However, the dopamine receptor explanation is limited. A neuroanatomical explanation for why this side effect was associated with olanzapine and not haloperidol or risperidone seems

also quite limited. There is no clear neuroanatomical substrate in blepharoclonus, as it has been described as associated with a heterogeneous group of neurologic signs or diseases.¹² However, the stimulation of the midbrain and the caudate nucleus have been shown to provoke rhythmic and rapid bursts of blinking.¹² Blinking is highly influenced by dopaminergic activity, and the D₂ blockade explanation is not satisfactory, as blinking activity would be reduced, as it is observed in Parkinson's disease.¹³ Moreover, this side effect never occurred with haloperidol or risperidone, which have higher or similar affinity for D₂ receptors. A possible explanation could be linked to the high anticholinergic properties of olanzapine. High dosage of olanzapine is associated with frequent anticholinergic side effects.¹⁴ The ocular dryness observed concomitantly is also probably due to an anticholinergic effect associated with a higher dosage of olanzapine with our patient. A higher anticholinergic activity was associated with increased aberrant motor behavior in patients with dementia and psychosis.¹⁵ An anticholinergic effect hypothesis seems therefore plausible.

In conclusion, the present report illustrates the severity of eyelid motor adverse events that may occur with atypical antipsychotics in young patients. Adult use of neuroleptic medication is more widespread than pediatric use, yet clinical experience and the large number of case reports would suggest that the child patient group is statistically more likely to encounter more frequent and severe adverse events. In the future, more specific information on how cerebral maturation influences neuroreceptors in the adolescent brain and how this differs from the adult brain would be helpful and possibly relevant to the underlying mechanism of this side effect. Our case study tends to confirm that clozapine has a favorable action regarding abnormal movements such as blepharoclonus. We would suggest that clinicians should be alert to the emergence of motor side effects with antipsychotic treatment, particularly with olanzapine. With regard to the vulnerability of children and adolescents, long-term complications induced by antipsychotic medication need our best efforts for documentation and risk estimation.

The authors report no financial affiliations or other relationships relevant to the subject of this letter.

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Physiologic Sleep Disorders Among Treatment-Responsive Depressed Patients With Residual Cognitive and Physical Symptoms

Sir: Fava and colleagues¹ informative work on persisting cognitive and physical symptoms in patients with major depressive disorder following long-term use of antidepressants theorizes that complaints such as memory and concentration difficulties and daytime fatigue and sleepiness are caused by medication side effects or residual symptoms of depression or both. A major strength of that study is the focus on patients who partially or fully responded to antidepressant medication. We would expect these patients to report less impairment; however, 53% reported forgetfulness and 52% reported sleepiness among several residual symptoms.¹

These outcomes are reminiscent of the medical school adage, "When you hear hoof beats, think horses, not zebras." Yet, from a sleep medicine perspective, Fava and colleagues' work evokes images of stripes. In our field, complaints of memory and concentration problems combined with fatigue and sleepiness are hallmarks of physiologically induced sleep fragmentation, most commonly caused by sleep-disordered breathing in the form of obstructive sleep apnea (OSA) or its variant, upper airway resistance syndrome (UARS). Both conditions cause hundreds of awakenings, arousals, or micro-arousals on the electroencephalogram of a sleep study recording (polysomnography), yielding lighter, nonrestorative sleep.² Poor sleep quality commonly produces cognitive and physical symptoms³ similar to those described in the study of Fava et al.¹

Building upon this critical link between compromised sleep quality and myriad health symptoms, emerging research suggests a remarkably high co-occurrence of sleep-disordered breathing and depression^{4,5}; several case series and randomized controlled trials demonstrate that aggressive treatment of sleep-disordered breathing improves depression symptoms.⁶ Thus, a more compelling hypothesis to explain the findings of Fava et al. might be the presence of undiagnosed and untreated OSA or UARS among those patients complaining of residual symptoms.

