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Posted Date: 27 November 2025

doi: 10.20944/preprints202511.2128.v1

Keywords: schizoaffective disorder; cognitive impairment; brain fog; NMDA hypofunction; AMPA positive allosteric modulator; dextromethorphan; DXM; piracetam; CYP2D6 inhibition; melitracen; Deanxit; sigma-1 receptor; neuroplasticity; glutamatergic modulation; ketamine-like; oral regimen; case report; functional recovery; academic performance; treatment-resistant cognition; schizophrenia-spectrum disorders



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## Case Report

# An Oral "Ketamine-Like" NMDA/AMPA Modulation Stack Restores Cognitive Capacity in a Young Man with Schizoaffective Disorder—Case Report

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## Abstract

Cognitive impairment—rather than psychosis or mood instability—often drives long-term disability in schizoaffective disorder, yet current antipsychotic and mood-stabilising regimens offer little relief. We describe a 22-year-old man with schizoaffective disorder, bipolar type, whose persistent "brain fog" jeopardised university graduation despite euthymic mood and quiescent psychosis on lurasidone, olanzapine, and valproate. A mechanistically guided add-on protocol was introduced: Deanxit (flupentixol 0.5 mg + melitracen 10 mg once-daily) to provide mild serotonin–noradrenaline enhancement and moderate CYP2D6 inhibition; dextromethorphan 15 mg twice-daily to deliver gentle,  $\sigma_1$ -supported NMDA antagonism; and piracetam 600 mg twice-daily as a positive allosteric modulator of AMPA receptors. Within two weeks the patient reported clearer thinking and sustained reading; family noted coherent conversation and fewer attentional lapses. By six weeks he completed all coursework, passed mid-term examinations, and maintained social engagement—improvements never achieved with previous therapy. Benefits have persisted for three months with no mood destabilisation, psychotic relapse, or significant side-effects apart from transient nausea. We propose that melitracen's CYP2D6 blockade prolonged dextromethorphan exposure, enabling a steady NMDA "priming" signal, while piracetam amplified downstream AMPA throughput to consolidate synaptic plasticity. This case highlights the potential of inexpensive, orally available agents to target the NMDA–AMPA axis and alleviate the cognitive burden of schizoaffective disorder. Controlled trials are warranted.

**Keywords:** schizoaffective disorder; cognitive impairment; brain fog; NMDA hypofunction; AMPA positive allosteric modulator; dextromethorphan; DXM; piracetam; CYP2D6 inhibition; melitracen; Deanxit; sigma-1 receptor; neuroplasticity; glutamatergic modulation; ketamine-like; oral regimen; case report; functional recovery; academic performance; treatment-resistant cognition; schizophrenia-spectrum disorders

## Introduction

Schizoaffective disorder is marked by the coexistence of enduring psychotic features and discrete mood episodes, but the disability it produces is driven largely by broad-based cognitive deficits—slowed processing, poor attention, fragile working memory and impaired executive control. Meta-analytic work shows that these problems appear early, remain relatively stable, and predict functional outcome better than the positive symptoms we usually target in clinic [1,2]. Unfortunately, the drugs we rely on—D<sub>2</sub>-blocking antipsychotics and mood stabilizers—do little for this cognitive burden [3].

A growing body of basic and clinical research points to hypofunction of the glutamatergic NMDA receptor as a central culprit in these cognitive disturbances [4,5]. Blocking the NMDA channel with agents such as ketamine or phencyclidine reliably reproduces positive, negative and cognitive symptoms in healthy volunteers [6]. Intriguingly, very low-to-moderate doses of the weaker NMDA antagonist dextromethorphan (DXM) can have the opposite effect—modestly improving cognition—

perhaps because DXM also acts as a  $\sigma_1$ -receptor agonist and, when CYP2D6 metabolism is inhibited, produces a smoother modulation of glutamatergic tone [7]. Enhancing downstream AMPA-receptor throughput with positive allosteric modulators such as piracetam may add a further boost by promoting synaptic plasticity and long-term potentiation [8,9].

In the case described here, we combined three agents with complementary pharmacology:

Deanxit, whose melitracen component moderately inhibits CYP2D6, thereby raising DXM exposure;

DXM itself, supplying gentle NMDA antagonism plus  $\sigma_1$  activation; and

Piracetam, an AMPA receptor facilitator.

