Examine.com

Mood & Depression Supplement Guide

Written by the editors of Examine.com

Updated December 05, 2017

Medical Disclaimer

This guide is a general-health document for adults over 18. Its aim is strictly educational. It does not constitute medical advice. Please consult a medical or health professional before you begin any exercise-, nutrition-, or supplementation-related program, or if you have questions about your health.

This guide is built on scientific studies, but study outcomes are never homogeneous: individual results do vary. If you engage in any activity or take any product mentioned herein, you do so of your own free will, and you knowingly and voluntarily accept the risks. While we mention major known interactions, it is possible for any supplement to interact with other supplements, as well as with foods and pharmaceuticals.

A product may not contain the exact compounds and amounts listed on its label. Before you decide whether to take it, investigate it and its manufacturer. More than isolated compounds, herbs are prone to batch-to-batch variability, which can alter their efficacy and safety.

For evidence supporting the claims mentioned in this guide, please visit Examine.com.

Table of Contents

02 Medical Disclaimer

04 How to Use This Guide

05 Core Supplements

09 Primary Options

12 Secondary Options

14 Inadvisable Supplements

15 Assembling Your Stack

17 FAQ

18 Precautions and Troubleshooting

How to Use This Guide

The Examine.com team has been publishing research on nutrition and supplementation since March 2011. Drawing from all we've learned, we've designed this Stack Guide to help you figure out which supplements can help you reach your health goal, and which can hinder you or just waste your money.

Core supplements have the best safety-efficacy profile. When used responsibly, they are the supplements most likely to help and not cause side effects.

Primary options may provide substantial benefit, but only in the right context. A primary option is not for everyone, but if you read the entry and find that you meet the criteria, consider adding the supplement to your stack.

Secondary options have less evidence for their effects. They could work or be a waste of money. Keep them in mind, but think twice before adding them to your stack.

Promising supplements are backed by tradition or by mechanistic, animal, epidemiological, or anecdotal evidence, but not yet by convincing human trials.

Inadvisable supplements are either potentially dangerous or simply ineffective, marketing claims notwithstanding. Do not add them to your stack. At best, they'll be a waste of money; at worst, they can cause you harm.

Now that you've been presented with various supplements worthy of your interest, the time has come to combine them based on your objective. We'll guide you in **assembling your stack**.

Then comes the **FAQ**, in which we cover common questions that may arise when assembling your stack.

Lastly, we include information on **precautions and troubleshooting**.

With all this combined, you should be able to identify and assemble the supplement stack best suited to your objective.

Core Supplements

SAMe

Why it's a core supplement

S-adenosylmethionine (SAMe) works with enzymes in a process called methylation: when a molecule in your body needs a methyl group in order to undergo a chemical reaction, SAMe provides that group.

As a supplement, SAMe has been found to be as potent as tricyclic antidepressants (TCAs). It can also enhance the action of selective serotonin reuptake inhibitors (SSRIs), which is usually seen as beneficial, although a high enough dose of both SAMe and SSRIs could cause a negative reaction.

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that helps process amino acids. If you have an MTHFR gene mutation, SAMe can still benefit your mood, but it may also cause a "backlog" of a potentially harmful metabolite known as homocysteine. In this scenario, it would be safer to replace SAMe by L-methylfolate (aka levomefolic acid, 5-methyltetrahydrofolate, and 5-MTHF).

Preliminary evidence suggests that ingesting choline or its derivative trimethylglycine (TMG, aka betaine) can raise SAMe levels, though to a lesser extent than ingesting SAMe. As an upside, both choline and TMG lower homocysteine levels in normal people, which makes them less likely than SAMe to raise homocysteine levels in people with an MTHFR gene mutation.

How to take it

First choice is SAMe; second, TMG; third, choline. If you have an MTHFR gene mutation, replace SAMe by L-methylfolate, with or without TMG or choline. Before using any of those supplements to fight depression, however, ***consult with a doctor*** — especially if you take serotonin-mediated pharmaceuticals.

Take 400 mg of **SAMe** thrice a day (i.e., 1,200 mg/day), with or without food.

