changes in the patient's medication regimen were made, continuing maintenance therapy with once-monthly injection of aripiprazole.

DISCUSSION

Psychiatric comorbid conditions are very common in patients with BD, although fewer data are available about the treatment of this significant clinical population.[1,2] The effectiveness of aripiprazole in BD is well documented, but to our knowledge, this is the first reported case in a patient who also had other 2 mental illnesses (comorbid BPD and substance abuse) treated successfully with aripiprazole LAI.

Prior to initiating treatment with aripiprazole LAI, the patient was receiving a mood stabilizer (valproic acid) combined with 2 atypical antipsychotics (quetiapine and aripiprazole) without achieving stabilization. When quetiapine was withdrawn, and the dose of oral risperidone was increased, we observed an improvement of psychiatric symptoms. However, it was not until the introduction of aripiprazole LAI in substitution of oral form that the patient achieved disease stabilization and improved quality of life. Moreover, given the good response observed with aripiprazole LAI, it was decided to discontinue valproic acid therapy. Because our patient had a high risk of developing valproate hepatotoxicity, its withdrawal reduced this risk, as well as other adverse effects and drug interactions. Disease stabilization and other patient symptoms were subjectively assessed by the physician. Thus, a limitation of this study includes the lack of rating scales to evaluate clinical status before and after aripiprazole LAI therapy.

As recommended in most clinical practice guidelines that suggest the use of 2 or more antipsychotics only as a last option,[8] our patient achieved stabilization with antipsychotic monotherapy, given the good response to aripiprazole LAI. Not only does polytherapy increase the risk of adverse events, but also the complexity of the medication regimen may discourage patients from taking medications as prescribed. Up to half of patients with BD are partially or completely nonadherent to antipsychotic treatment, resulting in poorer outcomes.[9] Although our patient was aware of the disease, adverse effects, especially those related to valproate, and the prescription of complex drug regimens probably contribute significantly to poor medication adherence. In this context, the present case report highlights how these factors can be addressed by the introduction of a long-acting formulation. It is worth noting that aripiprazole LAI functions as a partial agonist at dopamine D_2 and 5-HT_{1A} receptors and as an antagonist at the 5-HT_{2A} receptor.[6] Thus, its mechanism of action on the dopamine system might be beneficial in reducing craving, reward, and relapse because dopaminergic dysfunction is at the core of the substance abuse.[10] However, we should bear in mind that the better clinical outcome obtained with aripiprazole LAI may be due to the simple fact that this drug promotes better adherence compared with previously received treatments, which could potentially bias the assessed effects of aripiprazole LAI on this patient.

In addition, we currently know that involvement of the patient in the treatment decision-making process and therapeutic alliance with the doctor or medical team may be extremely useful for improving treatment adherence. Although our patient was initially afraid of injections, when he was switched to the LAI form, he reported being very satisfied with the decision and stated that he felt much better during the injection regimen.

To conclude, our case report highlights the improvement of the patient's psychiatric symptoms, as well as the patient's quality of life, with the introduction of aripiprazole LAI, thus enabling a reduction in the total amount of treatments needed. However, a 4-month observation period with aripiprazole LAI was too short for assessing the effects of long-term use. For this reason, further studies are needed to investigate the benefits of aripiprazole LAI in patients with comorbid mental disorders and substance use disorders.

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Efficacy of Vitamin B6 in Lithium-Associated Tremor
A Case Series

To the Editors:

Tremor associated with lithium treatment is probably the most prevalent drug-related tremor encountered in clinical practice.[1] This tremor can occur within therapeutic doses of lithium and is not limited to lithium intoxication.[2] The prevalence of lithium-associated tremor has been estimated to be between 10% and 18% by the Canadian Network for Mood and Anxiety Treatments and up to 65% by the World Federation of Society of Biological Psychiatry.[3,4] This tremor is a common complaint of patients receiving lithium. It has a significant social impact[5] and may be a major cause of poor adherence to lithium. In fact, the prevalence of patients who cease lithium

treatment because of adverse effects has been estimated to be between 18% and 53%.[6]

Lithium-associated tremor falls into the category of physiological tremor and primarily affects the hands.[1] Monitoring of serum lithium levels and switching to an extended-release form can reduce lithium-associated tremors.[4] When these strategies are ineffective, adjuvant treatment with β-blockers, especially propranolol, can be administered.[7] However, propranolol has contraindications including bronchial asthma, diabetes, sick sinus syndrome, sinus bradycardia, first-degree heart block, congestive heart failure, and chronic obstructive pulmonary disease. Importantly, these medical conditions are prevalent in patients experiencing bipolar disorder. In addition, adverse effects of propranolol include light-headedness, fatigue, impotence, and bradycardia. These contraindications and adverse effects can restrict the prescription of propranolol.