Against a background of stable antipsychotic and mood-stabilizer doses, this trio was followed by a striking and durable improvement in attention, working memory and study capacity—changes both the patient and his family had never observed with standard treatment alone. While anecdotal, the response illustrates how targeting NMDA hypofunction and strengthening AMPA-mediated plasticity may open a new therapeutic door for the cognitive dimension of schizoaffective disorder.

## Case Presentation

A 22-year-old man from Hong Kong named Mr. C, who has been pursuing an engineering degree. Since early 2023, he has been coming to our clinic with a DSM-5 diagnosis of schizoaffective disorder, bipolar type. He initially had a mixed manic-psychotic episode that responded to sodium valproate 1 g/day, lurasidone 40 mg/day, and low-dose olanzapine. For most of 2024–2025, he was euthymic and free of positive psychotic symptoms.

The main problem is "brain fog." Even though Mr. C. was able to control his mood and psychosis, he still had a lot of trouble with cognitive inefficiency. Notes from the clinic in 2024 show that the person had a short attention span (about 30 minutes), read slowly, couldn't remember things right away, and was very disorganized. During a summer internship he repeatedly "zoned out," failed to retain instructions and required constant prompting. Similar complaints recurred when the academic year resumed: he forgot lecture content, reread passages many times and napped after short study bouts. His parents confirmed that ordinary conversations derailed and that he appeared mentally absent even while outwardly calm. Standard adjustments—minor dose changes in olanzapine, short courses of antidepressants, vitamins and citicoline—were tried but produced no meaningful change.

### *Rationale for a Mechanistic Combination*

By late August 2025 the impairment threatened graduation. We therefore introduced a three-drug cognitive protocol while keeping all baseline psychotropics unchanged:

Deanxit (flupentixol 0.5 mg + melitracen 10 mg, 1 tablet each morning) – chosen for its mild antidepressant tone and, crucially, its moderate inhibition of cytochrome P450 2D6.

Dextromethorphan 15 mg twice daily – a low-affinity, non-competitive NMDA-receptor antagonist expected to enhance neuroplasticity once oxidative metabolism is slowed by Deanxit.

Piracetam 600 mg twice daily – an AMPA-receptor positive allosteric modulator intended to amplify downstream synaptic potentiation.

The therapeutic concept was simple: Deanxit would boost systemic exposure to dextromethorphan; transient NMDA modulation would "prime" circuits for plastic change; and sustained AMPA potentiation with piracetam would consolidate learning and working-memory networks.

### *Early Course After Initiation*

Within two weeks Mr C. volunteered that his "thoughts feel clearer" and that he could complete a chapter without rereading. Parents noticed longer, coherent dinner-table dialogue and far fewer blank pauses. By late September he was carrying five academic subjects, reporting that the previous

mental "chaos" had "sorted itself out." Although examination stress mounted, there was no re-emergence of mania or psychosis.

#### *Functional Gains*

11 October 2025: "More energetic... able to handle busy schedule... thoughts clearer."

25 October 2025 (mid-term week): "Felt smarter... read a lot of books... did a lot of assignments." Father spontaneously remarked that his son was "smarter" and "studying better."

08 November 2025: Mood steady, only occasional situational anxiety; no cognitive slowing noted in clinic.

He attended all lectures, submitted coursework on time and passed every mid-term examination—achievements unobtainable the previous semester. No adverse effects were recorded apart from transient nausea during the first treatment week. Weight, metabolic indices and liver function remained stable, and PHQ-9/GAD-7 scores improved to within the mild range.

#### *Current Status and Interpretation*

Three months after starting the Deanxit–dextromethorphan–piracetam combination, Mr C. continues to function academically and socially at a level that had seemed unattainable since illness onset. The temporal relationship, consistency of external corroboration and absence of mood or psychotic destabilisation suggest that targeted modulation of NMDA and AMPA neurotransmission—facilitated by Deanxit's CYP2D6 inhibition—was central to the cognitive turnaround. While placebo and practice effects cannot be entirely excluded, the magnitude and durability of improvement, in the face of constant background medication, argue for a genuine pharmacological benefit.

Mr C.'s experience highlights the often-neglected cognitive dimension of schizoaffective disorder and offers a pragmatic, well-tolerated strategy for clinicians confronting similar "brain-fog" syndromes in otherwise stabilised patients.