Take 1.5–2 g of **trimethylglycine** (TMG) twice or thrice a day (i.e., 3–6 g/

day). TMG can be consumed as a powder or simply through foods, notably wheat bran (1,339 mg of TMG per 100 g), spinach (600–645 mg of TMG per 100 g), and beetroot (114–297 mg of TMG per 100 g).

Most people get enough choline through their diet. Track what you eat for a week; if, on average, you are getting less than 80% of your Adequate Intake (AI), try eating more foods rich in choline before you consider taking 250–500 mg of **choline bitartrate** once a day with a meal.

Take 7.5–15 mg of **L-methylfolate** once a day.

Consult with a doctor before using any of the above supplements to fight depression, especially if you take serotonin-mediated pharmaceuticals.

Vitamin D

Why it's a core supplement

Suboptimal levels of vitamin D are common, especially in people whose exposure to sunlight (without clothes or sunscreen) is limited. Moreover, the darker your skin, the longer you need to expose yourself to sunlight to synthesize enough vitamin D. Very little vitamin D can be found naturally in foods, with fatty fish being a notable exception (particularly cod liver oil).

Preliminary evidence suggests Vitamin D can benefit mood when supplemented by people with less than optimal vitamin D levels. While this effect is not very powerful and would need to be more thoroughly investigated, vitamin D is a safe (and cheap) supplement.

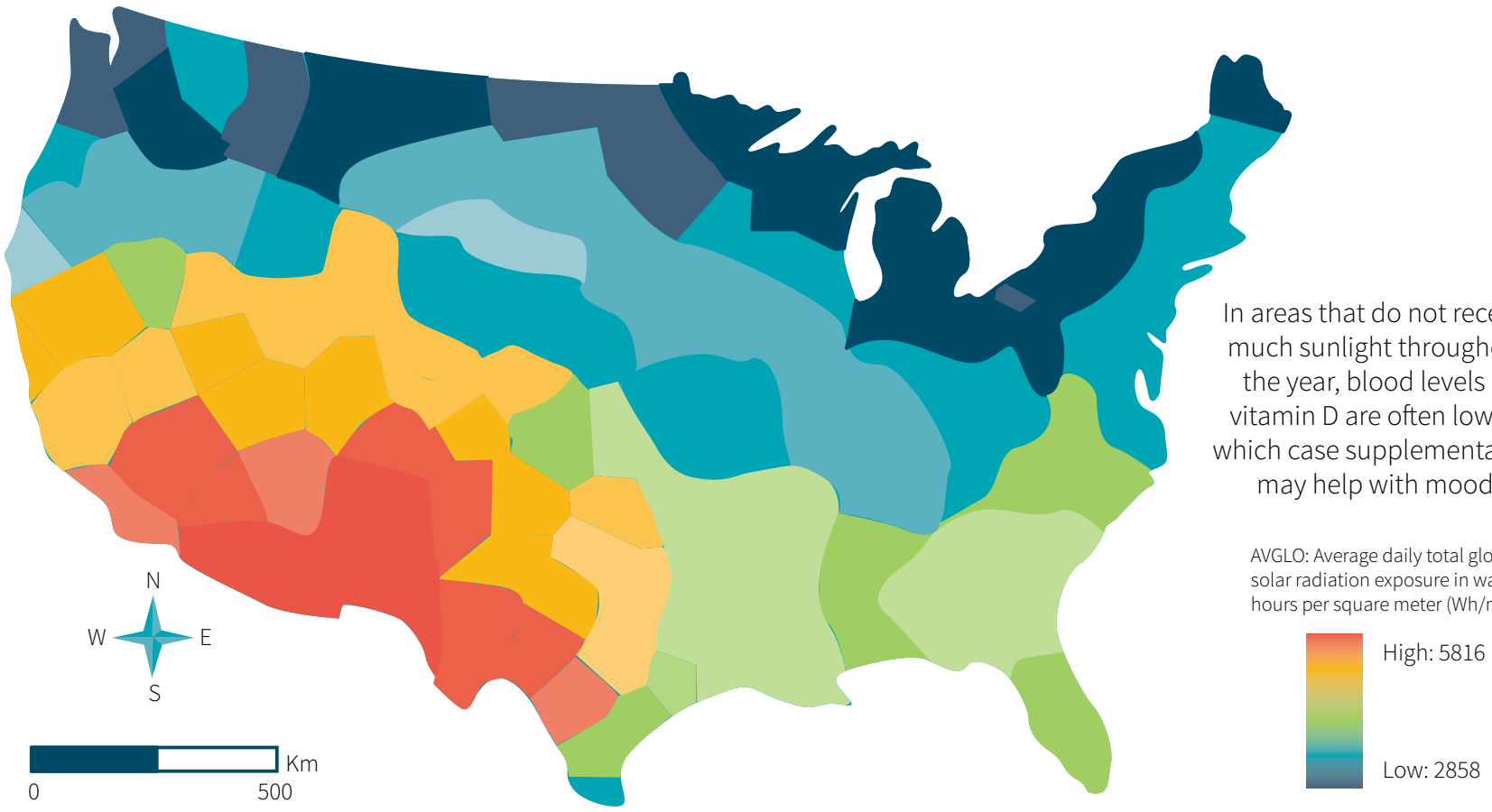
Vitamin D comes in two forms. Ergocalciferol (D_2) is obtained through the irradiation of some plants and fungi, whereas cholecalciferol (D_3) is the kind of vitamin D your body synthesizes from the cholesterol in your skin under the action of the sun's ultraviolet B (UVB).

