Examine®

Stress & Anxiety Supplement Guide

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Introduction

I gotta admit — I'm a little worried about writing this introduction. I have a bunch of other projects to tackle right now, but I'm under a deadline so I have to crank this out. But will the time pressure make me write a worse intro? I'm afraid that if I rush too much, I may miss something important!

But, maybe stressing out about writing this intro is perfectly normal! After all, I *am* anxious about something since I'm under some stress, right?

Presumably, you're turning to this guide because, like me and up to a third of the world,[1] you're experiencing some stress or anxiety in your life, and you want to know how to manage it. But in order to manage something effectively, we first have to understand it.

You may have noticed that I've been mixing up terms: "stress", "anxiety", "fear", and "worry" all refer to somewhat different things, but I've been using them interchangeably.

So, let's take a deep breath together, and dive into understanding these terms a bit better.

Stressing the science behind stress

Stress. Anxiety. Fear. Worry. Admittedly, all four of these words are a little fuzzy … as words usually are. And their definitions can evolve over time. For example, what "stress" is has been explicated and debated since the 19th century.[2] But just because these concepts aren't sharply defined doesn't mean we can't parse them out a bit better. Let's start with stress.

The modern concept of stress can be seen in Walter B. Cannon's work *The Wisdom of the Body*, first published in the early 1930s. In this book, Cannon summarizes some of his earlier work, in which he coined the term "homeostasis" — the body's way of trying to keep itself in balance when it experiences shocks.

Within this context, he came up with the famous "fight or flight" theory of stress, also called the acute stress response: when encountering an emergency, the activating, sympathetic part of the nervous system comes into play to give living creatures the energy they need to deal with the threat by either fleeing from or fighting it. This aspect of stress can be positive.

Later in the 1930s, Hans Selye, the founder of modern stress research, advanced the concept a lot further by noting that stress could be defined by a set of specific physiological reactions to potential threats — reactions that, if severe and prolonged, could lead to *general adaptation syndrome* (GAS).[3][4][5] This dark side of stress could lead to bodily damage in the long run.

🔍 ***Digging Deeper:*** **General adaptation syndrome**

General adaptation syndrome (GAS) is a hypothesis generated by Hans Seyle[3][4] on the basis of his experiments on rats.[5][6] GAS separates the reaction to stress into three stages:

The *alarm reaction* stage is Walter B. Cannon's "fight or flight" response: your body floods itself with chemicals that get you ready to either fight a perceived threat or flee from it.

If the source of stress doesn't disappear, you'll reach the *resistance* stage: your body adapts to some extent — but *only* to some extent. You may think you're getting used to stress, but in fact your body still produces above-normal amounts of stress hormones (the three main ones being cortisol, adrenaline, and norepinephrine) and your blood pressure remains elevated.

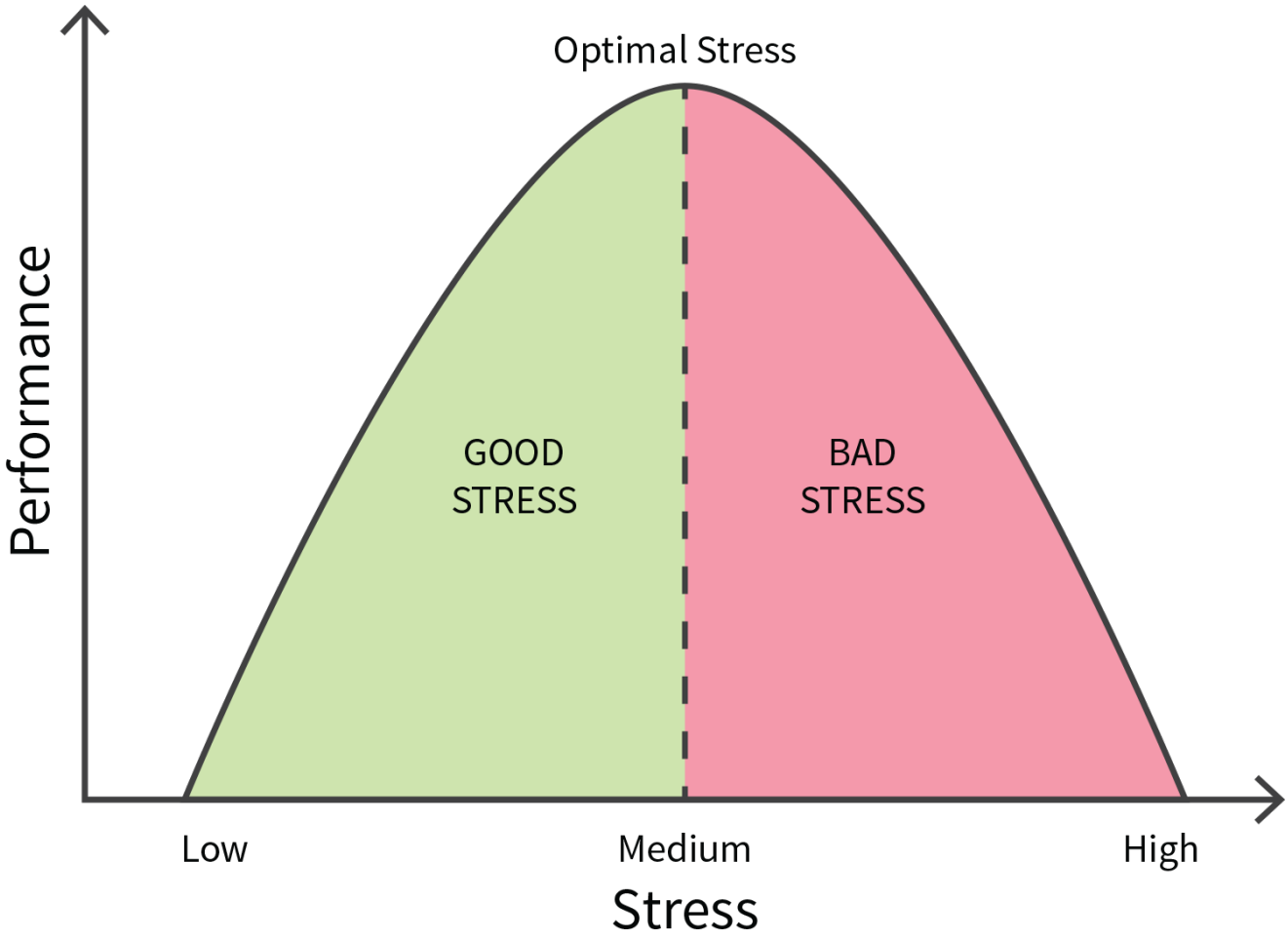
Then comes the *exhaustion* stage. Your body can no longer cope with the chronic state of high alert, your immune system takes a hit, your risk of high blood pressure and other diseases may go up,[7] and you may develop symptoms of depression.[8]

However, psychologists argued with Selye's emphasis on the *physio*logical aspects of stress, and instead (unsurprisingly) placed more emphasis on its *psycho*logical aspects.[9]

Nowadays, while the definition of "stress" is still not set in stone, stress is recognized as psychological and physiological reactivity to environmental factors.[10] What's also not quite set yet is whether some stress can benefit performance.

The famous Yerkes-Dodson law, first formulated in 1908 and illustrated below, states that some amount of stress can lead to optimal performance, whereas too much or too little can lead to worse outcomes.[11] In short: these results suggest that moderate amounts of stress can lead to better outcomes.

The (questionable!) Yerkes-Dodson Law



In Yerkes's and Dodson's original experiments, mice had to recognize a box. When they chose the wrong box, they got shocked at different strengths. Moderate shocks worked the best for learning, hence the inverted U-shaped curve.

This inverted-U shape, however, didn't generalize when similar experiments were tried in other animal models,[12][13] and the Yerkes-Dodson law wasn't tested rigorously in people. Nevertheless, some researchers in the 1950s hypothesized that the Yerkes-Dodson law would generalize to human stress and work performance.[14][15]

But the human evidence doesn't seem to strongly support this hypothesis. A review of the research performed in humans between 1975 and 2000 found that only 4% of the literature supported the inverted-U relationship between stress and performance, while close to half of all studies found that any amount of stress hurt performance.[16] The authors also identified some key problems in stress research up to that point.

