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Adenosine as the metabolic common path of rapid antidepressant action: The coffee paradox

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Yue, Luo, and colleagues discovered that adenosine signalling is the common underlying mechanism of rapid acting antidepressant therapies, unifying the effects of ketamine, ECT and acute intermittent hypoxia. They use genetically encoded sensors, along with extensive mechanistic dissection, to show that all three induce adenosine surges in mood-regulatory circuits via A1 and A2A receptor activation. The mechanism of action of ketamine primarily involves modulation of mitochondrial metabolism as opposed to NMDA receptor antagonism, thereby presenting the possibility for improvements in derivative products with better therapeutic indices. These outcomes offers a rational framework for gauging therapeutic benefit for depression and raise vexing questions about patterns of caffeine consumption in treatment resistant depression, specifically whether the chronic use has a protective effect or whether the acute use impedes treatment response.

As Claude Bernard understood in laying the foundations of experimental medicine, each scientific generation brings us closer to mechanistic truth, yet complete understanding remains elusive (1). This has been particularly evident in psychiatric therapeutics, where chance preceded knowledge for a long time. For over twenty years now, we had evidence suggesting that ketamine was a rapid anti-depressant. We knew the electrically charged scalpel of electroconvulsive therapy worked when nothing else did. And we had long suspected that depriving people of sleep benefited them in a transient way. All we were lacking was the mechanistic thread connecting these varied interventions, the common path which might allow for rational, instead of empirical, therapeutic development.

In a study that demonstrates what modern neuroscience can do when technical virtuosity meets conceptual clarity, Yue and colleagues led by Professor Min-Min Luo now provide that thread (2). Using genetically encoded adenosine sensors, a comprehensive genetic and pharmacological dissection, and immediate therapeutic translation they show that adenosine signalling is the convergent mechanism of rapid-acting antidepressant therapies. It is a new way of thinking about treatment-resistant depression and not just an incremental science.

The technical achievement

The precise timing is what gives the work its compelling quality. The authors applied GRABAdo1.0, a GPCR-based sensor for adenosine, to monitor online adenosine changes in mood-regulating circuits (2). Injection of ketamine (10 mg/kg) and application of electroconvulsive therapy resulted in a substantial spike in extracellular adenosine in the medial prefrontal cortex and hippocampus with peak amplitudes of ∼15% ΔF/F, which peaked in ∼500 s and lasted about 30 minutes above the baseline (Extended Data Fig. 1d–h in ref. 2). The specificity to regions is also telling. Even though adenosine increases occurred in the mPFC and hippocampus, no surge occurred in the nucleus accumbens, suggesting affective circuits, not reward circuits.

The dose-response-use relationships were clear-cut. When the doses of ketamine were 5 mg/kg, modest signals were seen. But then, at 10 and 20 mg/kg there were very clear effects. The higher doses increased the duration of response but had no effect on the peak amplitude. Two-photon imaging showed that the adenosine signal was spatially diffuse. The kinetics was different from that of acute hypoxia which was used by the authors as a positive control. Ketamine at the standard antidepressant dose (10 mg/kg) produced peak amplitudes of approximately 15% ΔF/F, while higher doses (20–50 mg/kg) reached approximately 35% ΔF/F, still substantially lower than the ∼60% ΔF/F observed with acute hypoxia. However, ketamine's decay rate was much slower, taking greater than 500s compared to the hypoxia decay rate of around 50s. The less pronounced peak but prolonged duration suggests that ketamine causes a sustained metabolic modulation rather than acute cellular stress.

This temporal resolution matters. Measuring constant receptor expression or a single-time point tissue sample would have led to missing the adenosine surge that would turn on and off. Only through continuous optics monitoring could it become possible to find a dynamic signal necessary for therapy.