Vitamin D_3 is both more stable and more bioavailable than vitamin D_2; as a supplement, it is usually derived from lanolin, a waxy substance secreted by the skin glands of woolly animals, but a vegan-friendly option (a lichen extract) is also available.

How to take it

Take 2,000 IU (50 mcg) of $\mathbf{D_3}$ with a meal containing fat, either year round or only during the colder, darker months, when you are least likely to synthesize enough vitamin D from sun exposure. If you spend a lot of time outside and live near the equator, supplementation is probably never a necessity.

Figure 1: Sunlight exposure in the US



Source: Tatalovich et al. *Cartography and Geographic Information Science*. 2013 March.

Doses higher than 2,000 IU may be warranted in cases of severe deficiency or non-response at lower doses, as ascertained by a blood test. Keep in mind that, over months, 10,000 IU/day can become toxic.

Zinc

Why it's a core supplement

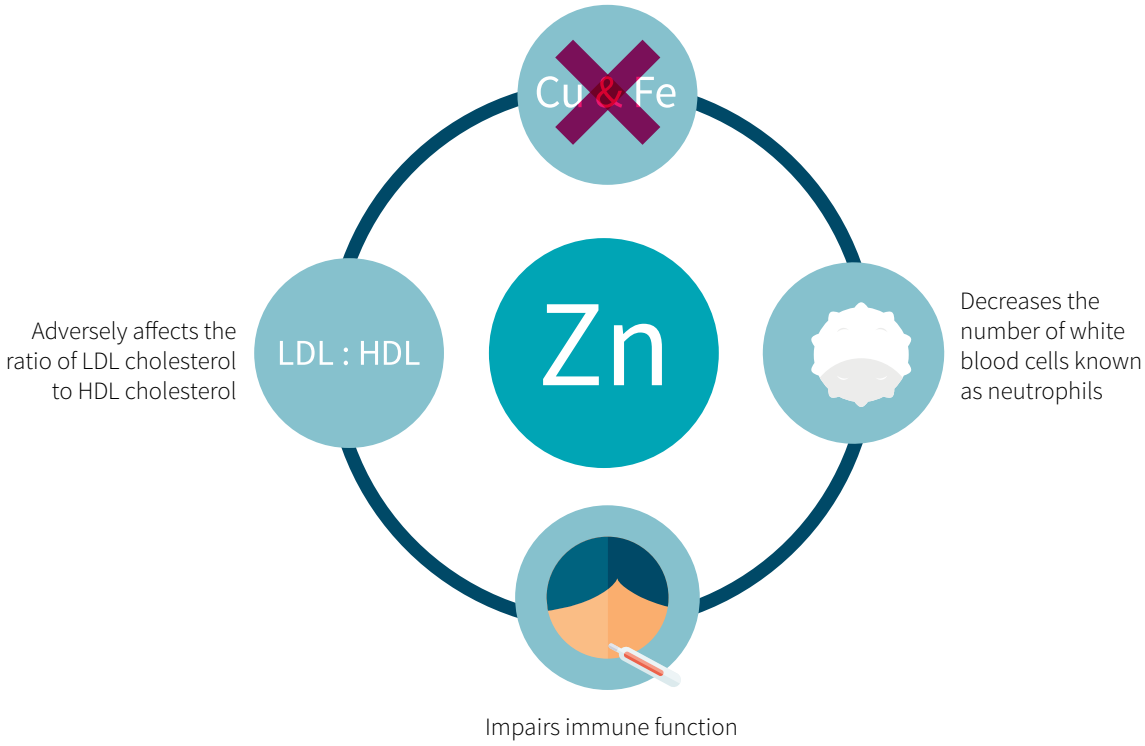
Zinc (Zn) is an important mineral for general health, and it may influence mood and depression.