More recent research has also spoken against the inverted-U relationship[17] or used more modern methods to explore stress's relationship to performance,[18] claiming that stipulating any two-dimensional relationship between stress and performance may be too simplistic.

While there's a lot of uncertainty around stress's psychology and effects on performance, at least one thing is relatively clear: high stress is associated with a wide range of negative mental and physical health outcomes.[19] This implies that, whatever stress is and however it affects performance, getting a handle on high, chronic stress is probably good for your long-term health.

Fear and worry in Las Vegas

Just like “stress”, “fear” and “worry” don’t have super-precise definitions. Still, their definitions are clear enough to allow us to differentiate those words from others like “stress” and “anxiety”.

Let’s start with “fear”. The online dictionary of the American Psychological Association (APA) defines it as “a basic, intense emotion aroused by the detection of imminent threat, … triggering a set of physiological changes” that strongly resemble the stress reaction we just described. Thus, fear is a lot like stress, but more emphasis is being placed upon its subjective, emotional component. The fifth edition of APA’s *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) also supports this emphasis on the emotional component, defining “fear” as “the emotional response to real or perceived imminent threat” (this emotional response coincides with the physiological fight-or-flight response).[20]

While fear shares a lot of features with stress, worry is something quite different, as it’s mostly cognitive: the emphasis is on what people are thinking. For instance, the *Textbook of Anxiety Disorders*, second edition, defines “worry” as a “preoccupation with negative events occurring in the future”,[21] whereas the APA dictionary defines it as “a state of mental distress or agitation due to concern about an impending or anticipated event, threat, or danger”.

The first definition places a heavier emphasis on ruminating about possible negative future events, whereas the second places a heavier emphasis on mental distress. However, both definitions agree that worry is mostly a *mental* phenomenon, unlike stress (physiological) and fear (emotional). Both also agree that worry has to do with future negative events — whereas fear is about events in the present.

In short: fear is what you feel when you go all-in on your poker bet in Vegas with a crappy hand. Worry is what you experience after you lose and have to figure out how to pay for the ticket back home.

Anxiety and anxiety disorders

While worry focuses mostly on what’s going on in your head when thinking about a negative future event, anxiety brings the body back into the picture. The APA dictionary defines “anxiety” as “an emotion characterized by apprehension and somatic symptoms of tension in which an individual anticipates impending danger, catastrophe, or misfortune”.

Those “somatic symptoms” the definition is referring to differ from what you feel when fear of something in the present moment arises. *DSM-5* associates anxiety with muscle tension and increased mental vigilance to keep an eye out for *future threats*. Fear, on the other hand, is sharper and focused on an *immediate threat*.

One thing to keep in mind is that anxiety and fear are normal parts of the human experience and not necessarily a problem. *DSM-5* lays out some specific criteria for when fear and anxiety cross the line to anxiety disorders:

- *When it’s persistent.* As a rule of thumb, fear and anxiety qualify as disorders if they last six months or more without a clear stressor. For instance, being anxious about an upcoming speech is probably normal; but being constantly anxious about appearing in public, even when there is no event planned, suggests a disorder.

- *When it's out of proportion to the actual threat.* For example, being afraid when stuck in an elevator can be considered normal; but refusing to ever get into an elevator is out of proportion to the actual risk. *DSM-5* is careful to note that since people with anxiety disorders are prone to overestimate the threat level of situations they dread, whether a threat is "out of proportion" should be determined by an experienced mental-health clinician. It also notes that the clinician should take culture and context into account when determining whether the fear or anxiety is actually out of proportion; there's no one-size-fits-all rule.

The types of anxiety disorders *DSM-5* recognizes are summarized in the table below. You'll notice one recurrent criterion: to rank as a disorder, the fear, anxiety, or avoidance behavior should interfere with living a normal life. After all, if something's not getting in the way of living the life you want, then it's not really a problem, is it?

> ⚠ ***Caution:*** **Don't self-diagnose**
>
> Diagnosing anxiety disorders is much, much more complicated than our summary suggests, so don't self-diagnose. If you suspect you're overstressed or overanxious, get the opinion of a mental-health clinician or your primary care doctor.

Anxiety disorders as classified by *DSM-5*

DISORDER	DEFINITION
Separation anxiety	High levels of fear and anxiety caused by separation from home or a particular person. Usually develops in childhood.
Selective mutism	Failure to speak in specific social situations where speaking is expected. Usually develops in childhood. Often accompanied by social anxiety disorder.
Specific phobia	Life-disrupting fear, anxiety, or avoidance behavior caused by a specific situation or object.
Social anxiety disorder	Life-disrupting fear, anxiety, or avoidance behavior caused by social situations.
Panic disorder	Frequent, regular panic attacks, and a fear of future attacks alongside avoidance behavior.
Agoraphobia	Strong fear in situations where escape feels difficult, such as crowded enclosed places or wide open spaces. Often accompanied by dysfunctional avoidance of those situations.
Generalized anxiety disorder	Excessive, disruptive fear or worry about a wide range of subjects.
Substance-, medication-, and disease-related disorders	Anxiety that can be specifically traced to another disease, a medicine, or substance withdrawal.
Other or unspecified disorders	Life-disrupting, troubling anxiety that doesn't fall into any of the categories above.

Reference: Diagnostic and Statistical Manual of Mental Disorders, fifth edition. American Psychiatric Association. 2013.[20]

🔍 ***Digging Deeper:*** **OCD and PTSD**

People familiar with anxiety disorders may be wondering at the absence, in the table above, of *obsessive-compulsive disorder* (OCD) and *post-traumatic stress disorder* (PTSD).

In *DSM-IV-TR*,[22] OCD and PTSD were still considered anxiety disorders. In *DSM-5*, however, OCD was moved to a new chapter on obsessive-compulsive and related disorders, whereas PTSD was moved to a new chapter on trauma- and stressor-related disorders.[23]

The authors of *DSM-5* state that OCD and PTSD have a lot in common with anxiety disorders, which is reflected by these two new chapters being placed just after the section on anxiety disorders. But they also believe, based on the current evidence, that OCD and PTSD differ enough from anxiety disorders (in development, diagnosis, and treatment) to warrant considering them separately.

What non-supplement interventions work?

Prescription drugs

When it comes to full-blown anxiety disorders, drugs work better, on average, than exercise and therapy, and they also boost the effectiveness of therapy.[24] However, some drugs work better than others, depending on the anxiety disorder.

For instance, duloxetine, a *selective serotonin-norepinephrine reuptake inhibitor* (SNRI), works really well for generalized anxiety disorder[25] but is no better than placebo for panic disorder, for which tricyclic antidepressants seem to work best.[26]

💡 ***Tip:*** **Make sure the evidence is relevant**

When taking a look at the evidence for what works and what doesn't, pay careful attention to who's being treated and what the outcome is. Something that works for general anxiety may not work as well for in-the-moment stress, and what works for agoraphobia may not work for social phobia.

⚠️ ***Caution:*** **Be patient**

While medicines *can* be quite effective for anxiety disorders, different people react differently to different medicines. For some people, no medicine will work well. For others, finding the right medicine can be a lengthy process of trial and error. Once you get a proper medical diagnosis from a health professional, work with your doctor to find what's best for you.

Therapy

Cognitive-behavioral therapy (CBT) works well for many anxiety disorders,[27][28] especially in combination with drugs.[24] Other therapies, such as relaxation therapy,[29] also work quite well and may give results on par with CBT.

While therapies are effective, that doesn't mean that face-to-face therapies are the only option. There's some evidence that iCBT (CBT delivered via the Internet by an individual or program)[30][31] and self-help methods can work well for anxiety disorders — and they're usually almost as good as face-to-face therapy.[32]

Meditation

The quality of the evidence on meditation's effects has been questioned.[33][34][35] Keeping that in mind, there is some evidence that meditation can reduce symptoms of anxiety,[36] especially among people for whom anxiety is a secondary concern.[37] It may also reduce physical signs[38] and mental symptoms[39] of stress.

