

Examine.com

Mood & Depression

Medical Disclaimer & Important Note

This guide is a general health-related information product, intended for healthy adults over the age of 18.

This guide is for educational purposes only. It is not medical advice. Please consult a medical or health professional before you begin any exercise, nutrition, or supplementation program, or if you have questions about your health.

Participating in exercise activities or using products mentioned in this guide may pose risks for people in poor health or with pre-existing physical or mental health conditions.

Do not use any products or participate in any activities if you are in poor health or have a pre-existing mental or physical health condition. If you choose to participate, you do so of your own free will, and you knowingly and voluntarily accept the risks.

While we will mention major known drug interactions, it may be possible for any supplement to interact with medications or other drugs. If you are currently taking medication, consult a health professional prior to using any supplement in this guide.

Specific study results described in this guide should not be considered representative of typical results. Not all supplements provide the exact amount of compounds as listed on the label. Always investigate supplement companies, as well as the supplement itself, before purchasing anything. Herbs, rather than isolated compounds, may also have some variability from one batch to the next that can alter the efficacy.

To read the evidence supporting claims mentioned in this guide, please visit [Examine.com](https://www.examine.com).

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How to use this Guide

The team at Examine.com has been publishing research on nutrition and supplementation since March 2011. In that time, we've learned a great deal about supplements, especially how they can work together to help you with health goals.

This stack guide help you figure out which supplements can help you and which will hinder and/or be a waste of your money for your desired goals.

The following four sections present information on supplements that are relevant to *Cardiovascular & Heart Health*:

1. Base Supplements
2. Proven Options
3. Unproven Options
4. Cautionary and Overhyped Options

Base Supplements are recommended for the majority of people with this goal. They are either effective on their own or are required to boost the effects of another supplement. These are the first supplements to consider for your stack. Base Supplements are more researched and have less adverse drug interactions than options.

Proven Options are supplements that will provide a lot of benefits, but only in the right context. They cannot be recommended for everyone, but if you read the entry and find that you meet the criteria, feel free to add the supplement to your stack.

Unproven Options are another group of potentially beneficial supplements, but they lack evidence for their effects. They cannot be recommended with the same confidence as proven options. They could work or be a waste of your money - there is not enough evidence to know for sure. Keep unproven options in mind, but approach them cautiously when incorporating them into your stack.

Cautionary and Overhyped Options are supplements that are claimed to provide benefits but have been shown to be ineffective. If a supplement is deemed too risky to be used, it will also be found in this section. **Do not** add these compounds to your stack; they tend to be a waste of money or potentially harmful to your health.

Once we have explained the various supplements that you need to be aware of, the **Assembling your Supplement Stack** section will outline how different supplements can be combined, based on your objectives.

After that, we follow up with the **Stack Modification 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 a supplement stack best suited for your goals and objectives.

Zinc

Why you should take it

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

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

High doses of zinc are potentially dangerous and should be avoided, but the standard dose will improve mood while also working with other antidepressant agents to increase their effects.

Some dietary minerals, like [chromium](#), also have antidepressant properties. It's recommended to focus on zinc supplementation first, since fixing a zinc deficiency will safely provide a variety of beneficial health effects.

Zinc can cause a copper deficiency over time, since it kickstarts the process of creating a protein called metallothionein, which binds to excess zinc while depleting copper. The extra zinc leaves the body as a waste product. This can happen after zinc superloading, but the doses below are too low to pose this risk.

How to take it

Zinc should be supplemented in the range of 25 - 30 mg of elemental zinc per day. Elemental zinc refers to the weight of zinc itself, and excludes the weight of the compound it is supplemented with to help absorption. For example, consuming 230 mg of zinc gluconate means consuming 30 mg of elemental zinc. The label displays the elemental dosage, not the total dosage.

Zinc should be taken with meals, since some people may experience nausea after supplementing zinc on an empty stomach. Do not pair zinc with minerals like [calcium](#), [magnesium](#), and iron in combined doses of 800 mg or more. Combining them at low doses is fine, but in high amounts the minerals will compete for absorption and limit the overall effectiveness of supplementation.

Note: This dose is commonly recommended for athletic people who have high zinc losses in sweat. If you are either sedentary, don't produce a large amount of sweat, or have a diet moderate to high in meat products this dose could be dangerous for long-term daily usage. If that is the case, then reduce the daily dose to the range of 10-20 mg once daily.