Though zinc in itself lacks a potent antidepressant effect, supplementation is known to increase the effectiveness of antidepressant therapies and to improve the mood of people who are not suffering from clinical depression.

Other dietary minerals, such as chromium, also have antidepressant properties. Focusing on zinc supplementation first is recommended, however, since fixing a zinc deficiency will safely provide a variety of health benefits.

Over time, high doses of zinc can irritate the gastrointestinal tract. They can also cause a copper deficiency, since zinc kick-starts the process of creating metallothionein, a protein that binds zinc but also other metals, notably copper; the bound metals then leave the body as waste products. Even higher doses of zinc can also damage the liver and kidneys, but the doses in this guide are too low to pose any of those risks.

Figure 2: The negative effects of too much zinc



How to take it

Zinc requirements vary according to diet and level of activity. Sedentary people who don't sweat much and eat enough meat might not need to supplement zinc at all, and should otherwise limit themselves to 10–20 mg/day. Vegetarians as well as athletes and other people who sweat a lot (which results in zinc loss) can take 25–30 mg/day.

Zinc should be taken with meals, so as to prevent potential nausea. Avoid taking calcium, iron, magnesium, and zinc at the same time in combinations of 800+ mg, since high amounts of these minerals will compete for absorption. Though to a lesser extent than magnesium, zinc may also impair the absorption of antibiotics, notably those in the tetracycline class (e.g., doxycycline) and quinolone class (e.g., ciprofloxacin), so consider taking zinc and antibiotics at least six hours apart.

Primary Options

Adaptogens

Why they're a primary option

Adaptogens are supplements that can reduce the mental and physical effects of stress, including fatigue, mood swings, irritability, and anxiety. They have only been shown to be effective at treating depression that stems from stress and anxiety.

The best-researched adaptogens with regard to mood disorders are Rhodiola rosea (which can prevent and relieve stress-induced burnout) and ashwagandha.

How to take them

To supplement ***Rhodiola rosea***, take 80–160 mg of SHR-5 (an extract standardized for 3% rosavins and 1% salidroside) with a meal.

Ashwagandha is commonly taken with breakfast, if only because night-time supplementation may cause insomnia. The usual dosage range for KSM-66 (a water-based extract standardized to 5% withanolides) is 300–600 mg/day. Should you purchase another extract standardized for withanolide content, aim for 15–30 mg of withanolides per day. Do not take more than 1,200 mg of KSM-66 (or 60 mg of withanolides) per day.

EPA

Why it's a primary option

Studies suggest that treatment-resistant depression is associated with low concentrations of eicosapentaenoic acid (EPA) in the brain. Though further research is needed to confirm this relationship, EPA supplementation may play a supporting role in the treatment of depression, and preliminary human evidence suggests it may also play a role in reducing anxiety.

EPA is a primary option for people suffering from severe (rather than

minor) depressive disorders. **Consult with a doctor** before using EPA as supporting therapy.

How to take it

Take 500 mg of EPA.

While EPA-only supplements exist, including vegan supplements, EPA is most often consumed as fish oil. Most 1-g fish oil softgels on the markets contain 180 mg of EPA, so 3 such softgels, taken all at once or separately, would make for a daily dose. You can choose to lower your dose on days you consume fatty fish, though this is by no means compulsory.

