Examine®

Mood & Depression Supplement Guide

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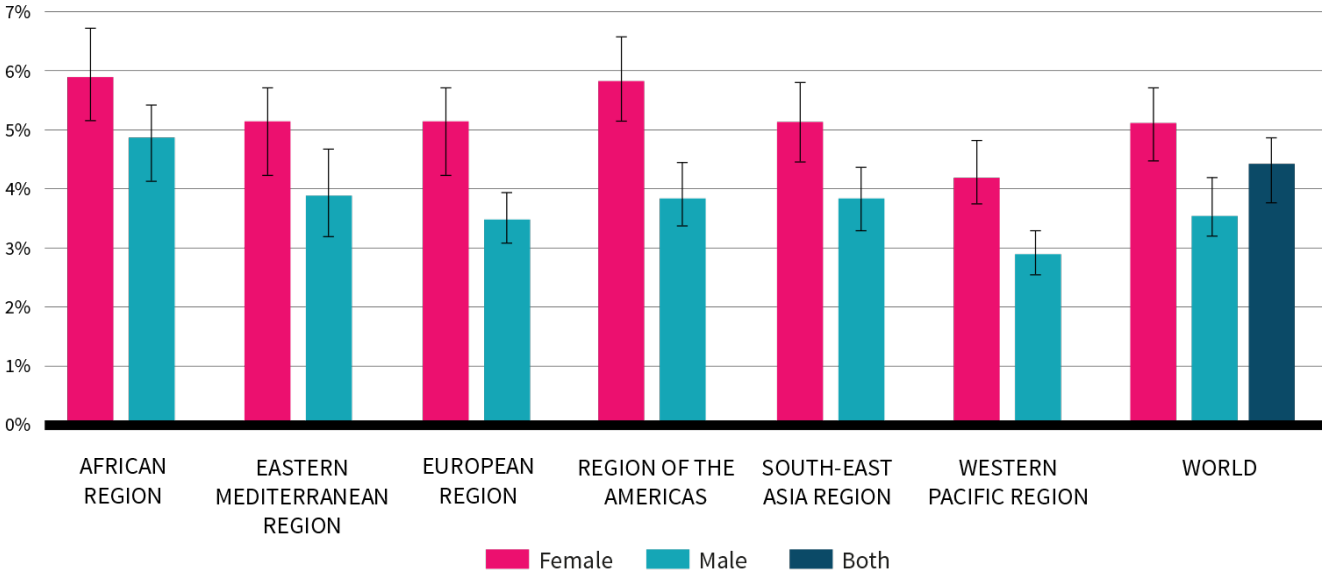
Introduction

From time to time, everyone feels down for some reason, such as failing at something or losing a job or a loved one. This downturn can be disabling and can prevent a person from performing normal, everyday tasks. And when “low mood” turns very severe or simply lasts too long, it is often classified as a mood disorder.

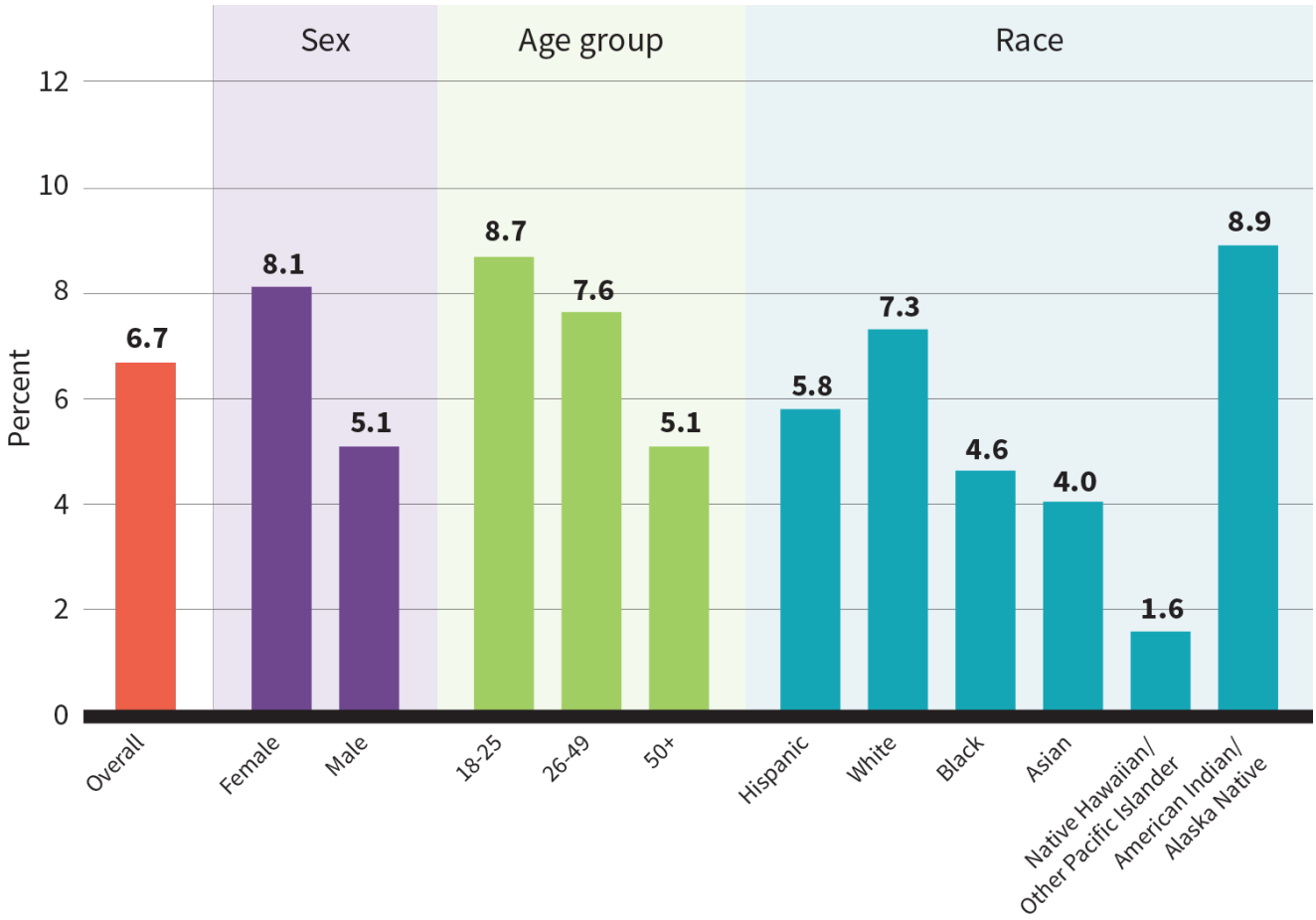
The most common mood disorder is *major depressive disorder* (MDD), a condition that affects nearly 322 million people worldwide[1] and is one of the largest contributors to global disability. The World Health Organization (WHO) estimates that the number of people living with depression increased by nearly 20% from 2005 to 2015. Although estimated to be more common in women[2] and adults of working age, depressive symptoms are frequently found in all sexes and age groups.[3]

Prevalence of depressive disorders (% of population) by WHO Region



Reference: World Health Organization. *Depression and Other Common Mental Disorders: Global Health Estimates*. Gov't Doc #: WHO/MSD/MER/2017.2

Prevalence of major depressive episodes (% of population) in the US



Reference: Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute of Mental Health (NIMH). 2013.

Although depression is a common ailment, it can be incredibly difficult to talk about, both because of the stigma around mental health[4] and because many people (including researchers) don't take it as seriously as they do ailments that can be objectively assessed, such as infections or diabetes.

Issues related to measurement and diagnoses

Mood disorders are difficult to diagnose, notably because they cannot be assessed objectively. Diagnosis of depression involves weighing subjective symptoms such as anxiety, fatigue, insomnia, and altered appetite.

Not only are those symptoms subjective, but not everyone living with depression will have them all, and their severity will also differ from one person to the next.[5] One person with depression may suffer from narcolepsy, serious fatigue, loss of interest, and some anxiety, whereas another may suffer from serious anxiety, very little fatigue, and insomnia.

This variation is especially problematic because the questionnaires used to assess depression tend to assign greater weight to the *number* of symptoms than to their *severity*.[6][7] For example, consider a 20-item questionnaire on which each item is a symptom graded from 1 to 4 (from least to most severe). In that instance, having 15 level-1 symptoms will yield a greater "depression total score" than having 3 level-4

symptoms (15 vs. 12 points), even though the latter scenario is probably more debilitating.[7]

🔍 Digging deeper: "Measuring" depression

To diagnose an illness, you have to assess *variables*.

Observable variables can be measured directly. For instance, we can assess people's risk of cardiovascular disease by measuring their blood levels of *low-density lipoprotein* (LDL). LDL levels are observable variables.

Latent variables cannot be measured directly — they must be inferred from observable variables (using mathematical models).[8] When it comes to assessing depression, the observable variables are usually answers to a questionnaire, some of which are filled by the patient and others by a clinician.

Two examples of patient-filled questionnaires

Beck's Depression Inventory II (BDI-II) is a 21-item multiple-choice questionnaire.[9] Each item refers to an area of life that could be affected by depression. For each item, there are 4 possible choices corresponding to 4 levels of severity — from nothing wrong (rated 0) to great distress (rated 3). The scores from all 21 items are then tallied up:

- 00–10 = no depression
- 11–16 = mild mood disturbance
- 17–20 = borderline clinical depression
- 21–30 = moderate depression
- 31–40 = severe depression
- 40–63 = extreme depression

The Self-Reported 30-item Inventory of Depressive Symptoms (IDS-SR30) is a 30-item questionnaire.[10] Each item refers to a specific symptom experienced over the past week. Most items are scored from 0 to 3, where 0 indicates an absence of symptoms and 3 indicates high severity and frequency. The scores from all 30 questions are then tallied up:

- 00–13 = no depression
- 14–25 = mild depression
- 26–38 = moderate depression
- 39–48 = severe depression
- 49–84 = very severe depression

Two examples of clinician-filled questionnaires

The Hamilton Depression Rating Scale (HDRS) is a 17-item questionnaire widely used to quantify levels of depression and evaluate recovery.[11] The interviewer rates the severity of symptoms such as anxiety, agitation, feelings of guilt, and weight loss. These measures have been shown to reliably track and quantify symptoms of depression. A score of 15 or higher indicates depression.

The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item questionnaire.[12] The interviewer rates from 0 to 6 the severity of symptoms such as inner tension, reduced sleep duration, and suicidal thoughts. The scores from all 10 questions are then tallied up:

- 00–06 = no depression
- 07–19 = mild depression
- 20–34 = moderate depression
- 34–60 = severe depression

The subjectivity and interindividual variability of depression symptoms make it difficult to establish robust, generalizable theories and find treatments that work for everyone. Also, they make it even more difficult for researchers to take depression seriously. This is worth keeping in mind as we explore hypotheses that have been proposed over the years.

⚠️ **Caution: Don't self-diagnose**

Although diagnosing depression often involves patient-filled questionnaires, it is a much more involved process than our summary suggests, so avoid self-diagnosis. A person who suspects that they are depressed should get the opinion of a mental-health clinician or primary care doctor.

Hypotheses of mood disorders

Neuroscientists and psychiatrists have searched for biological causes of depression (objective, observable variables) since the 1950s, especially to gain credibility within the medical community. One of the first major theories was that depression was caused by low levels of serotonin[13] (a neurotransmitter that notably helps regulate mood). This idea was heavily marketed by the pharmaceutical industry, which created several types of antidepressants designed to raise serotonin levels.[14]

