A Case of Worsening Bipolar Disorder With Tacrolimus in a Patient With Renal Transplant

Jessica B. Thai, BA[a,*]; Ashish Sharma, MD[b]; and Matthew K. Egbert, MD[b]

Management of psychiatric illnesses in patients with comorbid medical conditions may be challenging due to balancing pharmacokinetics of the psychotropic medications alongside pharmacodynamics of medications used for underlying medical illnesses. We present a case in which immunosuppressant tacrolimus (also known as FK506) worsened bipolar disorder in a kidney transplant patient.

Case Report

The patient, a 56-year-old man with a history of bipolar disorder (per *DSM-IV*) and a recent kidney transplant. He presented to the emergency department for increasingly erratic behavior. Per his family's report, the patient exhibited behavior suggestive of a manic episode (*DSM-5* criteria), with emotional lability and agitation, grandiosity, decreased need for sleep, and increased involvement in risky activities with high potential for painful consequences (ie, hypersexuality, irresponsible spending, attempting to buy a $500,000 house and expensive clothes, running around the house in his underwear) for several weeks. He also had increased appetite and paranoia. These behaviors were out of character for the patient, and he was admitted to the inpatient psychiatric unit.

The patient was diagnosed with bipolar disorder at age 17 years and had multiple inpatient psychiatric admissions. Substance use history was not significant. He had a stable job and family environment. His bipolar disorder was in remission for the past 20 years, and he was initially prescribed lithium followed by valproic acid. Unfortunately, he developed focal segmental glomerulosclerosis secondary to chronic lithium therapy for which he underwent a living donor kidney transplant. Since his transplant, he had been on tacrolimus 10 mg/d orally for immunosuppression.

At hospital admission, his tacrolimus level was 13.8 ng/mL, blood urea nitrogen was 208 ng/mL, creatinine was 1.258 ng/mL, and glomerular filtration rate was 60 mL/min. Other laboratory examinations were within normal range. Initially, the patient's manic symptoms persisted during his first week of admission while he was restarted on valproic acid and olanzapine, so doses of both medications were increased (Figures 1 and 2). He did not tolerate olanzapine due to sialorrhea and was switched to quetiapine (Figure 3). Valproic acid was titrated up to 500 mg orally in the morning and 2,500 mg orally at night. His quetiapine dose was titrated up to 300 mg orally at night. His total valproic acid level was in the therapeutic range: 84 mcg/mL. Over the course of hospitalization, his mania symptoms improved—insomnia was the first symptom to improve with the other symptoms following—and he became stable for discharge. At a follow-up visit 3 months after discharge, his symptoms were well controlled.

Discussion

Tacrolimus is an immunosuppressant that acts by inhibiting calcineurin, an enzyme that is involved in T-cell activation by binding to the immunophilin FKBP5.[1] Adverse effects of tacrolimus include seizures, encephalopathy, cerebellar ataxia, and hallucinations.[2]

There are limited data supporting worsening bipolar disorder in patients on tacrolimus. While there have been guidelines[3] for assessment of depression pre- and posttransplant, there are no such standards for the assessment of bipolar disorder. A proposed theory for the mechanism behind worsening bipolar disorder in patients on tacrolimus includes dopamine receptor antagonism.[4] Another hypothesis is that tacrolimus may cross the blood-brain barrier, attach to myelin, and produce nitrous oxide, which may cause a neurotoxic effect or edema.[5] Tacrolimus may also exacerbate neurotoxicity via hypertensive encephalopathy.[6] These neurotoxic effects may specifically damage the white matter in the parietal or occipital lobes.[7]

After searching PubMed for the keywords *tacrolimus* and *renal transplant*, we found 1 case report of a patient with bipolar disorder who developed psychotic symptoms without concurrent mood symptoms while on tacrolimus. This patient's psychosis developed while her tacrolimus level was within normal range, with recurrence of similar symptoms on rechallenge with tacrolimus. Her regimen was then changed to alemtuzumab as an effective rescue medication for rejection.[3] Another report[8] described a case of treatment-resistant mania in a patient on therapeutic levels of tacrolimus, which only improved after tapering of the tacrolimus and initiation of cyclosporine.

