

June

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QUETIAPINE-INDUCED HYPOTHYROIDISM

Quetiapine fumarate is an atypical neuroleptic indicated for the treatment of schizophrenia. It is also used as both a monotherapy for the acute treatment of manic episodes and as an adjunct to treatment with lithium or divalproex associated with bipolar type 1 disorder. Pharmacologically, it is an antagonist at serotonin (5-HT)_{1A} and 5-HT₂, dopamine (D)₁ and D₂, histamine H₁, and adrenergic α_1 and α_2 receptors.¹ According to the package insert,¹ in clinical trials of the drug there were small dose-related decreases in thyroid hormone, particularly total T₄ and free T₄; however, only 0.4% of subjects studied experienced significant increases in thyroid stimulating hormone (TSH) levels. In previously reported cases of quetiapine-induced hypothyroidism,²⁻⁶ most of the patients either had a history of compromised thyroid function or had normal TSH levels. In addition, no anti-thyroid antibody titers were measured in these studies. The following is a report of a depressed patient treated with quetiapine who developed hypothyroidism that remitted after drug discontinuation.⁷

A 49-year-old woman with a 20-year history of dysthymia and two major depressive episodes 14 and 5 years prior was admitted to the Psychiatric Unit at Eginition Hospital in Athens, Greece, for treatment of her disabling depression. Over the preceding 4 years she had been abusing high doses of zolpidem, up to 150 mg/day, which she reported not only alleviated her chronic insomnia but which had mood-elevating effects as well. Six months prior to admission, the patient was treated with the combination of venlafaxine 300 mg/day, paroxetine 30 mg/day, and quetiapine 800 mg/day, without benefit. At the time of admission, routine laboratory testing revealed that the patient, who had no prior history of thyroid disease but a positive family history of hypothyroidism in two siblings, had abnormal thyroid indices compatible with hypothyroidism as follows: total serum T₃ 0.77 (range 0.76–1.78 ng/mL), total serum T₄ 4.17 (range 6.09–12.23 μ g/dL), Free T₄ 0.53 (range 0.58–1.64 ng/dL), and TSH 6.78 (range 0.34–5.60 μ IU/mL). Clinical

symptoms and signs of hypothyroidism included modest weight gain, decreased appetite, voice hoarseness, expressionless face, slowing of intellectual and motor activity, and constipation. Due to concerns about its possibly inducing hypothyroidism, quetiapine was tapered to discontinuation over a 1-week period while the rest of the medication regimen was left unchanged. Over the next 2 months, there was a robust and progressive normalization of thyroid indices as follows: T₃ 1.13, 0.96 and 0.89 ng/mL, total serum T₄ 5.38, 6.77, and 5.74 μ g/dL, Free T₄ 0.61, 0.73, and 0.64 ng/dL, and TSH 4.75, 5.09, and 3.99 μ IU/mL, at 1 week, 1 month, and 2 months after quetiapine discontinuation, respectively. Moreover, anti-thyroid peroxidase autoantibodies, considered as the most sensitive and specific marker of thyroid autoimmunity, were 126.36 at 1 week after quetiapine discontinuation, but had declined to 74.40 by 2 months after quetiapine discontinuation (range <100 IU/mL). Concomitantly, there was steady mood improvement over this period as well.

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Disclosure: Dr. Ginsberg is a speaker for AstraZeneca, Bristol-Myers Squibb, Cyberonics, Forest, and GlaxoSmithKline; and has received research support from Cyberonics.

The temporal sequence of events is consistent with quetiapine-induced hypothyroidism. Possible mechanisms of action underlying this association include competitive metabolism of UDP-glucuronosyltransferase by quetiapine and thyroid hormones, a direct action of quetiapine on the hypothalamopituitary axis, or an immune reaction to quetiapine similar to the one sometimes observed in association with lithium treatment. It is also possible that the finding is purely coincidental, associated with the underlying affective illness and not due to quetiapine. While the incidence appears quite low, clinicians who prescribe quetiapine ought to be aware of the potential for development of hypothyroidism as an unintended adverse effect. **PP**

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PROPOFOL-INDUCED PRIAPISM

Previous "Psychopharmacology Reviews" columns have discussed reports on the successful off-label use of the intravenous anesthetic propofol, also known as 2,6-diisopropylphenol, for the management of delirium tremens.¹⁻³ Propofol is also sometimes used during administration of electroconvulsive therapy, and it potentiates both γ -aminobutyric acid and glutamate receptors. It has a rapid onset and short duration of action. In addition to its role as an anesthetic, propofol has antiemetic and antipruritic properties.⁴ Moreover, several case reports mark the successful use of propofol in treating status epilepticus.^{5,6} Paradoxically, in high doses, propofol has been reported to cause seizures.⁷ The following is a report of propofol-induced priapism.⁸