St. John's Wort

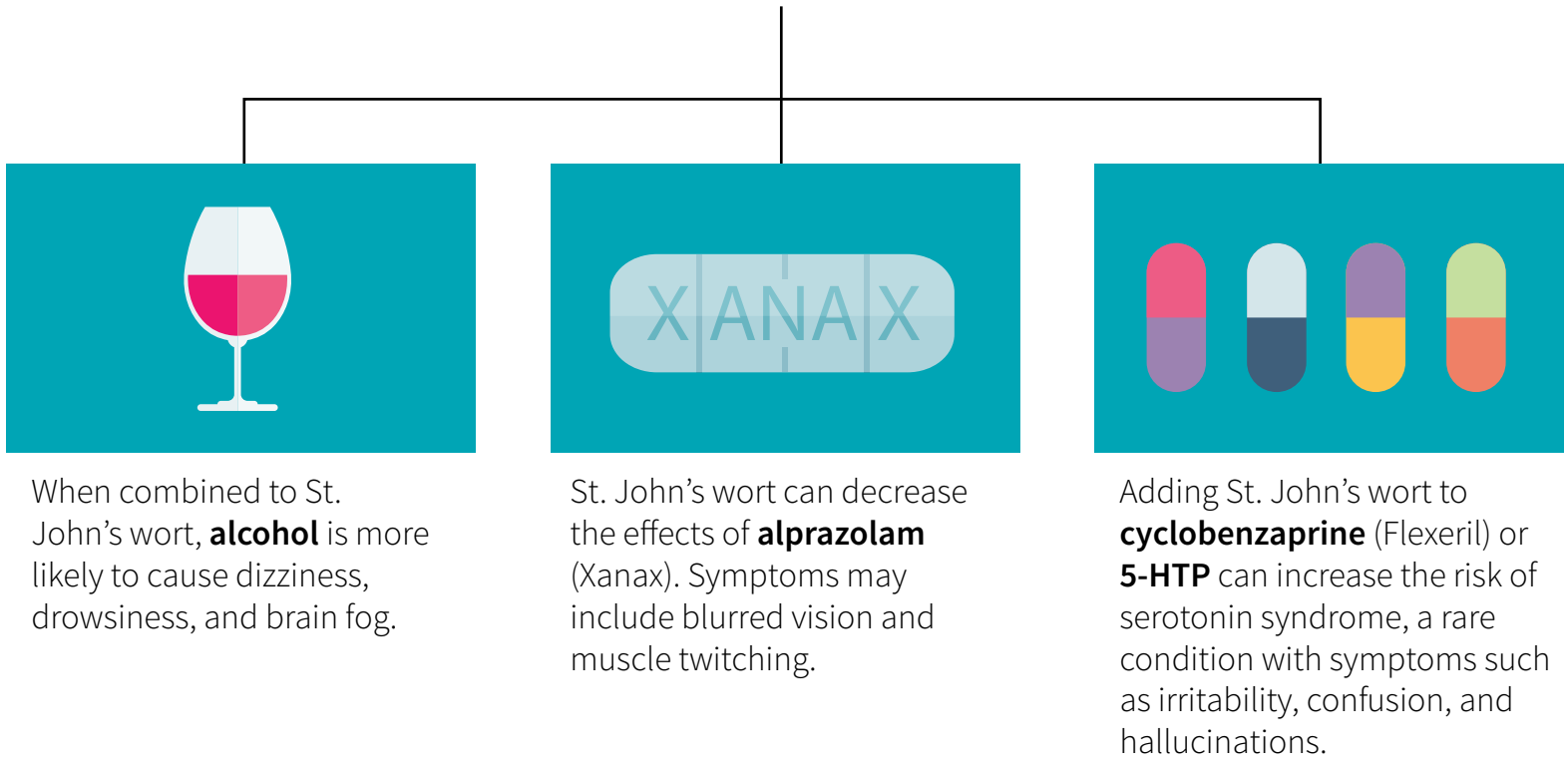
Why it's a primary option

St. John's wort (*Hypericum perforatum*), is one of the best-researched herbal antidepressants. It may be comparable to pharmaceutical alternatives, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

St. John's wort is recommended for people suffering from depressive symptoms but not taking medication. Supplementation may not benefit people suffering from major depressive disorder or people not suffering from depression but looking to improve their mood.

