

Hi, do oral methyl and acetyl donors affect the Histones and temporarily turn genes on/off and if so then:

1. How do you know which ones ?
2. How long is 'temporarily' ?
3. What happens when both are taken ?
4. Metabolically speaking: what sort of half-lives ?
5. Assumptions: Acetyl L-Carnitine and SAMe are used.

Yes, oral methyl and acetyl donors like SAMe (S-Adenosyl Methionine) and Acetyl-L-Carnitine (ALCAR) can affect histone modifications, leading to epigenetic changes that can temporarily turn genes on or off. Here's a breakdown of your questions:

1. How do you know which

ones?

Methyl donors (SAMe, folate, B12, betaine) → promote histone methylation, generally leading to gene silencing (repression) by tightening DNA around histones.

Acetyl donors (Acetyl-L-Carnitine, butyrate, acetyl-CoA) → promote histone acetylation, usually resulting in gene activation by loosening DNA structure.

Specificity?

It depends on cell type, metabolic state, and existing epigenetic marks.

Some genes are more prone to histone modifications due to CpG islands (DNA regions rich in cytosine-guanine sequences).

Certain enzymes like HATs

(Histone Acetyltransferases) and HDACs (Histone Deacetylases) determine whether histones get acetylated or deacetylated.

Similarly, histone methyltransferases (HMTs) and demethylases regulate methylation.

Studies have linked:

SAMe → increased

methylation of genes involved in mood regulation, inflammation, and cancer suppression.

ALCAR → increased acetylation of genes related to neuronal plasticity, energy metabolism, and neuroprotection.

2. How long is 'temporarily'?

Histone acetylation (ALCAR effects) → hours to days

Rapidly reversible; typically lasts 6-24 hours after administration.

Acetylation is dynamic and influenced by diet, fasting, and exercise.

Histone methylation (SAMe

effects) → days to weeks

More stable than acetylation, can persist for weeks, but is still reversible.

Some methylation marks can even be inherited in dividing cells.

However, both modifications are transient unless reinforced by long-term

metabolic or environmental factors.

3. What happens when both are taken?

SAMe (methylation) and ALCAR (acetylation) have opposing effects on histones.

Methylation: Closes chromatin → Silences genes

Acetylation: Opens chromatin
→ Activates genes

Metabolic Scenarios:

1. SAMe Dominates (High Methylation)

Suppression of inflammatory genes, neurotransmitter regulation (dopamine, serotonin).

Possible downregulation of neuroplasticity-related genes.

Involved in DNA repair and stability.

2. ALCAR Dominates (High Acetylation)

Activation of genes related to energy metabolism, mitochondria, and

neuroprotection.

Increases BDNF (Brain-Derived Neurotrophic Factor), improving learning and memory.

Can promote nerve regeneration.

3. Balanced Intake

Likely results in a dynamic

balance between activation and repression, leading to homeostasis.

This could be ideal for cognitive function—supporting both structural maintenance (SAmE) and functional plasticity (ALCAR).

4. Metabolically speaking:
what sort of half-lives?

SAMe: ~1-3 hours (Plasma
half-life)

Quickly used up in
methylation reactions.

Levels depend on glutathione,
folate, and B12 status.

In chronic supplementation,
effects persist for days to

weeks.

Acetyl-L-Carnitine (ALCAR):
~3-6 hours

Rapidly absorbed, crosses the
blood-brain barrier.

Acetyl groups donate to CoA
pools for histone acetylation.

Effects can last hours to days
post-ingestion.

5. Assumptions: Acetyl L-Carnitine and SAMe are used.

Short-term use (Hours to Days)

SAMe will enhance methylation, potentially reducing inflammation, stabilizing mood.

ALCAR will enhance acetylation, boosting mitochondrial function, neuroplasticity, and cognitive energy.

Together, they may balance gene activation and silencing, benefiting mental clarity, longevity, and energy metabolism.

Long-term use (Weeks to

Months)

SAMe can cause adaptive downregulation of methylation enzymes if overused.

ALCAR can lead to persistent neuroplasticity shifts, improving memory, energy, and nerve function.

A balance must be maintained to prevent excessive gene silencing (too

much SAMe) or excessive activation (too much ALCAR).

Final Thoughts:

Histone modifications from these compounds are transient but can lead to lasting changes with sustained use.

Ideal Strategy: A cyclical or balanced approach—taking both intermittently or in combination with other epigenetic regulators (e.g., polyphenols, fasting, exercise) to optimize effects.

