The authors' disclosures accompany the original article.

This letter (doi: 10.1176/appi.ajp.2010.10030391r) was accepted for publication in April 2010.

Treatment With Depot Olanzapine

To the Editor: I wish to expand on two points made in my editorial (1), published in the February 2010 issue of the *Journal*, and correct an error. An accidental injection of depot olanzapine into or near a vein can result from much of the dose being administered as one bolus, producing an overdose, which is manifested as confusion, disorientation, deliria, somnolence, dysarthria, ataxia, and coma or seizure (2). This occurs in approximately 0.07% (the correct value) of individuals per injection, or approximately 1% of patients each year, which cumulates year by year. Hopefully, clinicians will be meticulous about injection techniques, reducing the incidence. Eighty percent of the time, this syndrome starts within 1 hour after injection, 17% of the time within 1–3 hours, and 3% of the time after 3 hours, with the median time to incapacitation being 60 minutes (range: 10–300 minutes). There was no relationship of dose to seriousness of this adverse reaction. In addition, there were no fatalities. Patients completely recovered in a few days, and most agreed to go back on depot medication It is important to prevent the consequences of adverse effects (e.g., auto accidents) by observing the patient for 3 hours after the injection; having the patient leave the clinic with a responsible caregiver; being attentive to the nonspecific prodrome (feeling weak, dizzy, or generally bad); and avoiding sedative medications as well as epinephrine, dopamine, and other beta agonists because they may possibly worsen hypotension as a result of olanzapine's apha-1 properties.

I do not think there is sufficient evidence to recommend tapering or not tapering oral drug doses or using a loading or intramuscular booster dose when switching to depot olanzapine, based on the following evidence. It takes 3–5 injections to reach steady state. Plasma levels decrease after the first injection, to as low as 5%–20% of the levels observed with oral drug formulation, but the half-life of D_2 receptor blockade for oral and depot formulations is at least three times as long as that for plasma (3). Kane et al. (4) found the rate of relapse to be approximately 50% greater (not statistically significant) in the first few dosage intervals than the rate observed at steady state. The 405 mg per month dose was almost as effective as the dose of 300 mg every 2 weeks, indicating that monthly injection intervals can be of use.

The dosage of 150 mg every 2 weeks is too low for many patients, and may possibly double the number of relapses when the observed difference is projected over years.

References

1. Davis JM: The use of depot medications in the treatment of schizophrenia. Am J Psychiatry 2010; 167:125–126
2. Eli Lilly: Psychopharmacologic Drugs Advisory Committee Briefing Document: Zyprexa Olanzapine Pamoate (OP) Depot (Olanzapine Long-Acting Injection) Schizophrenia. Indianapolis, Ind, Eli Lilly, 2008
3. Mamo D, Kapur S, Keshavan M, Laruelle M, Taylor CC, Kothare PA, Barsoum P, McDonnell D: D2 receptor occupancy of olanzapine pamoate depot using positron emission tomography: an open-label study in patients with schizophrenia. Neuropsychopharmacology 2008; 33:298–304
4. Kane JM, Detke HC, Naber D, Sethuraman G, Lin DY, Bergstrom RF, McDonnell D: Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry 2010; 167:181–189

JOHN DAVIS, M.D.
Chicago, Ill.

The author reports no financial relationships with commercial interests.

This letter (doi: 10.1176/appi.ajp.2010.10030396) was accepted for publication in April 2010.

Substance Abuse and Switch From Depression to Mania in Bipolar Disorder

To the Editor: The recent Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) article by Michael J. Ostacher, M.D., M.P.H., et al. (1), published in the March 2010 issue of the *Journal*, identified an association between current or past substance abuse or dependence in bipolar disorder patients and a greater likelihood for affective polarity switch from depression to mania, hypomania, or mixed state relative to when comorbid substance use disorders were absent (1). Consistent with this finding, previous naturalistic data from a study that I co-authored (2) demonstrated that a history of comorbid alcohol or substance use disorders conferred an approximate 7-fold increased risk in bipolar disorder patients for developing antidepressant-induced mania, regardless of cotherapy with antimanic agents. Using multiple regression, similar findings during antidepressant therapy were reported by Manwani et al. (3). In light of this prior literature, it would have been informative within the STEP-BD database to determine whether the presence or absence of antidepressant use mediated the relationship between a comorbid substance use disorder and affective polarity switch from depression. Although STEP-BD subjects with comorbid substance use disorders were less likely to receive an antidepressant than those without substance use disorders, this comparison in itself does not address the question of whether depressed bipolar subjects with a substance use disorder were more likely to experience a polarity switch in the presence rather than absence of an adjunctive antidepressant.

Elsewhere, the STEP-BD randomized acute depression pathway (4) showed no increased risk for mood destabilization with antidepressants among bipolar depressed patients overall, but that investigation has not yet examined whether there may be distinct bipolar subgroups who are prone to affective polarity switch during antidepressant therapy. Insofar as Dr. Ostacher et al. identify bipolar disorder patients with comorbid substance use disorders as especially vulnerable to mood instability, yet no less likely to recover from a depressive episode as those without substance use disorder comorbidity, the potential safety versus efficacy of adjunctive antidepressants in this particular subset of individuals with bipolar depression warrants further examination.