S-adenosylmethionine (SAmE)

Why you should take it

S-adenosylmethionine (SAmE) is a compound that works with enzymes in the body in a process called methylation. Sometimes, a molecule needs a 'methyl' group to undergo a chemical reaction. SAmE provides that group and allows the reaction to proceed. Many of these reactions are involved in depression.

SAmE has been found to have a potency similar to tricyclic antidepressants (TCAs), and it can also increase the benefits seen with selective serotonin reuptake inhibitor (SSRI) therapy. This increase in benefit seen with SSRIs is normally considered a beneficial interaction, although a high enough dose of both supplements could cause a negative reaction. If you take antidepressants, consult with a medical professional before supplementing SAmE.

Both [trimethylglycine](#) (betaine) and [creatine monohydrate](#) have been found to increase SAmE levels indirectly after supplementation. Preliminary evidence suggests creatine may have the same antidepressant effects SAmE does. If SAmE is too expensive, creatine and trimethylglycine are worth looking into instead.

Creatine and trimethylglycine do not have negative interactions with serotonin-based medications.

SAmE is recommended as a base supplement (despite the potential SSRI interaction) because it is effective and can be replaced by alternate supplements by people taking antidepressants.

How to take it

The standard SAMe dose is 400 mg, taken three times a day for a total daily dose of 1,200 mg. It may take up to two weeks for SAMe supplementation to have significant effects on the body. SAMe should be taken with meals, and its usage alongside pharmaceuticals should be initially cleared by a medical practitioner.

To mimic SAMe's effects with creatine, take 2 - 5 g once a day, with a meal. This is the standard supplemental creatine dose.

Fish Oil

Why it is a proven option

Fish oil is often claimed to enhance cognition. However, it improves cognition reliably only in a few cases, such as when supplemented by people suffering from major depression. Fish oil does not provide any benefits for people with non-major depression, or people not suffering from depression but looking to improve their mood.

Studies suggest that treatment-resistant depression is associated with a lower concentration of fish oil eicosapentaenoic acid (EPA) in the brain. Further research is needed to confirm this relationship. Fish oil supplementation may play a supporting role for the treatment of depression, and preliminary human evidence suggests it may also play a role in reducing anxiety.

Fish oil should be considered as an option for people suffering from severe depressive disorders. Consult with a medical doctor before using fish oil as a supporting therapy. Fish oil should not be a major focus for people with minor depressive disorders.

How to take it

Higher than normal doses are needed to supplement fish oil for EPA content and brain health. Approximately 1 g of fish oil, taken once a day with a meal, will provide maximal benefits.

People that consume fatty fish multiple times a week can supplement 500 mg of fish oil instead.

St. John's Wort

Why it is a proven option

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

St. John's Wort is recommended for people not using medication but suffering from depressive symptoms. St. John's Wort interacts negatively with many pharmaceuticals and ***can render birth control pills ineffective***. Supplementation may not be beneficial for people that are suffering from major depressive disorder, or for people not suffering from depression but looking to improve their mood.

Since St. John's Wort can increase serotonin signaling in the brain, it especially should not be taken with antidepressants like selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), to avoid the risk of overdose.

How to take it

The standard dose for St. John's Wort supplementation is in the range of 300 - 900 mg a 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 herb to drug ratio of St. John's Wort is 3-7:1, which means supplements 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.

Adaptogens

Why it is a proven option

Adaptogens are a class of compounds that desensitize the body to future stress. These herbs are most effective when supplemented by stressed people.

Major symptoms of stress include acute depression, mood swings, and irritability. Since adaptogens fight stress, they play a supporting role in improving mood.

There are many adaptogens, but only a few have the evidence to support their use as supplements. The best researched adaptogens are [*Rhodiola rosea*](#) and [*ashwagandha*](#). *Rhodiola rosea* can prevent and relieve burnout induced by

stress. Ashwagandha is well-tested in athletes, and it may provide benefits for people suffering from social anxiety.

Adaptogens are only effective if the symptoms of depression and irritability being treated stem from stress and anxiety. People that do not suffer from stress do not need to supplement adaptogens.

Ashwagandha may also play a role in improving the effects of other anxiety-reducing agents.

