Systematic Review of Lithium Augmentation in Depression Resistant to at Least 2 Antidepressants

To the Editor: Refractory depression is common in clinical practice. At least 30% of patients fail to respond to initial antidepressant therapy.[1] In patients who have failed 1 course of antidepressants, there is evidence from 9 randomized controlled trials suggesting that approximately 50% of treatment-refractory patients do respond to lithium augmentation compared with placebo ($p < .001$).[2] The British Association for Psychopharmacology guidelines recommend that patients be treated with 2 antidepressants before an augmentation strategy is used.[3]

Our aim was to review the evidence for use of lithium in those patients who are resistant to treatment with 2 or more antidepressants at recognized therapeutic doses.

Method. A systematic review was undertaken of placebo-controlled, double-blind, randomized trials of lithium that assess its effectiveness in treatment-resistant depression. English-language studies of adults (aged 18 years or older; both sexes), suffering from major depressive disorder diagnosed by the *International Classification of Diseases, Tenth Revision (ICD-10),* the *Diagnostic Statistical Manual of Mental Disorders,* Fourth Edition *(DSM-IV),* or *Research Diagnostic Criteria (RDC)* were included. The following keywords were used: *lithium* OR *Camcolit* OR *Carbolith* OR *Duralith* OR *Eskalith* OR *Licarbium* OR *Liskonum* OR *Litarex* OR *Lithane* OR *Lithocarb* OR *Lithizine* OR *Lithonate* OR *Lithotabs* OR *Manialith* OR *Phasal* OR *Priadel* OR *Quilonorm* OR *Quilonum* OR *Li-Liquid* OR *resistant depression* OR *refractory depression* OR *treatment resistant depression* OR *treatment non respon(*) depression* OR *lithium augment(*).* Exclusion criteria were bipolar depression, previous prescription of lithium, co-morbid schizophrenia, or drug and alcohol dependence.

All participants should have received 2 antidepressants at recognized therapeutic doses (eg, 150 mg of imipramine daily) for a minimum of 4 weeks. Participants in the active arm should have received at least 4 weeks of lithium treatment at a minimum plasma level of 0.4 mmol/L or a dose of 600 mg daily.

The search included the computerized databases of the Cochrane Library, MEDLINE/PubMed (1966+), EMBASE (1980+), CINAHL (1982+), and PsycINFO (1974+). Reference lists were hand searched along with major books. Pharmaceutical companies were contacted. Leading researchers and experts in the field were also contacted. Methodological quality was categorized as (A) adequate, (B) uncertain, or (C) inadequate.

Results. A total of 12 randomized controlled trials involving lithium augmentation for resistant depression were identified, of which only 1[4] had ensured a trial of 2 antidepressants. There was little information given in the published reports regarding the methods used to achieve random allocation. Thus, on the basis of the published reports, the studies initially received a B rating according to the Cochrane criteria.

In the 1 study that included 2 antidepressants,[4] there were 18 patients in the lithium augmentation arm, of whom 2 dropped out. The proportion who responded to lithium augmentation in the completer and intent-to-treat (ITT) analyses were 12.5% and 11.1%, respectively. There was no statistically significant difference in scores on the 17-item Hamilton Rating Scale for Depression. The lithium group achieved a mean reduction of 6.3/5.5 points (completer/ITT). The mean reduction in the placebo group was 6.5/5.8 points (completer/ITT) ($p = .91$). The mean blood lithium level at week 2 was 0.63 mmol/L (range, 0.3–1.4 mmol/L) and at week 6 was 0.61 mmol/L (range, 0.6–0.9 mmol/L). The duration of the trial was 6 weeks.

In the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[5] there was no placebo group, and, as there was no significant difference to T_3 augmentation (which has not yet been demonstrated as being effective for treatment-resistant depression), we cannot conclude that either lithium or T_3 is an effective augmentation strategy for patients who are resistant to at least 2 antidepressants.

There is limited evidence to support the use of lithium augmentation after 2 or more failed antidepressant therapies. More research needs to be undertaken to compare lithium augmentation with other augmentation strategies. Those patients who have failed to respond to 2 or more antidepressants are a difficult group to treat.