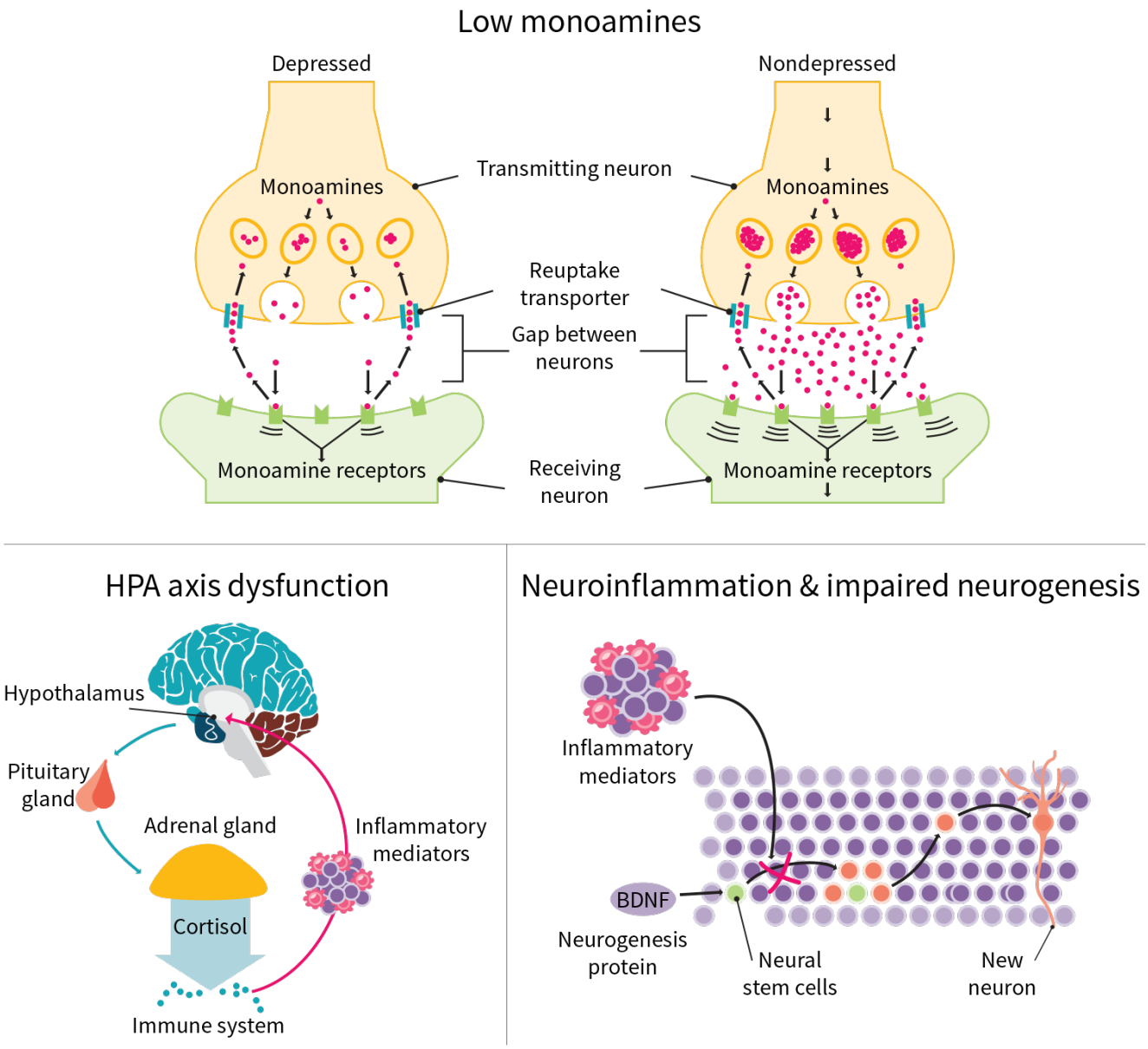
Presynaptic neurons are serotonergic: they produce serotonin, which activates postsynaptic neurons. *Selective serotonin reuptake inhibitors* (SSRIs), by far the most common class of antidepressants, prevent the presynaptic neurons from reabsorbing serotonin so that more is absorbed by the postsynaptic neurons.

However, more recent studies have contradicted this "low serotonin" hypothesis.[15] Some studies showed that SSRIs instantly increased serotonin levels but took weeks to result in any improvements in people with depression.[16] Other studies showed that using drugs to deplete serotonin in healthy individuals did not cause depression, but simply resulted in feelings of irritation or temporary insomnia.[17]

These results have led some researchers to posit that antidepressants actually work by mechanisms other than increasing serotonin, such as increasing *brain-derived neurotrophic factor* (BDNF), a molecule associated with brain growth.[18] For that reason, BDNF levels have been proposed as a better observable variable than serotonin levels to indicate the efficacy of antidepressant treatments. However, changes in BDNF levels don't appear to occur uniformly across all antidepressants.[19]

Today, the "serotonin" hypothesis has lost much of its credibility with neuroscientists and psychiatrists, and several new biological hypotheses of depression have emerged and gained traction, exploring the roles of neuroinflammation,[20] neurotoxicity (more precisely, excitotoxicity[21]), *hypothalamic-pituitary-adrenal* (HPA) axis dysfunction,[22] and circadian-rhythm abnormalities.[23]

Possible mechanisms involved in depression



References: Miller and Raison. *Nat Rev Immunol.* 2016.[24] ● Anacker et al. *Psychoneuroendocrinology.* 2011.[22] ● Delgado. *J Clin Psychiatry.* 2000.[25] ● Delgado and Moreno. *J Clin Psychiatry.* 2000.[26]

Additionally, observational studies have linked depressive symptoms to nutrient deficiencies[27] and seasonal decreases in sunlight exposure. Unfortunately, in either case, it is difficult to assess whether these links are causal because other variables might be at play — for instance, less sunlight is associated with less exercise, less sunlight and less exercise are associated with worse sleep,[28] and less exercise[29] and worse sleep[30][31][32] are associated with lower mood.

Finally, some researchers have argued that looking for biological causes of depression is a waste of time and that the focus should be on the environment and social connections.[33]

To summarize, numerous hypotheses of depression have been proposed (most of them biological), but unfortunately, many have been contradicted by newer evidence, and almost none have large support from researchers who study depression.

Treatments and their evidence

Today, antidepressants (chiefly SSRIs) are still the first-line treatment for depression, even though they've been incredibly controversial ever since they entered the market, with many researchers arguing that they are no better than placebo and have potential adverse effects.

In 2008, a psychiatric researcher conducted a meta-analysis of all the published clinical trials and, using the Freedom Act of Information, obtained unpublished data from pharmaceutical companies; the researcher concluded that although antidepressants were statistically more effective than placebo in reducing symptoms of depression, their benefits were not clinically meaningful because the size of the reduction in symptoms did not meet the guidelines set by some researchers.[34]

In 2018, the largest meta-analysis of antidepressants to date, which combined 522 controlled trials, found that antidepressants led to a small reduction in symptoms of depression but were also associated with higher study dropout rates as a result of adverse events.[35]

Some authors have disputed these results, however.[36] They've suggested that the benefits are actually much smaller and the risks much higher than reported because many of the analyzed trials suffer from poor study design and poor choice of method of statistical analysis, as well as the potential of publication bias[37] (meaning that studies with positive results, because they are considered more interesting, are more likely to get published).

Another problem is that most antidepressant trials are quite short. Even the "long-term" ones didn't last all that long (2–3 years at the very most). Moreover, as a rule, the participants take the antidepressant for the whole duration of the trial and aren't monitored afterward — and if they drop out of the trial because of an adverse event associated with the antidepressant, they are no longer part of the trial and thus are no longer monitored (or at least not in the same way), even though the trial is still ongoing. Therefore, we don't always know whether recorded adverse effects persist, lessen, or worsen after the participant stops taking the antidepressant, and if they do, for how long. It is also possible for adverse events to occur *after* cessation of the treatment, either because of the treatment itself or as a result of its cessation.

Another issue is that meta-analyses of antidepressant studies are likely to combine trials that used different questionnaires, in which case they may be adding noise rather than clarifying the effects of antidepressants.

Some researchers have proposed using "big data" and machine learning to find common patterns among people with depression, with the goal of tailoring drug protocols to specific patterns — which is to say, to specific subgroups of people with depression.[38] Although this approach sounds highly promising, especially given the heterogeneous nature of depression, determining true subgroups within a population is incredibly difficult due to the possibility of random noise showing up as systematic patterns.[39] Furthermore, with the use of big data and machine learning, the small biases of small trials may accumulate.

Another primary treatment for depression is *cognitive-behavioral therapy* (CBT),[40] which has been shown to be helpful in many trials.[41] There is still much uncertainty about its effects, however, and it can be inaccessible to many people due to cost and lack of information.[42]

🔍 Digging deeper: Behavioral therapies

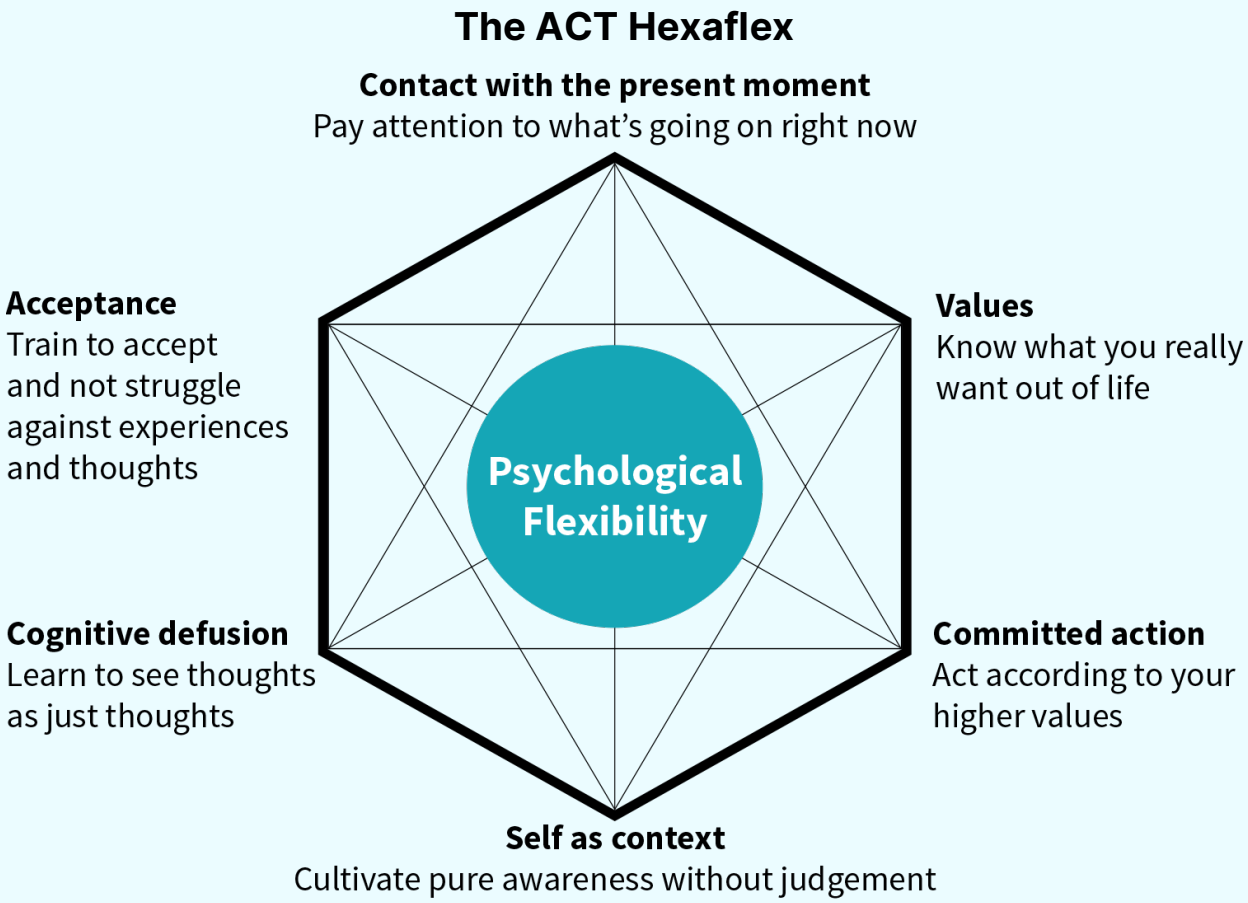
There have been three "waves" of behavioral therapies.

The first wave altered behaviors. Techniques such as exposure therapy for phobias fall into this category — in exposure therapy, people are either gradually or suddenly exposed (with their consent) to something that they fear, and the fear tends to subside with repeated exposure.

The second wave added thoughts to the equation, becoming *cognitive-behavioral therapy* (CBT). This family of therapies requires that people change not only their behaviors but also their thoughts — they must challenge their irrational, harmful thoughts and replace them by more rational thoughts based on the evidence.

The third wave takes a different approach to thoughts: instead of challenging and replacing them, people must be *mindful* of them. In other words, they must see the thoughts for what they are: fleeting thoughts, not enduring facts. They can then act according to their higher values rather than to their fleeting thoughts and the emotions that accompany them.

Acceptance and Commitment Therapy (ACT) is one type of third-wave behavioral therapy. It teaches people to use mindfulness-based methods to accept thoughts and feelings instead of fighting them, so that they can then act based on their higher values. ACT therapists tend to insist that this therapy be pronounced as an acronym (i.e., as one word: *act*) rather than as an initialism (i.e., as separate letters: *a, c, t*), to emphasize a commitment to action. There are 6 areas of training in ACT:



It should be noted that ACT is very new, so although it is a promising type of therapy, the supporting evidence is scarce (basically nonexistent compared to the evidence in support of CBT).

Depression is a complex, heterogenous mental disorder, and there are several barriers to measuring it and treating it. This means that taming depression may require some long-term work with a trained professional with good judgment to try various interventions that show promise. This is a sizable investment (in money, time, and effort), yet one that may be worth considering, given the potential to experience some relief from a debilitating disorder that can seriously impair quality of life.

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Combos

Disclaimer about supplement quality

We expect that readers will do their due diligence when choosing products. Depending on the manufacturer, supplements may have inaccurate labels (i.e., they contain too much or too little of the ingredients they claim or, in some cases, significant amounts of other ingredients not listed). They may also contain significant amounts of contaminants such as heavy metals or pesticides. It is also possible for supplements to contain ingredients that people are commonly allergic to, and it's important to be aware of the nonmedicinal ingredients as well. As a brief introduction to vetting manufacturers, we drew up a short list of steps you should take if a product has caught your interest.

💡 **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.

Core Combo

⚠️ **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 activities such as driving or operating heavy machinery, when impaired cognition may be a risk for personal safety and the safety of others.

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

First, it may be best to evaluate the overall diet and identify any instances of insufficient nutrient intake.

Although the evidence for vitamin D, zinc, and magnesium is not as strong as we would like, if a person's diet is critically low in any of these nutrients, or any other nutrients that could plausibly affect neurological function, it may be a significant factor in mood, and improving the diet/taking supplements to fill gaps is probably a good idea anyway.

It's also very worthwhile to test the effects of frequent exercise, especially for people who currently don't get enough.

More details about taking these nutrients can be found in the "How to take" sections of this guide.