Exercise

Aerobic exercise reduces anxiety in people who have clinical anxiety, with higher-intensity exercise tending to be more effective.[40] Resistance training has less evidence, but that evidence suggests that it can benefit people with anxiety disorders[41] and with overweight or obesity.[42]

Exercise is roughly on par with therapy, with regard to benefits, but generally lower than drug treatment.[24]

Wrapping up

I hope this tour of stress and anxiety has given you a better understanding of what they are and how they can be alleviated. Up next, you'll get a lot more info on which supplements can help.

Keep calm, and read on.

Greg Lopez, _NERD _editor in chief
MA in molecular biophysics, PharmD

Combos

⚠️ ***Caution:*** **Read this before taking any supplement**

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 anxiety. After a month or so, pause supplementation and keep a close eye on your state of mind. If your anxiety does not increase, discontinue the supplement permanently, unless it provides other benefits.

Core Combo

There is only one core supplement: magnesium.

Eating a variety of healthy foods like leafy green vegetables, nuts, and fish will provide enough magnesium to make supplementation unnecessary. If your diet does not provide you with enough magnesium and you cannot modify it so it does, a bedtime dose of 200–350 mg of magnesium (in a form such as citrate, gluconate, or diglycinate) will alleviate a deficiency. Magnesium oxide, the cheapest form of magnesium, is associated with intestinal distress and is thus not recommended.

If you elect to supplement magnesium, do so for a couple of weeks before you consider adding one of the following options.

💡 ***Tip:*** **Try one combo alone for a few weeks**

Taking too many supplements at once may prevent you from determining which ones are truly working. Start with just one of the combos suggested here for a couple of weeks before you consider making any modification, such as adding another supplement, altering a supplements dosage, or incorporating the supplements from an additional combo.

When adding another supplement to your regimen, be methodical. For example, you may wish to take all the supplements from two combos. Select the combo that you wish to try first and take this for a couple of weeks. Then, add one supplement from the second combo and wait another week to see how it affects you. Continue this process until you've added all the supplements you wish to.

If a supplement appears in two combos you wish to combine, don't stack the doses; instead, combine the ranges. For instance, if the range is 2–4 mg in one combo and 3–6 mg in the other, your new range becomes 2–6 mg. Always start with the lower end of the range — especially in this case, since the reason why one of the ranges has a lower ceiling in one combo may be due to a synergy with another supplement in the same combo. Reading through the full supplement entry may help you decide which dose to aim for, but if you're not sure, lower is usually safer.

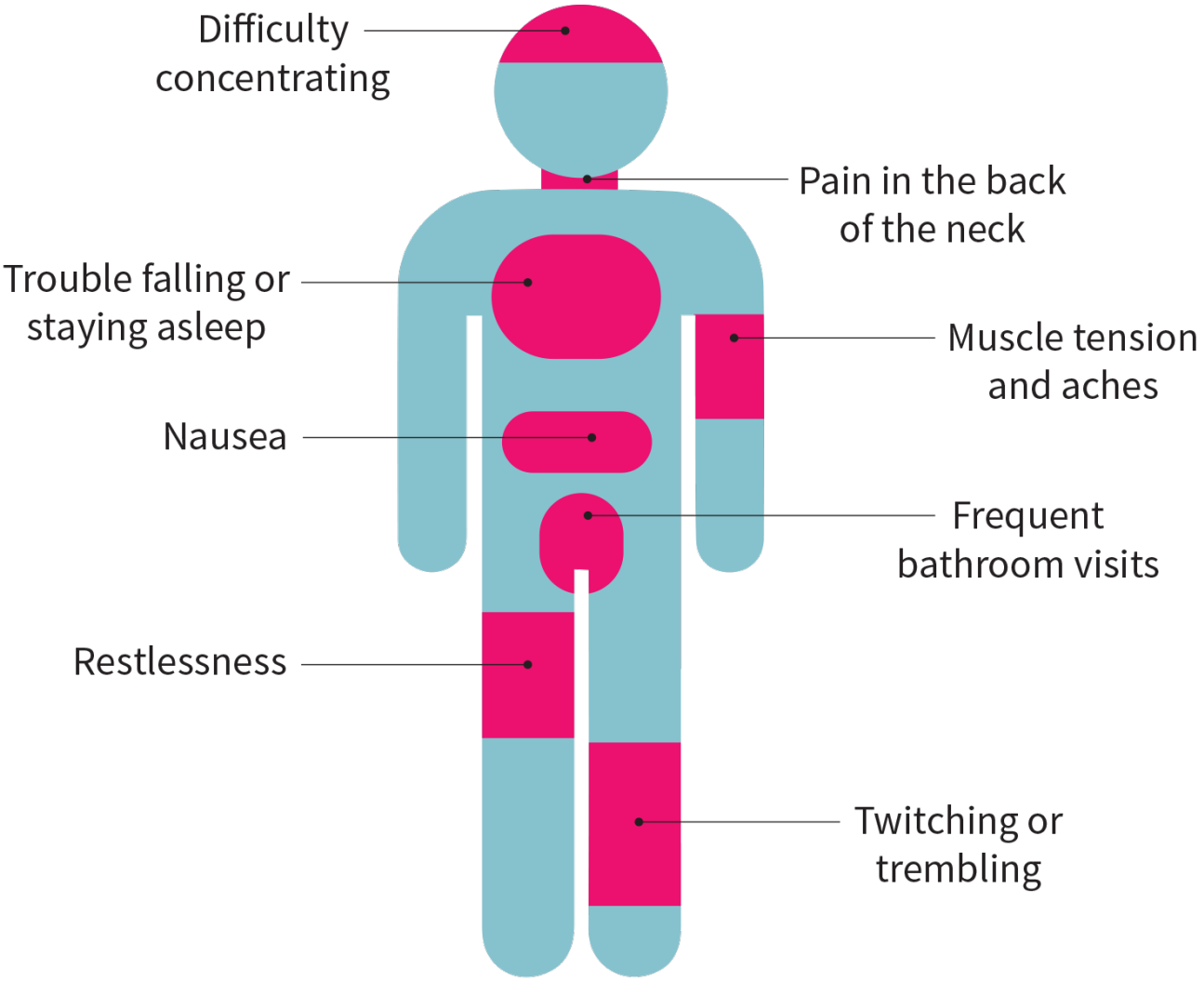
Specialized Combos

The following supplements should only be used to cope with anxiety and stress that established coping strategies have been unable to address.

For people with generalized anxiety disorder (GAD)

After supplementing magnesium for two weeks, to eliminate the possibility of the anxiety being caused by a magnesium deficiency, add lavender (starting with 80 mg of Silexan per day, working up to 160 mg/day over the course of a week if no lower dose proves effective) or kava (100 mg of the WS 1490 extract or 70 mg of kavalactones, three times a day).

Symptoms of generalized anxiety disorder



GAD can be defined as a constant state of restlessness and worry. People suffering from GAD are anxious about getting through the day, believing as they do that things will go poorly for them.

For people with anxiety linked to accumulated

stress

After supplementing magnesium for two weeks, to eliminate the possibility of the anxiety being caused by a magnesium deficiency, add ashwagandha (300–500 mg of the root powder or 15–60 mg of withanolides) once a day. Do not take ashwagandha in the evening, as it may cause insomnia. If you take your supplements in the evening, try replacing ashwagandha by *Rhodiola rosea* (80–160 mg of the SHR-5 extract) or *Panax ginseng* (100–200 mg of an extract standardized for 2–3% ginsenosides).

For people with state and trait anxiety

Take 1.25 g of arginine and 1.25 g of lysine twice a day (i.e., 2.5 g of each per day), with or without a meal. Effects can be felt after a week of supplementation.

For panic attacks and panic-related anxiety

Anxiety related to panic disorders may be reduced by taking inositol (14–18 g) as a daily supplement. Agmatine (1.62 mg/kg or 0.74 mg/lb) may also be beneficial — by itself or in conjunction with inositol — but there is no human evidence to support this claim.

For women experiencing anxiety related to PMS

Take *Vitex agnus-castus* once a day: either 150–250 mg of the dried berry, 20 mg of the Ze 110 extract, or 4 mg of the BNO 1095 extract.