A 17-year-old white male with a history of supraventricular tachycardia and Crohn's disease was admitted for cardiac ablation of an aberrant pathway. His medication regimen consisted of atenolol 100 mg/day (held prior to the procedure), mesalamine 1,000 mg/day, polyethylene glycol 17 g/night, mercaptopurine 30 mg/day, gabapentin 300 mg QID, and tramadol 50–100 mg every 6 hours PRN. Anesthetic agents for the ablation procedure included midazolam 4 mg,

propofol infusion at a rate of 2.8 mg/minute, cisatracurium infusion at a rate of 90 μ g/minute, sevoflurane inhalation, and nitrous oxide inhalation. Two hours after initiation of the propofol infusion (total dose 550 mg), the patient experienced engorgement of the penis. After 1 hour without resolution, a urology consult was obtained, propofol was discontinued, and sevoflurane was increased. The urologist injected 2 mL of lidocaine 0.5% with epinephrine 1:200,000 into each corpus, with prompt detumescence. The priapism lasted 2 hours and resolved promptly after treatment, with no blood loss or further complications. Anesthesia was maintained with sevoflurane, nitrous oxide, cisatracurium, and midazolam following the discontinuation of the propofol infusion. The ablation was successfully completed.

The next day, the patient underwent a routine post-ablation transesophageal echocardiogram. He received total doses of midazolam 3 mg, fentanyl 75 μ g, and propofol 40 mg over 20 minutes during this procedure. Thirty minutes after completion of the echocardiogram, the patient developed priapism, which resolved within 1 hour without medical intervention.

The temporal sequence of events described, including recurrence upon rechallenge, indicates that propofol was a highly probable causative agent of priapism in this patient. Priapism, characterized by abnormal, prolonged, painful erection of the penis, is a urological emergency. Complications may occur if not treated in time, including difficulty urinating, urinary retention, impotence, cavernosa fibrosis, and gangrene. Even with surgery, approximately 40% to 50% of patients with priapism will become impotent.⁹ Causes of priapism include blood dyscrasias, solid tumors, trauma, spinal cord injuries, and stroke. Medications may also cause priapism. In general, the medications most commonly associated with priapism are antihypertensives, anticoagulants, antidepressants, and antipsychotics.^{10,11} The case described here is the first published report of priapism in association with the intravenous anesthetic, propofol. While the frequency of this adverse effect appears to be rare, when it does occur it requires prompt intervention. **PP**

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VISUAL HALLUCINATIONS DUE TO THE ADDITION OF RILUZOLE TO MEMANTINE AND BUPROPION

Riluzole is a benzothiazole medication indicated for patients with amyotrophic lateral sclerosis to extend survival and/or time to tracheostomy.¹ Pharmacologically, riluzole reduces glutamate release, inactivates voltage-dependent sodium channels, and inhibits γ -aminobutyric acid reuptake.² Previous "Psychopharmacology Reviews" columns have reported on studies suggesting that riluzole may be effective in treating generalized anxiety disorder,³ treatment-resistant depression (TRD),^{4,5} obsessive-compulsive disorder,^{6,7} and borderline personality disorder.⁸ The following is a report of add-on riluzole for TRD resulting in new-onset visual hallucinations.⁹

A 43-year-old woman with a long history of TRD had a family history of alcoholism on her father's side and of depression on her mother's side. With a history of psychologic trauma dating to childhood, she had a lifelong pattern of low self-esteem and of fluctuating depressive symptoms, albeit ones which did not interfere with her functioning until immediately after the birth of her third child 6.5 years prior to the time of admission. Severe depression with suicidality necessitated the current hospitalization. After the onset of her depression she began abusing alcohol but had no history of delirium tremens or of alcohol-related hallucinations. She occasionally used marijuana, but denied use of other drugs including hallucinogens. Despite longstanding treatment with many agents, she never attained complete remission of her depression. Antidepressant trials included multiple selective serotonin reuptake inhibitors, mirtazapine, venlafaxine, dextroamphetamine, amoxapine, and bupropion. Augmentation agents included lithium, divalproex, gabapentin, and lamotrigine. The patient also completed 3 sets of electroconvulsive therapy with only modest benefit. Antipsychotic trials included risperidone, haloperidol, quetiapine, olanzapine, and clozapine. Of note, the clozapine trial had to be terminated early due to the occurrence of visual illusions that were described as "preseizure auras" but which did not progress to an actual seizure. Over the 7 years prior to the current admission, the patient had been hospitalized seven times, two of which were precipitated by superficial self-induced lacerations during a period of intoxication.

