Hypothesis

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Inducing BDNF and mTOR-Mediated Synaptogenesis via Oral Agents: A Hypothetical Prophylaxis for Alzheimer's Disease

Ngo Cheung *

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Inducing BDNF and mTOR-Mediated Synaptogenesis via Oral Agents: A Hypothetical Prophylaxis for Alzheimer's Disease

Ngo Cheung

Cheung Ngo Medical Limited, Hong Kong SAR, China; info@cheungngomedical.com; Tel: 98768323

Abstract

Ketamine's ability to lift mood and spur new synapse growth has put glutamate biology at the center of modern neurotherapeutics. Yet the drug's intravenous route, monitoring requirements, and dissociative effects make it a poor candidate for long-term prevention of Alzheimer's disease (AD). Here we advance a testable hypothesis: an all-oral "synaptogenic stack" could mimic ketamine's downstream benefits—namely, the rise in brain-derived neurotrophic factor (BDNF) and the activation of mTOR—while avoiding its toxicities. The stack combines three inexpensive agents that have decades of human use. First, dextromethorphan, kept in circulation with a small dose of a CYP2D6 inhibitor, provides gentle NMDA antagonism. Second, piracetam acts as a positive modulator of AMPA receptors, boosting fast excitatory transmission. Third, oral L-glutamine replenishes presynaptic glutamate stores and buffers against excitotoxic spill-over. Working in concert, these drugs should reduce extrasynaptic NMDA stress, enhance AMPA throughput, and preserve dendritic spine density in the ageing brain. If this mechanism proves sound, the regimen offers a low-cost, scalable way to delay the clinical onset of AD, particularly in people who already show prodromal biomarkers or genetic risk. Prospective trials are needed to evaluate safety, target engagement, and long-term cognitive outcomes.

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Background

Alzheimer's disease (AD) is now viewed less as a sudden loss of memory and more as a very long slide into synaptic failure that can start 20 or 30 years before a diagnosis [1,2]. In the earliest phase, two things go wrong with glutamate signalling. First, extrasynaptic NMDA receptors—especially those that carry the NR2B sub-unit—become hyperactive. At the same time AMPA receptors, which should sit in the synapse and pass the fast excitatory message, are pulled inside the neuron and degraded [3,4,5,6] Together these shifts set off calcium overload, oxidative stress, loss of long-term potentiation, spine shrinkage and, finally, cell death [7]. Drugs on the market today arrive late in that process and work on only half of the problem—for example, memantine mostly calms the rogue NMDA channels [8]. A better preventive approach would dampen toxic NMDA activity, rescue AMPA traffic and spark new synapse growth while the network is still salvageable.

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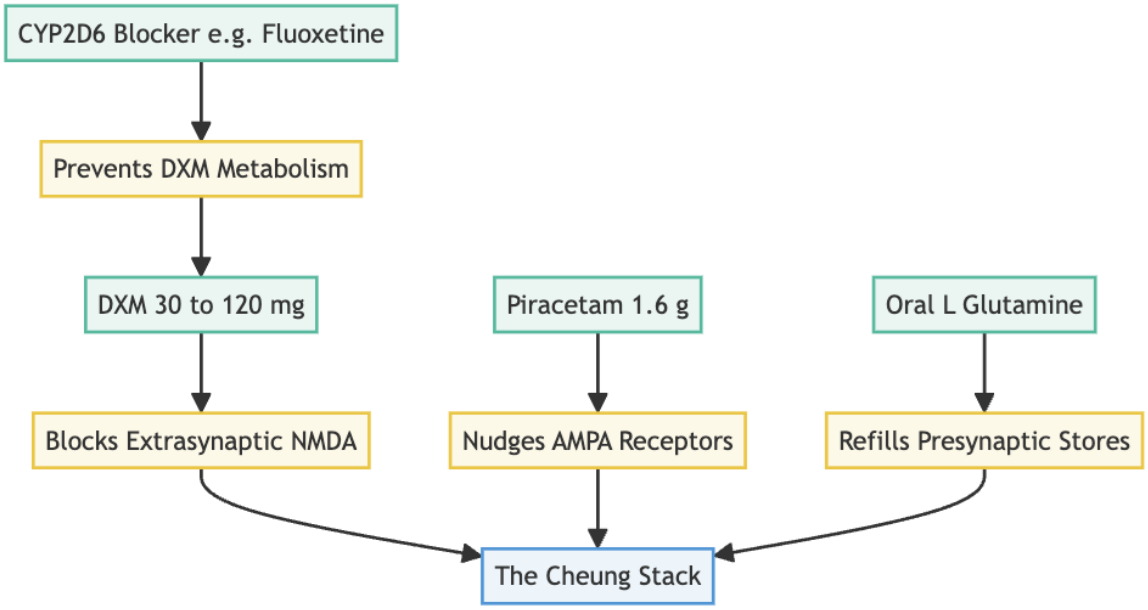
The Cheung Glutamatergic Regimen

Figure 1. The Four-Part Stack Overview

This diagram outlines the four specific components of the regimen and their primary roles.