Determining cause and effect in biology

The rigor of the mechanistic proof is exemplary. The importance of the mechanism indicated by the convergence of genetic and pharmacological approaches is shown by studies. Adora1$^{-/-}$ and Adora2a$^{-/-}$ mice lost all of the antidepressant efficacy of ketamine in two standard tests for depression. The first being the forced swim test which measures behavioral despair and the other the sucrose preference test which measures anhedonia (2). Results were not paradigm-specific. The necessity also applied in the chronic restraint stress model and the lipopolysaccharide model of inflammatory depression (3, 4). Post-hoc acute pharmacological blockade with selective antagonists PSB36 (A1) and ZM241385 (A2A) also completely stripped therapeutic responses to ketamine. This was the case at both 1-hour and 24 hours post-treatment.

The circuit-specificity is equally convincing. Scientists administered AAV-mediated CRISPR-Cas9 to internalize sgRNAs that target Adora1 and Adora2a within the mPFC. The loss of local receptor was sufficient to negate the effect of systemic ketamine (2). This confirms the mPFC as a key node—consistent with established mood and executive function roles, now established mechanistically.

The sufficiency experiments complete the logical circle. According to research, adenosine may act to prevent or reverse the onset of some diseases. In fact, direct infusion of adenosine into the mPFC produced antidepressant-like effects lasting 24 hours (2). More elegantly, optogenetic stimulation of astrocytes expressing cOpn5, optogenetic tools that trigger Ca^{2+}-dependent ATP release and subsequent CD73-mediated adenosine production, produces therapeutic actions, and this effect was extinguished in Nt5e$^{-/-}$ mice lacking CD73 (2, 5). Systemic delivery of

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selective agonists (CHA for A1, CGS21680 for A2A) produced rapid antidepressant responses, with A1-only action potent enough to sustain effects for 24 hours (2).

This mechanism was shown with a degree of thoroughness the field demands but rarely achieves.

Mitochondria, not neuronal hyperactivity

The upstream mechanism represents genuinely novel biology. Rather than generating adenosine through extracellular ATP hydrolysis, ketamine directly modulates mitochondrial function to increase intracellular adenosine, which then exits cells via equilibrative nucleoside transporters (ENT1/2). The authors demonstrate this in isolated mPFC mitochondria that are incubated with [$^{13}C_3$]pyruvate. Ketamine ($\geq$2 μM—therapeutically relevant concentrations) (6, 7) dose-dependently suppressed ^{13}C enrichment of TCA cycle intermediates fumarate, malate, and aspartate while causing accumulation of pyruvate (2).

This metabolic brake cascades into adenosine production. Using PercevalHR sensors to measure intracellular ATP/ADP ratios in vivo, they show that ketamine quickly decreases this ratio in CaMKII$^+$ pyramidal neurons (largest effect), GABAergic interneurons (transient reduction with rebound), and astrocytes (sustained decrease) (2). The timing is telling: the ATP/ADP ratio decrease comes before the extracellular adenosine surge, making metabolic perturbation upstream.

Critically, this occurs without neuronal hyperactivity. By analyzing calcium signaling response in pyramidal and GABAergic neurons to therapeutic doses of ketamine using GCaMP8s, it was found that ketamine at 10 mg/kg did not increase Ca^{2+} signaling in pyramidal neurons and actually decreased activity of GABAergic interneurons (2). This overturns the assumption that seizure-like neuronal hyperactivity is necessary for rapid antidepressant action. The mechanism is metabolic modulation driving adenosine efflux via equilibrative nucleoside transporters, not excitotoxic processes.

The authors demonstrate that dipyridamole, an ENT1/2 inhibitor, reduces the adenosine signal induced by ketamine, confirming the role of these transporters (2). In contrast, genetic depletion of CD73 (which hydrolyzes extracellular ATP to adenosine) has no effect on ketamine-induced adenosine surges.[1] The adenosine arises intracellularly and exits through ENT1/2 transporters in response to the concentration gradient produced by metabolic shifts.