The patient presented to the psychiatry research unit for elective participation in an ongoing trial of riluzole as an add-on therapy for TRD. At admission, she was profoundly dysphoric and minimally engageable with prominent psychomotor retardation, constricted affect, poverty of speech, and thought blocking. Baseline mood and anxiety ratings were in the severe range as follows: 39 on the Hamilton Rating Scale for Depression (HAM-D), 37 on the Beck Depression Inventory (BDI), and 20 on the Hamilton Rating Scale for Anxiety (HAM-A). The patient denied auditory or visual hallucinations and exhibited no delusional thought content, although depressive ruminations of nearly delusional proportions were present. She endorsed passive suicidality. Cognition was intact, with a Folstein Mini-Mental Status Examination score of 27/30. While her full-scale intelligence quotient was 89, she had marked gaps in autobiographical memory. Physical examination including vital signs were unremarkable. Laboratory studies, including chemistries, blood count, thyroid, and liver function tests, were normal. A urinalysis revealed a urinary tract infection. The patient denied use of alcohol for the 1 month prior to admission. Urine toxicology screen was negative.

Her preexisting medication regimen consisted of lithium 900 mg/day, bupropion 450 mg/day, amoxapine 250 mg/day, memantine 10 mg/day, tiagabine 12 mg/day, and diazepam 20 mg/day. In accordance with the study protocol, riluzole 50 mg BID was added to her current psychotropic medications. Shortly thereafter, the patient reported unequivocal subjective improvement of her depression. However, at the end of the first week of riluzole treatment she also began to report visual hallucinations. Initially, these consisted of a piece of multicolored rope floating and weaving in her room. Frequent elementary hallucinations were of patterns on the walls, which occurred in full light but which were more intense in the evenings regardless of whether or not the lights were on. During the evenings, the hallucinations became more complex, resolving into well-formed scenes "like a movie," which occasionally the patient was able to recount. At all times, reality testing remained intact, with good insight into the nature of both simple and complex hallucinations. While not frightening, the hallucinations were distressing. There was no evidence of a thought disorder. Repeat laboratory testing including chemistries and liver function tests were normal.

Due to concerns about a possible pharmacodynamic drug-drug interaction involving the glutamate release-inhibiting action of riluzole with the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonizing effects of memantine culminating in a ketamine-like hallucinogenic effect, memant-

tine was discontinued. Subsequently, the visual hallucinations resolved for 10 days, only to recur again as before, with occasional well-formed visual scenes in the evening. At this point, the patient was withdrawn from the study and riluzole was reduced to 50 mg/day. There was a slight reduction in hallucinations. Despite the reduced dose of riluzole, the depression improved, both by subjective report (BDI, 25) and by objective ratings (HAM-D, 27). Tiagabine was tapered to further simplify her medication regimen, with no appreciable effect on either the depression or the hallucinations. Next, the norepinephrine and dopamine reuptake inhibitor bupropion was also tapered to discontinuation due to the possible psychotomimetic effects. At this point, the visual hallucinations quickly declined, then completely remitted over the next 72 hours. Riluzole was then reincreased to a dose of 150 mg/day without any recurrence of hallucinations; however, there was also no further improvement in mood (HAM-D, 28; HAM-A, 22; BDI, 28).

As noted by the authors of this case report, the occurrence of visual hallucinations in a patient taking two ant glutamatergic medications combined with bupropion suggests that pharmacodynamic interaction between the glutamate and dopamine systems may be a potential mechanism. Other possible but less likely explanations for this patient's visual hallucinations include alcohol hallucinosis or seizures; however, the latter were not observed by the unit staff. In schizophrenia, deficits in the function of the NMDA glutamate receptor and hyperactivity of limbic dopamine systems have long been thought to contribute to psychosis.¹⁰⁻¹² Thus, psychopharmacologic regimens that duplicate this pattern of interaction, such as the combination of the ant glutamatergic medications lamotrigine, memantine, and riluzole with prodopaminergic medications like bupropion, pramipexole, and dextroamphetamine, may also increase psychosis risk. **PP**

