

Oral Glutamatergic Modulation With Dextromethorphan and Piracetam for Refractory Bipolar Disorder With Obsessive-Compulsive Disorder:

Three Consecutive Cases From Routine Practice

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The combination of bipolar disorder and obsessive-compulsive symptoms remains one of the most challenging clinical presentations in psychiatry.^{1–3} Standard treatments frequently fail or worsen mood instability: high-dose selective serotonin reuptake inhibitors (SSRIs) carry a substantial risk of manic switch, while mood stabilizers alone rarely touch the obsessions.^{4,5} Intravenous ketamine can produce rapid relief of both mood and intrusive thoughts,^{6,7} but cost, monitoring requirements, and transient dissociation limit its everyday use.

Case Report

Three consecutive adults (2 women aged 24 and 31 years and 1 man aged 46 years) seen in outpatient practice

in Hong Kong between May and November 2025 presented with DSM-5 bipolar disorder (2 bipolar I, 1 bipolar II) and severe, mood-congruent obsessive-compulsive features—trichotillomania with onychophagia, persistent bladder-emptying ruminations with checking, and compulsive arranging accompanied by somatic delusions. All had failed multiple prior trials of high-dose SSRIs/serotonin-norepinephrine reuptake inhibitors, atypical antipsychotics, and standard mood stabilizers.

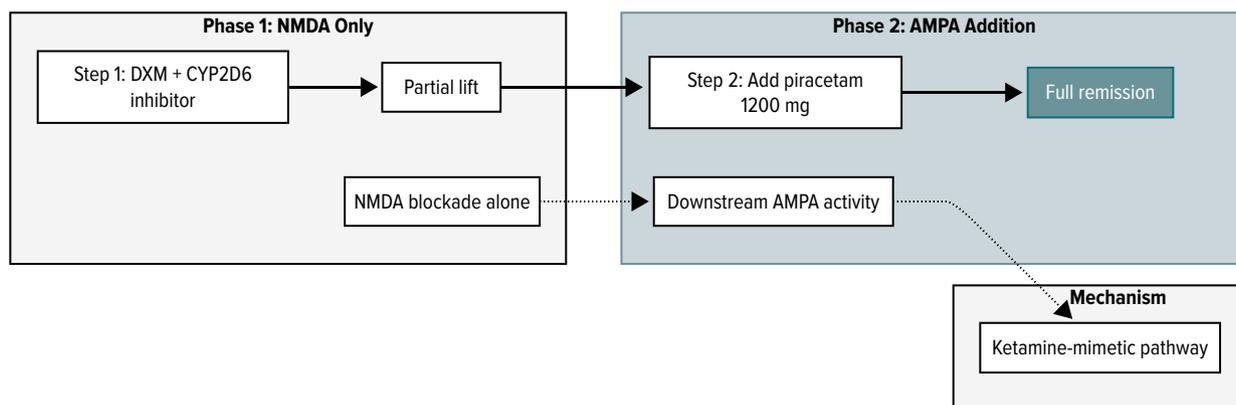
Each patient was started on an oral ketamine-mimetic protocol (the Cheung Glutamatergic Regimen)⁸ consisting of dextromethorphan (NMDA receptor antagonism, typically 30–120 mg/d), whose exposure was prolonged with

low-dose fluoxetine (10–20 mg/d) as a cytochrome P450 (CYP)2D6 inhibitor and augmented with piracetam (AMPA receptor positive allosteric modulation, 600–1,200 mg/d) and, when needed, L-glutamine (500–1,000 mg/d) for presynaptic glutamate support.⁸ Conventional mood stabilizers and low-dose antipsychotics were continued or adjusted as clinically indicated.

In all 3 cases, partial improvement occurred with dextromethorphan alone, but sustained remission of both depressive and anxious symptoms and obsessive-compulsive phenomena only followed the addition of piracetam (Figure 1). Transient hypomanic activation, when it occurred, was managed by reducing dextromethorphan dose while maintaining or increasing piracetam,

Figure 1.

Sequential Response Pattern Observed in the Cases^a



^aDextromethorphan—boosted by CYP2D6 inhibition—provides only partial relief. Consistent with animal models of ketamine action, full remission and “steady wellness” are achieved only after the addition of piracetam to facilitate downstream AMPA receptor activity.

alongside adequate mood stabilization.⁹ By late November 2025, scores on the Patient Health Questionnaire-9 (PHQ-9) scores had fallen markedly from baseline values of 14–27 to final values of 6–9, and Generalized Anxiety Disorder 7-item (GAD-7) scores had fallen from baseline values of 15–19 to final values of 6–9, and specific compulsive behaviors had largely resolved. Treatment was generally well tolerated; no serious adverse events were recorded.

Discussion

These naturalistic observations in routine care suggest that a fully oral, inexpensive NMDA–AMPA modulation strategy may offer a practical alternative for patients with the “bipolar obsessive-compulsive disorder” phenotype who respond poorly to conventional approaches.^{10,11} The consistent “second-step” effect of piracetam aligns with preclinical and clinical data indicating that downstream AMPA receptor activation is critical for the sustained antidepressant and antiobsessive actions of ketamine-like agents.^{12,13}

Controlled trials are now needed to confirm efficacy, establish optimal dosing, and clarify long-term safety in this difficult-to-treat subgroup.

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