Cheung's four-part oral stack was first built for stubborn mood and anxiety illnesses, yet its design maps neatly onto those early AD defects [9,10,11]. The plan is simple and inexpensive: dextromethorphan (DXM) at 30–120 mg a day; a low dose of a strong CYP2D6 blocker such as fluoxetine, paroxetine or high-dose duloxetine to keep DXM in the blood; piracetam 1.6 g a day to nudge AMPA receptors; and supplementary oral l-glutamine to refill presynaptic stores and curb excitotoxicity. Together, these agents reproduce the "NMDA-to-AMPA flip" that underlies ketamine's burst of plasticity [12,13,14].

Mechanistic Alignment with Early AD Pathophysiology

Selective dampening of extrasynaptic NMDA noise is the first pillar. Like low-dose ketamine or memantine, high but steady DXM blocks open NMDA channels in a voltage-dependent way and shows a clear preference for NR2B-rich receptors [8]. Because soluble Aβ forces exactly these receptors to the cell surface and even drives damaging metabotropic signals without ion flow ([15,7], DXM held in circulation by a CYP2D6 inhibitor [11] could blunt calcium overload and tau mis-chief long before plaques appear.

Figure 2. Pillar One: The NMDA Brake

How DXM and CYP2D6 blockers counteract the specific NMDA defects found in early Alzheimer's.

The second pillar is keeping AMPA receptors where they belong. Aβ promotes rapid tagging and internalisation of GluA1/GluA2 receptors, a change that tracks closely with memory loss [4,5,6].

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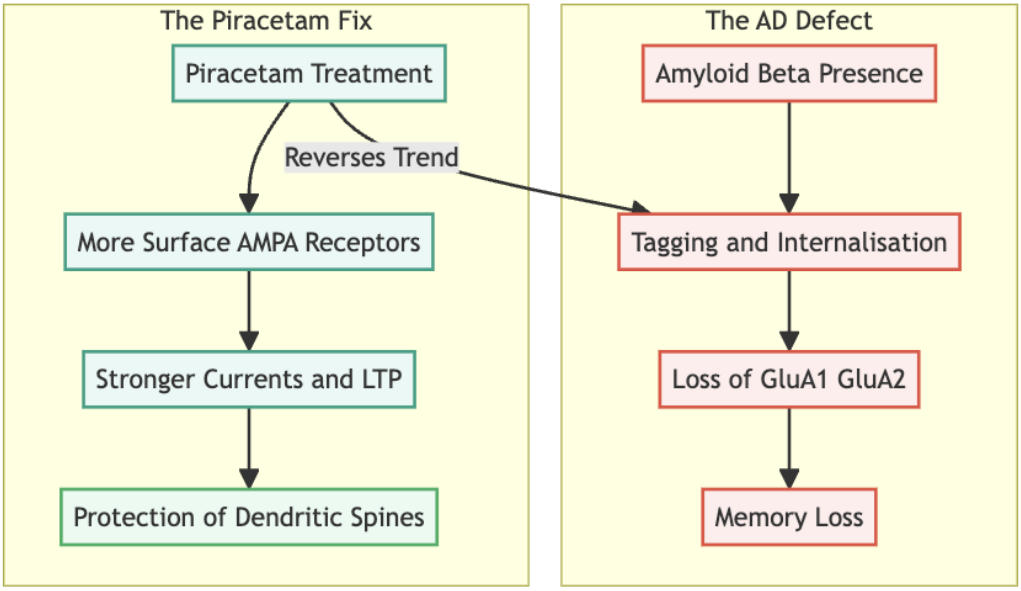
Piracetam reverses that trend: work in aged and amyloid-exposed systems shows more surface AMPA receptors, stronger currents and better LTP after treatment [16,17]. By preserving fast transmission, piracetam may protect dendritic spines through the long pre-clinical window.