> 💡 **Tip: Try one combo alone for a few weeks**
>
> Taking too many supplements at once may prevent a person from determining which ones are truly working. Start with just one of the combos suggested here for a couple of weeks before making any modification, such as adding another supplement, altering a supplement's dosage, or incorporating the supplements from an additional combo.
>
> When adding another supplement to a regimen, be methodical. For example, some people may want to take all the supplements from two combos. In this case, select a combo to try first and take this for a couple of weeks. Then, add one supplement from the second combo and wait another week and note its effects. Continue this process until all of the wanted supplements have been added.
>
> If a supplement appears in two combos selected for combination, 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, the new range becomes 2–6 mg. Always start with the lower end of the range — especially in this case, because 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 in deciding which dose to aim for, but in the case of uncertainty, lower is usually safer.

Specialized Combos

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

Consider whether the intakes or levels of essential nutrients are inadequate or deficient (read the core combos section).

After addressing that, and after consultation with a physician, add 1 g of EPA to the core supplements (if needed). Fish oil with DHA can be used as long as the amount of EPA reaches 1 g.

After that, there is a decision to make. It is often a good idea to add supplements slowly to see if more are truly needed or to try to discern whether or not they are effective. Two or three months is typically the minimum amount of time required to see the full benefits of an antidepressive intervention, and longer

durations may yield greater effects still. But it is also understandable if people don't want to wait that long before adding additional interventions.

After giving the aforementioned a solid chance, 30 mg of saffron (in two doses of 15 mg) can be added to the overall combo.

After months, if saffron proves to be insufficient, adding either 900 mg (300 mg 3 times per day) of St. John's Wort or 500-1500 mg of curcumin (as per the curcumin section of this guide) could yield additional benefits. It is worth noting that St. John's Wort, as far as we know, is potentially more effective but also interacts more potently with medications and supplements, whereas curcumin's drug interactions are more mild (except for when taken with piperine, which has strong drug interactions). Taking multiple herbal extracts is inherently risky and should be discussed with a physician.

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

If at all possible, get diagnosed by a mental-health clinician or primary care doctor. Without a clinical diagnosis, it's difficult to know specifically what might help, because it's possible that the symptoms aren't major depression and could be caused by any number of factors. For that reason, in addition to exploring other options and possibilities like exercise and psychotherapy, it's important to think about why a person might be experiencing depression symptoms. If it's related to another chronic health condition, life circumstances, or addictions, addressing those things may be the most important.

The core combo, with its focus on diet and essential nutrients, is probably the best place to start.

After that, adding saffron may be helpful. It is probably unwise to combine multiple herbs because they can potentially interact negatively with each other and pose a risk for adverse events.

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

Saffron and *Rhodiola rosea* both exhibit anti-stress/anxiety effects. Because saffron is so much more supported by evidence, it is the better option.

What has changed since the last time?

It should be noted that we changed the names of our ranking categories. "Core" (the highest) is now "primary", "primary" is now "secondary", and "secondary" is now "promising". This nomenclature has already been implemented for some guides, but this is the first update to the Mood & Depression Guide that uses this new terminology. For example, if it was a core supplement in the previous issue and now it's a secondary supplement in this issue, we'll say that it was a primary supplement in the previous issue and is now a secondary supplement.

Added:

- Saffron (primary)

- *Rhodiola rosea* (promising)
- Magnesium (promising)
- Chromium (unproven)
- Ashwagandha (unproven)
- Inositol (unproven)

Changed ranking:

Omega-3 fatty acids (formerly called EPA)

Increased from secondary to primary. Although EPA seems to be the main omega-3 fatty acid responsible for fish oil's antidepressant effects — and higher doses of EPA than DHA make sense — most studies use both, and so focusing only on EPA doesn't make sense. Although the effect size of omega-3 fatty acids is modest, they are also important nutrients to the body, and some small amount of depression can likely be blamed on an insufficiency.

Vitamin D

Downgraded from primary to secondary. Although the evidence from clinical studies supports a benefit, it is smaller than was previously thought.

SAMe

Downgraded from primary to promising. Although there has been a lot of research over the years, very little of it is of high quality, and the better studies are somewhat mixed on the efficacy of SAMe.

Zinc

Downgraded from primary to promising. There is insufficient evidence to call it a primary supplement, and much of the evidence was found in combination with antidepressant drugs, so we're especially not sure how effective it is in other contexts.

Removed:

Adaptogens

We decided not to combine adaptogens in one entry and instead write separate, proper, entries for both ashwagandha and *Rhodiola rosea*.

Primary Supplements

Omega-3 fatty acids

What makes *omega-3 fatty acids* a primary supplement

Omega-3 fatty acids, or specifically, the longer-chain family members *docosahexaenoic acid* (DHA) and *eicosapentaenoic acid* (EPA), are of interest for depression and mood because observational studies have reported that the consumption of greater amounts of omega-3 fatty acids (e.g., from fish) is associated with a reduced risk of mood disorders,[43][44][45][46] and people with depression or bipolar disorder have lower levels of omega-3 fatty acids in red blood cells.[47][48]

The positive effects of omega-3 fatty acids on depression and mood are thought to occur as a result of their incorporation into the cell membrane, resulting in changes in structure and function that promote reductions in inflammation and oxidative stress[49] and the regulation of neurotransmitter pathways and cell signalling.[50]

Supplementation with omega-3 fatty acids has been reported to improve depression symptoms to a small degree in people with major depressive disorder,[50] regardless of whether the supplement was taken as an adjunctive therapy or monotherapy. Whether this improvement is clinically meaningful is questionable, but the effectiveness of omega-3 fatty acids seems to be comparable to that of some antidepressants.[50][51][52] Thus, further studies directly comparing omega-3 fatty acids to antidepressants are warranted.

Supplementation with omega-3 fatty acids as a monotherapy has a small-to-moderate beneficial effect in perinatal depression, with the greatest benefits reported during the postpartum period.[53][54] Also, omega-3 fatty acids may have a small beneficial effect in bipolar depression when used as an adjunctive therapy.[55][56]

Warnings about *omega-3 fatty acids*

Omega-3 fatty acids are known to cause gastrointestinal side effects, including abdominal pain and diarrhea, in some people.[57][58] Taking omega-3 fatty acids with food may help avoid these unwanted side effects.[59]

Although rare, some cases suggest that fish oil interacts with anticoagulants like warfarin/Coumadin/Jantoven and antiplatelets like aspirin and can increase the risk of bleeding when used together.[60][61][62], especially at daily doses greater than 1 gram.[63] Taking fish oil alone does not appear to have this risk.[64][65] Consult with a prescriber or medical professional before taking fish oil with any of these medications.

🔍 **Digging Deeper: Oxidized fish oil**

Fish oil can become rancid and oxidize when exposed to oxygen, heat, or light. These oils are particularly susceptible to oxidation because of their very-long-chain polyunsaturated fatty acids. The oxidation level is measured using three values:

- *Peroxide value* (PV)
- *Anisidine value* (AV)
- *Total oxidation value* (TOTOX)

The PV is a measure of primary oxidation products (peroxides), and AV is a measure of secondary oxidation (aldehydes and ketones). The TOTOX value is calculated using the formula AV + 2PV. The lower the TOTOX value, the better the oil quality will be. The Global Organization for EPA and DHA Omega-3 recommends a TOTOX value of no more than 26.

Oxidation of fish oils can be highly variable. One 2015 study found that nearly 50% of commercial fish oils exceeded the maximum recommended TOTOX value,[66] whereas other studies have found very good compliance with the TOTOX limits.[67][68] Taken together, the divergent results demonstrate just how widely the quality of commercially available fish oil supplement can be.

Evidence for the health effects of consuming oxidized fish oils is a bit mixed. For healthy individuals, there is an absence of obvious short-term health damage from consuming oxidized fish oil. One study showed no difference in circulating levels of oxidized LDL-C or inflammatory markers after 7 weeks of supplementation with oxidized fish oil.[69]

However, in people with high levels of cholesterol and triglycerides, consumption of highly oxidized fish oils can minimize its efficiency in improving metabolic markers like fasting glucose, total cholesterol, and triglycerides.[70]

There is some evidence of omega-3 fatty acids increasing the risk of atrial fibrillation, as detailed elsewhere by Examine. The risk seems to be present even at dosages as low as 1 gram per day and may be greater with EPA-only supplements than with combined EPA and DHA supplements.[71] There are still many uncertainties, including the magnitude of risk and whether or not this risk is present in people without cardiovascular disease or who are not at a high risk of cardiovascular disease.

Although DHA is marginally better than EPA at reducing triglyceride levels, it can cause a modest increase in *low-density lipoprotein* (LDL-C, the "bad cholesterol").[72]

How to take *omega-3 fatty acids*

For *major depressive disorder* (MDD), the dose of omega-3 fatty acids should contain at least 1 gram of EPA,[73] either in the form of pure EPA or a supplement containing a 2:1 ratio of EPA to DHA,[49] with the potential to increase the dosage to 2 grams per day, if well tolerated.[73] The optimal dose of omega-3 fatty acids for perinatal depression is unclear, but there's also an absence of evidence to indicate that it should differ from the recommendation for MDD.[53]

More research is needed to determine the optimal dose of omega-3 fatty acids for bipolar depression.

Trials that have reported a positive effect have used vastly different interventions, including one that had participants take 1–2 grams of EPA per day[74] and another that involved roughly 9.6 grams of omega-3 fatty acids (6.2 grams of EPA and 3.4 grams of DHA) per day.[75]

Saffron

What makes *saffron* a primary supplement

Saffron is derived from the *Crocus sativus* L. plant and has been traditionally used to flavor food. It is a rich source of bioactive compounds with potential neuroprotective effects, most notably crocins, crocetin, picrocrocin, and safranal. Preclinical evidence in animals indicates that saffron could be useful for improving mood and depression through its ability to reduce oxidative stress and inflammation, modulate neurotransmitter pathways and hypothalamic–pituitary–adrenal (HPA) axis activity, and increase *brain-derived neurotrophic factor* (BDNF) levels.[76]

A number of meta-analyses have reported that saffron reduces depression symptoms in many users, ranging from people with subclinical depression to people with major depressive disorder.[77][78][79][80] The magnitude of effect reported in these studies is considerably greater than that of conventional treatments for depression,[51][52] but head-to-head comparisons between saffron and antidepressants have not found differences between groups.[77][78][80] Further research is warranted to determine whether saffron is as effective as antidepressants because the latter has a larger amount of scientific evidence and real-world data to support its use.

A potential limitation of this body of research is that the studies to date have been exclusively conducted in Iran, the world's primary producer of saffron. This doesn't invalidate the relatively consistent and impressive results; however, it highlights the need for replication from researchers in other geographical regions.

Warnings about *saffron*

There is mixed, weak evidence that saffron may modestly increase the risk of headaches, anxiety and anxiety-related symptoms, and gastrointestinal symptoms. It's still unclear how much saffron increases this risk, if it increases it at all.[78][81] However, GI effects tend to be more likely at doses greater than 1.2 grams of saffron. [82]

One study showed that daily supplementation with 60 mg of saffron for 26 weeks may reduce red and white blood cells and platelet levels. Also, daily supplementation with 60 mg of saffron for at least 8 weeks seemed to cause a drop in blood pressure along with sedation, overactive energy, and change in appetite. These effects increased as the duration of use increased.[83]

The natural chemicals in saffron can interfere with the activity of CYP2B, CYP2C11, and CYP3A enzymes, which could either reduce or increase the rate of metabolism for various drugs, potentially leading to negative interactions.[84] Saffron may reduce blood sugar, and the use of saffron along with diabetes medication could possibly lead to hypoglycemia. [85] Saffron may reduce blood pressure, and the use of saffron along with blood pressure medications could possibly lead to low blood pressure.[86][87]

The use of more than 10 grams of saffron by pregnant individuals has shown a potential abortive effect. However, this effect was reported in 1925 and could be due to the unwanted pollutants in saffron.[88]

How to take *saffron*

The vast majority of studies have had participants supplement with 30 mg of saffron extract (typically derived from the stigma of the *Crocus sativus* L. plant) daily, often taken as two separate 15 mg doses.