How to take it

Rhodiola rosea is supplemented through an extract called SHR-5 (a mixture of 3% rosavins and 1% salidroside). *Rhodiola rosea* can either be supplemented every day, or as a precaution for an upcoming stressor, like a presentation at work. To prepare for an future stressor, take 500 mg of SHR-5. To take *Rhodiola rosea* daily, take between 80 - 160 mg, preferably with a meal.

Ashwagandha is supplemented through a dry root extract. The standard dose is 300 - 500 mg, taken with breakfast. Supplementation at night may cause insomnia.

Vitamin D

Why it is an unproven option

Vitamin D is an essential vitamin. It is frequently recommended for supplementation and it is claimed to boost mood.

This claim has not been as investigated as other properties of vitamin D, but preliminary evidence suggests vitamin D can improve mood when supplemented by people with less than optimal vitamin D levels.

Though vitamin D's effect on mood is not very powerful and needs more evidence, it is a cheap, safe supplement.

How to take it

To supplement vitamin D, take 2,000 IU of vitamin D3 a day. Vitamin D should be taken with a meal.

N-Acetylcysteine

Why it is an unproven option

N-acetylcysteine (NAC) is used to treat a wide range of cognitive disorders, including those that concern mood and depression. However, it has not been directly tested for its effects on people with clinically diagnosed depression, nor has it been tested for improving mood in people that are not depressed.

Since NAC is safe and provides benefits for cognitive disorders like addiction, anxiety, irritability, and other conditions that affect mood, it should not be discounted completely. Due to a lack of direct evidence, it cannot be specifically recommended to alleviate depression and improve mood. Furthermore, it may have adverse interactions with nitroglycerin, which is used in the treatment of chest pain associated with cardiovascular disease.

NAC works by increasing the reuptake of a neurotransmitter called glutamate. It also reduces excitatory signaling in the brain. Most supplements that improve mood and reduce depression tend to excite the brain with

neurotransmitters like dopamine. Since NAC has the opposite effect, it may explain why it relieves symptoms of excitability like anxiety, irritability, and restlessness. NAC may also help relieve the anxiety, restlessness, and general bad mood that comes with a hangover.

How to take it

To benefit from NAC's cognitive benefits, take 900 – 2,400 mg, once a day. NAC can be taken with or without a meal. It has a sweet and sulfurous taste that most people do not like.

Doses in the range of 300 - 900 mg a day can also have an antioxidant effect.

Nigella sativa

Why it is an unproven option

Nigella sativa is a seed from a flowering plant frequently used in traditional medicines. It has recently been investigated for its effects on mood. More research is needed to determine its main mechanism of action, but current evidence points to a bioactive called thymoquinone.

Ingesting *Nigella sativa* has been found to greatly improve the quality of life for middle-aged men, which is attributed to a self-reported improvement in mood.

Nigella sativa is supplemented through a dry seed extract. It can also be used as a spice. *Nigella sativa* tastes somewhat similar to black pepper.

Nigella sativa is one of the few supplements (besides zinc) that has evidence supporting it as a mood enhancer for healthy adults that do not suffer from depression.

How to take it

Nigella sativa can be used as a food product. The product is called 'Black Cumin Seed.' Use approximately 3 g of this seed with meals each day.

Note: Cumin seeds are not related to Black Cumin Seeds.

Ideally, the seeds should be crushed with a mortar and pestle. Many seed-derived supplements need to be crushed to improve absorption. Further research is needed to determine if this applies to *Nigella sativa* as well, but unless conflicting evidence comes to light, it would be prudent to crush *Nigella sativa* before consumption.

Nigella sativa can also be supplemented. Look for a product that provides either 3 g of the dried extract, or 500 mg of the oil component.

Uridine

Why it is an unproven option

Uridine is a nucleotide found in many foods. It's vital for creating membranes for neurons, and may increase the growth of brain cells through growth factors. Unfortunately, supplementation is the only way to benefit from uridine, since most food contains very little of it.

Rodent tests suggest that uridine interacts with many neurotransmitters and pharmaceuticals. A lack of applied human testing and long-term safety data means uridine cannot be recommended specifically for depression and mood.

Uridine may act as a supporting therapy for other antidepressants, mood enhancers, and cognitive enhancers that rely on growth factors, like [blueberries](#) and [Bacopa monnieri](#). This claim is not backed by human evidence.

How to take it

The standard dose for uridine is 500 mg, though doses of up to 1,000 mg have been used effectively. Uridine is supplemented through uridine monophosphate disodium salt.