Other options

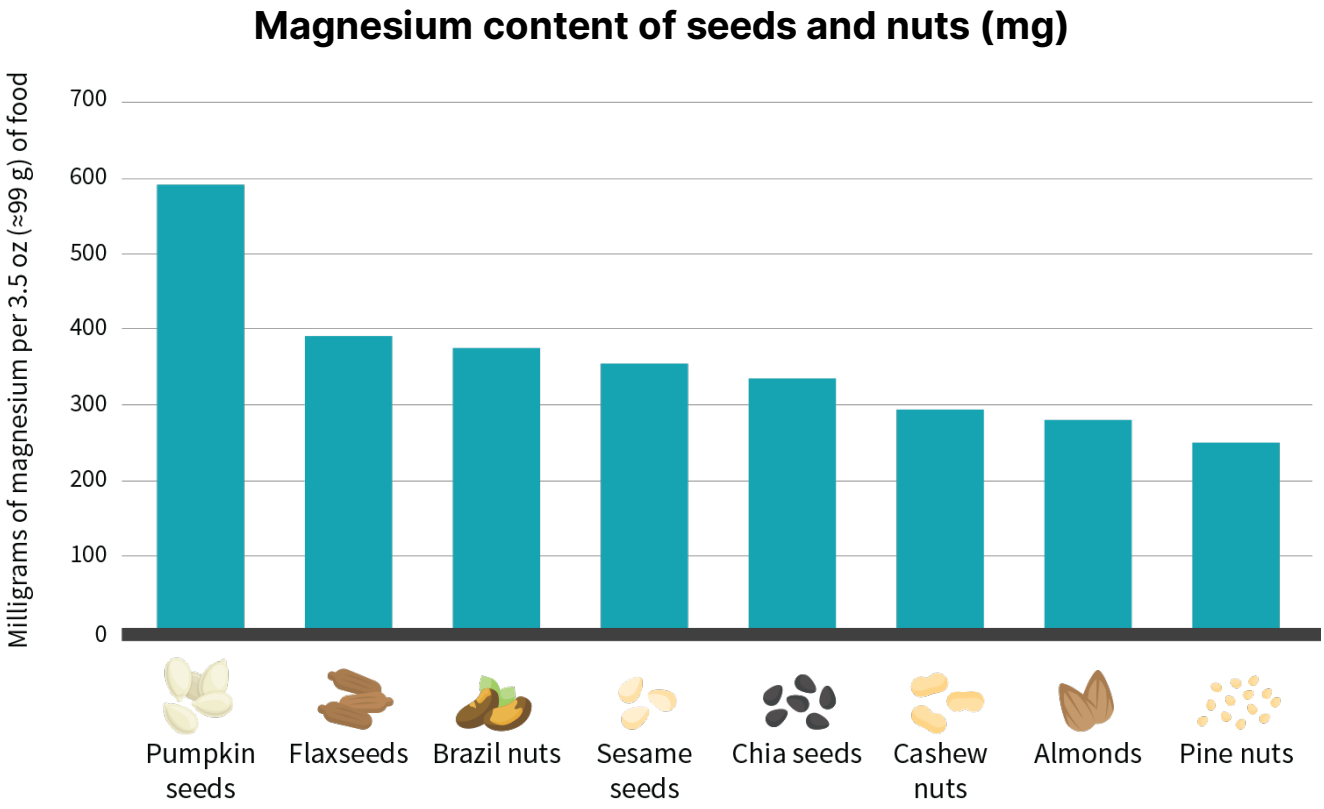
Alongside another anxiety combo, lemon balm (300–600 mg) or melatonin (0.5–5 mg) can be supplemented 30–60 minutes before bed if impaired sleep is contributing to anxiety. Start at the low end of the dosage range, then add 100 mg of lemon balm every couple of days or 0.5 mg (500 mcg) of melatonin every week until you reach the minimum effective dose. Do not take more than you need, and do not take more than the high end of the dosage range.

Primary Supplements

Magnesium

What makes *magnesium* a core supplement

Magnesium is a dietary mineral that plays an important role in the brain. Hypomagnesemia (subnormal magnesium levels in the blood) can result in abnormal neuronal excitations and thereby cause or increase anxiety. Studies have shown that inducing magnesium deficiencies also induces stress and anxiety, which can then be alleviated through magnesium supplementation. There is no reliable evidence to suggest that taking a magnesium supplement can help people who do not suffer from a magnesium deficiency.



Reference: USDA FoodData Central Database.

Who is more likely to have low magnesium levels?

- *Older people*, because they tend to have relatively low magnesium intakes[43] and may absorb less during digestion.[44]
- *People who sweat a lot*, because magnesium is lost through sweat. Athletes participating in sports requiring weight control may be especially vulnerable.
- *Type 2 diabetics.* It has been estimated that, over all adult ages in developed countries, hypomagnesemia affects less than 15% of healthy people but up to 50% of people with type 2 diabetes.[45]

In addition, certain diuretics, proton pump inhibitors, and the antifungal medication amphotericin B can cause significant magnesium loss.[46][47] However, potassium-sparing diuretics (e.g., amiloride, eplerenone/Inspra, spironolactone/Aldactone, triamterene/Dyrenium) may not.[46]

High doses of supplemental magnesium can cause diarrhea and general intestinal discomfort;[48] fortunately, magnesium obtained via food has not been seen to cause such problems.[48]

Tolerable Upper Intake Level (UL) for supplemental magnesium (mg)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–12 months	—	—	—	—
1–3 years	65	65	—	—
4–8 years	110	110	—	—
>9 years	350	350	350	350

Reference: Institute of Medicine. Magnesium (chapter 6 in *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. The National Academies Press. 1997. DOI:10.17226/5776)

Magnesium is a core supplement because it is cheap, safe, and provides a variety of health benefits. Taking magnesium for at least a few weeks is recommended before adding any other supplement, in case a magnesium deficiency is the cause of the anxiety.

How to take *magnesium*

There is no single agreed-on, satisfactory method for assessing magnesium status.[49] To get a better sense of your typical magnesium intake, you should track what you eat for a week. If, on average, you are getting less than 80% of your Recommended Dietary Allowance (RDA), supplementation becomes an option, but you should first try eating more foods rich in magnesium.

Recommended Dietary Allowance (RDA) for magnesium (mg)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–6 months	30*	30*	—	—
7–12 months	75*	75*	—	—
1–3 years	80	80	—	—
4–8 years	130	130	—	—
9–13 years	240	240	—	—
14–18 years	410	360	400	360
19–30 years	400	310	350	310
31–50 years	420	320	360	320
>50 years	420	320	—	—

* Adequate intake (AI)

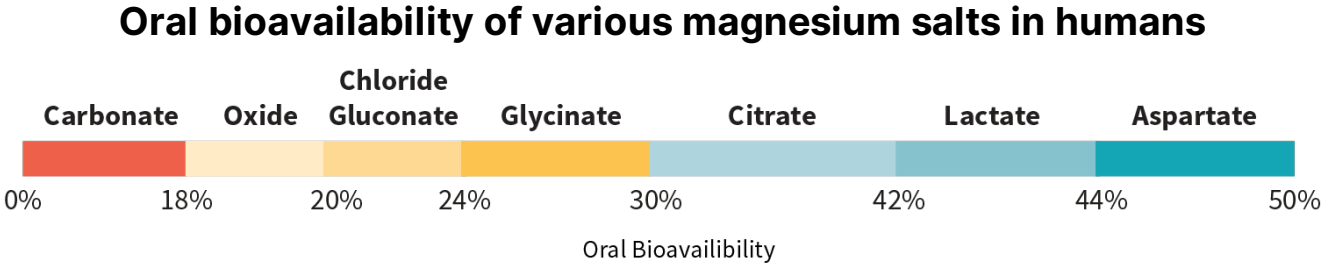
Reference: Institute of Medicine. Magnesium (chapter 6 of *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. The National Academies Press. 1997. DOI:10.17226/5776)

A diet comprising magnesium-rich foods (such as those seen in the figure above) renders supplementation unnecessary, at least for the purpose of preventing anxiety. In case of magnesium deficiency, adding or increasing dietary sources of magnesium should be the first option, but in the absence of practical ways of doing so, supplementation can be used.

If you cannot get enough magnesium through foods, start supplementing with *200 mg* of magnesium once a day. Capsules with 400 mg are common, but keep in mind that the Tolerable Upper Intake Level (UL) for supplemental magnesium for adults is 350 mg. The higher the dose, the higher the risk of gastrointestinal issues.