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ARIPIPRAZOLE-INDUCED DYSTONIA

Aripiprazole is an atypical neuroleptic indicated for the treatment of schizophrenia and acute manic and mixed episodes associated with bipolar disorder. A potent dopamine partial agonist, aripiprazole acts as an antagonist at dopamine (D)₂ receptors under hyperdopaminergic conditions and as a D₂ agonist under hypodopaminergic conditions. It has been theorized that dopamine partial agonists may be able to stabilize the dopaminergic system without inducing a hypodopaminergic state, thereby reducing the risk of side effects associated with pure blockade of dopamine receptors. In addition to these effects, aripiprazole also acts as a partial agonist at 5-hydroxytryptamine (5-HT)_{1A} receptors and as an antagonist at 5-HT_{2A} receptors. The most commonly reported side effects in association with use of aripiprazole include insomnia, anxiety, headaches, nausea, vomiting, and somnolence.¹

Acute dystonia is a distressing and sometimes life-threatening form of extrapyramidal symptoms that in the vast majority of cases occurs within a few days of initiation of antipsychotic medication. Acute dystonias are among the most frightening side effects of antipsychotic drugs. Occurring in upwards of 10% of patients, often within the first few hours or days of treatment, these involuntary movements result from slow, sustained muscular contractions or spasms. Dystonias may involve the eyes, neck, jaw, tongue, or the entire body. Risk factors include male gender, young age, and use of intramuscular doses of high-potency antipsychotics.² The following is the first published report of aripiprazole-induced dystonia in an adult.³

An 18-year-old male with Tourette's disorder had a history of developing phonetic tics when he was 9 years of age, which included blurting out words without any simple utterances. These resolved by the time he was 17 years of age. At 15 years of age, he began to experience simple involuntary movements such as shoulder shrugs and mouth grimaces. At the time of presentation, the patient had only simple motor tics. At baseline, his motor score on the Yale Global Tics Severity Scale was 9/16, his phonic score was 0/25, and his impairment score was 30/50. These scores indicated a moderate severity of Tourette's disorder.⁴ Otherwise, the patient was in good health and had not received any medication for at least 2 years. In the past, he had received supportive psychotherapy

and benzodiazepines. Aripiprazole 10 mg/day was initiated. By the second day, the patient reported significant improvement. However, on the third day he experienced an acute episode of dystonia with facial muscle spasm, oculogyric crisis, and torticollis. These adverse effects resolved after a single 5 mg intramuscular injection of the anticholinergic medicine biperidine. Aripiprazole was discontinued. One month later the patient was assessed by phone. During a direct follow-up visit to the service 2 months later, he reported a significant decrease of 50% to 70% in both the severity and frequency of tics. At this time his Yale Global Tics Severity Scale baseline motor score was 3/16, his phonic score was 0/25, and his impairment score was 10/50. In addition, there were no residual side effects from his previous exposure to aripiprazole.

The temporal sequence of events described above is consistent with aripiprazole-induced dystonia. While patients with Tourette's disorder are known to be very sensitive to antipsychotic adverse effects, other reports of severe extrapyramidal symptoms in association with aripiprazole include that of a 3-year-old child⁵ and another of an adolescent with a previous history of such symptoms.⁶ While short-term clinical trials of aripiprazole reported a very low incidence of extrapyramidal symptoms,⁷ with akathisia being the most common, clinicians ought to be aware of the possibility of such adverse effects, particularly in more vulnerable patient populations. *PP*

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CLOZAPINE-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

Clozapine is a dibenzodiazepine derivative that has greater potency in blocking dopamine (D)₁ compared with D₂ receptors. Clozapine also has potent dopaminergic anti-D₄, anti-serotonergic (5-hydroxytryptamine type 2), antimuscarinic, anti-adrenergic (α_1 and α_2), and antihistamine (H₁) effects, and enhances dopamine release in the striatum.¹ The first of