When sleep specialists invoke this hypothesis to connect sleep disorders to symptoms in mental health patients, a frequent rebuttal asserts that the sample was properly screened for sleep breathing problems. The screening, though, only seems to “round up the usual suspects,” focusing on snoring, choking or gasping for breath, witnessed apneas, patient age (older), sex (male), or weight (obesity). As recently shown, these factors are unreliable in raising suspicions for a diagnosis of sleep-disordered breathing in psychiatric patients with sleep complaints.⁷

In a comparison of 2 groups of sleep-disordered breathing patients,⁷ 89 apnea patients were contrasted with 89 patients with moderate to severe posttraumatic stress disorder. The former group presented with classic features of sleep apnea, whereas the trauma group presented with classic features of psychiatric insomnia. Yet, all participants in both groups, matched for age and sex, were objectively diagnosed with sleep-disordered breathing. The cardinal findings of the study showed that the trauma patients’ sleep breathing problems were masked by several atypical features.⁷ The trauma patients were not overweight, less than 25% reported snoring or other breathing symptoms, and insomnia was pervasive and severe, as often seen in mental health patients, averaging a sleep efficiency of less than 70% and a total sleep time of less than 5½ hours. Because of this atypical presentation among trauma patients, the more reliable indicators raising suspicion for a sleep breathing condition were the common (typically present in 50% or more of the sample) end-organ symptoms routinely linked to OSA or UARS, including daytime fatigue and sleepiness, memory and attention deficits, nocturia, dry mouth upon awakening, and morning headache.⁷

To test this hypothesis in the sample of Fava et al.¹ or other depressed patients with residual symptoms, polysomnography—the gold standard of objective sleep analysis—must be conducted to assess OSA and UARS.² Polysomnography coupled with advanced respiratory monitoring (e.g., pressure transducers) must be used for these tests to accurately measure sleep breathing episodes.⁸ No other claims about objective sleep can be validated until these data are analyzed in appropriate samples.

Polysomnography will also uncover periodic limb movement disorder in some depressed patients taking antidepressants. Patients taking selective serotonin reuptake inhibitors show marked increases in leg jerks during sleep studies.⁹ Although the clinical significance of this finding is debatable, at our sleep centers we often find high rates of leg jerks on polysomnography among patients taking escitalopram, fluoxetine, paroxetine, or venlafaxine. Among some patients, periodic limb movement disorder diminishes restorative sleep and appears to cause impairment.

In sum, the concerns of Fava et al. are well-founded: “our field has not paid sufficient attention to the presence of cognitive [and physical] symptoms emerging or persisting during long-term antidepressant treatment. . . .”^{11(p1757)} In juxtaposition, our field is concerned that psychiatry does not pay sufficient attention to the potential comorbidity of mental health and sleep disorders.¹⁰ In treated depressed patients with residual symptoms, we recommend inclusion of sleep breathing and movement conditions in the differential diagnosis, after which the sound of hoof beats may herald the presence of sleep disorders of all stripes.

This letter was shown to Dr. Fava, who declined to reply. —Editor
The study discussed in this letter was funded by Cephalon, Inc.

Dr. Krakow’s disclosure involves 3 commercial Web sites:

www.sleepdynamitherapy.com, www.sleep-treatment.com, and www.nightmare-treatment.com, which offer products and services for sleep disorder patients, and 3 books: Sound Sleep, Sound Mind; Insomnia Cures; and Turning Nightmares Into Dreams.

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Aripiprazole-Induced Psychosis: A Case Report of Reexposure by Stepwise Up-Titration

Sir: Aripiprazole is a new atypical antipsychotic with a partial agonist activity at D₂ and 5-HT_{1A} receptors and with potent 5-HT_{2A} receptor antagonism. Dose titration is considered necessary by some authors,¹ but not by others.^{2,3} Recently, multiple cases of worsening of psychotic symptoms after add-on treatment with aripiprazole have been reported.^{4,8} Therefore, slow and cautious up-titration in patients with schizophrenia has been suggested.⁷ This report describes a patient treated with risperidone whose psychotic positive symptoms worsened dramatically after add-on of 15 mg/day aripiprazole, nearly subsided after aripiprazole discontinuation, and reappeared after aripiprazole reexposure, even though this reexposure was done very slowly by stepwise up-titration.

Case report. Mr. A, a 37-year-old white man with ICD-10–defined paranoid schizophrenia since the age of 20 years, was admitted to our inpatient unit in 2006. He described chronic auditory hallucinations and had the feeling that someone was breathing through him. His delusional thoughts fluctuated in intensity and were accompanied by agitation, anger, and aggressiveness against neighbors and their cars. Mr. A had been treated with a daily dose of 6 mg risperidone by mouth for 26 months prior to admission. This therapy significantly reduced the paranoid delusions and auditory hallucinations, but had no

impact on the concomitant lack of motivation, flat affect, and social withdrawal.

In order to improve these negative symptoms, he was prescribed a morning dose of aripiprazole 15 mg by his psychiatrist as an add-on therapy. After 3 days of aripiprazole intake, hallucinations, paranoid symptoms, and aggressive and suicidal ideations increased dramatically, and Mr. A was hospitalized on our ward. Aripiprazole was stopped immediately and risperidone was increased to 9 mg/day. The psychotic symptoms declined gradually within 10 days, suicidal ideation disappeared, and the total Positive and Negative Syndrome Scale (PANSS)⁹ score (on a 1–7 scale) declined from 78 to 56.