If your magnesium intake is very low, take up to *350 mg* of magnesium once a day.

Commonly supplemented forms include citrate, gluconate, and glycinate. To increase absorption, magnesium gluconate should be taken with food; other forms can be taken on an empty stomach. *Avoid magnesium oxide.* It has poor bioavailability (rats absorbed only 15% in one study;[50] humans, only 4% in another[51]) and is especially liable to cause intestinal discomfort and diarrhea.[51][52][53]



Reference: Ranade et al. *Am J Ther*. 2001.[54]

Since calcium, iron, magnesium, and zinc compete for absorption, it is better to take them at least one hour apart from each other. magnesium may impair the absorption of other pharmaceuticals, notably bisphosphonates and antibiotics, especially those in the tetracycline class (e.g., doxycycline) or quinolone class (e.g., ciprofloxacin).[55] Take magnesium at least 6 hours apart from bisphosphonates or antibiotics.

Because magnesium might have a sedative effect and improve sleep quality, it is best to take it before bed.

> 💡 ***Tip:*** **Why don't you recommend brands or specific products?**
>
> For two reasons:
>
> - We don't test physical products. What our researchers do — all day, every day — is analyze peer-reviewed studies on supplements and nutrition.
> - We go to great lengths to protect our integrity. As you've probably noticed, we don't sell supplements, or even show ads from supplement companies, even though either option would generate a lot more money than our Supplement Guides ever will — and for a lot less work, too.
>
> If we recommended any brands or specific products, our integrity would be called into question, so … we can't do it. That being said, in the interest of keeping you safe, we drew a short list of steps you should take if a product has caught your interest.

Secondary Supplements

Arginine with Lysine

What makes *arginine with lysine* a primary option

State and trait anxiety is a form of anxiety that can occur in otherwise healthy individuals in response to minor stressful events, such as a presentation. More precisely, state anxiety is defined as an unpleasant emotional arousal in response to a stressor, whereas trait anxiety is indicative of an individual's general tendency to respond with state anxiety when stressors arise.

People suffering from state and trait anxiety have been found to benefit from supplementing arginine and lysine in combination.

Since research on these two amino acids has focused on state and trait anxiety in otherwise healthy adults, it is uncertain if they hold any benefit with regard to other forms of anxiety, such as *generalized anxiety disorder* (GAD).

How to take *arginine with lysine*

Take 1.25 g of arginine and 1.25 g of lysine twice a day (i.e., 2.5 g of each per day), with or without a meal. Effects can be felt after a week of supplementation.

Kava

What makes *kava* a primary option

Kava (*Piper methysticum*) is an herb traditionally used to reduce anxiety, with effects occurring quickly after oral supplementation. It is well researched and has evidence to support its use as an anti-anxiety supplement. In fact, some studies show it works about as well as low-dose benzodiazepines, which is surprising since supplements seldom reach pharmaceutical-level potency.

Like lavender, kava is an effective supplement for people with GAD. It has also been tested in the context of other kinds of anxiety, with promising results.

Some concerns have been raised about the safety of kava because of reports of liver damage. Such reports are numerous enough to be cause for concern, yet it is still unclear whether and in which cases kava can be blamed. The current view is that kava at high doses, for prolonged periods of time, or combined with other medications might increase the risk of liver damage. In some cases, the damage may have been due to the poor quality of the kava supplement.

How to take *kava*

Most studies on kava used an extract called WS 1490. Study participants took 100 mg three times a day (i.e., 300 mg/day). If supplementing with other products, select one that specifies its kavalactone content (kavalactones being the active molecules in kava). Take 70 mg of kavalactones three times a day (i.e., 210 mg/day).

Kava does not need to be taken with meals.

Lavender

What makes *lavender* a primary option

Lavender (*Lavandula*) is traditionally used in aromatherapy to reduce anxiety. Its purported calming and sedative effects have been linked to two of its constituents: linalool and linalyl acetate.[56] Lavender is usually administered in the form of an essential oil distilled from the flower. This oil can be used orally, topically, or through inhalation.

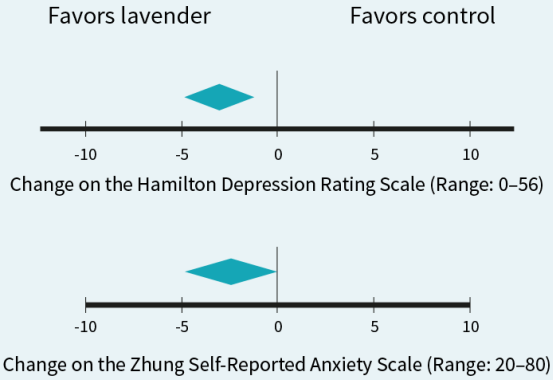
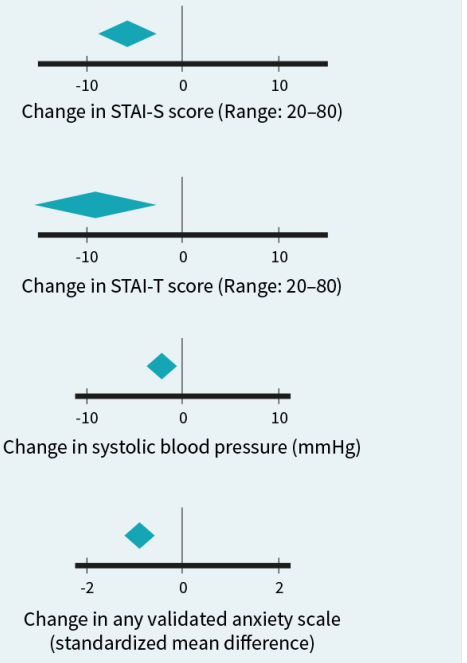
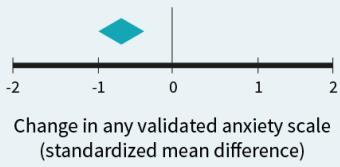
A 2019 meta-analysis looked at 37 *randomized controlled trials* (RCTs). Some settings were highly anxiety-inducing (e.g., patients in an intensive care unit) and others milder (e.g., students taking a test).[57] To account for differences in anxiety assessment and lavender administration (oral, topical, or inhaled), the study's authors conducted seven meta-analyses, whose findings are summarized in the graphic below.

Lavender was associated with an overall improvement in anxiety, but the RCTs were highly heterogeneous, and most exhibited a high risk of bias. The inability to conduct blinded aromatherapy studies does contribute to the risk of bias.

Oral administration showed the most robust results, due to a standardized extract and dose: Silexan™ seems as efficacious as SSRIs and benzodiazepines, without the adverse effects of those anti-anxiety pharmaceuticals (who are still backed, however, by sturdier evidence).

In studies examining oral supplementation, lavender oil has been found to benefit people with *generalized anxiety disorder* (GAD), a condition characterized by frequently occurring symptoms of anxiety unrelated to specific stress or situations. While lavender and lemon balm have been shown to be synergistic, more research is needed to confirm this effect.

Results of a lavender meta-analysis

DELIVERY METHOD	EFFECT ON ANXIETY	STUDIES AT HIGH RISK OF BIAS?	HETEROGENEITY?
OIL IN CAPSULES 		Around half Over half	High Very low
INHALED OIL 		Around half Over half Over half Over half	Very high Very high Very low Very high
MASSAGE OIL 		Around half	High

Reference: Donelli et al. *Phytomedicine*. 2019.[57]

Because anxiety is prevalent in younger women, anxiety treatments are often taken along with contraceptive pills. One study has shown that lavender doesn't interact with a type of estrogen-based birth control: ethinyl estradiol with levonorgestrel.

Yet lavender may have hormonal effects. The Endocrine Society and the National Institutes of Health (NIH) warn that lavender oil has estrogenic properties that may cause gynecomastia (enlarged breasts in males).

Three case studies of prepubertal gynecomastia have previously been attributed to topical administration of a cologne with lavender as an ingredient.[58][59] More recently, a case-series reported three prepubertal girls and one boy with clinical evidence of estrogenic action associated with a history of using lavender-

based fragrance.[60] While the precise development of these conditions can be multifactorial, the gynecomastia resolved once the use of the products was discontinued. Additionally, there is *in vivo* evidence of estrogenic and antiandrogenic properties of both lavender and tea tree essential oils.[59]

If you are using lavender and your breasts become tender, cease use.