From mechanism to molecules

This work goes beyond descriptive neuroscience in its immediate therapeutic translation. Adenosine dynamics appear to act as a functional biomarker in their hands. Based on this observation, the authors synthesized 31 ketamine derivatives by inducing systematic changes in chemical groups affecting their metabolism and receptor binding (2). Screening identified deschloroketamine (DCK) and deschloro-N-ethyl-ketamine (2C-DCK) as compounds showing 40-80% stronger adenosine signals than ketamine at equivalent doses.

The effects of this drug on behavior were noticed immediately. DCK produced significant antidepressant effects at 2 mg/kg (compared to 10 mg/kg for ketamine) with only a little hyperlocomotion at this dose (2). This shows a dissociation between therapeutic and psychomimetic effects. In particular, DCK at therapeutic doses showed only a small amount of locomotor activation. On the other hand, ketamine at 10 mg/kg produced significant hyperlocomotion. The enhanced therapeutic index indicates that promoting signaling downstream of adenosine rather than optimizing NMDA receptor nonspecific blockade broadens the safe window.

The authors provide clear evidence for the dissociation between NMDAR antagonism and the release of adenosine. Studies showed that compounds such as 3'-Cl-ketamine blocked NMDARs with high potency (IC_{50} comparable to ketamine in cortical slice recordings) but did not induce adenosine surges and are ineffective as an antidepressant (2). The correlation between the estimated in vivo NMDAR inhibitions (derived from the ex vivo IC_{50} values and brain tissue concentrations) and adenosine modulation was non-significant (Pearson r, $P = 0.097$).[1] Therefore, NMDAR antagonism is neither necessary nor sufficient; the therapeutic action operates via ketamine's direct mitochondrial actions.

This metabolic evidence is consistent with the parent compound driving adenosine release. In contrast, ketamine's primary metabolites—norketamine and (2R,6R)-hydroxynorketamine—do not produce adenosine responses at equivalent doses (2). Notably, hydroxynorketamine does have antidepressant properties in some studies (8). Inhibition of metabolism is important: CYP3A4 inhibitors (ketoconazole, ritonavir) potentiated the adenosine signal, whilst CYP2B6 inhibition (ticlopidine) did not (2).

Electroconvulsive therapy and beyond

The adenosine framework extends beyond ketamine. Seizures induced by electroconvulsive therapy (ECT) in anesthetized mice (40 mA, 100 Hz, 10s) mediated an adenosine surge in medial prefrontal cortex (mPFC) comparable in magnitude to that of ketamine but with faster kinetics (2). That is, the onset and decay of adenosine signaling are faster, consistent with the idea that ECT produces intense but brief neuronal firing. According to the authors, the requirement for adenosine to mediate these antidepressant effects is also the same. Adora1$^{-/-}$ mice (lacking the adenosine receptor A1) and Adora2a$^{-/-}$ mice (lacking the adenosine receptor A2A) did not respond to ECT with reductions in immobility in forced swim test or restored preference for sucrose in sucrose preference test (2).

The researchers found that acute intermittent hypoxia (aIH), which is a controlled reduction in oxygen that consists of 5 cycles of 9% O_2 for a duration of 5 min, interspersed with 21% O_2, when done daily for 3 days produces antidepressant effects that were entirely reliant on adenosine signaling.[1] Most importantly, from a clinical perspective, aIH is non-invasive, has been shown to be safe in other clinical contexts (9), does not require any complex machinery as long as oxygen can be controlled, and could be rolled out in low-resourced settings. Adenosine receptor knockout mice had no antidepressant effects from aIH, which indicates that aIH, ketamine, and ECT share identical mechanistic dependence on adenosine signaling (Figure 1) (2).

The coffee question: Clinical and mechanistic insights

It is certainly a paradoxical sort of story worth noticing. The most commonly consumed psychoactive drug in the world is caffeine, which functions as an adenosine receptor antagonist (Figure 2). The study makes it clear that "the possibility of dietary caffeine interfering with these treatments (2, 10, 11)." The warning has mechanistic grounding: if activation of adenosine receptors is necessary for therapeutic effectiveness, and caffeine is an adenosine receptor antagonist, then coffee drinking can be expected to blunt treatment response.