the "atypical" neuroleptics Food and Drug Administration-approved for the treatment of schizophrenia, clozapine is known to have a lower risk of causing parkinsonism^{2,3} and tardive dyskinesia⁴ in schizophrenic patients. It is indicated for treatment-resistant schizophrenia and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder. Clinical trials of clozapine have revealed numerous side effects including sedation, constipation, hyperthermia, sialorrhea, gastrointestinal upset, myoclonus, and weight gain. Agranulocytosis occurs in 1% to 2% of patients, typically within the first 6 months of treatment. With careful clinical monitoring leading to early recognition of agranulocytosis and to discontinuation of drug, most patients will fully recover. Among cardiovascular side effects are tachycardia, reversible electrocardiogram (ECG) changes such as ST segment depression or inverted T waves, orthostatic hypotension, hypertension, venous thromboembolism, cardiomyopathy, and fatal myocarditis.⁵⁻¹² In addition, elevated erythrocyte sedimentation rate (ESR),¹³ acute interstitial nephritis,^{14,15} eosinophilic colitis,¹⁶ allergic vasculitis,¹⁷ and the tetrad of pericarditis, polyserositis, rash, and pericardial tamponade¹⁸ have also been described in association with the use of clozapine. The following is a report of clozapine-induced systemic lupus erythematosus (SLE).¹⁹

A 32-year-old white woman with schizophrenia who had lived in a psychiatric facility for 9 years had first presented to the hospital in 1996 with clinical characteristics and laboratory markers consistent with drug-induced lupus. One year prior to that she had been started on clozapine. Specifically, work-up at the time had revealed strongly positive antinuclear antibodies (ANA) and inflammatory myopathy suggestive of collagen disease. Subsequently, she was taken off clozapine, which was suspected as a possible offending agent, and switched to an alternate antipsychotic medication. Naproxen was also added. Discharged with a diagnosis of autoimmune disease, by the time of her next follow-up visit 3 months later she appeared well and the ANA had disappeared.

In 2004, 1 month after rechallenge with clozapine for uncontrolled, catatonic schizophrenia, the patient again developed symptoms and signs consistent with drug-induced lupus. Physically healthy until 3 weeks prior to admission, she subsequently developed fatigue, myalgia, and arthralgia of the ankle and small joints of the hands. Three days prior to admission, her temperature had been 38.3° C. A complete blood count done at the psychiatric hospital had shown a drop in hemoglobin from 12.3 to 9 g/dL and an ESR of 126 mm/h. The patient denied using other medications, including estrogens and dietary supplements.

Upon admission, vital signs included temperature at 38.8° C, heart rate at 103 beats/minute and regular, respiratory rate at 18 breaths/minute, blood pressure at 110/65 mm Hg, and oxygen saturation at 97% on room air. The patient appeared ill. Her weight was 62 kg (136.4 lb). No rash or lymphadenopathy was noted. Although the patient complained of pleuritic chest pain, her lungs were clear. The abdominal skin was loose, consistent with recent weight loss. There was symmetrical swelling and tenderness at the ankles and small hand joints, with nonpitting edema. The rest of the physical examination, as well as a chest X-ray and ECG, were unremarkable. Urinalysis showed trace blood and protein. Hemoglobin was 9.6 g/dL, with mean corpuscular volume of 84 μm^3 , and the ESR was 94 mm/h. Unbound plasma hemoglobin was slightly elevated, as were ferritin (340 ng/mL) and haptoglobin (235 mg/dL). Direct Coombs test was negative, while thyroid function was normal. Lactate dehydrogenase was elevated at 950 U/mL (range 300–620), while creatine kinase was within normal limits. Aspartate aminotransferase was mildly elevated to 85 U/mL (2–60). A bone marrow biopsy revealed hypercellularity with clusters of rich cytoplasm (“tissue paper”) macrophages—a finding usually found in Gaucher’s disease, which this patient did not have. Abdominal computed tomography scan was normal. A test for ANA was strongly positive (+4 of +4) with a diffuse homogenous pattern. Antihistone antibodies were found (1.6 units; negative <1, weak positive 1–1.5, moderate positive 1.6–2.5, strong positive >2.5). Extractable nuclear antibodies were elevated to 15 U/mL (normal 0–10) while anti-deoxyribonucleic acid antibody test results were within normal limits. Complement levels showed a normal C3 of 67 mg/dL (50–120) but a reduced C4 of 11 mg/dL (20–50). Again, as with the previous episode 8 years prior, discontinuation of clozapine resulted in remission within 2–3 months.

The temporal pattern of events consisting of appearance of symptoms shortly after drug introduction, resolution after drug discontinuation, prompt recurrence after rechallenge, and remission after discontinuation is strongly suggestive of clozapine-induced SLE. Although there are at least two prior published reports of clozapine-induced SLE,^{20,21} none were diagnosed with the strict criteria used in the case reported here. While the risk of developing SLE in association with clozapine appears to be very low, its seriousness requires that clinicians be aware of the possibility of its occurrence. **PP**

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