> 🔍 ***Digging Deeper:*** **Why you should care about heterogeneity**
>
> Heterogeneity within a meta-analysis (usually represented as I2) represents the degree of variation among the included studies. An I2 value can range from 0% to 100%, with high percentages representing considerable variation — in the intervention (e.g., delivery method, dosage), population studied (e.g., age, sex, health issues), or study methodology. If you meta-analyze studies that are too different (i.e., highly heterogeneous), you wind up comparing apples and oranges.
>
> When heterogeneity is identified, it is common to explore the cause by conducting subgroup analyses. For example, you could analyze the results from males and females separately. It must be noted that explorations of heterogeneity done after the fact (that is, after heterogeneity has been identified) should be interpreted with caution, especially if there are very few studies or people in each subgroup.

How to take *lavender*

Studies on lavender and GAD have used 80 mg of Silexan™, a proprietary lavender oil preparation standardized for the active component linalool at 25–46% of total weight. This supplement is taken once a day, usually with breakfast. After two weeks, if no benefit has been observed, the dose can be increased to 160 mg (this is the *maximum* dose).

Lavender oil is also used in aromatherapy — burned as a candle, heated, placed in a vaporizer, or added to a hot bath. The number of variables (product concentration, proximity of the user to the source, size of the room …) makes recommending dosages exceedingly difficult, but studies have used at least thirty minutes of exposure in a well-ventilated room.

Vitex Agnus-Castus

What makes *vitex agnus-castus* a primary option

Vitex agnus-castus (VAC) is a very specific anti-anxiety supplement. An extract of the plant is used to reduce the anxiety that can occur during the menstrual cycle, as well as to alleviate the symptoms associated with premenstrual syndrome (PMS). VAC may also reduce irritability and improve sleep during PMS, which can in turn improve mood and indirectly reduce anxiety.

VAC has no effect when supplemented by women not currently experiencing PMS and has not been tested in men for anxiety.

How to take *vitex agnus-castus*

To supplement VAC, take 150–250 mg of the dried berry once a day with breakfast.

VAC extracts with a higher percentage of the active compounds may provide benefits at a lower dosage. To supplement VAC through the Ze 110 extract, take 20 mg once a day. To supplement VAC through the BNO 1095 extract, take 4 mg once a day.

Promising Supplements

Agmatine

What makes *agmatine* a secondary option

Agmatine is a neurotransmitter produced from arginine, an amino acid. If alcohol reduces anxiety, it is notably by causing the body to release agmatine. This often results in increased anxiety the next day, when the body's reserves of agmatine are depleted. Giving rodents agmatine helped mitigate this "hangover anxiety". Agmatine may also make opioids more effective for pain relief as well as less addictive.

Though agmatine is a promising supplement, human studies are needed to determine if the anti-anxiety effects observed in rodents will occur reliably in humans.

How to take *agmatine*

Studies on people with nerve pain used as much as 3.2 g/day, with no reported side effects, yet this dose seems unnecessarily high to treat anxiety, especially since rodent studies found that very high oral doses could actually *worsen* anxiety. The optimal anti-anxiety agmatine dose for rats was 10 mg/kg, which translates to approximately 1.62 mg/kg (or 0.74 mg/lb) in humans, so about:

- 110 mg for a 150-lb person
- 150 mg for a 200-lb person
- 180 mg for a 250-lb person

More research is required to determine the optimal time to supplement agmatine. The few human studies on nerve pain had their participants take agmatine with a small breakfast.

Ashwagandha

What makes *ashwagandha* a secondary option

Ashwagandha (*Withania somnifera*) is an adaptogen, commonly defined as a supplement that can reduce the mental and physical effects of stress, including anxiety. It is only a secondary option because studies specifically on ashwagandha and anxiety are rare, but the results are promising. Furthermore, studies on ashwagandha and social functioning suggest that this adaptogen could be especially beneficial to people suffering from social anxiety.

Studies looking at the effects of ashwagandha when participants have at least mild-moderate anxiety have been largely positive, though some of the studies only show a minor effect.[61][62][63][64][65][66] Of 4 studies that were able to be included in an analysis, the average reduction compared with placebo in Hamilton Anxiety

Scale was 4.14, which is a small effect, though the two other studies had large effects according to their respective scales. While research is generally supportive, it's still in its early stages, and higher quality studies with more participants, particularly for more severe forms of anxiety would give us a better understanding how effective it is, and when it's the most effective.

When it comes to subclinical stress, the studies that we have are in agreement that it was reduced by ashwagandha.[62][63][67][68] The average reduction on the perceived stress scale was 4.54 (7.94, -1.14) in people with at least moderate stress levels, which is small but meaningful and was potentially higher in those with the most stress. Overall, there's not enough clear, high-quality evidence to be confident in ashwaganda's ability to have a notable effect on stress, but what we have is supportive.

How to take *ashwagandha*

To supplement *ashwagandha*, find a product with KSM-66 (a proprietary water-based extract standardized to 5% withanolides). The usual dosage range is 300–600 mg/day. Do not take more than 1,200 mg of KSM-66 (or 60 mg of withanolides) per day. Ashwagandha is usually taken with breakfast, if only because night-time supplementation may cause insomnia.

To supplement *Rhodiola rosea*, find a product with SHR-5 (a proprietary extract standardized to 3% rosavins and 1% salidroside). To supplement SHR-5 in anticipation of a stressful event, take 500 mg one hour before the event. To supplement SHR-5 continuously, take 80–160 mg once a day, preferably with a meal.

To supplement *Panax ginseng* continuously, take 100–200 mg of an extract standardized for 2–3% ginsenosides, once a day.

Inositol

What makes *inositol* a secondary option

Inositol encompasses nine vitamin-like compounds that are structurally similar to blood glucose. The most common of those, in nature as well as in health stores, is called *myo*-inositol. Supplemental myo-inositol is often called just "inositol" or sometimes "vitamin B_8" (a misnomer, as inositol is not related to the B vitamins, nor is it a true vitamin).

Inositol usually refers to _myo-_inositol, which has been shown to help in some disorders of glucose metabolism, like polycystic ovary syndrome (PCOS). It has also been investigated for its beneficial effects on anxiety and depression, with some evidence to support its use specifically to alleviate panic attacks. High doses of inositol (18 g) have been compared to fluvoxamine in potency.

Initial evidence is promising, yet more research is needed before inositol can become a primary option to fight anxiety.

Studies haven't reported notable adverse effects from taking inositol, though they haven't been particularly meticulous about their accounting.[69] Myo-inositol might cause some gastrointestinal discomfort, but this is not a frequent occurrence.

In pregnant females taking up to 4 g of myo-inositol, no notable adverse effects were noted in the females or in their babies at birth.[70][71][72] There is insufficient evidence on the effects of taking myo-inositol while breastfeeding.

How to take *inositol*

As an anti-anxiety supplement, take 14–18 g/day, in one or more doses, with food.

When taking softgels, only some 30% of the powder dose is required, so 4.2–5.4 g of inositol.

Lemon Balm

What makes *lemon balm* a secondary option

Lemon balm (*Melissa officinalis*) is actually a light sedative, not an anti-anxiety supplement *per se*, but people with anxiety issues can use it to help fall asleep.

Though quality sleep is a great way to reduce general anxiety, it can be difficult to get if anxiety strikes near bedtime. It is all too easy to get stuck in a cycle of anxiety that both causes sleep deprivation and is fueled by it. If you have already tried and failed to establish healthy sleep habits (see the *Sleep* Supplement Guide for more information), a minor sedative such as lemon balm can help break the anxiety-and-sleep-deprivation cycle.

Lemon balm may act synergistically with lavender, but more research is needed to confirm this effect. Since the point of lemon balm supplementation is to improve sleep, other supplements that can induce sleep, such as melatonin, can also be used.