The epidemiological literature paints a different picture. The findings of a number of meta-analyses indicate that chronic coffee consumption protects against depression. One meta-analysis found that RR coffee 0.757, RR caffeine 0.721 (12). Another one found RR 0.76, with an optimal protective effect at ~400 mL/day (13). In comparison to many drug treatments that have an effect size in this range, this is not a small effect size. A risk reduction of 20 to 25% is quite impressive.

Ideas based on known pharmacology, but not yet directly

One might find answers in the tonic and phasic adenosine signaling and if there is any receptor reserve. Ongoing caffeine use will cause a modest (~20%) upregulation of A1 receptors, but crucially, this upregulation does not interfere with any functional signaling capacity of the receptor upon binding of adenosine (14). The receptors are still functional; there are just more of them.

Furthermore, adenosine receptors show a significant "spare receptor" reserve, with A2A receptor reserve estimated to be 70–90% and 10–64% for A1 receptors. It means a 5–10% occupancy of the receptor can give rise to approximately a 50% maximal effect (15, 16). An antagonist must occupy more than 95% of the receptors to block any effect when spare receptors are present (15).

The pharmacokinetics of caffeine is relevant here. Caffeine has a half-life of 3–7 hours and a peak concentration 45–60 minutes after ingestion,

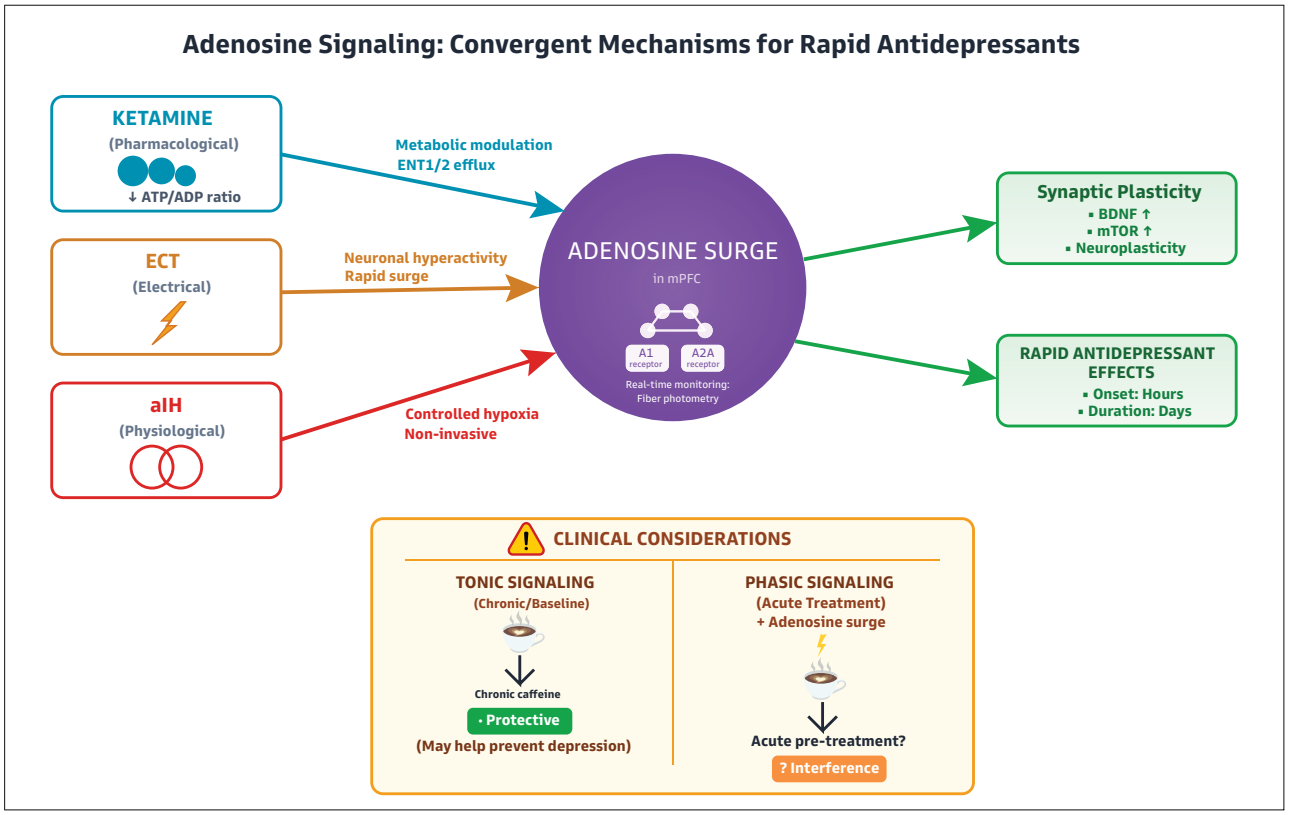

Figure 1. Adenosine Signaling: Convergent Mechanisms for Rapid Antidepressants. Three distinct interventions—ketamine (pharmacological), electroconvulsive therapy/ECT (electrical), and acute intermittent hypoxia/aIH (physiological)—converge on a common mechanism: adenosine surges in the medial prefrontal cortex (mPFC). Ketamine triggers adenosine release through metabolic modulation (decreased ATP/ADP ratio) and ENT1/2-mediated efflux, without causing neuronal hyperactivity. ECT produces adenosine surges via neuronal hyperactivity and rapid metabolic demand. aIH generates adenosine through controlled hypoxia in a non-invasive manner. All three interventions activate A1 and A2A adenosine receptors in the mPFC, detected in real-time using fiber photometry with genetically encoded sensors (GRABAdo1.0). This adenosine signaling triggers