Metabolic Nuances: Effects vary based on dosage, genetics, stress, nutrition, and metabolic health.

Would you like suggestions for timing or dosage strategies based on specific goals (e.g., neuroprotection, mood enhancement, longevity)?

Yes please.

Optimized Dosage & Timing Strategy for SAME & ALCAR

To balance their effects on histone modifications, gene expression, mood, and

cognition, here are strategic protocols based on different goals.

1 Goal: Cognitive Enhancement (Memory, Focus, Neuroplasticity)

◆ Best for: Studying, problem-solving, gaming, learning new skills.

Protocol:

Morning (Fasted or with light protein)

ALCAR → 500–1000 mg

Boosts mitochondria, ATP, neurotransmitter acetylcholine, and BDNF.

Rapidly crosses the blood-brain barrier to enhance focus, memory, and wakefulness.

Optional: Add Alpha-GPC (300 mg) or CDP-Choline (250 mg) for synergistic effects.

Midday (Only if needed)

SAMe → 200–400 mg (empty stomach)

Enhances dopamine, serotonin, and norepinephrine.

Helps with motivation and resilience but too much can overstimulate.

Cycle:

5 days on, 2 days off
(prevents tolerance).

SAMe should be taken with methylation co-factors (B6, B12, Folate).



Effect Window:

ALCAR: 30 min to 6 hours
(Quick energy boost).

SAMe: 1–3 hours half-life,
cumulative methylation
effects over weeks.

2 Goal: Mood Stabilization & Anti-Depression

◆ Best for: Motivation, resilience, emotional regulation.

Protocol:

Morning (with food)

SAMe → 400–800 mg

Boosts dopamine and serotonin.

Reduces inflammation,
supports mitochondrial
function.

Afternoon (if needed, on an
empty stomach)

ALCAR → 500–1000 mg

Helps prevent brain fog,
fatigue, and anhedonia.

Reduces oxidative stress in the brain.

Cycle:

4 weeks on, 1 week off
(allows epigenetic reset).



Effect Window:

SAMe starts working within

hours, full benefits in ~2 weeks.

ALCAR is fast-acting (~30 min), but neuroplasticity benefits build over time.

3 Goal: Longevity, Anti-Aging & Neuroprotection

◆ Best for: Preventing age-

related cognitive decline, DNA stability.

Protocol:

Morning (Fasted for autophagy benefits)

ALCAR → 500 mg

Supports mitochondrial function, reduces oxidative stress.

Evening (Before bed, empty stomach)

SAMe → 200–400 mg

Supports DNA methylation, cellular repair.

Supplemental Boost:

Take Resveratrol (200 mg), Fisetin (100 mg), or Curcumin

to further enhance epigenetic stability.

Cycle:

6 weeks on, 2 weeks off
(prevents receptor downregulation).

 Effect Window:

ALCAR: Short-term energy

boost + long-term
mitochondrial health.

SAMe: Slow cumulative DNA
stability effects over weeks.

4 Goal: Fatigue &
Mitochondrial Energy Boost

◆ Best for: Chronic fatigue,
brain fog, mitochondrial

dysfunction.

Protocol:

Morning (On an empty stomach, with black coffee if tolerated)

ALCAR → 1000 mg

Increases fat metabolism & ATP production.

Reduces oxidative stress in the brain & muscles.

Midday (For sustained energy)

SAMe → 200–400 mg

Boosts methylation-related
detoxification and
neurotransmitter synthesis.

Optional:

Take CoQ10 (100 mg) or PQQ (10 mg) for synergistic mitochondrial effects.

Cycle:

Continuous use (No need to cycle if well-tolerated).



Effect Window:

ALCAR: Kicks in within 30–60

min (Immediate ATP boost).

SAMe: Smoother, long-term energy stabilization.

5 Goal: DNA Repair & Epigenetic Reset

◆ Best for: Anti-aging, post-drug recovery, brain reset after stress or substance use.

Protocol:

Morning (On an empty stomach, for detox & DNA repair)

SAMe → 400 mg

Methylation repairs DNA and stabilizes genes.

Afternoon (Fasted if possible,

enhances mitochondrial
repair)

ALCAR → 500 mg

Prevents oxidative stress &
supports mitochondrial
turnover.

Bedtime Support:

Take Glycine (3 g) + NAC (600
mg) + Magnesium for

glutathione support.