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Quetiapine-Induced Bradycardia Without QT Interval Prolongation in an Elderly Woman

To the Editor: Bradycardia has recently been reported as a rare but severe adverse effect of atypical antipsychotics like risperidone,[1,2] olanzapine,[3] and clozapine.[4] Most case reports describe bradycardia with QT interval prolongation.[1–5] Until now, the mechanism of this bradyarrhythmogenic character of atypical antipsychotics has not fully been understood. Interference with K^+ transport inward ven-

tricular cells was suggested by Magyar et al.[6] Quetiapine is increasingly used in the treatment of elderly patients and those with relevant comorbidity because of its apparently lower incidence of side effects. Among others, Gareri et al[7] stated in their review article on adverse effects of atypical antipsychotics that no electrocardiogram (ECG) monitoring was required, because of infrequent QTc time alterations on using quetiapine. Here, however, we present a case of an elderly woman with paranoid schizophrenia treated with quetiapine who suffered from asymptomatic bradycardia without QT interval prolongation that resolved after withdrawal.

Case report. Ms A, a 63-year-old woman diagnosed with paranoid schizophrenia according to *DSM-IV* criteria, was admitted in November 2006 to the gerontopsychiatric unit of De Gelderse Roos Mental Health Care. She had previously received several antipsychotics, both classical and atypical, and at admission was receiving quetiapine at a daily dose of 1,000 mg. Despite this high dose, the psychosis persisted, but she did not experience any physical complaints except fatigue. At physical examination, we found a slow irregular pulse rate (52 bpm) and a blood pressure of 115/77 mm Hg without orthostasis.

In the following days, the bradycardia persisted with pulse rates varying from 40 to 55 bpm. The ECG showed a sinus bradycardia with normal conduction times (PQ interval = 123 ms, QT interval = 440 ms) and some ventricular extrasystoles. During exercise, the bradycardia persisted, and at laboratory examination no abnormalities were found, with findings including a plasma quetiapine concentration (160 mg/mL) within normal limits. The bradycardia and the lack of antipsychotic effect forced us to reduce the quetiapine dose. During a 6-week taper, the bradycardia persisted but completely disappeared 6 days after full cessation with the pulse rate increasing to over 60 bpm.

On prescription of clozapine, the bradycardia did not return. The Holter ECG showed only a few 3- to 4-second pauses during the night. No tachycardias were registered. The echocardiography showed normal left ventricular function and normal aortic valve dimensions. Therefore, a sick-sinus syndrome or atrioventricular node dysfunction as a cause of the bradycardia—although not fully ruled out—is less likely.

To our knowledge, this is the first case of quetiapine-induced bradycardia unrelated to the QT interval. According to the criteria proposed by Naranjo et al,[8] it is a probable cause. Although quetiapine is assumed to be safe in elderly patients and patients with comorbidity, this report indicates that it needs to be prescribed with the same precautions as other antipsychotics. Since it is still unknown which patients are at risk for developing bradycardia, we support the advice of Stollberger et al[5] of routinely monitoring the ECG when prescribing atypical antipsychotics. At least at baseline and after the introduction of the drug, both QT interval and heart rate need to be documented.

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Oxcarbazepine-Induced Reversible Anorgasmia and Ejaculatory Failure: A Case Report

To the Editor: Psychotropic drugs are well known to affect sexual functioning[1] and may contribute to patient noncompliance. The serotonin reuptake inhibitor antidepressants are particularly known for their effects on orgasm.[2] Much less is known about adverse sexual effects of anticonvulsants, although a few case reports suggest that topiramate,[3] gabapentin,[4] and carbamazepine[5] may cause ejaculatory failure, though these cases are mainly from patient populations with epilepsy. Here, we report a case of oxcarbazepine-induced anorgasmia and ejaculatory failure in a patient with schizoaffective disorder.

Case report. Mr A, a 28-year-old man, has a long history of *DSM-IV* schizoaffective disorder. Upon his initial presentation to the outpatient mental health clinic in 2008, he was being prescribed quetiapine 600 mg/d and paliperidone 6 mg/d. Despite this, he remained preoccupied by paranoid delusions and complained of feeling depressed and hopeless with neurovegetative symptoms, sleep disturbance, and severe anxiety. Though he endorsed intermittent passive death wishes, he denied suicidal thoughts, intent, or plan to harm himself or others. His history revealed episodic increased energy, decreased need for sleep, increased goal-directed activities, disorganized behavior, and worsening psychotic symptoms that seemed consistent with mania.