downstream synaptic plasticity mechanisms (BDNF upregulation, mTOR activation, neuroplasticity), resulting in rapid antidepressant effects with onset in hours and duration lasting days. Clinical Considerations: The adenosine mechanism raises important questions about caffeine consumption patterns. *Tonic signaling* (chronic/baseline coffee consumption) appears protective against depression and may help prevent depressive episodes. *Phasic signaling* (acute pre-treatment coffee) raises mechanistic concerns about potential interference with the adenosine surge during ketamine/ECT administration, though this remains speculative and requires clinical validation. The dual nature of caffeine's effects—protective chronically, potentially interfering acutely—reflects the distinction between tonic baseline adenosine receptor modulation and phasic adenosine surge responses to rapid-acting treatments.

Figure 2. The coffee paradox in adenosine-mediated antidepressant action. Depression (left) and coffee consumption (right) are both linked through adenosine signaling (center), creating a pharmacological paradox: chronic coffee drinking appears protective against depression through tonic adenosine receptor modulation, while acute pre-treatment caffeine may attenuate the phasic adenosine surge required for rapid antidepressant responses to ketamine and electroconvulsive therapy.

with a receptor occupancy of ~50%–65% between doses in regular consumers (11, 17).

When there is chronic consumption, there is usually a tonic effect which results in more receptors being upregulated in addition to a maintained spare receptor reserve. While there is partial occupancy on the receptors, there is no complete occupancy. The fundamental adenosinergic tone might be augmented in the presence of the antagonist consistent with epidemiological protection from depression.

Prior consumption of caffeine (phasic blockade) must be overcome by the adenosine surge following ketamine or ECT application. When caffeine occupies 50–65% of receptors, there's still considerable receptor reserve available. This means the adenosine surge has to work harder to overcome the blockade, weakening the signal without wiping it out completely. With considerable but not infinite receptor reserve, adenosine signal decreases but does not get obliterated.