[a]College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska

[b]Department of Psychiatry, University of Nebraska Medical Center, Omaha, Nebraska

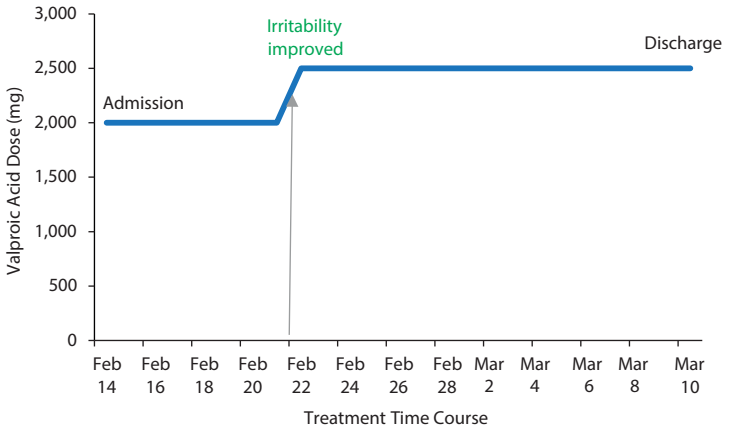
*Corresponding author: Jessica B. Thai, BA, 985575 Nebraska Medical Center, Omaha, NE 68198-5578 (jessica.thai@unmc.edu).

Prim Care Companion CNS Disord 2020;22(1):19l02473

To cite: Thai JB, Sharma A, Egbert MK. A case of worsening bipolar disorder with tacrolimus in a patint with renal transplant. *Prim Care Companion CNS Disord*. 2020;22(1):19l02473.

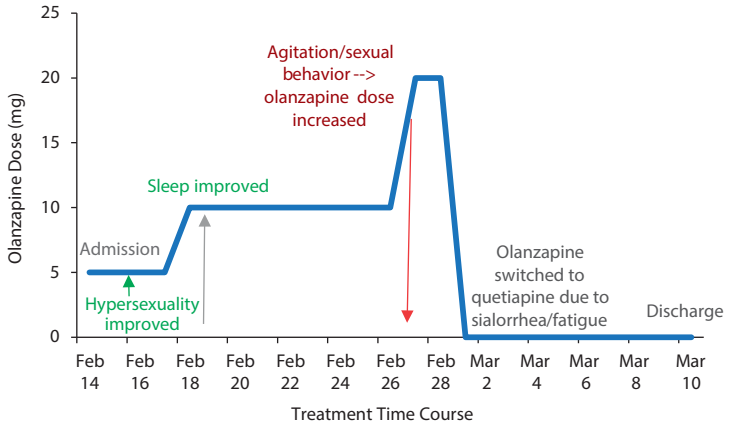
To share: https://doi.org/10.4088/PCC.19l02473

Figure 1. Response With Valproic Acid[a]



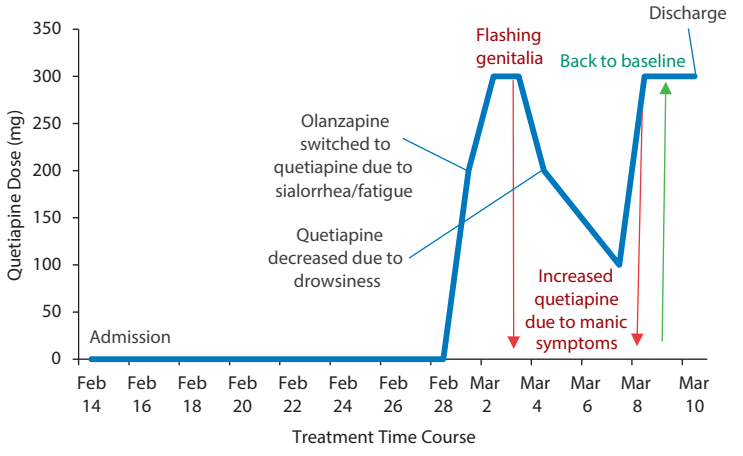
[a]The patient was started on 2,000 mg valproic acid at admission, which was titrated to 2,500 mg. His irritability improved with the increased dose.