A stepwise reexposure to aripiprazole as add-on treatment to risperidone was started with 2.5 mg aripiprazole as morning dose on day 14, with a gradual increase by 2.5-mg steps up to 15 mg/day on day 33. On day 33, the plasma level of aripiprazole was 198 ng/mL (expected range, 150–250 ng/mL)¹⁰ and risperidone/9-hydroxyrisperidone was 98 ng/mL (expected range, 20–60 ng/mL).¹¹ At this point, only occasional auditor hallucinations occurred, the patient showed improved affective reactivity, and discharge from the hospital was discussed. However, during the following 6 days, without changes to the dose of risperidone (9 mg/day) or aripiprazole (15 mg/day), the patient again developed increasing anxiety and auditory hallucinations with aggressive and suicidal contents. Aripiprazole was discontinued on day 39.

Four days later, Mr. A's PANSS score had dropped to 60, suicidal ideations ceased, and the patient was discharged from the hospital. In the following 5 months, no further deterioration of psychotic symptoms, suicidality, or aggressiveness occurred.

We think that in this patient the described worsening of psychotic symptoms was clearly associated with the add-on treatment with aripiprazole. The patient adhered to his medications as proven by plasma levels. A spontaneous fluctuation of his psychosis was unlikely since the worsening of symptoms occurred twice, each time in close temporal relationship to the administration of a daily dosage of 15 mg aripiprazole. Furthermore, the discontinuation of aripiprazole resulted twice in immediate improvement of psychotic symptoms.

The worsening of the psychotic symptoms after the add-on therapy with aripiprazole 15 mg might be explained by the characteristics of dopaminergic binding of this drug. In subjects treated with potent D₂-receptor blocking substances like risperidone, D₂-receptors may become hypersensitive and might even increase in density. Thus, one of the mechanisms of the above described aripiprazole-induced psychosis might be an enhancement of dopamine neurotransmission due to the drug's D₂-agonistic effects on hypersensitive postsynaptic D₂-receptors.^{4,5,7,12,13} We had expected to reduce this overstimulation of sensitized D₂-receptors by a stepwise up-titration of aripiprazole. However, this case suggests that the worsening of psychotic symptoms in vulnerable patients may be unavoidable even with slow titration.

Another explanation is that aripiprazole is a weaker D₂-antagonist than risperidone and could displace risperidone from the receptors, leading to a decreased D₂ blockade resulting in worsened symptoms.

A review of the literature suggests that many patients benefit from aripiprazole. However, as the reported case shows, there are certain patients who may develop an increase in positive psychotic symptoms. We recommend close monitoring of patients with paranoid schizophrenia during the first weeks of aripiprazole titration as an add-on to existing treatment with D₂-blocking antipsychotics, regardless of duration of up-titration.

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Is Smoking Associated With Suicide in Bipolar Patients?

Sir: Ostacher et al.¹ published an interesting article suggesting that smoking is independently associated with suicide attempt in patients suffering from bipolar disorder. All new hypotheses leading to a best comprehension about suicide behavior in bipolar-disordered patients are welcomed, particularly because suicide rates are higher in people with bipolar disorder than in all other psychiatric-diagnosed subjects²; if this hypothesis holds true, it turns out to be even more important since it is known that cardiovascular and respiratory causes of death are greater in bipolar patients than in the general population and that a well-established association exists between those conditions and smoking.³

However, we must proceed with extreme caution in attributing smoking as an independent risk factor for suicide. The well-conducted study carried out by Ostacher et al.¹ has some limitations that are inherent with retrospective studies, and many of them were addressed by the authors themselves. However, there are other aspects that were not covered by them.

Initially, Ostacher et al.¹ did not assess comorbid cluster B personality disorder, which is highly prevalent in bipolar disorder, affecting 30% to 50% of those patients, and confer additional risk of suicide behavior in bipolar-disordered patients.⁴ These patients tend to exhibit more impulsivity/aggression, and we could speculate that the prevalence of smoking in cluster B personality disorder could be higher than in bipolar disorder patients without this comorbidity. If so, the increased suicidality observed in bipolar smokers is probably related to this comorbidity and not to smoking itself.