References

1. Ostacher MJ, Perlis RH, Nierenberg AA, Calabrese J, Stange JP, Salloum I, Weiss RD, Sachs GS; for STEP-BD Investigators: Impact of substance use disorders on recovery from episodes of

depression in bipolar disorder patients: prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2010; 167:289–297
2. Goldberg JF, Whiteside JE: The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002; 63:791–795
3. Manwani SG, Pardo TB, Albanese MJ, Zablotsky B, Goodwin FK, Ghaemi SN: Substance use disorder and other predictors of antidepressant-induced mania: a retrospective chart review. J Clin Psychiatry 2006; 67:1341–1345
4. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME: Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356:1711–1722

JOSEPH F. GOLDBERG, M.D.
New York, N.Y.

Dr. Goldberg has served on the speaker's bureaus of AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck, and Pfizer; he has received honoraria for lectures for Janssen-Cilag; and he has served as a consultant to or on the scientific advisory board for Cephalon and Eli Lilly.

This letter (doi: 10.1176/appi.ajp.2010.10030367) was accepted for publication in April 2010.

Reply to Goldberg Letter

To the Editor: We thank Dr. Goldberg for calling our attention to the findings suggesting that switch risk is increased in patients with bipolar disorder who also have substance use disorders and are treated with antidepressants. Whether the risk we observed is specific to antidepressant-treated patients is an important issue that merits further investigation.

MICHAEL J. OSTACHER, M.D., M.P.H.
ROY H. PERLIS, M.D., M.Sc.
Boston, Mass.

The authors disclosures accompany the original article.

This letter (doi: 10.1176/appi.ajp.2010.10030367r) was accepted for publication in April 2010.

Pregabalin Abuse, Dependence, and Withdrawal: A Case Report

To the Editor: Pregabalin is a novel gamma-aminobutyric acid (GABA) analog that is approved for the treatment of neuropathic pain and partial-onset seizures. While there are reports about the addictive potential of another novel antiepileptic drug (gabapentin [1, 2]), we present the first case of pregabalin dependence.

"Mr. B" was a 47-year-old man who asked for admission to the department for addiction medicine. At the time of his admission, he was consuming 25 capsules (equivalent to 7,500 mg) of pregabalin per day as well as alcohol and cannabis at irregular intervals. Attempting to wean himself off pregabalin, he developed vegetative withdrawal symptoms, including sweating, unrest, arterial hypertension, tremor, and craving for pregabalin. He fulfilled all seven DSM-IV dependence criteria. The patient reported a history of alcohol and cannabis abuse as well as heroin dependence but had been abstinent from heroin since he was released from prison 7 years ago. Two years ago, a friend suffering from neuropathic pain recommended that he use pregabalin, which in high doses would induce "very good feelings." Mr. B took some pregabalin capsules and experienced euphoric feelings. In the following weeks, his pregabalin use became regular, and he developed tolerance and withdrawal symptoms, which is why he finally increased the dosage to 25 capsules per day.

After admission to the unit, the patient's withdrawal symptoms were only insufficiently controlled by benzodiazepines. On the first day, we had to add pregabalin in high doses to achieve significant clinical improvement. His blood analysis immediately after admission showed a pregabalin level of 29 mg/l (therapeutic range: 0.5–16 mg/l). A breathalyzer test for alcohol was negative, urine drug test was positive for cannabis, and the patient stated that alcohol withdrawal symptoms were unknown to him. Standard laboratory, ECG, cranial magnetic resonance imaging, and abdominal ultrasound results were without pathological findings. An EEG revealed general alterations, probably because of the pregabalin's effect. Consecutively, pregabalin capsules were slowly reduced by two capsules a day. Within 12 days, Mr. B's plasma levels decreased from 29 mg/l to 9.8 mg/l. He repeatedly complained of a heavy craving for pregabalin, discontinued the treatment prematurely, and relapsed immediately at home by taking 20 capsules of the drug. Further attempts to motivate him for detoxification in our outpatient unit failed, and he continued taking up to 20 capsules per day.

Pregabalin is a GABA-analog that selectively binds to the alpha$_2$ delta subunit of voltage-gated calcium channels. It inhibits the release of excitatory neurotransmitters and increases neuronal GABA levels. Like some other compounds that modulate GABA-ergic neurotransmission, pregabalin might have a potential for abuse. Our patient had a history of drug addiction, which may be important in the reward effect of pregabalin. We therefore recommend being especially cautious when using pregabalin to treat patients with a history of drug or alcohol dependence.

References

1. Pittenger C, Desan PH: Gabapentin abuse, and delirium tremens upon gabapentin withdrawal. J Clin Psychiatry 2007; 68:483–484
2. Vicctorio-Vigneau C, Guerlais M, Jolliet P: Abuse, dependency and withdrawal with gabapentin: a first case report. Pharmacopsy 2007; 40:43–44

MARTIN GROSSHANS, M.D.
JOCHEN MUTSCHLER, M.D.
DERIK HERMANN, M.D.
OLIVER KLEIN, M.D.
HARALD DRESSING, M.D.
FALK KIEFER, M.D.
KARL MANN, M.D.
Mannheim, Germany

The authors report no financial relationships with commercial interests.

This letter (doi: 10.1176/appi.ajp.2010.09091269) was accepted for publication in January 2010.