Secondary Supplements

St. John's Wort

What makes *St. John's Wort* a secondary supplement

St. John's Wort (*Hypericum perforatum*) is a perennial herb that has been traditionally used to treat mood disorders. The main bioactive compounds in St. John's Wort (to which the herb's mood-enhancing properties have been attributed) are hyperforin (a lipophilic phloroglucinol) and hypericin (a naphthodianthrone). Although the exact mechanism of action is not fully understood, St. John's Wort is thought to have a mechanism similar to *selective serotonin reuptake inhibitors* (SSRIs) — it increases the levels of brain chemicals that are known to play important roles in regulating mood.[89]

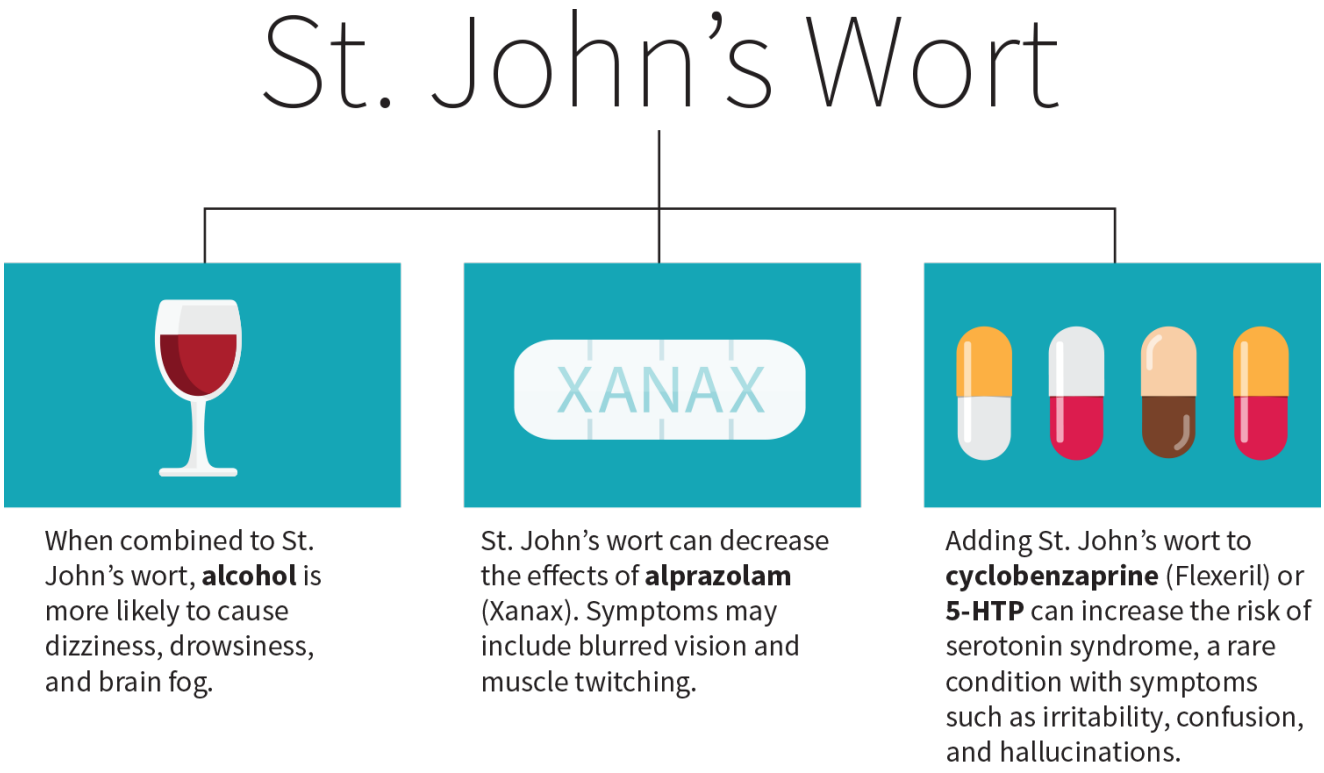
According to a fairly large body of scientific evidence, the effects of St. John's Wort on symptoms of depression in individuals with mild or moderate depression are likely comparable to those of pharmaceutical antidepressants such as SSRIs.[90][91][92] Moreover, fewer side effects related to neurologic, psychiatric, and sexual functions have been reported with the use of St. John's Wort compared to those of pharmaceutical antidepressants.

That said, most trials examining the antidepressant properties of St. John's Wort are of questionable methodological quality. Also, one of the aforementioned meta-analyses rated the certainty of the evidence on the effect of St. John's Wort on symptoms of depression as moderate or low.[91] For these reasons, St. John's Wort can only rank as a secondary supplement.

Warnings about *St. John's Wort*

St. John's Wort is generally well tolerated.[93] Approximately 1% to 3% of patients experience some side effects associated with St. John's Wort such as anxiety, dry mouth, dizziness, gastrointestinal symptoms, fatigue, headache, skin reactions, and sedation.[94] Taking St. John's Wort with other antidepressant medications may cause serotonin syndrome.[95] If St. John's Wort is taken in large doses or by people with chronic illnesses like hepatitis C, it may cause sensitivity to sunlight. Few instances of allergic skin reactions have been noted.[94] St. John's Wort interacts with many medications. Therefore, individuals who are taking any medication should talk to a doctor before taking St. John's Wort. St. John's Wort is a CYP3A4 inducer. Thus, St. John's Wort alters and decreases the concentration and the efficacy of drugs that are metabolized by CYP3A4 such as immunosuppressant medications (tacrolimus and cyclosporine), oral contraceptives, certain statins (atorvastatin and simvastatin), certain cancer medications (imatinib and irinotecan), anticonvulsants (mephenytoin), protease inhibitors, and omeprazole.[96] St. John's Wort is also a CYP2C9 inducer. Thus, St. John's Wort decreases the concentration and efficacy of drugs that are metabolized by CYP2C9 such as warfarin.[97][96] Another study showed that St. John's Wort decreased digoxin levels by 25%. This decrease could be linked to P-glycoprotein transporter induction.[98] Additionally, St. John's Wort can cause adverse neurological symptoms when combined with alcohol and alprazolam (Xanax).

St. John's wort — drug interactions



St. John's Wort should be avoided by people with HIV and AIDS who are receiving protease inhibitors. St. John's Wort should also be avoided during pregnancy and breastfeeding because there is not enough data to support its use during these stages and some evidence to suggest that it may cause problems.[99][100] Soil contamination is common with herbal medications. Nickel is the most common element in soil. Nickel contamination affects St. John's Wort efficacy.[101]

How to take *St. John's Wort*

The most commonly used daily dosage for St. John's Wort in trials examining its effects on symptoms of depression is 300 milligrams taken 3 times per day, for a total daily dose of 900 milligrams.

Most of the extracts used in clinical trials had been standardized to contain 2%–5% hyperforin and 0.3% hypericin.

Vitamin D

What makes *vitamin D* a secondary supplement

Vitamin D receptors are distributed throughout the body, including in the brain.[102] Through binding to these receptors, vitamin D influences the expression of numerous genes in a variety of pathways.[103] Relevant to depression and mood, vitamin D is involved in the synthesis of monoamine neurotransmitters, the regulation of several neurotrophic factors, and neuroprotection (via maintaining calcium homeostasis and exerting anti-inflammatory and antioxidant effects),[104][105] which may explain why observational evidence suggests that lower blood vitamin D levels are associated with an increased risk of depression.[106]

A number of meta-analyses have investigated the effect of supplementing with vitamin D on depression

symptoms. Collectively, these studies generally indicate that supplemental vitamin D has a small-to-moderate beneficial effect in people with depression,[106] particularly if they also have inadequate vitamin D levels.[107] Vitamin D also seems to be useful as an adjunct therapy to antidepressants.[108][109]

Supplemental vitamin D might be beneficial during the perinatal period, with evidence of an improvement in depression symptoms in studies of women without depression at baseline,[110] as well as in women with postpartum depression,[111] but more research is needed.

In contrast, vitamin D does not appear to have much of an effect in healthy people without depression.[107] Additionally, in what appears to be the only trial on this topic, supplemental vitamin D did not enhance the effects of psychotropic drugs on depression symptoms in people with bipolar depression.[112] Further research is needed on the effects of supplemental vitamin D in people with bipolar depression.

Warnings about *vitamin D*

Vitamin D is a fat-soluble vitamin that can accumulate to toxic levels with prolonged excessive intake. Vitamin D toxicity, also called hypervitaminosis D, results in hypercalcemia and a whole host of symptoms including nausea, muscle weakness, loss of appetite, thirst, and excessive urination, to give an incomplete list. It can lead to kidney stones, irregular heartbeat, and sometimes renal failure. The tolerable upper limits for vitamin D intake according to the NIH are listed below.

Tolerable Upper Intake Level (UL) for vitamin D (mg)

AGE/SITUATION	DOSE (IU)
0–6 months	1,000
7–12 months	1,500
4–8 years	2,500
9–13 years	3,000
14–18 years	4,000
>18 years	4,000
Pregnant and breastfeeding	4,000

Exceeding these limits won't necessarily lead to vitamin D toxicity, and higher doses have been shown to be safe in the short-term, without increasing calcium levels to a harmful degree.[113] However, in the long-term, especially without frequent vitamin D testing, it is unwise to exceed the amount of vitamin D needed for healthy bodily functions, as it all ultimately comes down to vitamin D status, and people with already sufficient levels may be especially at risk of overdoing it.

There are some studies that suggest an increase in falls for elderly participants taking vitamin D supplements in doses greater than 1,000 IU/d.[114][115][116] It's currently unclear why this happens or if it might be mitigated by other fat-soluble vitamins such as K and A, so caution is warranted.

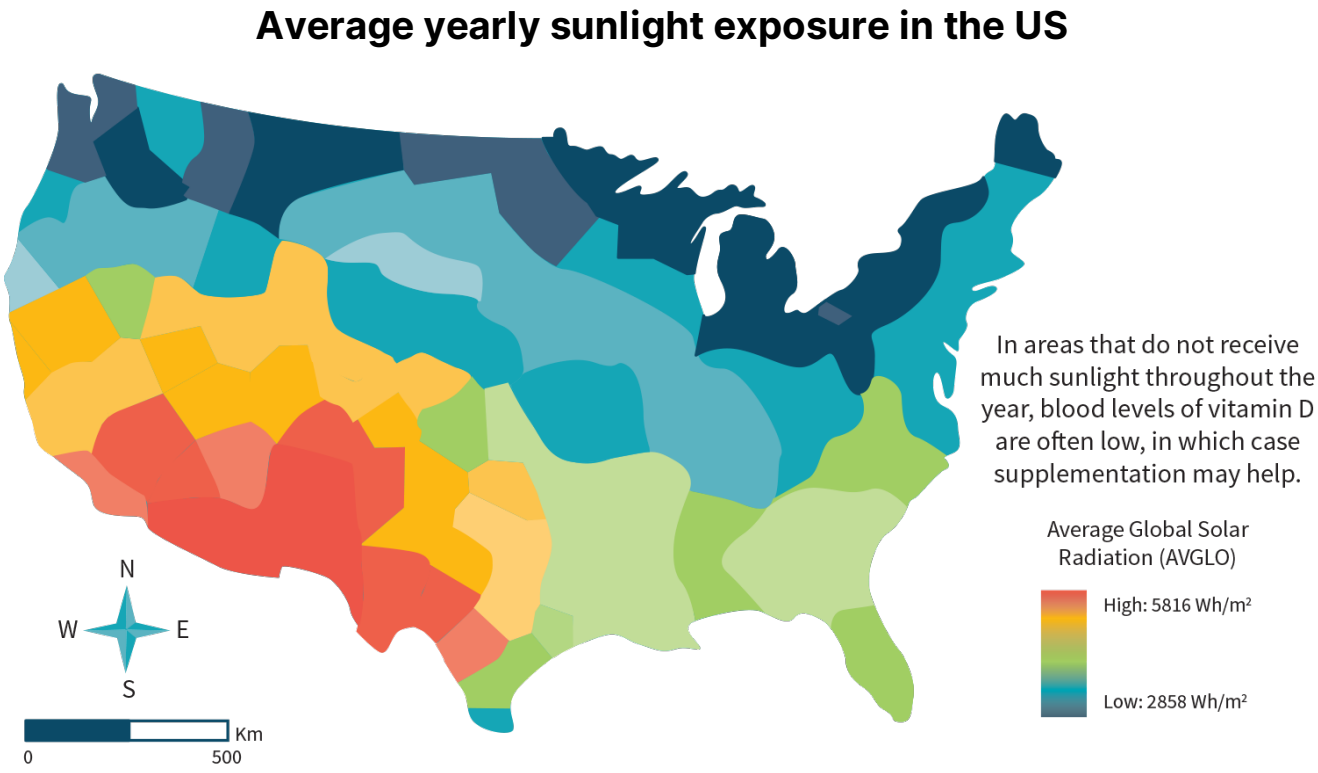
How to take *vitamin D*

Because supplemental vitamin D seems to be most effective in people with inadequate blood vitamin D levels, it's prudent to first determine whether a person's vitamin D levels are adequate. If vitamin D levels are indeed inadequate, the first step should be to increase the intake of vitamin D via whole foods and/or

increase exposure to sunlight. If these strategies are not feasible, supplementation may be considered. In case of outright *deficiency*, a medically supervised intervention will be needed. *Do not begin any intervention without discussing it with a physician.*

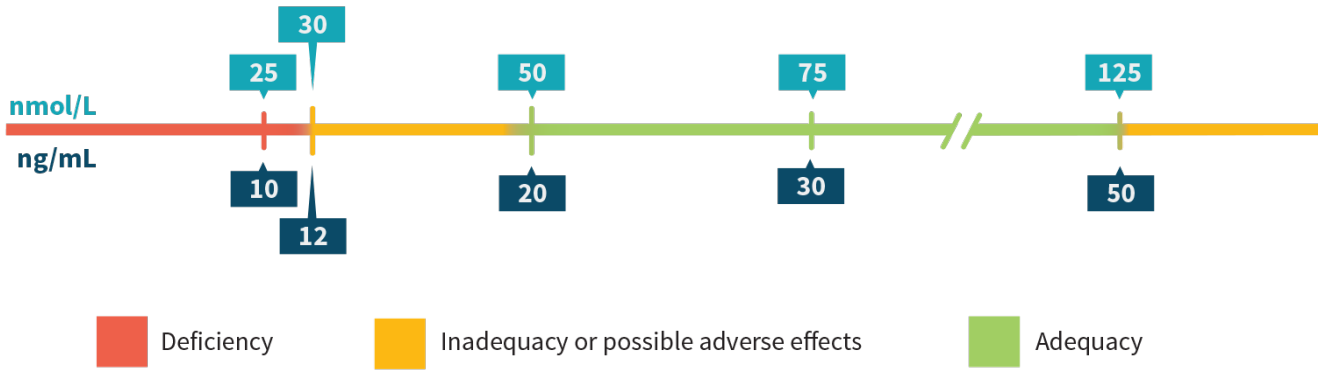
Virtually all studies have had the participants supplement with vitamin D_3, specifically. The optimal dose of vitamin D is likely to differ between individuals, depending on their current vitamin D levels and body mass index (people with overweight or obesity seem to have an impaired response to vitamin D supplementation[117][118] and need higher amounts[119]), among other factors, so an intervention tailored and supervised by a medical professional is recommended. Nevertheless, the available evidence suggests that somewhere between 2,000 and 4,000 IU per day works best, on average.[107]

Such high doses are unlikely to be needed if simply maintaining sufficient vitamin D levels. Suboptimal levels of vitamin D are common, especially in people whose skin exposure to sunlight (meaning without protection from clothes or sunscreen) is limited. Moreover, the darker a person's skin, the longer they need to expose themselves to sunlight to synthesize enough vitamin D, which is why people with darker skin are at an increased risk of suboptimal vitamin D levels.[120]



Adapted from Tatalovich et al. *CaGIS*. 2006. DOI:10.1559/152304006779077318

The situation doesn't improve with age. The older a person gets, the less efficient their body becomes at synthesizing vitamin D, the less time they're likely to spend outside, the less vitamin D they're likely to get through food, and the more likely they are to carry extra fat (belly fat has been linked to vitamin D deficiency).[121][122]



Reference: Institute of Medicine. Overview of Vitamin D (chapter 3 in *Dietary Reference Intakes for Calcium and Vitamin D*. The National Academies Press. 2011. DOI:10.17226/13050

Vitamin D is commonly available in two forms. *Ergo*calciferol (vitamin D_2) is available in a few plants and fungi whose vitamin D_2 content can be increased dramatically when exposed to *ultraviolet B* (UVB) radiation,[123][124] whereas *chole*calciferol (vitamin D_3) is synthesized from the cholesterol in the skin when exposed to the sun's UVB rays.[125][126][127]

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 wooly animals, but a vegan-friendly option (a lichen extract) is also available.