St. John's wort interacts negatively with many pharmaceuticals. Since it can increase serotonin signaling in the brain, it especially should not be taken with serotonin-related medication, such as serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and MAOIs, so as to avoid the risk of overdose. Also, ***St. John's wort can render birth control pills ineffective***.

Figure 3: St. John's wort — drug interactions



How to take it

Take 300–900 mg/day. Start with the low end of the dose and slowly increase until the desired effects are achieved. The most common maintained dose is 600 mg.

The ideal extract ratio lies between 3:1 and 7:1, which means the extract should contain 3–6% hyperforin and 0.1–0.3% hypericin.

Further research is needed to determine if St. John's wort should be taken at a specific time, though it is commonly supplemented with breakfast.

Secondary Options

NAC

Why it's a secondary option

N-acetylcysteine (NAC) is used principally to treat acetaminophen overdose (by increasing the body's production of the antioxidant glutathione) and to loosen thick mucus. It is also being researched for the treatment of a wide range of cognitive disorders and affective disorders.

Most supplements that benefit mood excite the brain with neurotransmitters (such as dopamine). NAC does the opposite: By increasing the reuptake of glutamate, it decreases the synaptic levels of this neurotransmitter, thus reducing excitatory signaling in the brain. This explains why it can relieve symptoms of excitability, such as irritability and restlessness (or the general "bad mood" that comes with a hangover).

However, NAC has not been directly tested for its effects on people with clinically diagnosed depression, nor for its effects on the mood of people who are not depressed. In addition, it may interact adversely with nitroglycerin, which is used in the treatment of chest pain associated with cardiovascular disease. This makes two reasons why, as a mood-enhancer, NAC should only be considered a secondary option.

How to take it

NAC in the range of 300–900 mg/day can support the body's levels of glutathione, the primary antioxidant produced by the cells. To benefit from NAC's cognitive and mood-related benefits, however, you'll need to take 900–2,400 mg/day.

NAC can be taken once a day or in divided doses, with or without a meal. It has a sweet and sulfurous taste that most people dislike.

Uridine

Why it's a secondary option

Uridine is required to create neuronal membranes. It can also increase the rate of neuronal growth and turnover. There is little uridine in food. While the body can synthesize enough to satisfy its basic needs, supplementation can bring additional benefits.

Rodent studies suggest that uridine interacts with many neurotransmitters and pharmaceuticals. While uridine on its own might help with depression, it is more likely to support the action of those antidepressants, mood enhancers, and cognitive boosters that rely on growth factors, such as blueberries and Bacopa monnieri.

At the end of the day, however, a dearth of human studies and long-term safety data means that, as a mood enhancer, uridine is at best a secondary option.

How to take it

Uridine is usually supplemented through uridine monophosphate (**UMP**), which is ⅔ uridine. The standard dosage for uridine is 250–500 mg twice a day (i.e., 500–1,000 mg/day), which translates as 375–750 mg of UMP twice a day (i.e., 750–1,500 mg/day).

Other options include triacetyluridine (TAU) and CDP-choline. Following oral supplementation, both appear to be effective in reaching the brain in humans.

If **TAU** is indeed seven times more bioavailable than an equimolar amount of uridine, as one study noted, then much lower doses could be used: 35–70 mg twice a day (i.e., 70–140 mg/day). Research on this compound is still scarce, however, which makes it hard to recommend.

As for **CDP-choline**, it is a source both of cytidine, which the body converts to uridine, and of choline, which the brain converts to acetylcholine. To supplement CDP-choline for its pro-uridine content, high doses are required: 500–1,000 mg twice a day (i.e., 1–2 g/day).