More tailored approaches instead of outright bans are suggested by this pharmacologcial analysis.

- Regular caffeine/coffee use pre-ketamine is probably not contraindicated. Epidemiological data suggest a possible benefit of that use.
- Having coffee just before the treatment is more concerning. Patients may be recommended caffeine washout to achieve optimal adenosine receptor availability during the critical adenosine spike.
- Drinking coffee after treatment is probably safe once the first plasticity mechanisms are already established.

Can we test whether regular coffee drinkers show blunted ketamine responses? Does controlled caffeine washout enhance outcomes? Is there a link between caffeine use and the response? The current paper offers the mechanistic foundation to pose such questions rigorously.

But these things are still open empirical questions, sadly. This system has not yet undergone quantitative pharmacology that links chronic receptor modulation with acute receptor reserve and surge amplitudes large enough to overcome partial blockade. Yue et al. clarify mechanisms to ensure that scientists pose the right questions.

What remains unknown

What makes this piece valuable is its honesty about the boundaries of its work. Several questions merit attention.

The mechanisms linking acute adenosine surges to sustained plasticity are not well defined. The authors demonstrate that the upregulation of BDNF [a key transducer of antidepressant effects (18)] produced by ketamine requires the A1 and A2A receptors (2), linking adenosine to established pathways of neuroplasticity. Still, more elaboration is needed on how a surge of adenosine for ~30 minutes produces antidepressant effects extending over days-to-weeks. HOMER1A activation and stimulation of the mTOR pathway are cited in the paper as likely downstream effectors (2, 19, 20) but the full signalling pathway has yet to be defined.

Second, the hippocampal story is incomplete. After ketamine, adenosine levels soared in the hippocampus in a manner comparable to that in the mPFC (2). It should be noted that optogenetic initiation of adenosine and the direct infusion of adenosine into the dorsal hippocampus did not produce an antidepressant effect (2). This suggests functional heterogeneity, possibly along the dorsal–ventral axis. With the ventral hippocampus having greater associations with mood circuits and the dorsal hippocampus serving cognitive and spatial functions. The authors rightly highlight the need for an investigation of this complex matter.

We will need to incorporate these into our understanding of the relationship between adenosine and the other proposed ketamine mechanisms. In this area, there has been interest in NMDAR antagonism (21), AMPA receptor potentiation (22), mTOR activation (23) and various metabolite effects (8). The current work shows that adenosine is necessary and sufficient and that the NMDAR block dissociates from therapeutic action across derivatives. lthough the position of adenosine in the signaling cascade remains unclear, whether it operates in parallel with, upstream of, or downstream from other mechanisms, the authors' data suggest that adenosine may be the primary initiating signal and that other mechanisms are downstream consequences but this is yet to be validated.

To apply this finding to treatment resistant depression in humans, we have to keep in mind the heterogeneity that clinical psychiatry so well knows. Some patients do not respond to ketamine and not all respond to ECT. Do nonresponders have defects in how they produce adenosine, express receptors, or couple receptor signaling? Can adenosine dynamics—appraised with PET tracers for A1 and A2A receptors and, if predictive, using peripheral biomarkers—sample patients likely to respond? These questions ultimately determine clinical utility.

A framework for rational development

Unfortunately, psychiatry has depended much more on serendipity than mechanism for a long time. The monoamine hypothesis was discovered accidentally (as with iproniazid and imipramine). The atypical antipsychotics resulted from chemical modifications aimed at fewer side effects. Finally, the discovery of ketamine's antidepressant properties occurred by accident during studies of its properties. We have been, in Baudrillard's concept, cartographers mapping territories we have not yet crossed: "The territory no longer precedes the map, nor survives it. Henceforth, it is the map that precedes the territory (24)." We say we know what works without knowing why.