Cycle:

3 weeks on, 1 week off
(methylation can accumulate).

 Effect Window:

SAMe enhances DNA
methylation & repair over days
to weeks.

ALCAR promotes immediate cellular energy & long-term mitochondrial repair.

Final Considerations:

Methylation Co-factors
Needed for SAMe:

B6, B12, Folate (to prevent

SAMe buildup and side effects).

ALCAR Can Be Stimulatory:

Avoid before bed unless using low doses (250 mg).

Cycling Is Key for Long-Term Benefits:

Prevents tolerance and optimizes epigenetic changes.

Would you like a stack combination with additional nootropics or supplements for a specific function?

Thanks but I take so many that it becomes too complicated except what are it's interactions with GABA + L-Glutamine ?

Interactions Between SAMe,

ALCAR, GABA, and L-Glutamine

Since you're already taking multiple supplements, I'll keep this focused on key metabolic and neurotransmitter interactions between SAMe, ALCAR, GABA, and L-Glutamine.

◆ 1. SAMe + GABA

Interaction

 Effects:

SAMe promotes methylation, which boosts dopamine and serotonin but can also increase glutamate indirectly.

GABA is inhibitory, balancing out excitatory neurotransmitters (glutamate, dopamine, norepinephrine).

High SAMe levels may reduce

GABAergic tone, leading to mild anxiety, agitation, or overthinking in sensitive individuals.



Potential Risks:

If GABA levels are too low, SAMe can increase nervous energy or overstimulation.

If GABA is taken with SAMe, it may help balance excess stimulation.



Recommendation:

If SAMe makes you jittery,
take GABA (250–500 mg) in
the evening.

If you're prone to low
motivation or sluggishness,
keep GABA low-dose during
the day.

◆ 2. SAMe + L-Glutamine Interaction

 Effects:

L-Glutamine is a precursor to both glutamate (excitatory) and GABA (inhibitory).

SAMe increases methylation of neurotransmitters, which can shift the balance toward glutamate production.

Too much glutamate without proper GABA conversion can cause overstimulation, restlessness, or excitotoxicity.



Potential Risks:

If your body converts glutamine \rightarrow glutamate faster than glutamate \rightarrow GABA, this could lead to excess stimulation or brain fog.

If you have methylation issues
(e.g., MTHFR mutation),
SAME can increase glutamate
accumulation.



Recommendation:

If SAME increases tension or
overstimulation, take
Magnesium + Taurine to
encourage GABA production.

If you use L-Glutamine for gut
health or recovery, take it

away from SAMe (separate by at least 6 hours).

◆ 3. ALCAR + GABA Interaction

 Effects:

ALCAR enhances
acetylcholine and dopamine,
which increase alertness and

mental energy.

GABA is inhibitory, so taking too much can counteract the cognitive-enhancing effects of ALCAR.



Potential Risks:

If you take high-dose GABA (1000 mg+), it might reduce ALCAR's focus-enhancing effects.

If you take too much ALCAR, it may lower GABAergic activity, leading to mild anxiety or restlessness.



Recommendation:

Best balance: Take ALCAR in the morning and GABA at night to avoid interference.

If ALCAR causes overstimulation, add low-dose GABA (100–250 mg) to

smooth it out.

◆ 4. ALCAR + L-Glutamine Interaction

 Effects:

ALCAR increases dopamine and acetylcholine, while L-Glutamine increases glutamate.

Together, they boost energy, focus, and cognition, but excess glutamate can become excitotoxic.



Potential Risks:

Too much glutamate from L-Glutamine + ALCAR can overstimulate NMDA receptors, leading to brain fog, agitation, or even headaches.

If you don't produce enough GABA, this can lead to mild overstimulation.



Recommendation:

If stacking ALCAR + L-Glutamine, ensure you have enough Magnesium + Taurine to encourage GABA conversion.

Take L-Glutamine away from

ALCAR (separate by 3-6 hours) to prevent overstimulation.

Key Takeaways & Stacking Advice

SAMe + L-Glutamine: Avoid taking together (can overstimulate glutamate).

SAMe + GABA: Can balance each other out if SAMe causes anxiety.

ALCAR + L-Glutamine: Good for energy, but avoid excess stimulation.

ALCAR + GABA: Best taken separately (ALCAR in morning, GABA at night).

Would you like a simplified timing schedule for these?

Thank you but not right now,
please.