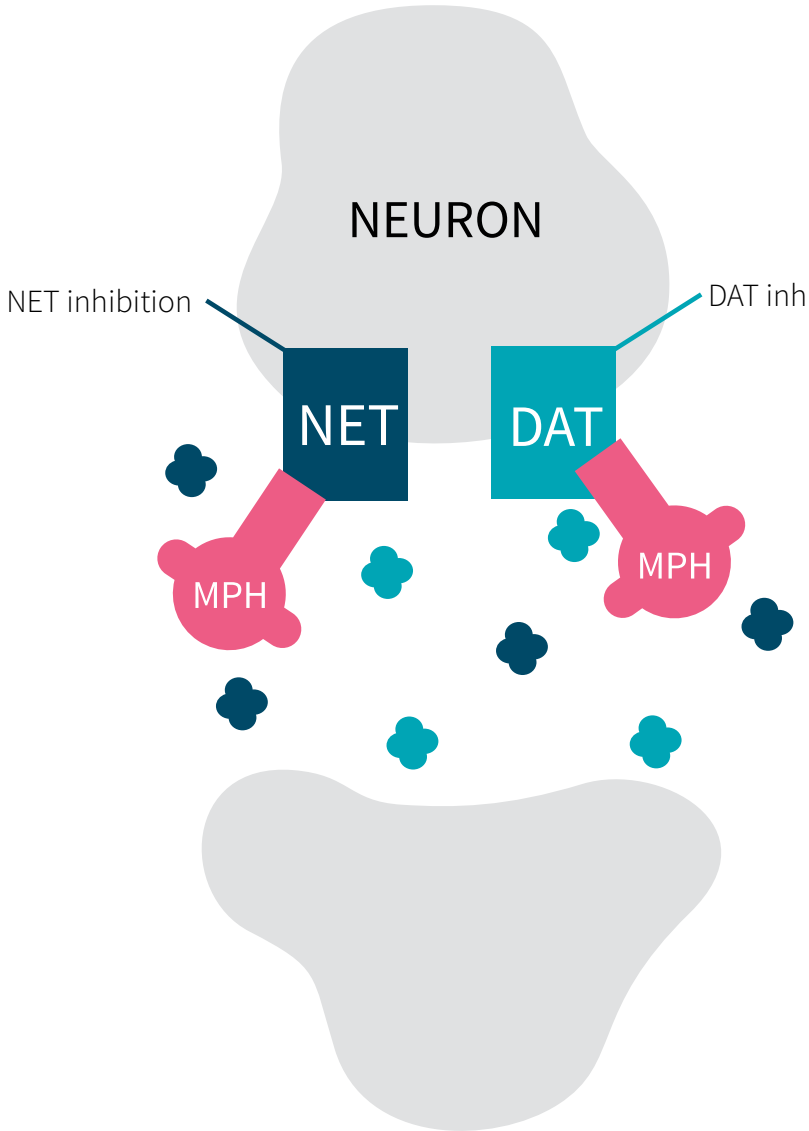
Further research is needed to determine if taking uridine with food is more effective than taking it on an empty stomach.

Inadvisable Supplements

Psychostimulants

Psychostimulants are supplements or pharmaceuticals, such as methylphenidate (Ritalin) and dextroamphetamine, that temporary benefit cognition and mood. Psychostimulants may even induce euphoria. However, used too frequently, they are likely to cause the original depressive symptoms to worsen. This warning applies to supplements as well as pharmaceuticals.

Figure 4: Mechanisms of action for methylphenidate (Ritalin)



Methylphenidate temporarily blocks the norepinephrine and dopamine transporters, which causes norepinephrine and dopamine to increase in the synaptic space. These increases can lead to increased alertness and provide short-term mood and cognitive enhancements.

DAT – Dopamine Transporter
NET – Norepinephrine Transporter
MPH – methylphenidate (Ritalin)

Source: Wilens TE. *J Clin Psychiatry*. 2006.

Assembling Your Stack

Incorporating Core Supplements

With a meal containing fat, take 50 mcg of vitamin D_3 (2,000 IU) and 25–30 mg of zinc. Three times a day, with or without food, take 400 mg of SAMe (i.e., 1,200 mg/day).

If your diet is rich in zinc, zinc supplementation may not be necessary. Similarly, if you get plenty of sun, consider skipping the vitamin D.