People without a deficiency/insufficiency, before turning to supplementation, should try incorporating some foods rich in vitamin D into their diet. Unfortunately, very few foods contain appreciable amounts of naturally occurring vitamin D, with fatty fish as a notable exception (cod liver oil, in particular). For that reason, milk is commonly fortified with either vitamin D_2 or, more recently, vitamin D_3. Why milk? Because milk is rich in calcium, which vitamin D helps the intestines absorb. For the same reason, yogurt, cheese, and breakfast cereal are also commonly fortified with vitamin D_2 or D_3. Other commonly fortified foods include bread, margarine, and fruit juice (orange juice, in particular). As usual, which foods get fortified, if any, varies by country, based on local laws and policies.

Recommended Dietary Allowance (RDAs) for vitamin D (IU*)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–12 months	400**	400**	—	—
1–13 years	600	600	—	—
14–18 years	600	600	600	600
19–50 years	600	600	600	600
51–70 years	600	600	—	—
>70 years	800	800	—	—

* 40 IU = 1 µg | ** Adequate intake (AI) *Reference:* Institute of Medicine. [https://www.nap.edu/read/13050/chapter/7](Dietary Reference Intakes for Adequacy: Calcium and Vitamin D) (chapter 5 in *Dietary Reference Intakes for Calcium and Vitamin D*. The National Academies Press. 2011. DOI:https://doi.org/10.17226/13050)

Because vitamin D is fat-soluble, it is better absorbed when taken with a fat-containing food or supplement

(e.g., fish oil).

In case of *high* vitamin D levels (which can cause adverse effects), seek the help of a medical professional. Of course, stop taking any supplement containing vitamin D, unless otherwise instructed by a medical professional.

Promising Supplements

Rhodiola rosea

What makes *Rhodiola rosea L.* a promising supplement

Rhodiola rosea L., or Rhodiola, is a well-known adaptogen with a long history of use in traditional and, more recently, alternative medicine. Rhodiola's roots and rhizome have been shown to contain approximately 140 potentially bioactive compounds, ranging from various glycosides, monoterpenes, flavonoids, and flavonlignans to proanthocyanidins and gallic acid derivatives.[128]

Rhodiola's mood-lifting and antidepressant effects are often ascribed to its salidroside content. [129][130] Accordingly, supplement manufacturers have sought to produce extracts with preferably high concentration of this tyrosol glucoside.

With only 6 studies, the evidence on Rhodiola's mood-improving and antidepressant effects is limited. However, the results are equivocally positive. All 6 mood- and depression-related studies published before September 2022 observed statistically significant improvements on the Hamilton Rating Scale for Depression (HAM-D), [131][132][133] the Profile of Mood States Inventory (POMS),[134] and the mood-related parameters in the Maslach Burnout Inventory (MBi-D).[135] Most of the 503 participants (476 completers) in 5 randomized controlled trials (all but one were double blinded) and a noncontrolled, open-label exploratory study from 2017[135] had mild to moderate depression. One study was conducted in participants with mood disorders or depression.[134] Two studies recruited participants with diagnosed fatigue syndrome or "burnout".[136][135] The study durations ranged from 14 days (1 study) to 12 weeks (3 studies). The median treatment dosage was 680 mg per day, and the dosages ranged from 340 to 1360 mg per day.

As already hinted at, the results of the mostly publicly funded studies were promising, with significant or even highly significant improvements compared to placebo. Depression-related indices improved by 13%–35%, and mood-related and fatigue-related indices improved by 6%–33%. One study that compared Rhodiola to placebo and to Sertraline (Zoloft) found similar, albeit somewhat less pronounced, effects for Rhodiola and the commonly prescribed SSRI.[133] Effects from study duration and dosage seem to exist. However, high-dose vs. low-dose (340 mg/day vs. 680 mg/day) regimens were compared in only 2 studies.[131] [132]

In view of the overall low number and high methodological heterogeneity of the input studies, it seems unwarranted to formulate evidence-based conclusions that go beyond very general qualitative assertions such as "longer treatment duration (>12 weeks) and higher dosages (640 mg/day vs. 340 mg/day) seem to yield better results". Overall, the existing evidence warrants Rhodiola's classification as a "promising" and generally well-tolerated mood-elevating and antidepressant supplement. This conclusion is based on only 6 studies in a total of 503 participants, of whom all but the 80 participants in an industry-funded 2015 study [134] had preexisting depression and/or fatigue. Whether the average, healthy supplement user can derive statistically significant, let alone practically relevant, improvements in mood from Rhodiola supplements remains questionable.

Warnings about *Rhodiola rosea*

Rhodiola may cause dizziness and dry mouth,[137] but it has been found to be well tolerated for the most part.[138] However, more evidence is needed to evaluate its safety of long-term use.[139]

Rhodiola may interact with losartan based on its ability to inhibit the metabolic effect of CYP2C9.[140] Rhodiola is mainly used for mental health, and Rhodiola has been shown to inhibit CYP2C9 activity. This interaction could lead to a decrease in the metabolism of antidepressant medications that are metabolized by CYP2C9, such as amitriptyline and fluoxetine, and an increase in their risk of toxicity.[141] A 68-year-old woman developed a serotonin syndrome after taking Rhodiola in combination with paroxetine.[142] Rhodiola may interact with antidiabetic medications, causing lower sugar levels in animals, though the extent hasn't been evaluated in humans.[143]

Although Rhodiola is generally safe, there is a theoretical toxicity concern based on the chemicals in *Rhodiola rosea* plants. *Rhodiola rosea* plants contain highly toxic cyanogenic compounds such as rhodiocyanosides and lotaustralin.These compounds release nitrile, which could lead to theoretical toxicity.[144]

There is limited evidence on the effect of Rhodiola on specific conditions.

How to take *Rhodiola rosea*

Take 340 mg doses of a standardized Rhodiola extract per day for 6–12 weeks. Choose products that are standardized for a high salidroside content of 2.5% or more. A note on proprietary extracts: Four of the studies under review used products based on SHR-5. [145][146] Vitano® (Rosalin WS® 1375) was used in 2 exploratory studies that support its effect on mood improvement and relief from burnout.[134][135] As of fall 2022, reliable evidence on the efficacy of other alternative proprietary blends found on the market is not available.

N-Acetylcysteine

What makes *NAC* a promising supplement

N-acetylcysteine (NAC) is probably best known by the general public for its mucus-dissolving effects. However, scientists and supplement enthusiasts are more excited over NAC's ability to promote the levels of the master antioxidant glutathione (GSH) in our cells, its ability to scavenge free radicals, and its proven ability to soothe inflammation in various organs and disease states. Unlike supplemental GSH and its precursor (the nonacetylated semi-essential amino acid L-cysteine), NAC effectively crosses the blood–brain barrier. Once in the brain, NAC has been shown to strengthen the brain's antioxidant defenses, lower inflammation, and modulate essential neurotransmitter systems.[147][148] Pertinent studies have investigated and still are investigating NAC's effects in various neurodegenerative diseases and, more recently, psychiatric illnesses — including several forms of (pre)clinical depression.[148]

Psychologists and neuroscientists are still debating the physiological processes that are responsible for the

onset, progression, and persistence of depression and related pathological mood disorders. However, most researchers agree that many of the various forms of depression can be traced back to abnormal mitochondrial activity in the brain that is triggered by oxidative stress and chronic inflammation.[149][150] In *in vitro*, animal, and even clinical trials, NAC has been shown to ameliorate similar states of neuroinflammation and has thus emerged as a promising agent for the treatment of various neurodegenerative and neuropsychiatric diseases ranging from autism to Alzheimer's disease and multiple sclerosis, to bipolar disorder, substance addiction, and depression.[151][152][153]

Thus far, research on NAC's potential role in depression and mood enhancement has largely focused on people with bipolar disorder with moderate or severe depression. The 4 contemporarily available meta-analyses draw on a largely overlapping pool of randomized clinical trials that lasted for 8–24 weeks and compared the participants' response to 1–3 grams per day of NAC, taken either alone or in combination with previously prescribed medication, to placebo treatments.[154][155][156][157] In regards to NAC's antidepressant effects, the meta-analyses that were published between 2016 and 2022 yielded mixed results. In Kishi et al. (2020) and Pittas et al. (2021), 2 meta-analyses were unable to confirm consistent, statistically significant effects on symptoms, functioning, and quality-of-life scales in moderate-to-severely depressed participants. [155] [157] In contrast, other meta-analyses that report favorable effects of NAC, Fernandes et al. (2016) and Nery et al. (2020), noted small-to-moderate effects (SMD) of 0.37 (95% C.I.: 0.19–0.55) on the MADRS and HDRS and 0.45 (95% C.I.: 0.06–0.84) based on the HAMD and MADRS scales, respectively. [154] [156]

What all of the meta-analyses share is that they rely on data from the same small and largely overlapping pool of studies. Against that background, the inconsistent effect sizes and difference in statistical significance of the meta-analyses' results may come as a surprise — a surprise that can be explained by the small number of input studies. As a consequence, both the weighting and the inclusion/exclusion of a single study can have a relevant effect on the final outcome of the meta-analyses. Let's take the meta-analysis by Pittas et al. as an example. It is the only one to include a small-scale (17 participants) study by Magalhães et al.,[157] which reported an almost incredible effect size of 2.33 (p = 0.008) and an average reduction of the MADRS score of 10 participants with bipolar disorder who were treated with 2x1 grams of NAC per day, from clearly pathologic 27.80 ± 10.00 points to 9.60 ± 5.50 points (note: levels below 7 points indicate remission and were achieved by 40% of the participants in the treatment group). That result is in stark contrast to the rather mediocre if not insignificant benefits that were observed in the other studies that were included in Pittas et al. and contributes decisively to the substantial heterogeneity (I^2=83%) of the meta-analysis, which drops to I^2=0% for the primary outcome when the Magalhães study is removed.

The previously discussed example may be considered extreme; nevertheless, it must be noted that all available meta-analyses are plagued by a high heterogeneity with respect to their primary outcomes (I^2 = 49%-93%). This makes it impossible to label N-acetylcysteine supplements as anything more than a "promising supplement" among the over-the-counter supplements with purported antidepressant effects, specifically a "promising supplement" for the rather small group of individuals (ca. 2.4% of the population) [158] with bipolar disorder. Future clinical studies will hopefully help us identify whether other groups of people with depression can benefit as well. Pertinent clinical evidence may also enable us to determine for whom NAC supplements are most useful and whether practical relevant effects can also be observed in healthy, nonclinically depressed individuals looking for improvements in mood during particularly stressful chapters of their lives.

Warnings about *NAC*

N-Acetylcysteine has been found to be well tolerated. N-Acetylcysteine does not cause adverse reactions

with daily doses up to 800 mg (by mouth). Mild adverse effects such as nausea, vomiting, and heartburn and musculoskeletal complaints such as back and joint pain are possible.[159][154]

N-Acetylcysteine currently does not have any known drug interactions.[159]. Some studies have shown that N-acetylcysteine may interact with nitroglycerin. Nitroglycerin can dilate blood vessels and increase blood flow. N-Acetylcysteine enhances the pharmacological effect of nitroglycerin, causing low blood pressure. In conclusion, avoid this combination or use it with caution.[160][161]

N-Acetylcysteine has an anticoagulant and platelet-inhibiting effect. People with bleeding disorders, who are undergoing surgery, or who are taking blood thinning medications may want to avoid N-acetylcysteine because it could increase the risk of bleeding.[162][163]

In instances of acetaminophen poisoning, N-acetylcysteine should be avoided in the presence of coma or vomiting or if activated charcoal has been given by mouth.[164]

How to take *NAC*

Take 1–3 grams of plain N-acetylcysteine per day for 8–24 weeks. To avoid gastrointestinal side effects, split the dose into 2 or 3 smaller servings.