Lemon balm's effect on mood

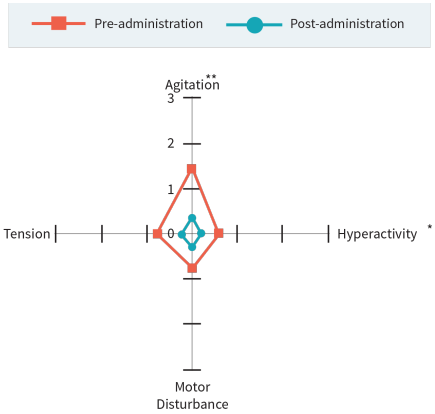


Figure 2a: Anxiety manifestations before and after 15 days of treatment with 600 mg of Cyracos (300 mg twice a day) in 20 volunteers affected by anxiety disorders and sleep disturbances. *p < 0.05 ; **p < 0.01

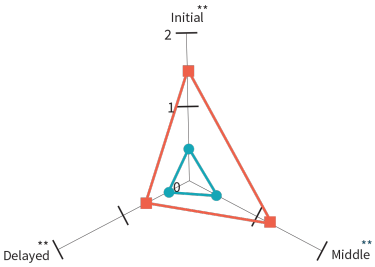


Figure 2b: Insomnia parameters before and after 15 days of treatment with 600 mg of Cyracos (300 mg twice a day) in 20 volunteers affected by anxiety disorders and sleep disturbances. **p < 0.01

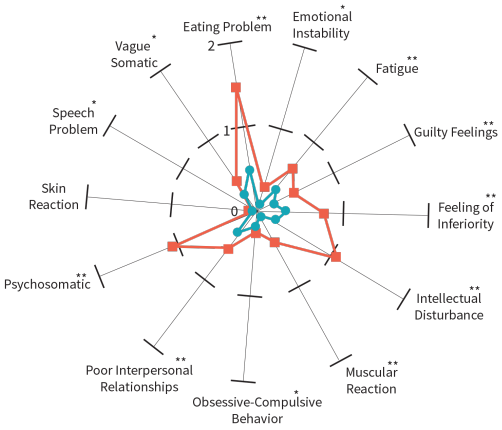


Figure 2c: Anxiety-associated symptoms before and after 15 days of treatment with 600 mg of Cyracos (300 mg twice a day) in 20 volunteers affected by anxiety disorders and sleep disturbances. *p < 0.05 ; **p < 0.01

Reference: Cases et al. *Med J Nutrition Metab.* 2011.[73]

Unlike benzodiazepines, lemon balm is not potent enough to have addictive or habit-forming properties. Nevertheless, any supplement with a sedative effect can disrupt working memory, reduce attention span, and increase reaction time. Do not drive or operate heavy machinery after taking lemon balm or any other supplement with a sedative effect. Do not take lemon balm during the day.

How to take *lemon balm*

Take 300–1,200 mg of *lemon balm* 30–60 minutes before bed. Start with 300 mg; ramp up to 600 mg over

the course of a week if no lower dose proves effective. Only take a dose larger than 600 mg if it provides noticeably greater benefits. Lemon balm is also used in aromatherapy, but studies tend to examine oral supplementation because it is a more reliable delivery method.

Alternatively, take 0.5 mg (500 mcg) of *melatonin* about 30 minutes before bed. Increase by 0.5 mg each week until you find the lowest effective dose that works. Do not take more than 5 mg. Time-release melatonin may be more effective at sustaining sleep throughout the night.

Passionflower

What makes *passionflower* a secondary option

Passionflower (*Passiflora incarnata Linneaus*) is one of the oldest herbal anxiolytics. Researchers are not sure which bioactive compound in this plant exerts the anxiety-reducing effect, although it is thought to be water-soluble, since passionflower is also effective as an infusion. Chrysin and benzoflavone are good candidates, as each could exert an anxiolytic effect by increasing the efficiency of the neurotransmitter gamma-aminobutyric acid (GABA) by acting on its receptors.

In contrast to other options, passionflower does not appear to be that effective acutely, but rather shows steady benefits after a month or more of daily supplementation.

Passionflower seems to affect anxiety in general rather than a type of anxiety in particular, which can be seen as an advantage but also means that human studies are all over the place and specific protocols seldom replicated. For that reason, it is considered a secondary option.

How to take *passionflower*

The ideal dosage is not yet known, but studies have found success with 500 mg of passionflower extract. Passionflower infusions, consumed at least twice a day, also appear to be effective.

Unproven Supplements

Of the supplements we have reviewed, none currently fit the above description.

Inadvisable Supplements

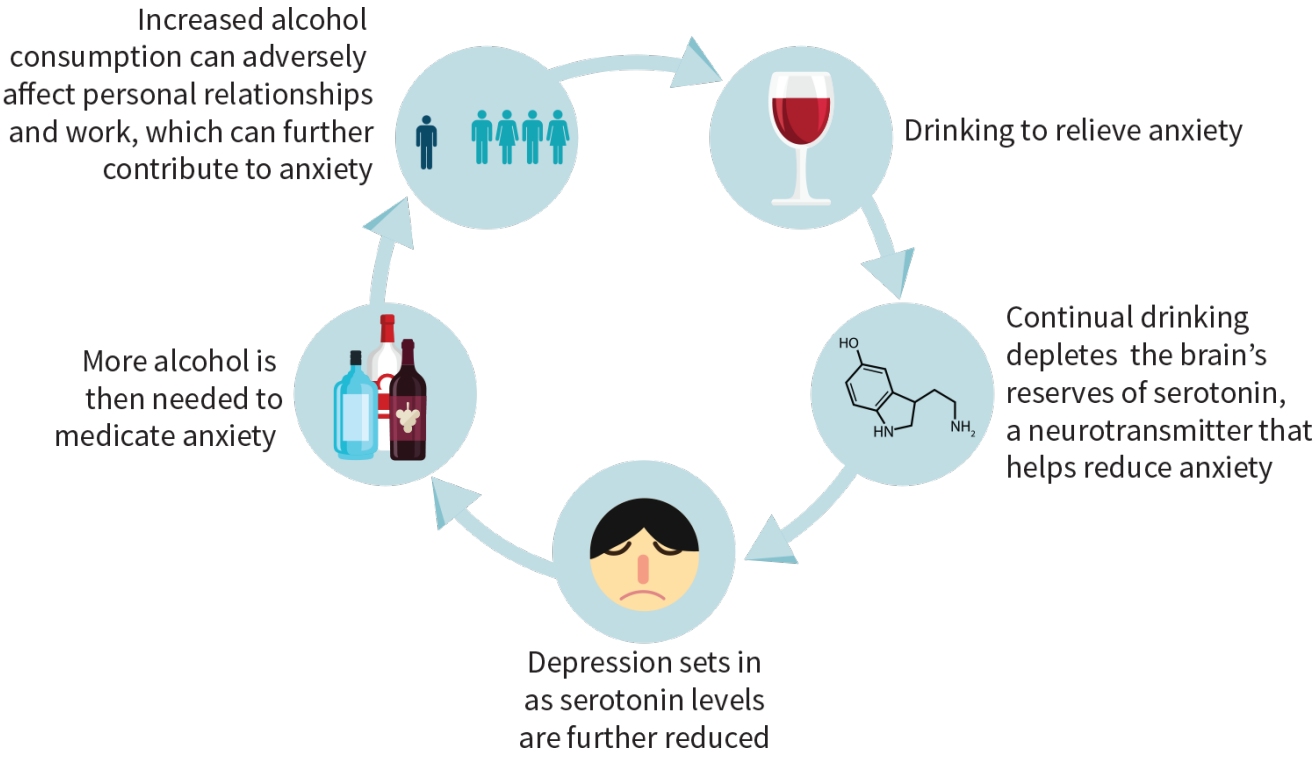
Alcohol

What makes *alcohol* an inadvisable supplement

Alcohol is popular worldwide, notably as a means to stave off anxiety. Like nicotine abuse, however, alcohol abuse results in exacerbated anxiety symptoms. While reasonable consumption is not unhealthy, relying on alcohol to alleviate anxiety is not recommended because of the health hazards associated with high-dose or high-frequency alcohol intake.

Self-medicating with an addictive substance is not a healthy solution to anxiety or other problems, nor is it sustainable. Long-term reliance on alcohol results in acquired tolerance and subsequent withdrawal, which greatly exacerbates anxiety. Moreover, since hangovers worsen anxiety, any attempt at medicating anxiety with alcohol is likely to backfire even in the short term. In brief, alcohol has negative consequences for anxiety in both the short and long terms.