Three other biases should be examined before attributing smoking as an independent suicide risk factor. First, nicotine can accelerate the metabolism of many drugs generally used in bipolar patients such as antidepressants, antipsychotics, and benzodiazepines.⁵ It is conceivable that smoker patients had lower plasma concentrations of drugs used to treat bipolar-disordered patients, and this was associated with poor outcome and more suicide attempts. Second, number of admissions in inpatient units is an important factor to be assessed. In many psychiatric units, the consumption of cigarettes is allowed, and, in this sheltered environment, some patients could learn to smoke at the first admission when in contact with older smokers. Thus, the number of more serious episodes of suicide attempt, those normally requiring hospitalization, could be directly associated with suicidality by instead following smoking habits. Third, it is conceivable that some personality traits, like impulsivity, that are classically associated with suicide behavior, might underlie both suicide behavior and smoking. Kollins et al.⁶ showed that symptoms related to attention-deficit/hyperactivity disorder such as impulsivity significantly increase the likelihood of smoking in adulthood. Robbins and Bryan⁷ showed that individuals with higher impulsivity are more prone to engage early in life in high-risk activities such as alcohol abuse, sexual relations without condom use, and smoking.

Finally, suicide itself is a rather complex phenomenon, with biological, environmental, developmental, and learning contributing factors. In view of this complexity, a detailed characterization of the suicide attempt is always of major interest given that some factors could play a major role in some categories of suicidal behavior (e.g., violent or impulsive or repetitive ones) but not in every single one. In other words, even if some association exists between smoking and suicide attempts in bipolar patients, this association could be actually found only in some types of suicide attempts but not in others. In addition, the way in which the lifetime suicide attempt history is assessed is of pivotal importance since a significant degree of past suicidal behavior is not usually recorded, unless a specific structured screening instrument is used.⁸

Drs. Neves and Correa report no financial or other relationship relevant to the subject of this letter.

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Dr. Ostacher and Colleagues Reply

Sir: We thank Drs. Neves and Correa for their thoughtful response to our article. We do not in our paper state that smoking is an “independent risk factor for suicide” in patients with bipolar disorder; we have no data to support such a conclusion, nor do we suggest it.¹ We agree that an impulsivity/aggression factor may be a common pathway to both smoking and suicide attempts and may be more prevalent in patients with bipolar disorder who are smokers, and, indeed, we suggested as much in our article. A limitation of our article, as we have written, is that we do not have data on Axis II comorbidity in our sample and could not determine whether it would have attenuated the association between a history of cigarette smoking and a history of suicide attempts. Rates of smoking among people meeting criteria for personality disorders are elevated in general population studies.²

It is plausible that smoking can lower levels of some drugs in patients with bipolar disorder, and this merits further study. Our findings suggest, nonetheless, that the risk of suicide attempts in smokers with bipolar disorder is independent of mood.

Finally, Drs. Neves and Correa suggest that there is a need for accurate measurement of suicidal behavior, that not all suicide attempts are equivalent, and that different types of suicide attempts might occur in patients with bipolar disorder who smoke. We concur that these observations raise potentially important questions. Even in the absence of such data, the difference in the rate of past suicide attempts that we found in smokers (49%) compared to nonsmokers (25%) to us remains striking. By understanding the risk factors for suicidal behavior associated with smoking in patients with bipolar disorder, we hope to identify an area for inquiry that may ultimately lead to improved detection and treatment for this highly morbid group.

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Corrections

In the article “Efficacy and Tolerability of Adjunctive Ziprasidone in Treatment-Resistant Depression: A Randomized, Open-Label, Pilot Study” by David L. Dunner, M.D., et al. (July 2007 issue, pp. 1071–1077), the acknowledgment statement incorrectly identified Dr. Edward Schweizer as an employee of Pfizer Inc. Dr. Schweizer is an employee of Paladin Consulting Group. He received funding from Pfizer Inc for his editorial assistance in the preparation of the draft manuscript.

In the article “A Meta-Analytic Review of Double-Blind, Placebo-Controlled Trials of Antidepressant Efficacy of Omega-3 Fatty Acids” by Pao-Yen Lin, M.D., Ph.D., and Kuan-Pin Su, M.D. (July 2007 issue, pp. 1056–1061), the acknowledgment statement that both authors contributed equally to the work was omitted.

In the letter to the editor “Ziprasidone in the Acute Treatment of Borderline Personality Disorder in Psychiatric Emergency Services” by Juan C. Pascual, M.D., et al. (September 2004 issue, pp. 1281–1283), the authors’ affiliation with the Universidad Autònoma de Barcelona (UAB) was omitted.

The online versions of these articles have been corrected.