Figure 2. Response With Olanazapine[a]



[a]The patient's manic symptoms generally improved with olanzapine. Two days after starting olanzapine 5 mg at admission, his hypersexuality improved, and after increasing olanzapine to 10 mg, his sleep improved. After exhibiting agitation and increased sexual behavior, olanzapine was increased to 20 mg but was eventually switched to quetiapine due to sialorrhea and fatigue.

Figure 3. Response With Quetiapine[a]



[a]Olanzapine was switched to quetiapine due to sialorrhea and fatigue. Quetiapine was decreased due to drowsiness but was later increased again due to reappearance of manic symptoms.

Lithium's nephrotoxic side effects include reversibly reduced glomerular filtration rate and permanently reduced maximal urinary concentrating capacity, progressing to nephrogenic diabetes insipidus.[9,10] Patients on lithium have also exhibited focal segmental glomerulosclerosis and increased proteinuria and have developed end-stage renal disease.[10–12] These patients were more likely to be older men, to have concurrent hypertension and diabetes mellitus, and to have taken lithium for over 15 years.[10–12] It is suggested that transplant candidates switch from lithium to other mood stabilizers or atypical antipsychotics that do not rely on renal metabolism.[13] New medications should continue for at least 3 months to ensure symptoms and side effects are controlled.[11] However, medications may remain unpredictable for transplant patients due to graft-host interactions and diuretic and dialysis use.[14]

Published online: February 13, 2020.

Potential conflicts of interest: None.

Funding/support: None.

Patient consent: Written informed consent was obtained from the patient for publication of this case report, and information was de-identified to protect anonymity.

REFERENCES

1. Ellsworth KA, Wang L. FKBP5 (FK506 binding protein 5). Atlas of Genetics and Cytogenetics in Oncology and Haematology website. http://atlasgeneticsoncology.org/Genes/GC_FKBP5.html. Accessed January 7, 2020.
2. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int*. 2000;13(5):313–326.
3. Dave V, Mulley W, Kanellis J, et al. Managing psychosis in a renal transplant recipient with bipolar affective disorder and allograft rejection. *Nephrology (Carlton)*. 2015;20(suppl 1):2–5.
4. Rushlow WJ, Seah C, Sutton LP, et al. Antipsychotics affect multiple calcium calmodulin dependent proteins. *Neuroscience*. 2009;161(3):877–886.
5. Chopra A, Das P, Rai A, et al. Catatonia as a manifestation of tacrolimus-induced neurotoxicity in organ transplant patients: a case series. *Gen Hosp Psychiatry*. 2012;34(2):209.e9–209.e11.
6. Singh N, Bonham A, Fukui M. Immunosuppressive-associated leukoencephalopathy in organ transplant recipients. *Transplantation*. 2000;69(4):467–472.
7. Appignani BA, Bhadelia RA, Blacklow SC, et al. Neuroimaging findings in patients on immunosuppressive therapy: experience with tacrolimus toxicity. *AJR Am J Roentgenol*. 1996;166(3):683–688.
8. Ithman M, Malhotra K, Bordoloi M, et al. Treatment-refractory mania with psychosis in a post-transplant patient on tacrolimus: a case report. *Clin Med Res*. 2018;16(1–2):47–49.
9. Bendz H, Aurell M, Balldin J, et al. Kidney damage in long-term lithium patients: a cross-sectional study of patients with 15 years or more on lithium. *Nephrol Dial Transplant*. 1994;9(9):1250–1254.
10. Bendz H, Schön S, Attman PO, et al. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney Int*. 2010;77(3):219–224.
11. Presne C, Fakhouri F, Noël LH, et al. Lithium-induced nephropathy: rate of progression and prognostic factors. *Kidney Int*. 2003;64(2):585–592.
12. Bendz H, Sjödin I, Aurell M. Renal function on and off lithium in patients treated with lithium for 15 years or more: a controlled, prospective lithium-withdrawal study. *Nephrol Dial Transplant*. 1996;11(3):457–460.
13. Moss MC, Kozlowski T, Dupuis R, et al. Lithium use for bipolar disorder post renal transplant: is mood stabilization without toxicity possible? *Transplantation*. 2014;97(3):e23–e24.
14. Levy NB. Use of psychotropics in patients with kidney failure. *Psychosomatics*. 1985;26(9):699–701, 705, 709.