To better control the psychotic symptoms, Mr A's paliperidone was increased to 9 mg/d. At his next appointment, Mr A felt his psychotic symptoms were largely under control with the paliperidone and the quetiapine but continued to complain of low mood, anxiety, sleep disturbance, and low energy. It was recommended that Mr A undergo a trial with a mood stabilizer. Mr A initially refused to take lithium, valproic acid, or carbamazepine, as he did not want to undergo the laboratory work required to monitor the blood levels of these drugs. However, he was agreeable to a trial of oxcarbazepine 300 mg PO bid, despite the fact that this medication would still require occasional laboratory work.

Within a week, Mr A felt that his mood had improved, but he complained of concerning sexual side effects, specifically an inability to experience orgasm or ejaculate. He denied having cloudy urine after sexual activity, making retrograde ejaculation less likely. Neither libido nor erection was affected. Mr A stopped oxcarbazepine treatment due to these concerns, and within a few days the sexual side effects abated. After a few days, he resumed oxcarbazepine 300 mg twice daily. Again, he experienced anorgasmia and ejaculatory failure. Due to these symptoms, which Mr A found intolerable, oxcarbazepine treatment was stopped at the next visit. At the following appointment, orgasm and ejaculatory abilities had returned to normal. During this time period, Mr A denied taking any illicit drugs or any alcohol abuse, and no other new medications had been initiated.

This case demonstrated a clear on/off phenomenon of anorgasmia and ejaculatory failure related to oxcarbazepine. We have found no previous reports of anorgasmia and ejaculatory failure associated with oxcarbazepine, although it has been associated with sexual side effects. In a study of its use in epilepsy, 17% of men reported sexual dysfunction.[6] Anticonvulsant medications may interact with sex hormones,[6] and central-acting drugs such as oxcarbazepine may cause anorgasmia in conjunction with sedation.

It is difficult to determine a mechanism by which oxcarbazepine (keto analogue of carbamazepine with no significant anticholinergic or sympatholytic activity) could cause ejaculatory failure, but its use should be reconsidered if troublesome ejaculatory failure develops. We usually ask questions about decreased sexual function with selective serotonin reuptake inhibitors, but not with anticonvulsants. Physicians should be vigilant and should evaluate patients for sexual dysfunction with anticonvulsant treatment.

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Risperidone-Induced Priapism: A Case Report

To the Editor: Priapism is a prolonged, painful, and persistent penile erection usually not associated with sexual stimulation. Priapism results from an obstruction in the venous drainage of the corpora cavernosa of the penis sparing the glans penis and corpora spongiosa; thus, only the corpora cavernosa are turgid without affecting the other 2 components. It is this finding that distinguishes priapism from a normal penile erection.[1]

Priapism is a relatively rare condition, but due to its potentially serious and long-term consequences and its potential as an adverse effect of many common medications, it is a matter of serious concern for clinicians. Impotence may occur in 50% of patients with an episode of priapism,[2] and it is considered a urologic emergency. We present a case of a patient who developed priapism during treatment with risperidone, an atypical antipsychotic medication, and the treatment decisions that followed.

Case report. Mr A, a 31-year-old African American man, had a 10-year history of schizophrenia, chronic, paranoid type, diagnosed using the *DSM-IV* criteria. The patient had been followed at our outpatient clinic since 1997 and had been compliant with the treatment recommendations. His symptoms of schizophrenia were under fairly good control with risperidone. There was no history of psychiatric inpatient hospitalization. The patient had never been married and had no children. He lived by himself and worked 1 day a week doing newspaper advertising inserts. He had been attending a community-based day program 1 day a week for 10 years. He was a high school graduate with some community college training in computers. The patient was a nonsmoker and a nondrinker and had no history of any illicit drug use. His medical history was significant for obesity, hypercholesterolemia, keloid on his neck, and tonsillectomy at age 6 years. His only medication was risperidone 2 mg in the morning and 3 mg at bedtime.

The patient presented to the emergency room in 2005 with a 10-day history of a persistent and painful penile erection. It was sudden in onset while the patient slept, and he awoke with a painful erection. The patient was not sexually active; there was no history of penile, genital, or pelvic trauma; and there was no evidence of any infection or malignancy. There was no change in his current medications and no reported use of any over-the-counter medication or any herbal preparation. The patient had a similar complaint 2 years earlier, but it resolved within a few hours and he did not seek medical care.