In contrast, Yue et al. provide an extraodinary map after exquisitely researching the territory. With adenosine as the mechanistic target, the authors have already demonstrated proof-of-principle: derivatives with enhanced adenosine signaling show improved therapeutic indices.[1] The path forward involves:

- **Medicinal chemistry optimization** of adenosine-enhancing compounds, prioritizing metabolic mitochondrial modulators over NMDAR antagonists.
- **Allosteric modulation** of A1 and A2A receptors to enhance endogenous signaling without tonic activation.
- **Non-pharmacological interventions** (aIH, potentially others) that leverage adenosine biology.
- **Biomarker development** for patient stratification and response prediction.
- **Combination strategies** targeting complementary nodes in the adenosine-plasticity cascade.

The technical platform is robust: genetically encoded sensors provide real-time functional readouts for compound screening; the behavioral assays are well-validated; the genetic models allow mechanistic dissection; the therapeutic endpoints (onset, duration, side effects) are clinically meaningful.

Most critical is that the work establishes that rapid antidepressant action is not a pharmacological curiosity of a dissociative anesthetic. A reproducible neurobiological phenomenon, adenosine-driven plasticity in mood-regulatory circuits, can be triggered by multiple routes. This converts an empirical observation (ketamine works fast) into a biological principle (adenosine surges trigger antidepressant plasticity) that guides rational therapeutic development (Table 1).

Conclusions

As we have previously written about the psychotherapeutics, it is only time that will tell how far our conceptions of causation are from physical reality. Yue et al. have greatly shortened that distance. The overarching mechanism or platform refers to elements including genetically encoded sensors, validated targets, proof-of-principle molecules, non-drug alternatives and the general model explaining disparate interventions.

The adenosine hypothesis can be tested with readily available tools and immediate therapeutic implications. Yue et al. have given the field the aerial view after decades wandering through the forest of empirical psychopharmacology and not looking beyond the next tree.

Perhaps the most intriguing implication of this work lies in an unexpected connection: the most rigorous mechanistic dissection of rapid antidepressant action identifies adenosine as the critical mediator, yet adenosine receptors are the primary target of caffeine, the world's most widely consumed psychoactive substance. Is this merely coincidence, or