Curcumin

What makes *curcumin* a promising supplement

Curcumin is a component of turmeric (*Curcuma longa*). By regulating monoamine neurotransmission, reducing oxidative stress in the brain, modulating hypothalamic–pituitary–adrenal (HPA) axis function, and attenuating neuroinflammation, supplementation with curcumin may reduce symptoms of depression.[165]

Indeed, meta-analyses that examined the effect of supplementation with curcumin on symptoms of depression have generally reported positive results.[166][167] That said, the size of the effect was small to moderate and was statistically significant only in subgroups of participants with *major depressive disorder* (MDD). It's also worth noting that, in one of the meta-analyses, the effect of curcumin on symptoms of depression was statistically insignificant when only trials of high methodological quality were considered.[167]

For the reasons above, curcumin can only rank as a promising supplement.

Warnings about *curcumin*

Curcumin seems to be well tolerated. Some studies have reported a small amount of gastrointestinal-related side effects.[168][169] Rare, individual reports of hepatitis associated with taking turmeric have also occurred.[170][171] The reason for this effect is unclear, but it is possible that it involves contamination (e.g., formulations with a high heavy metal content). It is unclear whether the same concerns apply to curcumin extract, but regardless, it is important to only buy from companies whose products have been tested independently.

Piperine is a potent inhibitor of a variety of cytochrome P450 enzymes, which is one part of what makes it a curcumin enhancer and of potential use for augmenting the effects of other drugs; in other words, it can

reduce the rate of drug metabolism.[172][173][174] However, this property may make some medications more potent and lead to excessive effects. As such, it may be prudent to talk to a doctor or pharmacist before combining piperine and medications.

The same goes for curcumin itself, which has the ability to inhibit a variety of cytochrome P450 enzymes, albeit to a lesser extent.[172][175]

Curcumin may increase the risk of bleeding by interacting with anticoagulants such as warfarin and with antiplatelets such as aspirin.[176][177] Taking curcumin with diabetes medication such as glyburide may increase the risk of low blood sugar.[178]

Some athletes use curcumin to fight muscle inflammation. In theory, curcumin should have effects similar in nature and potency to those of aspirin, and rodent studies on this aspect are promising, but human studies are needed for confirmation.

How to take *curcumin*

By itself, curcumin is poorly absorbed. Among the methods devised to address the absorption issue, the two most common (and most often tested) methods are to pair curcumin with piperine (a black pepper extract) or to combine it with lipids (such as in BCM-95®). For either of these, most trials have examined daily doses of 500–1,500 milligrams.

To supplement with curcumin + piperine, take 500 mg of curcumin with 20 mg of piperine three times per day (i.e., a total of 1,500 mg of curcumin and 60 mg of piperine per day).

To supplement with *BCM-95®*, a patented combination of curcumin and essential oils, take 500 mg twice per day (i.e., a total of 1,000 mg/day).

To supplement with *Meriva®*, a patented combination of curcumin and soy lecithin, take 200–500 mg twice per day (i.e., a total of 400–1,000 mg/day).

Curcumin is usually taken together with food.

Zinc

What makes *zinc* a promising supplement for medically treated clinical depression only

Zinc is an essential mineral in the human diet and is an indispensable constituent of hundreds of vital enzymes and proteins. Thus, zinc is essential for the proper function of over 300 biological processes in the human body, including fundamental cellular processes such as DNA replication, transcription, protein synthesis, maintenance of cell membranes, cellular transport, as well as in the endocrine, immunological, and neuronal systems.[179] [180] [181]

Recently, there has been increasing scientific interest in the role of zinc in central neuronal function and signaling.[182][183] With the emerging consensus that depression is characterized by a severe imbalance

between the main excitatory (glutamatergic) and inhibitory (GABAergic) systems in the brain, researchers generally seem to agree that zinc's inhibitive effect on the NMDA receptors in our brains could explain the antidepressant effects of this essential trace mineral in preclinical and clinical studies.[184][183] Because the majority of these trials were conducted with zinc as an adjunct to conventional therapy with antidepressants, scientists can only speculate that the provision of zinc alone may have mood-enhancing and antidepressant effects as a standalone treatment and/or in nonclinically depressed individuals.[185]

The results of 2 recent meta-analyses, in the previously mentioned group of medically treated individuals with moderate to severe depression, are generally promising.[186][187] However, because their authors rely on the same, very limited evidence base, even the usefulness of coadministering zinc with antidepressant drugs must still be considered preliminary. Moreover, the additional effect of zinc supplements seems to be rather small.

In a methodologically solid (preregistered, followed PRISMA and PICOS standards) 2021 meta-analysis of 5 randomized clinical trials with durations ranging from 10 to 24 weeks, da Silva et al. reported a small beneficial effect of zinc supplements, as evidenced by a standard mean difference of −0.36 (95%CI, -0.67 to -0.04), indicative of a small effect, on the Beck Depression Inventory in 182 adults with clinically diagnosed major depression. That doesn't sound like much, but in 3 of 5 studies, this effect reflected an absolute reduction of the mean BDI score from values of 30 points or more, indicative of severe depression, to scores below 18 which signify a practically relevant alleviation of mild-to-moderate depression that was not observed in the control groups.[188][189][190]

In further subgroup analyses, da Silva et al. were able to show that the effect sizes increased with the average age of the subjects. from nonsignificant, small effects (standardized mean difference/SMD)] of −0.20; p=0.086) in participants below the age of 40 to statistically significant, moderately sized effects in those aged 40 or older (SMD of −0.61; p = 0.010). Whether that result is due to a higher prevalence of zinc deficiency in older individuals remains speculative and will have to be elucidated in future trials. Da Silva et al.'s overall positive results are in line with the observations of the other previously cited meta-analysis, by Donig and Hautzinger,[187] that used the Hamilton Depression Rating Scale instead of the BDI as the primary outcome and included only 3 out of 5 of the papers in da Silva's previously discussed meta-analysis. Their analysis of the data revealed a moderate effect size of g = −0.67 (p = 0.03) in response to supplements that provided 25 mg of elemental zinc per day. With a total study population of 124 participants in 3 clinical trials, the significance of the data remains questionable.

With the existing evidence in favor of mood-enhancing effects of zinc supplements — coming from clinical trials in participants with moderate to severe clinical depression who received the zinc supplements as an adjunct to conventional antidepressant therapy — zinc can be classified as a "promising" supplement only for this rather small group of individuals. Evidence of mood-enhancing effects in the absence of medically treated clinical depression, on the other hand, is lacking.

Warnings about *zinc*

Zinc is considered safe for adults in amounts less than 40 mg per day.[191] When this level of intake is exceeded, nausea, vomiting, stomach cramps, and even diarrhea can occur.[191]

Effects of low, adequate, and high zinc intake

At the same time, insufficient zinc intake can also cause gastrointestinal issues; it's all about balance. If too much zinc is taken — generally, more than 100 mg — for a long time, it can also decrease levels of copper, an important mineral needed for iron absorption and red blood cell formation.[192] Chronic zinc consumption or very high doses over a short period may also decrease the immune response[193] and reduce levels of HDL-C.[191] Zinc can also interact with quinolone and tetracycline antibiotics such as ciprofloxacin and doxycycline.[194][195] Taking zinc along with these antibiotics can reduce the amount of each that is absorbed. To reduce this effect, the antibiotic should be taken at least 2 hours before or 4–6 hours after zinc.[196][197] Other medicines, such as chlorthalidone and hydrochlorothiazide, can increase zinc in urine, so taking these thiazide diuretics could decrease the amount of zinc in the body.[198] Knowing what dietary supplements a person takes is important for doctors and pharmacists so that they can check for any interactions.

Tolerable Upper Intake Levels (ULs) of zinc in milligrams

AGE	MALE OR FEMALE (including pregnant or lactating women)
0–6 months	4
7–12 months	5
1–3 years	7
4–8 years	12
9–13 years	23
14–18 years	34
>18 years	40

Reference: Zinc[191]

How to take *zinc*

To support the medical treatment of clinical depression, take a supplement that provides 25 mg of elemental zinc per day for at least 10 weeks. Although dietary protein enhances the absorption of zinc, avoid taking zinc with foods that are high in phytate, such as nuts, seeds, legumes, (whole) grains, and cereals.[199] Due to their improved bioavailability, water-soluble zinc salts such as zinc sulfate, zinc citrate, or zinc gluconate are preferred over common zinc oxide supplements.[200] Soluble complexes of zinc with amino acids or zinc-chelating peptides from protein hydrolysates, such as zinc histidine or zinc bisglycinate, seem to be even better tolerated,[201][202] but whether this makes a practically relevant difference with respect to zinc's putative beneficial effect on medically treated clinical depression has yet not been evaluated in clinical trials.

Warning: Avoid taking supplements containing significantly more than the previously recommended 25 mg of elemental zinc because high doses of supplemental zinc (> 50 mg/day) have been linked to copper and/or iron deficiency.[203] [204]

In view of zinc's (literally) vital role for human health, it is truly disconcerting that researchers estimate the risk and prevalence of zinc deficiency worldwide at 17%–30%, with higher deficiency rates in lower-income countries and lower rates in higher-income countries such as the U.S., for which scientists estimate that roughly 10% of the population is at risk of zinc deficiency due to zinc intakes that are 50% or more below the recommended dietary allowance (RDA) — 11 mg per day for men and 8 mg per day for women.[205][206][207] Foods that are high in zinc include meat, fish, and seafood. Much smaller quantities of zinc can be found in eggs and dairy products, as well as seeds, nuts, legumes, and whole grains; the high phytate content of grains has yet been suggested to impair the bioavailability (absorption and use) of this essential trace element.[208][209]

SAMe

What makes *SAMe* a promising supplement

S-Adenosylmethionine (SAMe) works with enzymes in a process called methylation — when a molecule in the body needs a methyl group to undergo a chemical reaction, SAMe can provide that group.[210] This affects the function of numerous neurotransmitters, and insufficient methylation has been mechanistically implicated in various neurological disorders, including depression.

Although preliminary trials have suggested meaningful benefits for participants with major depressive disorder,[211][212][213][214] their different methods make it difficult to be confident in these findings. More recent studies have found mixed results, and while one trial found comparable effects with a common antidepressant[215] and two found an augmentation effect when combined with antidepressants,[216][217] other trials haven't found evidence of a significant benefit for the purpose of augmentation or on its own.[218][219] Therefore, although it's entirely possible that SAMe could yield meaningful benefits in some contexts, it is unclear whether it's worthwhile for most people, especially compared with other options within this guide, and more research is needed — particularly, more trials with highly rigorous methodologies.

For these reasons SAMe is only a promising supplement.

Warnings about *SAMe*

SAMe is well tolerated and has adverse effects similar to those of a placebo.[220]. Instances of mania, pruritus, and headache have been reported with the use of 1,600 mg of SAMe.[211]. Mild adverse effects such as headache, anxiety, nausea, and diarrhea are possible.[221][222]

SAMe has been shown to be safe in treating intrahepatic cholestasis during pregnancy.[223] Despite the mild evidence that it could be safe during pregnancy, longer-term information isn't available, so caution during pregnancy is still advisable. SAMe did not cause any adverse events in breastfed infants over 2 months old, which provides limited evidence that it could be safe during breastfeeding, but there isn't enough data to support using it during this stage, so avoid using it during breastfeeding.[224] SAMe should be avoided by individuals with bipolar disease because it appears to increase mania and anxiety.[225][226] SAMe should also be avoided by individuals with Parkinson's disease because it decreases the effect of levodopa.[227]

How to take *SAMe*

Before using any supplements, *consult with a physician* — especially if taking pharmaceuticals that mediate serotonin.

Take 800 mg of *SAMe* twice per day* (i.e., 1,600 mg/day), with or without food. Starting with a small dose (200 or 400 mg) and gradually increasing it over the course of weeks may reduce the likelihood of side effects.

Magnesium

What makes *magnesium* a promising supplement

Magnesium is an essential dietary mineral that acts as a coenzyme (an activator) for several hundred different enzymatic reactions, many of which are critical for proper functioning of the central nervous system.[228] Interest in magnesium for mood disorders stems from evidence from observational studies that people with depression have lower serum magnesium levels,[229] and diets with higher (adequate) magnesium intake are associated with a reduced risk of depression.[230]

Preclinical evidence in animals indicates that magnesium may have beneficial effects on mood and depression through several mechanisms, such as inhibiting NMDA receptors in the brain (thus modifying glutamatergic neurotransmission), increasing *brain-derived neurotrophic factor* (BDNF) levels, regulating hypothalamic–pituitary–adrenal (HPA) axis activity, and modulating monoaminergic neurotransmission.[231][229] Also, because magnesium deficiency is linked to increased levels of inflammation and oxidative stress,[228][232] magnesium may have protective effects against depression by keeping inflammation and oxidative stress at bay.

Only a few studies have investigated the effect of supplemental oral magnesium on mood and depression, and this small group of studies have used heterogeneous study designs. Two studies in participants with depression reported that supplementing with magnesium improved depression symptoms and increased serum magnesium levels, compared to a placebo.[233][234] In addition, a study in older adults with type 2 diabetes and newly diagnosed depression found that supplemental magnesium was as effective as imipramine for improving depression symptoms.[235]

Similarly, the results of a study in women with obesity and mild-to-moderate depression also suggested that supplementing with magnesium reduced depression symptoms to a slightly greater extent than a placebo.[236] However, there are a couple of limitations worth noting, namely, that the participants were vitamin D deficient and that the trial was not statistically powered to detect differences in depression symptoms between groups.