The cyclical process of drinking to relieve anxiety



Nicotine

What makes *nicotine* an inadvisable

supplement

Nicotine is known to reduce anxiety in new users. Tolerance builds up with frequent use, however, leading to a reduction of the anti-anxiety effect. Tolerance also leads to nicotine withdrawal, which greatly increases anxiety.

Nicotine's addictive properties vary depending on the dose taken and the speed at which it enters the bloodstream. When inhaled, nicotine reaches the blood quickly, which makes this delivery method especially addictive. At the other end of the spectrum, patches are the least addictive delivery method, but they act too slowly to ward off anxiety (unless said anxiety is related to nicotine withdrawal).

When it comes to speed of delivery, nicotine gum holds the middle ground. By itself, it would not prevent a panic attack, but it could be chewed during the practice of coping mechanisms (2 mg of nicotine at a time, no more than 10 mg in one day). Making this a daily habit, however, would allow tolerance to develop, and only ceasing supplementation entirely (for a couple of weeks) would allow sensitivity to return. Increasing the dose instead would, sooner or later, lead to nicotine withdrawal and greatly increased anxiety. Even the minimum dose, taken regularly, is potentially addictive, and thus potentially harmful, especially for people suffering from anxiety.

Of course, tobacco is still the most noxious source of nicotine, and not just because it contains some thirty carcinogens. As noted above, when inhaled, nicotine reaches the blood quickly, which makes it especially addictive. In addition, several other compounds in tobacco, such as monoamine oxidase inhibitors (MAOIs), amplify the addictive effects of nicotine. Finally, the acquired need to suck on something contributes to the addictive properties of cigarettes, cigars, and smoking pipes (and thumbs, for little children).

While most anti-anxiety supplements have a sedative effect, nicotine acts as a stimulant.

Yohimbine

What makes *yohimbine* an inadvisable supplement

Yohimbine is an alkaloid found in the bark of the African tree yohimbe (*Pausinystalia johimbe*). It is used to treat erectile dysfunction and to aid in fat loss.

Alas, yohimbine is associated with a variety of side effects, one of which is anxiety. In fact, this side effect is so reliable that many studies on anxiety use yohimbine to _induce _anxiety and panic attacks. People who are susceptible to panic attacks or have panic disorders are especially susceptible to anxiety caused by yohimbine.

FAQ

Q. What about the supplements not covered in this guide?

Our guides are regularly updated, often with new supplements. We prioritize assessing (and reassessing) the most popular of them and those most likely to work. However, should there be a specific supplement you'd like to see covered in a future update, please let us know by filling out this survey.

Q. Can I add a supplement not covered in this guide to my combo?

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

Q. Can I modify the recommended doses?

If a supplement has a recommended dose 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. Taking less could render the supplement ineffective, yet starting with half the regular dose could be prudent — especially if you know you tend to react strongly to supplements or pharmaceuticals.

Q. At what time should I take my supplements?

The answer is provided in the "How to take" section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Starting with half the regular dose can help minimize the harm a supplement may cause when taken during the day (e.g., fatigue) or in the evening (e.g., insomnia).

Q. Should I take my supplements with or without food?

The answer is provided in the "How to take" section of a 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.

Q. What are DRI, RDA, AI, and UL?

The Dietary Reference Intakes (DRIs) is a system of nutrition recommendations designed by the Institute of Medicine (a US institution now known as the Health and Medicine Division). RDA, AI, and UL are part of this system.

- Contrary to what the name suggests, a *Recommended Dietary Allowance* (RDA) doesn't represent an *ideal* amount; it represents the *minimum* you need in order to avoid deficiency-related health issues. More precisely, it represents an amount just large enough to meet the minimum requirements of 97.5% of healthy males and females over all ages — which implies that the RDA is too low for 2.5% of healthy people.
- The *Adequate Intake* (AI) is like the RDA, except that the number is more uncertain.
- The *Tolerable Upper Intake Level* (UL) is the maximum safe amount. More precisely, it is the maximum daily amount deemed to be safe for 97.5% of healthy males and females over all ages — which implies that the UL is too high for 2.5% of healthy people.

As a general rule, a healthy diet should include at least the RDA of each nutrient — but less than this nutrient's UL. This rule has many exceptions, though. For instance, people who sweat more need more salt (i.e., sodium), whereas people who take metformin (a diabetes medicine) need more vitamin B12.

Moreover, the DRIs are based on the median weight of adults and children in the United States. Everything else being equal (notably age, sex, and percentage of body fat), you likely need a lesser amount of nutrients if you weigh less, and vice versa if you weigh more. The numbers, however, are not proportional — if only because the brains of two people of very different weights have very similar needs. So you can't just double your RDIs for each nutrient if you weigh twice as much as the median adult of your age and sex (even if we overlook that people weighing the same can differ in many respects, notably body fat).

Q. What's the difference between elemental magnesium and other kinds of magnesium?

"Elemental" refers to the weight of the mineral by itself, separately from the compound bound to it. For instance, ingesting 500 mg of magnesium gluconate means ingesting 27 mg of elemental magnesium.

Product labels display the elemental dosage. On a label, "27 mg of magnesium (as magnesium gluconate)" means 27 mg of elemental magnesium (and 473 mg of gluconic acid).

Q. As an athlete with a low dietary intake of magnesium, I supplemented 350 mg and experienced diarrhea. Why is that?

If magnesium is indeed the culprit, then your diarrhea was probably caused by too large a dose reaching the colon. Alternatively, it could mean that your body's levels of magnesium are in fact sufficient, making supplementation unnecessary.

In the future, split your daily dose into multiple doses. If the problem persists, reduce your daily dose to 200 mg. If you are using magnesium oxide, switch to a different form of magnesium.

Q. Should I stop using stimulants if I have anxiety?

Though stimulants do not always cause anxiety, many create a stress response that could worsen existing symptoms. People with anxiety might not need to stop using stimulants entirely, but they may want to avoid frequent use, especially if symptoms worsen.

Caffeine is the stimulant least likely to cause anxiety. Ideally, 100–200 mg of caffeine should be paired with an equal dose of theanine, an amino acid that can tame the anxiety caused in some people by caffeine without impairing caffeine's stimulatory effect. In fact, the improvements in concentration (focus and attention span) induced by caffeine and theanine respectively have been shown to be synergistic.

Yohimbine and yohimbine-containing products — as well as supplements that have a similar mechanism, such as rauwolscine — should be avoided.

Q. What kinds of coping strategies are effective at alleviating anxiety?

Deep breathing, muscle relaxation, and stretching are typical methods to cope with anxiety. The most effective stress-reducing activities, however, are highly dependent on the individual. Some people will soothe their anxiety through quiet rituals (knitting, tea ceremony ...), while others will quell it through high-intensity exercising (weight lifting, boxing ...).

Regular contact with nature (gardening, trekking, laying out in the sun ...) has shown benefits for most people.

Cognitive Behavioural Therapy (CBT) is highly effective in alleviating some forms of anxiety, as a substitute or a complement to supplements or pharmaceuticals.

Q. Can yoga alleviate anxiety?

The movements and poses in yoga incorporate the basic anti-anxiety coping strategies: deep breathing, muscle relaxation, and stretching. Yoga is also a form of meditation, and meditation has been shown to reduce anxiety.

Q. Are there specific species of lavender that have more active constituents?

Lavender is a plant from the *Lamiaceae* family that includes various different species. Most lavender species share similar major chemical constituents, consisting of terpenes, alcohols, ketones, and polyphenols.[74] While constituents and properties are similar among species, lavender essential oil extracts can range from 26–57% linalool and 4–35% linalyl acetate,[75] with linalool considered the primary active

constituent.[56]

Q. What other things might lavender be helpful for?

Beside inducing relaxation, lavender is traditionally known for treatment of parasitic infections, burns, insect bites, and spasms.[76] Lavender oil might be anti-fungal,[77] reduce headache severity[78] and hair loss,[79] improve wound healing,[80] and alleviate premenstrual symptoms.[81] However, much more research is needed to really tease out an effect.

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