Table 1. Clinical Implications of Adenosine-Based Antidepressant Mechanisms

Clinical Domain	Key Finding	Clinical Action
Caffeine & Treatment Timing		
Chronic consumption	Protective: 20–25% risk reduction (12, 13)	Continue usual intake; may prevent depression
Acute pre-treatment	Occupies 50–65% receptors for 3–7 h (15, 16)	Consider 12–24 h washout before ketamine/ECT*
Mechanistic basis	Tonic signaling (baseline) vs. phasic signaling (treatment surge)	Distinguish chronic protective effects from acute interference potential*
Novel Therapeutics		
Improved derivatives	DCK: 5 × lower dose, reduced side effects (2)	Monitor clinical trials of optimized compounds
Non-pharmacological	aIH produces adenosine-dependent effects (2)	Consider for drug-intolerant patients; scalable alternative to ECT
A1 receptor agonists	Sufficient for 24 h antidepressant action (2)	Potential monotherapy or adjunct strategy
A2A receptor role	Contributes to acute effects; less sustained than A1 (2)	May complement A1 activation in combination approaches
Mechanistic Insights		
Mitochondrial targeting	Ketamine modulates metabolism directly, not primarily via NMDAR (2)	Focus drug development on metabolic modulators over NMDAR antagonists
ENT1/2 transporters	Mediate adenosine efflux from intracellular compartment (2)	Consider ENT modulation as therapeutic strategy
Metabolic brake	Decreased ATP/ADP ratio precedes adenosine surge (2)	Target upstream metabolic pathways for novel interventions
Patient Stratification		
Genetic predictors	A1/A2A polymorphisms may predict response	Consider genotyping in treatment-resistant cases*
Biomarker development	Real-time adenosine monitoring validated; peripheral markers possible (2)	Research protocols for response prediction; drug screening platform
Treatment history	Chronic caffeine users may have upregulated receptors with preserved reserve (14–16)	Caffeine history as potential predictor (requires validation)*
Treatment Optimization		
Mechanism separation	Antidepressant ≠ psychomimetic effects (2)	Lower doses reduce dissociation/abuse risk
Circuit specificity	mPFC adenosine necessary & sufficient (2)	Future: regional targeting strategies; hippocampal effects require further study
Temporal dynamics	∼30 min adenosine surge → days of benefit (2)	Optimize inter-treatment intervals; single surge sufficient for sustained effects
Dose-response	Higher doses prolong duration without increasing peak (2)	Titrate for optimal balance of efficacy and side effects
Safety & Side Effects		
Therapeutic window	DCK effective at 2 mg·kg^{-1} with minimal hyperlocomotion vs. ketamine 10 mg·kg^{-1} (2)	Enhanced safety profile possible with adenosine-optimized compounds
Dissociation avoidance	Adenosine mechanism separable from NMDAR psychotomimetic effects (2)	Target adenosine pathway to minimize dissociative experiences
Non-Pharmacological Interventions		
aIH advantages	Non-invasive, safe profile in humans, no complex equipment required (9, 2)	Implement in low-resource settings; option for treatment-resistant patients
ECT mechanistic insight	Adenosine mediates ECT effects; A1/A2A receptors required (2)	Optimize ECT protocols based on adenosine dynamics; predict responders*
Sleep deprivation	Known to increase adenosine (20)	Investigate adenosine monitoring during sleep deprivation therapy*
Biomarker Applications		
Drug development	Adenosine dynamics as functional readout for compound screening (2)	Use GRABAdo sensors for phenotypic drug discovery
Response prediction	PET tracers for A1/A2A available; peripheral markers under investigation	Develop clinical-grade adenosine monitoring protocols*
Treatment monitoring	Real-time adenosine measurement feasible (2)	Potential for dose optimization during treatment*
Combination Strategies		
With existing SSRIs	Adenosine pathway may complement monoaminergic effects	Investigate sequential or concurrent administration*
With psychotherapy	Rapid symptom relief may enhance therapy engagement	Time psychotherapy sessions to peak neuroplasticity window*
Multi-modal approaches	Combine pharmacological + aIH for additive effects	Pilot studies of combination protocols*

*Mechanistic speculation requiring clinical validation. All other recommendations based on published evidence.
Abbreviations: aIH, acute intermittent hypoxia; DCK, deschloroketamine; ECT, electroconvulsive therapy; ENT, equilibrative nucleoside transporter; mPFC, medial prefrontal cortex; NMDAR, NMDA receptor; PET, positron emission tomography; SSRI, selective serotonin reuptake inhibitor.
Numbers in parentheses refer to references in the main text.

does it reveal something fundamental about why humans have gravitated toward caffeine consumption across cultures and millennia? The epidemiological protection that chronic coffee drinking confers against depression may represent an inadvertent form of adenosinergic modulation operating at population scale. Yet the same mechanism that provides tonic benefit might interfere with phasic therapeutic surges during acute treatment.

The coffee paradox demands resolution through carefully designed clinical studies. Do regular coffee drinkers show altered responses to ketamine or electroconvulsive therapy? Does pre-treatment caffeine washout enhance therapeutic outcomes? Can we develop dosing strategies that preserve the protective effects of chronic consumption while optimizing acute treatment responses? The convergence of the world's most prevalent psychoactive drug with the mechanistic lynchpin of our most effective rapid antidepressants is unlikely to be accidental. Understanding this intersection may illuminate both the widespread appeal of caffeine and the optimization of adenosine-targeted therapeutics. The next generation of clinical trials should systematically examine caffeine consumption patterns as a critical variable in treatment response, transforming an apparent pharmacological complication into a therapeutic opportunity.

Author contributions

Both authors contributed equally and fully to this article.

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Author disclosures

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