On this occasion, the erection persisted, and on the 10th day he presented to the emergency room. Routine laboratory tests were performed that included complete blood count, basic metabolic profile, and a coagulation study, and all the results were within normal limits. A diagnosis of priapism was made, and the urology service was consulted. They performed irrigation with normal saline followed by an injection of phenylephrine to the corpora cavernosa to reduce the priapism. There was some improvement in the patient's priapism, and he was transferred to the internal medicine floor. On the second day, his symptoms worsened, and he was offered a second phenylephrine injection, which he refused due to pain. He was then transferred to the operating room where a Winter shunt was placed between corpora cavernosa and corpora spongiosa to relieve his symptoms. His priapism resolved completely within a few hours with the shunt placement. Sickle cell anemia was a potential cause of his priapism, so a hematology consult was obtained. In the absence of any history of anemia, pain crisis, or blood transfusion, a diag-

nosis of sickle cell anemia was considered unlikely and was ruled out by testing, but the patient was found to be a carrier. While in the hospital, his risperidone treatment was continued. The patient was discharged to home on the fourth day to be followed up in our outpatient psychiatry clinic. Risperidone was the only known causative factor, and despite its efficacy for this patient, it was discontinued. The patient's treatment was changed to aripiprazole in a cross-tapering manner over 3 weeks. The priapism had not returned when the patient was followed up 2 months later.

Although priapism can occur in all age groups, it occurs more frequently in the third and fourth decades, often early in the morning, and is noticed on waking.[3] The cause is unknown 50% of the time, and the rate of recurrence is 30%–40%.[3] The exact pathophysiology is still unclear, and it is considered to be multifactorial in origin. However, among all the reported cases of priapism, 15%–26% are linked to the use of antipsychotic medications.[4] Priapism may occur at any time during the treatment course of psychotropic medications and may occur even without a change in the medication dosage.[5]

Priapism is a result of an obstruction in the venous drainage from the corpora cavernosa of the penis. Priapism is commonly divided into 2 subtypes,[6] high-flow and low-flow priapism. High-flow subtype results from a rupture of a cavernous artery that leads to an abnormal blood flow in the penis. This condition is rare and is usually painless due to lack of ischemia, has a favorable prognosis, and is generally not considered a true emergency.[7]

In low-flow priapism, there is a reduction or absence of the venous drainage from the emissary venules, which results in hypoxia, acidosis, and ischemia. This subtype is painful, accounts for the majority of the cases, and can lead to irreversible fibrosis of the cavernosal spaces if not treated urgently.[7] Low-flow priapism is associated with the use of antipsychotic medications. The exact mechanism underlying antipsychotic-induced priapism is still unclear and is considered multifactorial in origin.[7] The histaminic system[8] and hypersensitization of the β-adrenergic receptors[9] have been proposed as important influences in this phenomenon.

The commonly proposed mechanism of antipsychotic-induced priapism is related to the α-adrenergic system. Arterioles in the penis that supply blood to the corpora cavernosa are in a tonic state of contraction during the flaccid state of penis, a condition mediated by the α-adrenergic activity.[10] During erection, there is a relaxation of the cavernous and the arteriolar smooth muscle leading to an increase in the blood flow into the sinusoidal spaces.[11] Priapism is proposed to be mediated by α receptors located in the corpora cavernosa of the penis,[8] and the α-adrenergic antagonist properties found in many psychotropic medications[12] could very well explain the mechanism underlying priapism induced by these medications. It has also been proposed that the corpora cavernosa in some men are exceptionally sensitive to α-blocking agents.[8,13]

Several other causes of priapism include perineal trauma, some antihypertensives, phosphodiesterase type 5 inhibitors, other behavior medications (trazodone), anticoagulants, and hematologic disorders including sickle cell anemia, leukemia, lymphoma, and thrombocytopenia.[7] However, the only medication our patient was taking was risperidone, which is known to possess α_1- and α_2-adrenergic antagonist properties,[14] and as there was no indication of any other medical illness or causative factor, we propose his condition of priapism to be related to the use of risperidone.

Priapism is a urologic emergency, and treatments, including ice packs, enemas, medications, and anesthesia, generally do not produce consistent results.[15]

Management usually includes intracavernous injection of an α-adrenergic agonist.[7] This patient needed to be maintained on an antipsychotic regimen, which posed a particular problem given the high degree of risk for priapism with these medications. At the time of our patient's follow-up, the only medication not reported to be associated with priapism was aripiprazole.

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