Reducing lithium-associated tremor has the potential to improve patient quality of life, adherence to medication, and overall prognosis of bipolar disorder. Consequently, alternative strategies are being explored. The effectiveness of vitamin B6 at reducing lithium-associated tremor was demonstrated in a preliminary open-label clinical trial.[8] However, evidence of vitamin B6 efficiency remains limited. Vitamin B6 is an essential vitamin that plays an important role in amino acid metabolism. It is hypothesized that the antioxidant properties of vitamin B6 could ameliorate movement disorders.[8] The 3 natural forms are pyridoxine, pyridoxal, and pyridoxamine. Pyridoxine is the most commonly used form in pharmaceutical preparations and dietary supplements.

Patients included in this case series experienced bipolar disorder type 1 (N = 1) or type 2 (N = 6) according to DSM-IV-TR Criteria without comorbid substance-use disorder. Patients were undergoing lithium monotherapy as a mood stabilizer and experienced tremor, scored as "distressing" on the PRISE-M Scale (Rush and Asberg, unpublished rating scale). Tremor imputation to lithium has been established according to the criteria defined by Morgan and Sethi.[9] These criteria are (1) the exclusion of other medical causes of tremor (hyperthyroidism and hypoglycemia), (2) a timed relation to the start of treatment with the medication, (3) a dose-response ratio (ie, increasing the dose of drug aggravates tremor or decreasing the dose improves tremor), and (4) the lack of worsening across time. Patients with eating disorders, malnutrition, impaired intestinal absorption, or avitaminosis were excluded from this case series. A monthly assessment of the tremor was performed by a clinical examination of the hands. The presence of tremor was defined as an oscillation of the end of the hands while the patient was voluntarily maintaining arm posture against gravity. Moreover, we used the PRISE-M Scale as a self-administered questionnaire.

Seven patients (56.6 ± 9.9 years, 4 women and 3 men) were included in this case series. Lithium dosage was 1.2 ± 0.8 g/d at the start of the study. The mean serum lithium level was 0.7 ± 0.2 mEq/L, and mean intraglobular lithium level was 0.2 ± 0.1 mEq/L. The duration of lithium treatment before vitamin B6 averaged 48.6 ± 69.6 months. Patients received adjuvant treatment with pyridoxine (750 mg–1 g per day) for an average of 7.3 ± 5.8 months (1–18 months). Five of the 7 patients had subjective and objective clinical reductions of their lithium-associated tremor during pyridoxine treatment. Two patients presented a total resolution of lithium-associated tremor. Another patient reported a significant improvement in quality of life with improvement in scribing and other daily activities. Before beginning pyridoxine treatment, 2 patients had been receiving propranolol (40 mg) for 3 and 7 years to treat lithium-associated tremor. In both these patients, the addition of vitamin B6 reduced tremors and allowed a reduction and cessation of propranolol. For 2 patients, tremor was reduced by vitamin B6 and then remained stable while they increased their dose of lithium during the vitamin B6 treatment. The time before effectiveness of vitamin B6 was 49.2 ± 57.3 days (6–150 days), suggesting that several weeks of treatment are needed to obtain a treatment response.

All patients showed a recurrence of tremor when vitamin B6 treatment was discontinued while lithium was continued. Three patients reported that their tremor after cessation of vitamin B6 was similar to what it had been before treatment. None of the patients presented clinical or biological adverse effects during or after vitamin B6 treatment.