Figure 3. Pillar Two: The AMPA Accelerator

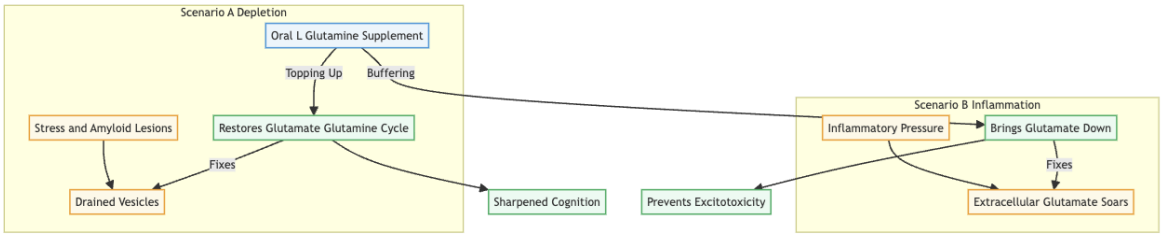
Illustrating how Piracetam fights the internalization of AMPA receptors caused by Amyloid Beta.



Third, presynaptic glutamate stores need topping up. Stress and early amyloid lesions drain vesicular glutamate and weaken release probability [18,19]. Oral l-glutamine quickly restores the glutamate–glutamine cycle, normalises excitatory postsynaptic currents and sharpens cognition in stressed or amyloid-bearing animals [18,19]. Curiously, when extracellular glutamate soars under inflammatory pressure, high-dose glutamine can actually bring it down [20,19], providing a two-way safety net against excitotoxicity.

Figure 4. Pillar Three: The Two-Way Safety Net

How L-Glutamine acts as a buffer, helping in both low-energy states and high-inflammation states.



Finally, the pairing of an NMDA brake with an AMPA accelerator triggers a well-studied plasticity cascade: BDNF release and mTOR-dependent spine formation [12,21]. Because BDNF/TrkB signalling falters early in AD, repeated activation through the Cheung stack could hold synaptic density steady in people at risk [9].

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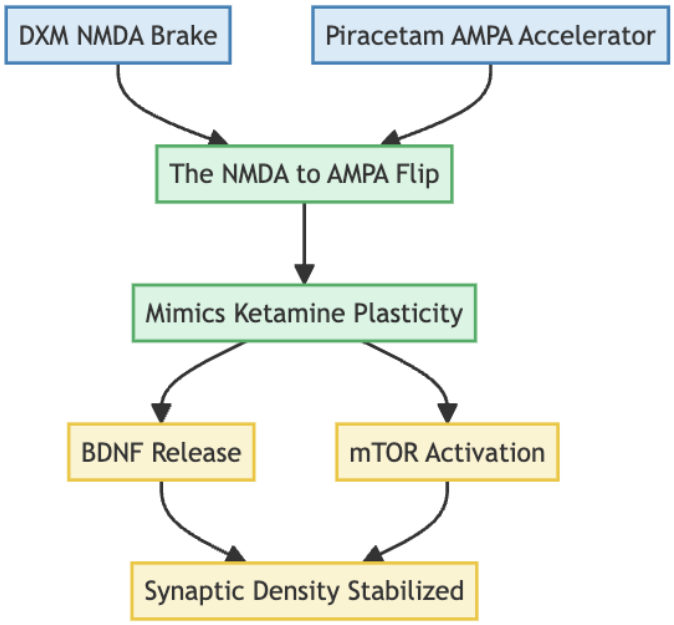
Figure 5. Pillar Four: The Plasticity Cascade

The final result: How combining the "Brake" and the "Accelerator" mimics the Ketamine effect.



Emerging Clinical Signals Relevant to Cognition and Neuroprotection

Case reports already hint at brisk cognitive gains with the full or partial regimen. Patients describe clearer thinking, faster processing and stronger working memory within weeks—improvements that mirror the subtle executive losses seen years before an AD diagnosis [22,23,24,25]. One young man with schizoaffective disorder said the stack "cleared decades of mental sludge" after everything else had failed [23]. Although anecdotal, such stories match the known importance of healthy AMPA throughput for high-order cognition.

Feasibility for Long-Term Prevention

All four ingredients are off-patent, cheap (well under two dollars a day), taken by mouth and backed by decades of safety data. Side-effects tend to be mild—occasional insomnia, jitters or stomach upset—and usually ease with dose adjustment [9,11]. Because many clinicians already prescribe the stack off-label, it is uniquely positioned for pragmatic prevention trials in APOE-ε4 carriers, people with subjective cognitive decline or biomarker-positive preclinical AD.

Conclusions

The earliest biology of Alzheimer's looks like a tilt from a balanced NMDA–AMPA partnership toward runaway extrasynaptic NMDA activity and dwindling AMPA support. The Cheung Glutamatergic Regimen addresses both faults at once: sustained DXM plus a CYP2D6 blocker reins in toxic NMDA signalling; piracetam revives AMPA strength; glutamine refuels presynaptic stores and cushions against spill-over damage. Given its low cost, oral delivery and growing clinical experience, the regimen deserves fast-tracked trials as a primary or secondary preventive for Alzheimer's disease.