Supplemental magnesium may also have beneficial effects on mood outside of people with depression, as evidenced by improvements in negative affect in women with premenstrual syndrome.[237] In contrast, a study in postpartum women without depression reported that supplemental magnesium did not affect depression symptoms.[238]

Concerning the effectiveness of supplemental magnesium as an adjunct therapy to antidepressants, one study reported that supplemental magnesium did not enhance the effectiveness of antidepressant therapy.[239] However, a potential limitation of this trial was that there were no differences between groups for changes in serum magnesium levels.

The limited evidence available suggests that supplemental magnesium has a beneficial effect on depression symptoms in people with depression, particularly when serum magnesium levels are low. However, more studies are needed to strengthen confidence in these findings. As a result, magnesium is ranked as a promising supplement as of 2023.

Warnings about *magnesium*

High doses of supplemental magnesium can cause diarrhea and general intestinal discomfort;[240] fortunately, magnesium obtained via food has not been seen to cause such problems.[240] Magnesium is excreted through the kidneys, and therefore, excess magnesium that is present in food and beverages is usually removed via urine. However, magnesium in dietary supplements and medications should not be consumed in amounts greater than 350 mg daily for adults. Excessive intake of magnesium has primarily been shown to cause diarrhea; however, other mild gastrointestinal effects such as nausea and abdominal cramping have been reported as well. Similar to other supplements, magnesium can also interact with other medications. For example, diuretics (e.g., hydrochlorothiazide can also increase or decrease magnesium.[241] Medications used to treat osteoporosis (e.g., bisphosphonates)[242] and also antibiotics (e.g., quinolones[243] and tetracyclines[244]) are not well absorbed when high amounts of magnesium are consumed, and thus their doses should be separated. High doses of zinc may also interfere with the absorption abilities of magnesium and should be separated as well.[245] Therefore, it is important that doctors and pharmacists should be informed about all dietary supplements, for safety.

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.[240]

How to take *magnesium*

Before considering a magnesium supplement, it's prudent to determine whether it is actually needed, which involves checking total serum magnesium or red blood cell magnesium levels. If magnesium levels are inadequate, then diet should be assessed to determine whether it's feasible to increase the intake of magnesium from whole foods. If this approach isn't possible, a magnesium supplement is worthy of consideration.

In studies that have reported positive effects of supplemental magnesium in participants with depression, a dosage of 250 mg of magnesium oxide taken twice per day with meals was most commonly used.[233][234] Further research is warranted to determine whether other forms of magnesium or other dosage strategies produce superior effects. This dosage exceeds the tolerable upper intake of magnesium, and so it is likely not sustainable, and any long-term use should probably be guided by testing of magnesium levels. Long-term magnesium supplementation shouldn't exceed 350 mg per day for people older than 9 years, based on the tolerable upper intake.

Who is more likely to have low magnesium levels?

- *Older people*, because they tend to have relatively low magnesium intakes[246] and may absorb less during digestion.[247].
- *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,*because it has been estimated that in all adult ages in developed countries, hypomagnesemia affects less than 15% of healthy people but up to 50% of people with type 2 diabetes.[248]

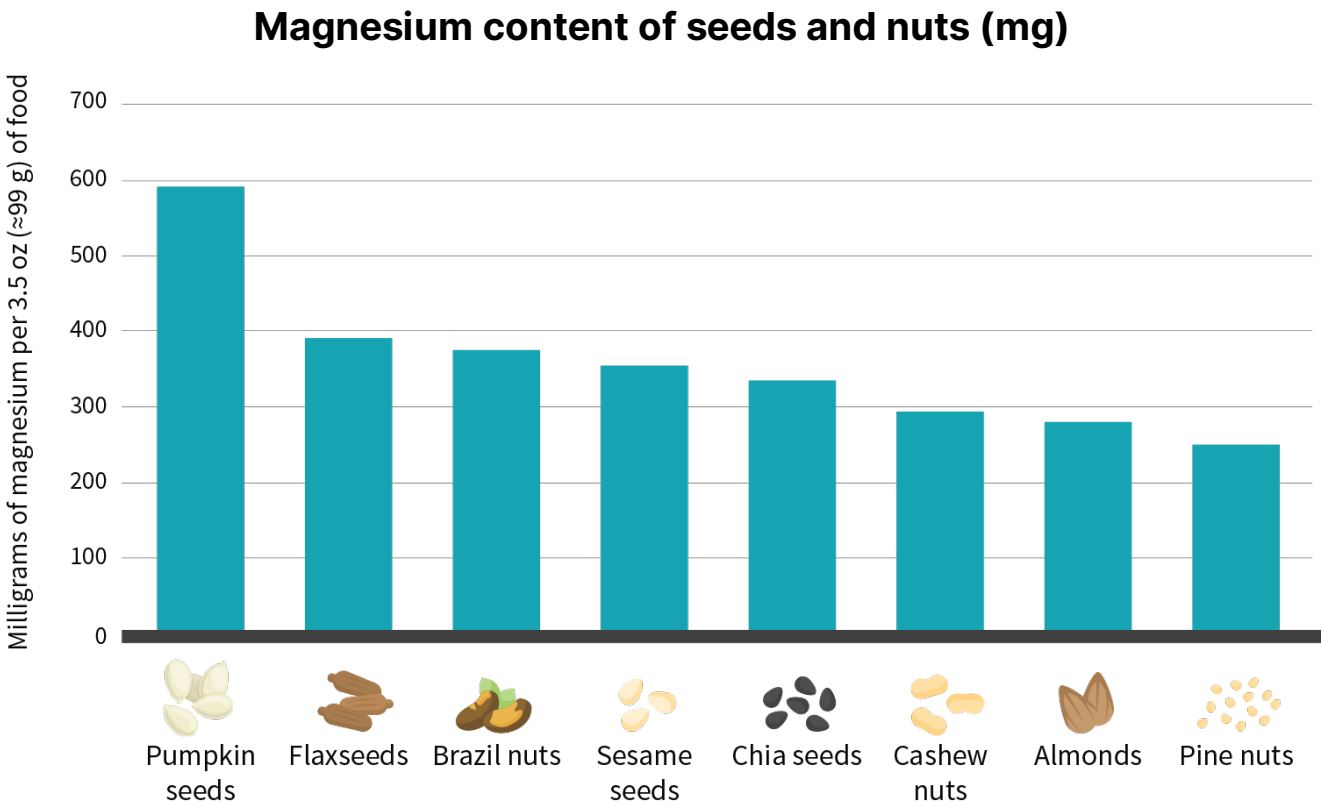
There is no single agreed on and satisfactory method for assessing magnesium status.[249] To get a better sense of typical magnesium intake, an individual should track what they eat for a week. If, on average, a person is getting less than 80% of the Recommended Dietary Allowance (RDA), supplementation becomes an option, but a first step should be 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)



Reference: USDA FoodData Central Database.

Unproven Supplements

Chromium

What makes *chromium* an unproven supplement

Chromium is an essential micronutrient with particular relevance for metabolic health,[250][251][252] In individuals with diabetes, chromium supplements have shown significant insulin-sensitizing effects.[253] Due to an existing relationship between central serotonergic activity and insulin sensitivity,[254] researchers have speculated that chromium supplements may normalize the levels of serotonin and thus trigger significant improvements in mood and alleviate symptoms of depression in both generally healthy and chronically depressed individuals.[255]

Evidence that the previously outlined “chromium-insulin-serotonin” connection holds is still scarce, to say the least. Very few industry-funded studies have reported improvements on various indices for within-group comparisons, but all have failed to detect statistically significant differences in inter-group comparisons. In fact, none of the studies that had a proper control group found statistically significant between-group differences in mood-related and depression-related indices such as the 29-item Hamilton Depression Rating Scale (HAM-D-29) or the Clinical Global Impressions Improvement Scale (CGI-I) in participants with atypical depression or premenstrual dysphoric disorder.[256][257][258] Additionally, evidence of chromium's putative mood-lifting effects in healthy individuals simply does not exist.

As convincing as the chromium-insulin-serotonin connection may sound, scientific evidence that the mere provision of 400–600 µg per day of chromium picolinate can significantly alleviate symptoms of depression — let alone lift the mood of otherwise healthy supplement users — simply doesn't exist. As of fall 2022, the use of chromium picolinate supplements as mood enhancers is thus clearly unproven.

Uridine

What makes *uridine* an unproven supplement

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

Rodent studies suggest that uridine interacts with many neurotransmitters and pharmaceuticals. Although uridine on its own might help with symptoms of depression — as evidenced by one small-scale noncontrolled study [259] — 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*.

Overall, a lack of human studies and long-term safety data means that, as a mood enhancer, uridine is at best an unproven supplement.

Ashwagandha

What makes *ashwagandha* an unproven supplement

Ashwagandha (*Withanian somnifera*) is the most prominent herb used in Ayurvedic medicine.[260] It is considered an adaptogen, meaning that it purportedly enhances the body's resilience to stress. The health benefits of ashwagandha are attributed to the density of bioactive compounds in the plant (predominantly in the roots), most notably a group of steroidal lactones known as withanolides.[261]

Ashwagandha may have positive effects on mood and depression through its antistress effects because stress can cause changes in the brain that have been implicated in the development of many mental health conditions.[262][263] The proposed mechanisms of action for these effects include reductions in inflammation and oxidative stress in the brain and modulation of hypothalamic–pituitary–adrenal (HPA) axis function and GABAergic neurotransmission.[264]

Only a few studies have examined the effects of ashwagandha on depression symptoms, and each of these studies focused on a different population. In participants with reportedly elevated levels of stress, supplementing with ashwagandha meaningfully improved depression symptoms.[265] In contrast, ashwagandha was not found to benefit depression symptoms in people with bipolar disorder.[266] However, depression symptoms (assessed using the Montgomery-Åsberg Depression Rating Scale) were either absent or mild at baseline, greatly limiting the potential for improvement via supplementation.

Ashwagandha might be a useful adjunct to antipsychotics in the treatment of schizophrenia, as evidenced by a moderate improvement in depression symptoms in one study.[267] However, the study was not designed to detect changes in depression symptoms, so the results should be interpreted with caution.

Due to the limited number of studies, as well as heterogeneity in the populations studied, ashwagandha is ranked as an unproven supplement at this time.

Inositol

What makes *inositol* an unproven supplement

Inositol refers to a group of molecules that are structurally similar to glucose. Myo-inositol is the most notable molecule of the bunch, and herefafter, "inositol" will primarily refer to "myo-inositol".

Inositol is naturally present in the body — including in the brain, where levels are much higher than that in plasma[268] — and is obtained through the diet, mostly via consumption of fruits, beans, grains, and nuts.[269] Inositol is mainly of interest for mood and depression because these molecules act as second messengers for several neurotransmitter systems,[270] and some evidence suggests that inositol levels in cerebrospinal fluid and the brain are reduced in people with mood disorders.[271][272][273] Inositol may also provide benefits through its antioxidant properties.[274]

Evidence for the beneficial effects of inositol in improving depression symptoms in people with major depressive disorder is extremely limited.[275] Furthermore, inositol does not appear to be useful as adjunct

therapy to antidepressants in this population.[276][277]

With respect to bipolar depression, inositol has been primarily examined as an adjunct therapy. One study reported no effect of inositol on average depression symptom scores, compared to placebo; however, there was a nonsignificant difference between groups in the number of participants who achieved a 50% or greater improvement in depression symptom scores in favor of the inositol group (50%–67% vs. 30%–33%, depending on the rating scale used).[278] Similarly, a separate study reported that inositol did not affect average depression symptom scores, compared to placebo, but 44% of participants in the inositol group experienced a 50% or greater improvement in depression symptom scores, whereas 0% achieved this feat in the placebo group.[279]

In a study that had participants with treatment-resistant bipolar depression take inositol, lamotrigine (mood-stabilizing drug), or risperidone (antipsychotic drug) as an adjunct therapy, the rate of recovery (defined as no more than 2 symptoms that met the criteria for a mood episode and no significant symptoms for 8 weeks) was similar between groups.[280]

Mixed results have also been reported in women with premenstrual dysphoric disorder, with 1 study reporting that supplemental inositol improved depression symptoms[281] and 1 study reporting no effect.[282]

As of this writing, the available evidence is simply too limited and conflicting to rank inositol beyond an unproven supplement.