Our case series confirms the potential utility of vitamin B6 in the treatment of lithium-associated tremor. Only 1 small 4-week open-label clinical trial of 5 patients with bipolar disorder on lithium monotherapy has demonstrated the efficacy of vitamin B6 in this context.[8] The main outcome was reducing tremor rated by 2 scales: the tremor subscale from the Simpson Angus Scale and the Subjective Clinical Improvement Impression Scale (Clinical Global Impression Scale adapted by the authors). Oral dosages of vitamin B6 were administered at 900 to 1200 mg/d over a period of 4 weeks. Four patients presented a reduction of Simpson Angus Scale and Subjective Clinical Improvement Impression Scale scores at the end of the follow-up. One patient did not present any improvement of tremors. A recurrence of tremors was observed in 3 of 4 patients after discontinuation of vitamin B6. No adverse effects were reported during the study.[8] Interestingly, 3 randomized double-blind clinical trials with crossover design versus placebo showed efficacy of vitamin B6 on tardive dyskinesia associated with neuroleptics in patients with schizophrenia or schizoaffective disorder.[10–12] Vitamin B6 dosage was 400 mg/d[10,11] or 1200 mg/d.[12] Adverse effects were reported by 2 of 50 patients (acne and light itch) after 2 months of treatment with vitamin B6 at 1200 mg/d.[12] As a consequence, it is recommended to consider these adverse effects because these could reduce treatment adherence. The relationship between lithium-associated tremor and extrapyramidal symptoms due to antipsychotics remains unclear. However, these studies suggested that extrapyramidal effects may be because of free radicals, and that the mechanism of action of vitamin B6 may be through its antioxidative effects.[13]

Despite the absence of severe adverse events in previous reports using vitamin B6 as an adjuvant treatment for adverse effects in psychiatric disorders, it is worth noting that high doses of pyridoxine may be toxic. This toxicity seems to be dose dependent and occurs primarily after chronic exposure in humans.[14] Schaumburg et al[15] described sensory neuropathy in 7 patients who took very high doses of pyridoxine (greater than 2 g/d for 2–40 months). Other clinical cases of sensorimotor ataxia in patients who consumed excessive oral vitamin B6 (600 mg/d over 3–10 years) have also been reported.[16] Additional adverse effects have also been reported: sensation of tingling that proceeds down the neck and legs,[15] vesicular dermatosis on regions of the skin exposed to sunshine, dizziness, nausea, breast discomfort or tenderness, and photosensitivity on exposure to sun.[17] Unlike pyridoxine, pyridoxal 5-phosphate has not been associated with adverse effects even at dosages up to 1200 mg/d.[15,18]

In conclusion, our case series reinforces the potential utility of vitamin B6 treatment in reducing tremors associated with lithium. Dosages between 750 mg and 1 g/d seem to be well tolerated and effective after several weeks of treatment. The optimal treatment duration after efficacy achievement remains to be explored, and we as well as others have observed a relapse of tremor on cessation of vitamin B6.[8] As a consequence, this therapeutic alternative deserves further exploration, both in terms of effectiveness in randomized controlled trials and in terms of tolerance and clinical management.

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Intranasal Ketamine and Cognitive-Behavioral Therapy for Treatment-Refractory Obsessive-Compulsive Disorder

To the Editors:

Refractory obsessive-compulsive disorder (OCD) is a common and vexing clinical problem. Agents that modulate glutamate, including the *N*-methyl-D- aspartate antagonist ketamine, have been the focus of recent interest for the treatment of this population,[1] but experience to date has been mixed.[2,3] Ketamine is a rapid-acting antidepressant that enhances cellular mechanisms associated with neural plasticity in prefrontal circuitry associated with extinction learning.[4] This raises the intriguing possibility that ketamine may potentiate extinction-based psychotherapy for OCD.[5]

CASE

A.L.[a] is a white man in his late 20s with a principal diagnosis of OCD, comorbid major depressive disorder (MDD) with chronic suicidal ideation, social anxiety disorder, and a history of bulimia nervosa. A.L. has been refractory to pharmacological treatments (clomipramine, venlafaxine, fluvoxamine, sertraline, citalopram, fluoxetine [+/− aripiprazole], risperidone, olanzapine, alprazolam, clonazepam, diazepam, bupropion, riluzole, and n-acetylcysteine). Detailed dosage history was not available for all agents, but fluoxetine (60 mg) and citalopram (60 mg) were given at a therapeutic dose for more than 2 months with minimal benefit and significant adverse effects; similarly, 200 mg clomipramine was prescribed, but was discontinued because of serious adverse effects. A.L. was also refractory to both residential and outpatient cognitive-behavioral therapy (CBT) with expert providers. Because of the failure of standard treatments, we initiated concurrent ketamine and CBT treatment, seeking a synergistic benefit. A.L. provided informed consent prior to beginning treatment.

A.L. was treated for 8 weeks on an inpatient psychiatric unit and for 8 weeks as an outpatient. He received intensive CBT throughout his inpatient stay; he met with his CBT provider every weekday and completed approximately 1 to 2 hours of CBT homework every day. Cognitive-behavioral therapy focused on

[a]The patient's real initials were not used in this case report. A.L. provided verbal consent to publish his treatment details.