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

Psychostimulants

Psychostimulants are supplements or pharmaceuticals, like methylphenidate (Ritalin) and dextroamphetamine, that provide temporary benefits for mood and cognition. Using a psychostimulant may even provide the feeling of euphoria. Though this would normally be therapeutic, psychostimulant use can intensify depression if used too frequently.

Self-administration of compounds that cause euphoria is not recommended. Despite the apparent benefits, continuous psychostimulant use can cause the original depressive symptoms to worsen. This warning applies to both pharmaceuticals and supplements.

Assembling Your Supplement Stack

The following outlines how to incorporate this supplement stack into your daily nutrition habits.

Incorporating Base Supplements

This stack contains two base supplements: the mineral (zinc) and the methylation agent (SAmE or creatine). If you are currently using antidepressants you must consult your doctor prior to using any supplements.

Both supplements should be taken with food, at the same time. Beginners are advised to try creatine before using SAmE, since SAmE can be expensive.

The base supplements should be taken consistently for a week before any modifications are made. If your diet contains a lot of zinc, zinc supplementation may not be necessary. It is very difficult to attain the levels of creatine needed for antidepressant effects from diet alone, so creatine supplementation should continue regardless of dietary changes.

Creatine (5g) with zinc (25-30mg)

Incorporating Supplement Options

For people who are medicated/diagnosed with major depressive disorder:

Add **fish oil** (1,000 mg EPA equivalent) to the base **creatine** (5 g) or **SAmE** (1,200 mg) and the base **zinc** (25-30 mg) after consultation with medical staff.

For people with self-diagnosed depression, not currently on any medication, and not using any drugs that affect the brain

Add **St. John's Wort** (600 mg of a 3-6% hyperforin and 0.1-0.3% hypericin standardized extract) to the base **creatine** (5 g) or **SAmE** (1,200 mg) and the base **zinc** (25-30 mg).

Assembling Your Supplement Stack (cont.)

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

Add an **adaptogen** (Ashwagandha or *Rhodiola rosea*) to the base stack of **creatine** (5 g) or **SAMe** (1,200 mg) and the base **zinc** (25-30 mg).

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

Add **N-Acetylcysteine** (2,400 mg) to the base stack of **creatine** (5 g) or **SAMe** (1,200 mg) and the base **zinc** (25-30 mg).

Other Options

People at risk for low **vitamin D** levels should consider taking vitamin D (2,000 IU) once a day, with a meal. Most people do not get enough vitamin D. If you live near the equator and get a lot of sun, you may not need to supplement vitamin D.

How do I add supplements to my stack that are not covered in this guide?

Before adding a new supplement to your stack, supplement your current stack for a few weeks to determine if you need to make a new addition. If you want to make multiple changes to your stack, pick one supplement to add at a time. Identify the stack change that you think will be the most effective, and do your research:

1. Use [Examine.com](https://www.examine.com) to determine if that supplement would have a negative interaction with your current stack. Talk to your doctor about including a new supplement in your stack.
2. Introduce the new supplement at half of the regular dose.
3. After a week with the new supplement, slowly increase the dose to the recommended dose if you are not experiencing the effects you want.

Stacks are intended to be synergistic, which means taking two supplements together may provide more effects than the supplements by themselves. New supplements should be added carefully, since even low doses can be powerful if other supplements in your stack improve their effects.

Can I modify the recommended doses?

If a supplement has an established advised dosage range, stay within that range. If a supplement has a recommended dose, and not a range, stay within 10% of that dose. Halving or doubling an advised dose could be ineffective or even dangerous.

The safest way to add dietary supplements to your life is one at a time. If you are considering purchasing several supplements, purchase only one and add the others after a week or two of supplementation. This will limit the risk of new supplements, and it will also make it easier to figure out what supplements are providing you with your newfound benefits.

Precautions & Troubleshooting

The safest way to add dietary supplements to your life is one at a time. If you are considering purchasing several supplements, purchase only one and add the others after a week or two of supplementation. This will limit the risk of new supplements, and it will also make it easier to figure out what supplements are providing you with your newfound benefits.

It is important to fully understand the effects of a supplement, particularly those that influence mood or depression. After a period of supplementation, stop using the supplement and keep a close eye on your mood. In some cases, halting supplementation of a mood-boosting supplement does not reduce mood. In these cases, supplementation should only continue if the supplement provides other benefits.