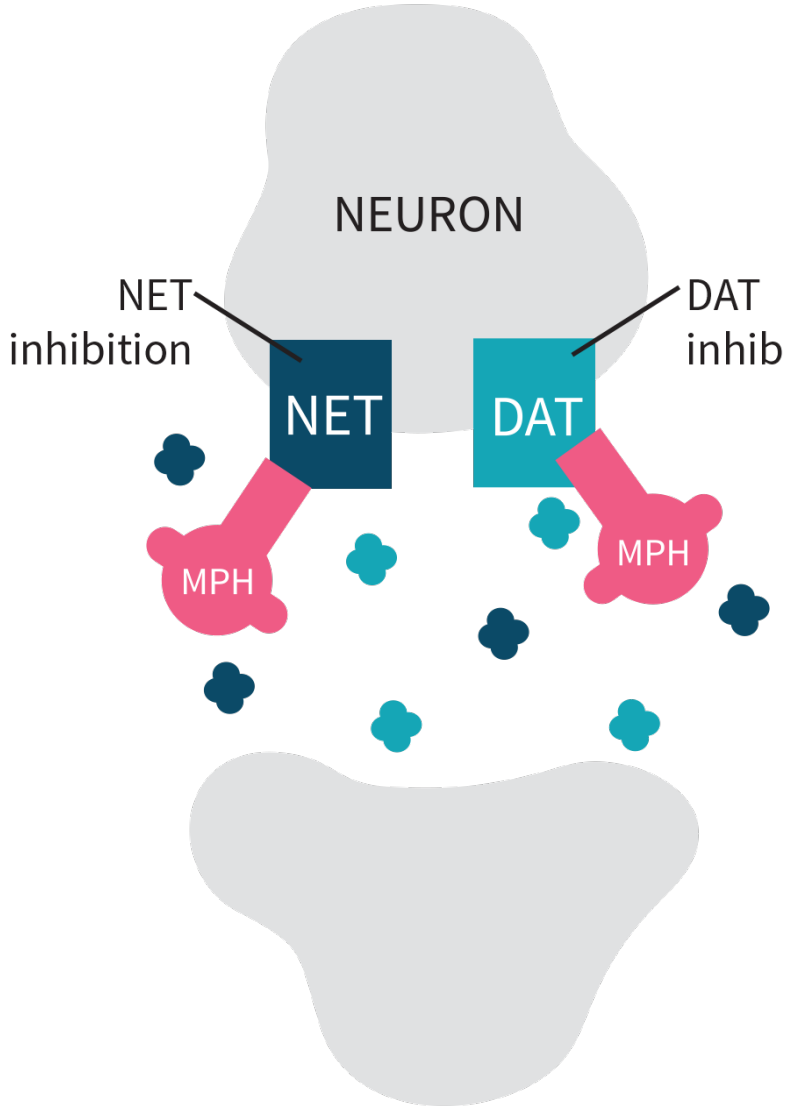
Inadvisable Supplements

Psychostimulants

What makes *psychostimulants* an unproven supplement

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

Mechanisms of action for Ritalin (methylphenidate)



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)

Reference: Wilens. *J Clin Psychiatry*. 2006.[283]

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, if there is 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 and 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 B_{12}.

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 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, "7 mg of zinc (as zinc gluconate)" means 7 mg of elemental zinc (and 43 mg of gluconic acid).

Q. Can I combine creatine and TMG?

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

Q. Will supplementing or consuming turmeric yield the same benefits as curcumin supplementation?

Curcumin is the active ingredient in turmeric that yields many of the benefits currently seen, but both are poorly absorbed in the gastrointestinal tract and usually require some enhancement to increase bioavailability.[284] Typically, a compound found in black pepper, known as piperine, is supplemented alongside curcumin to increase this bioavailability.[285] Other products increase bioavailability by using specialized formulations, such as the use of nanotechnology or a blend of essential oils.

It is unlikely, however, that simply consuming turmeric in small amounts through the diet will yield the same benefits as supplementing large doses of curcumin, due to the small dosage and poor bioavailability. It is also worth noting that turmeric has been found in some studies to be contaminated with heavy metals like lead.[286]

Q. Are curcumin's anti-inflammatory effects responsible for its beneficial effects on depression and anxiety?

Although it is possible that the general anti-inflammatory effects may be at play, it is hard to pin down curcumin's exact mechanism of action because it is a compound that can often result in false positives in mechanistic studies[287] and therefore may mislead researchers into producing false hypotheses.

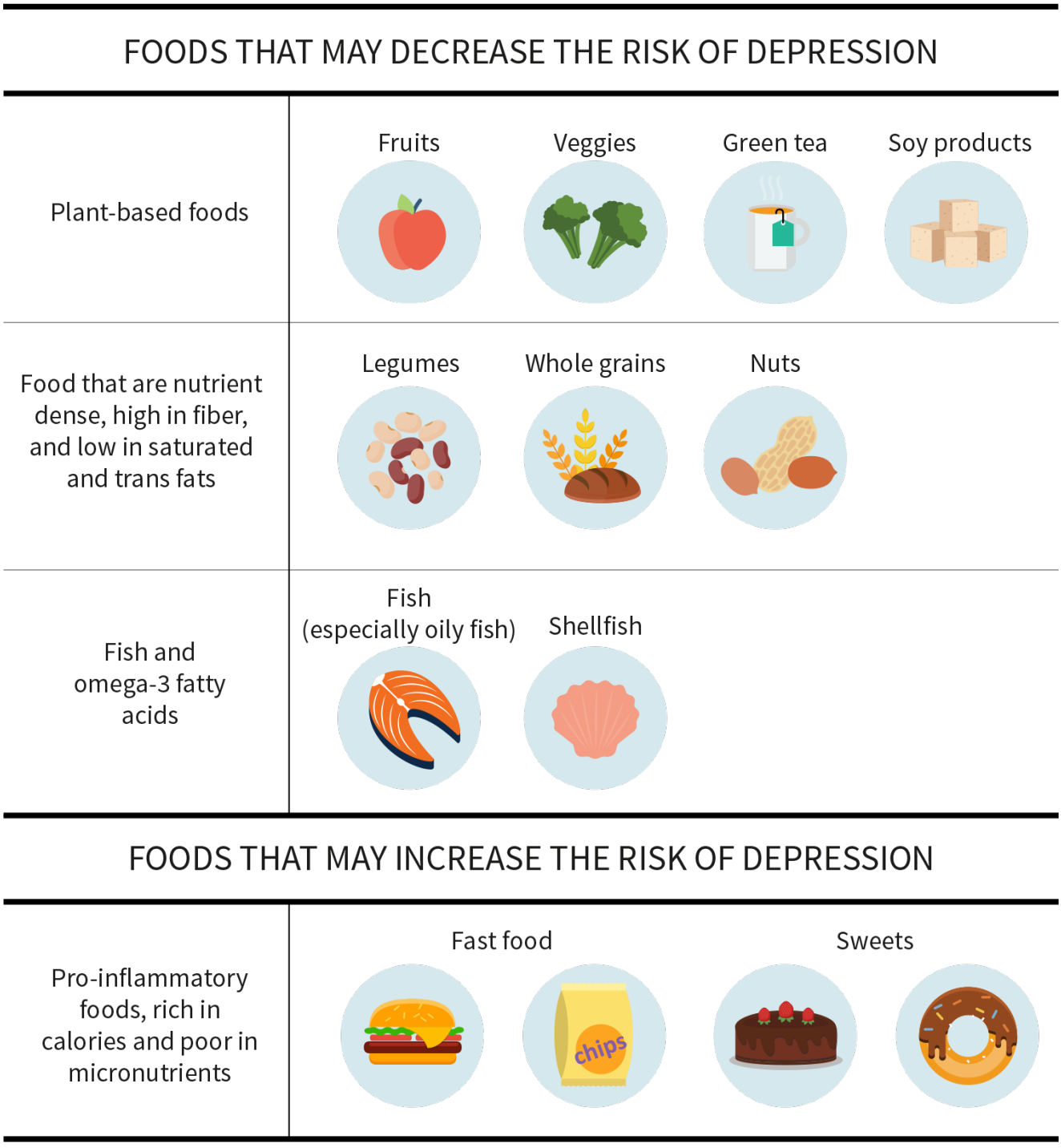
Q. Is there a best diet for depression?

The best way to answer this question would be through head-to-head trials or a network meta-analysis. Unfortunately, this information isn't available yet. However, dietary trends appear to emerge across dietary intervention trials investigating changes in depressive symptoms and several align with a Mediterranean-type diet pattern.

Increases in fruit and vegetables, nuts and seeds, and fish intake appear to be beneficial.[288] In addition, decreases in processed meats, refined carbohydrates, and other highly processed foods have previously been found to be associated with greater mental well-being.[289]

Even though the state of the evidence isn't ideal, there is some evidence that certain food groups, summarized below, may impact the risk of depression.

Foods that are associated with depressive risk



Reference: Opie et al. *Nutr Neurosci.* 2017.[290] ● Phillips et al. *Clin Nutr.* 2018.[289]

Q. How does exercise compare to antidepressant medication or psychotherapy for treating depression?

Exercise seems to compare at least comparably with the current medical standard of care for depression.[291][292] In one clinical trial, researchers randomly assigned 156 moderately depressed men and women to an exercise intervention, medication, or a combined exercise and medication group.[293]

- The *exercise* group walked or jogged on a treadmill for 30 minutes, 3 times per week for 16 weeks.

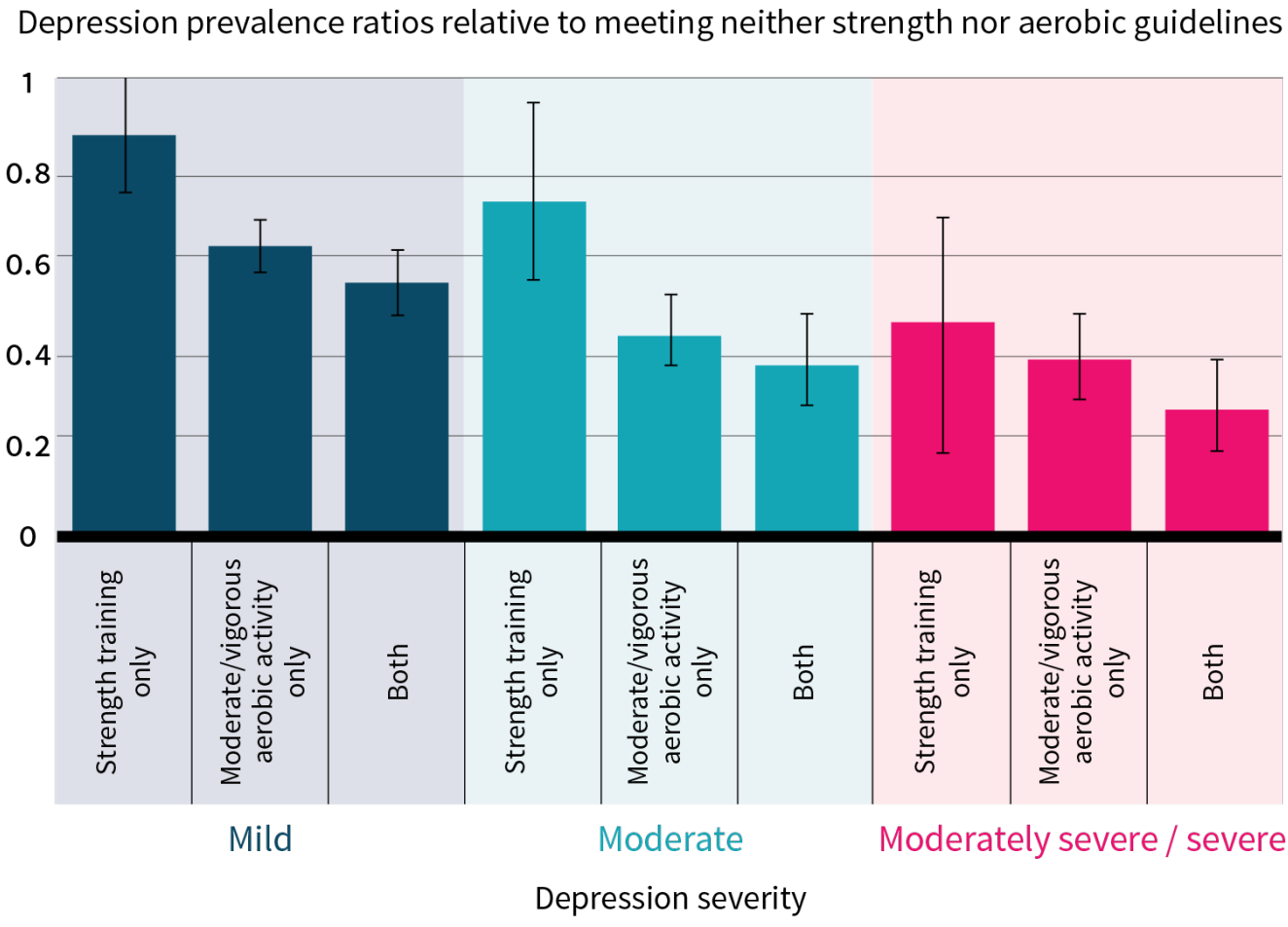
- The *medication* group received the common *selective serotonin reuptake inhibitor* (SSRI) sertraline (Zoloft)
- The *combination* group received the medication and performed the exercise program concurrently.

Results showed that the medication worked more quickly to reduce symptoms of depression, but exercise was equally effective at the end of the 16-week program and created more lasting alleviation of depression at a 10-month follow-up.[294]

Q. Is there a best type of exercise to protect against depression?

A large-scale observational study of nearly 18,000 individuals compared self-reported moderate to vigorous-intensity aerobic physical activity, muscle-strengthening exercise, and a combination of the two.[295] The researchers observed that individuals who met Centers for Disease Control and Prevention (CDC) guidelines for both aerobic and muscle-strengthening exercise[296] had the lowest prevalence ratios for depressive symptom severity. The results can be seen below, which are sorted by depression severity.

Impact of meeting CDC activity guidelines on depression



Reference: Bennie et al. *Prev Med*. 2019.[295]

Despite the considerable number of individual studies on this topic, further work is needed to refine potential recommendations to account for the following:

- Aerobic versus non-aerobic physical activity versus a combination of the two
- Type(s) of physical activity that may confer the greatest benefit
- Differences between men and women

- Differences across age groups
- Severity of the depression
- Comorbidities

Furthermore, it would be helpful to know the minimum duration and intensity of physical activity that still exerts a meaningful level of protection from depression.

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