If you have an MTHFR gene mutation, replace the SAMe by 7.5–15 mg of L-methylfolate once a day and 1,500–2,000 mg of TMG twice or thrice a day (i.e., 3–6 g/day). TMG can be consumed as a powder or simply through foods, notably wheat bran (1,339 mg of TMG per 100 g), spinach (600–645 mg of TMG per 100 g), and beetroot (114–297 mg of TMG per 100 g).

If you are using an antidepressant, consult your doctor prior to taking any supplement, especially a methylation agent (such as SAMe, L-methylfolate, TMG, or choline).

The core supplements are recommended for most people; their efficacy and safety are backed by a significant body of evidence. Take them for a couple of weeks before you consider making any modification, such as adding one of the following options.

Incorporating Options

For people who are medicated or have been diagnosed with a major depressive disorder:

After consultation with your doctor, add EPA (500 mg) to the core supplements.

For people with self-diagnosed depression who currently do not take any medication or drug that affects the brain:

In addition to the core supplements, take St. John's wort (600 mg of an extract containing 3–6% hyperforin and 0.1–0.3% hypericin).

For people who want to improve their mood and reduce stress:

In addition to the core supplements, take an adaptogen, either *Rhodiola rosea* (80–160 mg of the SHR-5 extract) or ashwagandha (300–600 mg of the KSM-66 extract). Do not take ashwagandha in the evening, as it may cause insomnia.

For people who want to improve their mood and reduce agitation and irritability:

In addition to the core supplements, take NAC (2,400 mg).

Other options

While uridine shows promise, human evidence is currently too scarce to warrant the inclusion of this supplement in any of the above stacks.

FAQ

Can I add to my stack a supplement not covered in this guide?

Supplement your current stack for a few weeks before attempting any change. Talk to your doctor and research each potential new addition in advance. Check for known negative interactions with other supplements in your current stack, but also for synergies. If two supplements are synergistic or additive in their effects, you might want to use lower doses for each.

Can I modify the recommended doses?

If a supplement has a recommended dosage range, stay within that range. If a supplement has a precise recommended dose, stay within 10% of that dose. Taking more than recommended could be counterproductive or even dangerous.

Should I take my supplements with or without food? And at what time?

Answers are provided in each supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Besides, a supplement's digestion, absorption, and metabolism can be affected differently by different foods. Fat-soluble vitamins (A, D, E, K), for instance, are better absorbed with a small meal containing fat than with a large meal containing little to no fat.

Starting with half the regular dose can help minimize the harm a supplement may cause when taken during the day (e.g., tiredness) or in the evening (e.g., insomnia).

What's the difference between elemental zinc and other kinds of zinc?

"Elemental" refers to the weight of the mineral by itself, separately from the compound bound to it. For instance, consuming 50 mg of zinc gluconate means consuming 7 mg of elemental zinc. ***Product labels display the elemental dosage.*** On a label, "30 mg of zinc (as zinc gluconate)" means 30 mg of elemental zinc (and 200 mg of gluconic acid).

Can I stack creatine and TMG?

Those two methylation agents work through the same channel. With regard to mood and cognition, stacking them will not provide additional benefits.

Precautions and Troubleshooting

Stack components are seldom studied together. The safest way to add supplements to your daily routine is one at a time, at least a couple of weeks apart, to better assess the effects (and side effects) of each new addition. Start at half the regular dose for a week, then slowly increase to the regular dose if you are not experiencing the desired effects.

Since minerals and vitamins (especially the fat-soluble vitamins: A, D, E, and K) can accumulate in the body, it is best to consider supplementation only after a dietary evaluation. Track what you eat for a week; if, on average, you are getting less than 80% of your Recommended Dietary Allowance or Adequate Intake, supplementation becomes an option, though first you should try eating more foods rich in the desired vitamin or mineral.

Any supplement that can affect the brain, especially supplements with a stimulatory or sedative effect, should first be taken in a controlled situation. Do not take a dose, least of all your first dose, before events such as driving or operating heavy machinery, when impaired cognition may be a risk for your safety and the safety of others.

It is important to fully grasp the effects of a supplement, especially on your behavior, thoughts, and feelings. After a month, pause supplementation and keep a close eye on your mood. If it does not suffer, discontinue the supplement permanently, unless it provides other benefits.