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References

1. Mota SI, Ferreira IL, Rego AC. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. Neuropharmacology. 2014;76 Pt A:16-26.
2. Wang R, Reddy PH. Role of Glutamate and NMDA Receptors in Alzheimer's Disease. J Alzheimers Dis. 2017;57(4):1041-1048.
3. Chang EH, Savage MJ, Flood DG, et al. AMPA receptor downscaling at the onset of Alzheimer's disease pathology in double knockin mice. Proc Natl Acad Sci USA. 2006;103(9):3410-3415.
4. Hsieh H, Boehm J, Sato C, et al. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron. 2006;52(5):831-843.
5. Zhang Y, Guo O, Huo Y, et al. Amyloid-β Induces AMPA Receptor Ubiquitination and Degradation in Primary Neurons and Human Brains of Alzheimer's Disease. J Alzheimers Dis. 2018;62(4):1789-1801.
6. Lu K, Li C, Liu J, et al. Impairments in endogenous AMPA receptor dynamics correlates with learning deficits in Alzheimer's disease model mice. Proc Natl Acad Sci USA. 2023;120(40):e2303878120.
7. Ortiz-Sanz C, Balantzategi U, Quintela-López T, et al. Amyloid β / PKC-dependent alterations in NMDA receptor composition are detected in early stages of Alzheimer´s disease. Cell Death Dis. 2022;13(3):253.
8. Danysz W, Parsons CG. Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine--searching for the connections. Br J Pharmacol. 2012;167(2):324-352.
9. Cheung N. Clinical experience and optimisation of the Cheung glutamatergic regimen for refractory psychiatric diseases. Preprints. 2025. https://doi.org/10.20944/preprints202511.2246.v1
10. Cheung N. DXM, CYP2D6-inhibiting antidepressants, piracetam, and glutamine: Proposing a ketamine-class antidepressant regimen with existing drugs. Preprints. 2025. https://doi.org/10.20944/preprints202511.1815.v1
11. Cheung N. Ultra-low-dose paroxetine as CYP2D6 inhibitor enables safe OTC glutamatergic augmentation in a depressive patient on lisdexamfetamine. Preprints. 2025. https://doi.org/10.20944/preprints202512.0057.v1
12. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010;329(5994):959-964.
13. Maeng S, Zarate CA Jr, Du J, et al. Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry. 2008;63(4):349-352.
14. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature. 2016;533(7604):481-486.
15. Kessels HW, Nabavi S, Malinow R. Metabotropic NMDA receptor function is required for β-amyloid-induced synaptic depression. Proc Natl Acad Sci USA. 2013;110(10):4033-4038.
16. Cohen SA, Müller WE. Effects of piracetam on N-methyl-D-aspartate receptor properties in the aged mouse brain. Pharmacology. 1993;47(4):217-222.
17. Winblad B. Piracetam: a review of pharmacological properties and clinical uses. CNS Drug Rev. 2005;11(2):169-182.
18. Son H, Baek JH, Go BS, et al. Glutamine has antidepressive effects through increments of glutamate and glutamine levels and glutamatergic activity in the medial prefrontal cortex. Neuropharmacology. 2018;143:143-152.
19. Baek JH, Park H, Kang H, et al. The Role of Glutamine Homeostasis in Emotional and Cognitive Functions. Int J Mol Sci. 2024;25(2):1302.
20. Guerrero-Molina MP, Morales-Conejo M, Delmiro A, et al. High-dose oral glutamine supplementation reduces elevated glutamate levels in cerebrospinal fluid in patients with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome. Eur J Neurol. 2023;30(2):538-547.

 doi:10.20944/preprints202512.0729.v1

21. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012;338(6103):68-72.
22. Cheung N. Clearing the fog with the Cheung's regimen: A case of OTC glutamatergic augmentation in a student with depression, somatic symptoms and cognitive dysfunction. Preprints. 2025. https://doi.org/10.20944/preprints202512.0122.v1
23. Cheung N. An oral "ketamine-like" NMDA/AMPA modulation stack restores cognitive capacity in a young man with schizoaffective disorder—Case report. Preprints. 2025. https://doi.org/10.20944/preprints202511.2128.v1
24. Cheung N. Case series: Marked improvement in treatment-resistant obsessive–compulsive symptoms with over-the-counter glutamatergic augmentation in routine clinical practice. Preprints. 2025. https://doi.org/10.20944/preprints202511.2223.v1
25. Cheung N. Oral glutamatergic augmentation for trauma-related disorders with fluoxetine-/bupropion-potentiated dextromethorphan ± piracetam: A four-patient case series. Preprints. 2025. https://doi.org/10.20944/preprints202511.1788.v1