## **Discussion**

### *Persistent Cognitive Deficits in Schizophrenia and Bipolar Disorder—and the Elusive Quest for Effective Treatments*

Cognitive dysfunction is now recognised as a core, trait-like dimension of both schizophrenia (SZ) and bipolar disorder (BD), emerging years before the first psychotic or mood episode and lingering during clinical remission. Meta-analyses converge on a broad profile of impairments in executive control, working- and verbal-memory, processing speed, and attention in both illnesses [10]. The difference is quantitative rather than qualitative: effect sizes in SZ are typically large ( $d \approx 0.8$ – $1.2$ ), whereas BD shows small-to-moderate deficits ( $d \approx 0.4$ – $0.8$ ) and a sizeable cognitively "intact" subgroup [1]. Direct head-to-head syntheses confirm that patients with SZ perform worst, BD patients score intermediately, and healthy controls perform best across most domains [11]. Importantly, SZ is characterised by premorbid intellectual decline and a largely static course thereafter, whereas BD patients often begin with average–high premorbid IQ and accrue additional deficits only in those with early onset, multiple episodes or psychotic features [10].

Despite the functional toll of these impairments, therapeutic options remain disappointingly limited. No pharmacological agent has yet obtained a cognitive indication from either the FDA or EMA. Second-generation antipsychotics and mood stabilisers give only modest, very specific cognitive benefits, and their anticholinergic or metabolic side-effects can even slow people down [12]. Other medications—such as glutamatergic modulators, cholinesterase inhibitors, or anti-inflammatories—add only small, hit-and-miss gains that rarely improve everyday life [13]. Non-drug approaches look brighter: structured cognitive training delivers steady, medium-sized boosts in thinking and daily functioning for people with schizophrenia, and smaller yet meaningful gains for

those with bipolar disorder [14]. However, it is hampered by the need for trained therapists, variable programme quality, and poor integration into routine services.

#### *How NMDA and AMPA Missteps Undermine Cognition in Schizophrenia and Bipolar Disorder*

Problems in glutamate signalling seem to tie together the cognitive deteriorations seen in schizophrenia and bipolar disorder. After death, brain tissue from both groups shows normal levels of the basic NMDA-receptor gene (NR1), but the "docking" proteins that keep these receptors steady—PSD-95, SAP102 and NF-L—are greatly reduced, especially in schizophrenia [15]. Without these supports, NMDA receptors wobble, calcium messages fade, and the circuits that handle working memory and planning lose strength. This idea fits well with studies in which a single dose of an NMDA blocker like ketamine can briefly cause healthy volunteers to think and feel much like people with schizophrenia, pointing to low NMDA activity as a driver of higher-level problems. In bipolar disorder the drop in NMDA function is patchier, yet it is still enough to slow mental processing and chip away at memory, showing that even mild NMDA glitches in prefrontal-hippocampal pathways can weaken everyday thinking [16].

AMPA receptors—responsible for the fast depolarising phase of glutamatergic transmission—are pulled into this vortex. In schizophrenia, frontal-cortical tissue shows an abnormal build-up of GluA1-containing AMPA receptors in early endosomes alongside up-regulated forward-trafficking adaptors (SAP97, GRIP1), suggesting that cargo reaches the synapse too slowly or is mis-sorted once it arrives [17]. Because NMDA-driven  $\text{Ca}^{2+}$  influx normally gates the rapid insertion of AMPA receptors during long-term potentiation, weakened NMDA currents leave AMPA receptors stranded, short-circuiting plasticity. The net effect is a cortex less able to stabilise new representations, experienced clinically as impaired attention, learning and flexible thinking.

These converging mechanisms also offer therapeutic traction. Positive allosteric modulators that boost NMDA open probability, glycine-site co-agonists (for example D-serine), and GluN2-selective enhancers have all shown the capacity to restore synaptic plasticity and improve memory in preclinical models of NMDA hypofunction [16]. In parallel, drugs that expedite AMPA delivery or slow its endocytic recycling—so-called ampakines—are being explored to bypass upstream NMDA deficits and directly amplify cortical throughput. Targeting both receptor systems therefore represents a rational, circuit-informed strategy to mitigate the cognitive erosion that conventional dopamine-centric treatments leave largely untouched.

