Delayed and Recurrent Calcineurin Inhibitor–Induced Psychosis With Agents in the Same Class and in the Absence of Supratherapeutic Levels

Nicole M. Khanna, BA, and Aniruddha Deka, MD

Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are commonly used antirejection drugs in organ transplantation. Though their neuropsychiatric side effects—mania, psychosis, catatonia, and akinetic mutism—are well documented, these effects are typically described as early onset and dose related.[1,2] We report a case of delayed and recurrent CNI-induced psychosis with both tacrolimus and cyclosporine, highlighting the need to better understand host vulnerability and risk stratification.

Case Report

The patient is a 50-year-old man with granulomatosis with polyangiitis (GPA) and end-stage renal disease, status post–renal transplant 7 years ago, with no prior psychiatric history. He presented with 1 month of insomnia and persecutory delusions that the FBI was out to get him. His home medication included tacrolimus 1 mg twice daily. Notably, his symptoms started after being diagnosed with *Clostridioides difficile* diarrhea and completing antibiotics with symptomatic resolution. His tacrolimus level was 5 ng/mL (within normal range). Three years prior, he had developed tremors, anxiety, and nightmares when his tacrolimus dose was increased to 2 mg twice daily (level: 10 ng/mL, within normal range), resolving after dose reduction.

Workup, including head computed tomography, complete blood count, complete metabolic panel, electrocardiogram, urine toxicology, serum ethanol, HIV, and thyroid-stimulating hormone, was unremarkable. He declined antipsychotics, and symptoms improved after switching from tacrolimus to cyclosporine within 2 days of initiation.

He remained psychiatrically stable until 3 years later, when he presented with 2 weeks of paranoia and insomnia. His cyclosporine level was 88 ng/mL (within normal range). The repeat workup was once again unrevealing. He was transitioned to sirolimus with symptomatic improvement and started on olanzapine, escitalopram, and prazosin. Olanzapine was discontinued on an outpatient basis with no symptomatic recurrence.

One year later, his anxiety was managed on an outpatient basis with mirtazapine, escitalopram, and short-term adjuncts (clonazepam, bupropion, and aripiprazole in augmentation doses), which were later discontinued. He remains psychiatrically stable on sirolimus, mirtazapine, and escitalopram, with no recurrence of psychosis.

Discussion

This case highlights several underappreciated aspects of CNI-induced psychosis. The patient developed new-onset psychotic symptoms after years of stable use, first on tacrolimus and later cyclosporine. In both episodes, serum drug levels were within therapeutic range, and symptoms resolved upon discontinuation, suggesting that serum concentration alone is not predictive of neurotoxicity. Using the Naranjo Adverse Drug Reaction Probability Scale, a score of 5 suggests a "probable" causal relationship.[3] This is the first reported case, to our knowledge, demonstrating all 3 of the following features: delayed-onset psychosis on CNIs, occurrence at therapeutic levels, and recurrence despite a within-class switch.

The mechanism of CNI-induced psychosis is poorly understood, but downstream modulation of dopamine and *N*-methyl-D-aspartate receptor systems is implicated.[4] CNIs are lipophilic, allowing them to cross the blood-brain barrier (BBB), which becomes an important consideration in infections, inflammation, or metabolic derangements, which can potentially compromise the barrier.[2] We considered whether our patient's GPA may have increased this susceptibility. GPA is associated with hypertrophic pachymeningitis, which can destabilize the BBB, allowing lipophilic CNIs to access central receptors in pathological quantities.[5] We also considered whether *Clostridioides difficile* infection during the initial psychotic episode may have transiently increased BBB permeability or otherwise potentiated neurotoxic effects.

The recurrence of psychosis after switching from tacrolimus to cyclosporine is noteworthy. A within-class switch is commonly recommended when CNI-induced neurotoxicity is suspected, as cyclosporine is considered less neurotoxic than tacrolimus.[5]

For patients with risk factors for compromised BBB or history of neurotoxicity, the threshold for considering non-CNI alternatives, such as sirolimus, should be lower. Furthermore, the potential role of prophylactic antipsychotics in high-risk patients warrants further exploration. This case reinforces the importance of considering CNI-induced psychosis—even in delayed presentations, in the absence of supratherapeutic levels, and across agents within the same class.

To Cite: Khanna NM, Deka A. Delayed and recurrent calcineurin inhibitor–induced psychosis with agents in the same class and in the absence of supratherapeutic levels. *Prim Care Companion CNS Disord* 2026;28(1):25cr04090.

Author Affiliations: Rush Medical College, Rush University Medical Center, Chicago, Illinois (Khanna); Department of Psychiatry, Rush University Medical Center, Chicago, Illinois (Deka).

Corresponding Author: Nicole M. Khanna, BA, Rush Medical College, Rush University Medical Center, Chicago, Illinois (nicole_m_khanna@rush.edu).

Financial Disclosure: None.

Funding/Support: None.

Previous Presentation: Presented at the Illinois Psychiatric Society Annual Meeting, October 2024, Chicago, Illinois, and the Trainee Research Day at Rush University, April 2025, Chicago, Illinois.

Patient Consent: Written informed consent was obtained from the patient to publish the case report, and information has been de-identified to protect patient anonymity.

Article Information

Published Online: February 17, 2026. https://doi.org/10.4088/PCC.25cr04090

Prim Care Companion CNS Disord 2026;28(1):25cr04090

Submitted: September 21, 2025; accepted November 4, 2025.

References

1. 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.
2. Gunther M, Jiang S, Banga A, et al. Delayed-onset psychosis secondary to tacrolimus neurotoxicity after lung transplant: a case report and systematic review. *J Acad Consult Liaison Psychiatry*. 2023;64(6):550–561.
3. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
4. Miao S, Yang M, Li W, et al. Efficacy and safety of calcineurin inhibitors (CNIs) for septic patients in ICU: a cohort study from MIMIC database. *Front Pharmacol*. 2024;15:1394553.
5. Choi HA, Lee MJ, Chung CS. Characteristics of hypertrophic pachymeningitis in patients with granulomatosis with polyangiitis. *J Neurol*. 2017;264(4):724–732.