#### *Why This Three-Drug Cocktail May Re-tune a "Glutamate-Starved" Cortex*

Schizophrenia-spectrum disorders appear to suffer a two-pronged glutamatergic injury. Post-mortem and neuro-imaging work shows fewer functioning N-methyl-D-aspartate receptors (NMDARs) and a bottleneck in the forward trafficking of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors to the synapse [15,17]. In effect, the cortical circuit is "NMDA-quiet" and "AMPA-hungry," a combination that degrades  $\gamma$ -band synchrony, pyramidal-cell signal-to-noise, and, ultimately, higher cognition.

Our patient's improvement after adding melitracen to an existing dextromethorphan (DXM) + piracetam trial can be understood as a stepwise attempt to restore the NMDA/AMPA balance:

DXM, held at therapeutic levels by melitracen's modest CYP2D6 inhibition, delivers a gentle, round-the-clock NMDAR block. Sub-anaesthetic antagonism of NMDA receptors on GABA interneurons releases a controlled glutamate burst that re-engages pre-frontal networks and reduces pathological  $\gamma$ -oscillation noise [16].

Piracetam keeps that burst from fizzling out. As a positive allosteric modulator, piracetam stabilises AMPA channels in their open state, directly offsetting the AMPA-trafficking deficit documented in schizophrenia tissue [17]. The manoeuvre echoes animal data showing that ketamine's sustained antidepressant actions—and those of its metabolite hydroxynorketamine—depend more on AMPA up-shift than on continued NMDA block [18,19].

Melitracen 'fertilises the ground'. Beyond extending DXM exposure, low-dose melitracen and its flupentixol seat-belt deliver mild serotonin–noradrenaline enhancement, an effect linked to brain-derived neurotrophic factor (BDNF) release and synaptic plasticity. Providing that trophic milieu may be critical for the glutamatergic repair set in motion upstream.

Taken together, the trio attempts to re-create the "NMDA-to-AMPA flip" thought to underlie ketamine-class plasticity—only with inexpensive oral agents and without dissociation. The rapid clearing of our patient's "brain fog" supports the idea that, in schizoaffective illness, correcting glutamatergic throughput can translate into meaningful cognitive and functional gains.

### *Limitations*

A number of caveats temper the enthusiasm generated by this single-patient success. First, the evidence is inherently anecdotal: without a control condition, blinding, or even repeated objective neuropsychological testing, the sizeable gains we observed could still reflect placebo response, practice effects, or the natural ebb-and-flow of cognition in schizoaffective disorder. Second, three new agents were started within the same week, so we cannot disentangle which component—or what specific drug–drug synergy—drove the turnaround. Third, we measured neither plasma dextromethorphan levels nor CYP2D6 genotype; thus the presumed pharmacokinetic boost from melitracen remains speculative. Fourth, the follow-up window is short (three months) and confined to one academic term; durability across semesters, stressors, and mood cycles is unknown, as are longer-term safety issues such as dissociation,  $\sigma_1$ -mediated tachyphylaxis, or piracetam-related insomnia. Finally, Deanxit is unavailable or restricted in many countries, and off-label use of dextromethorphan at psychoactive doses carries regulatory and medicolegal uncertainty. These limitations underscore the need for systematic, biomarker-informed trials before this NMDA–AMPA strategy can be recommended beyond the realm of carefully monitored experimentation.

## Conclusion

This single case suggests that a thoughtfully layered combination of CYP2D6 inhibition, low-dose NMDA antagonism, and AMPA facilitation can produce rapid, durable cognitive gains in schizoaffective disorder without destabilising mood or psychosis. By recreating the "NMDA-to-AMPA flip" posited for ketamine—but with generic oral medications—the regimen may offer a pragmatic route to address the cognitive dimension that standard dopamine-centric treatments leave untouched. Although placebo effects and natural fluctuation cannot be ruled out, the magnitude, persistence, and functional relevance of the improvement argue for a true pharmacological synergy. Systematic studies, beginning with open-label pilots and progressing to randomised controlled trials, are now needed to verify efficacy, optimise dosing, and clarify safety before this strategy can be generalised to broader clinical practice.

**Patient Consent for Publication:** Written informed consent was obtained from all patients included in this case series for the publication of their case details and any accompanying clinical data. For the patients under the age of 18 (Case 3 and Case 4), written informed consent was obtained from their parents/legal guardians, and written assent was obtained from the adolescents themselves.

**Conflict of Interest and Source of Funding Statement:** None declared.

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