Examine®

Mood & Depression Supplement Guide

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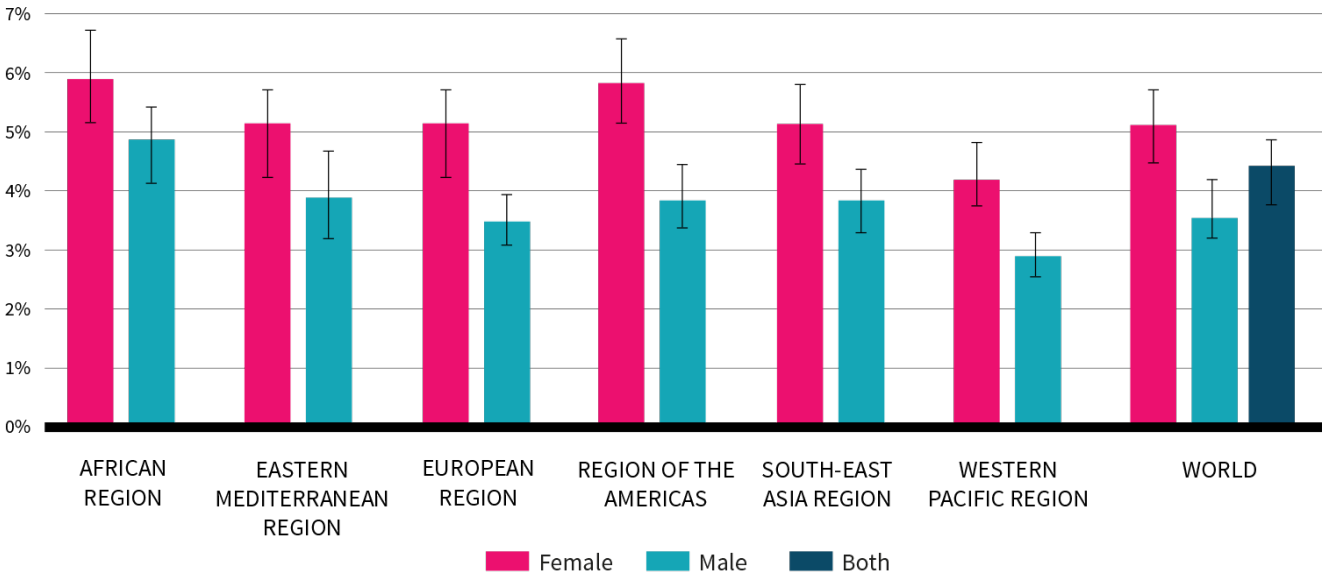
Introduction

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, preventing you from performing normal, everyday tasks. And when it turns very severe or simply lasts too long, it is often classified as a mood disorder.

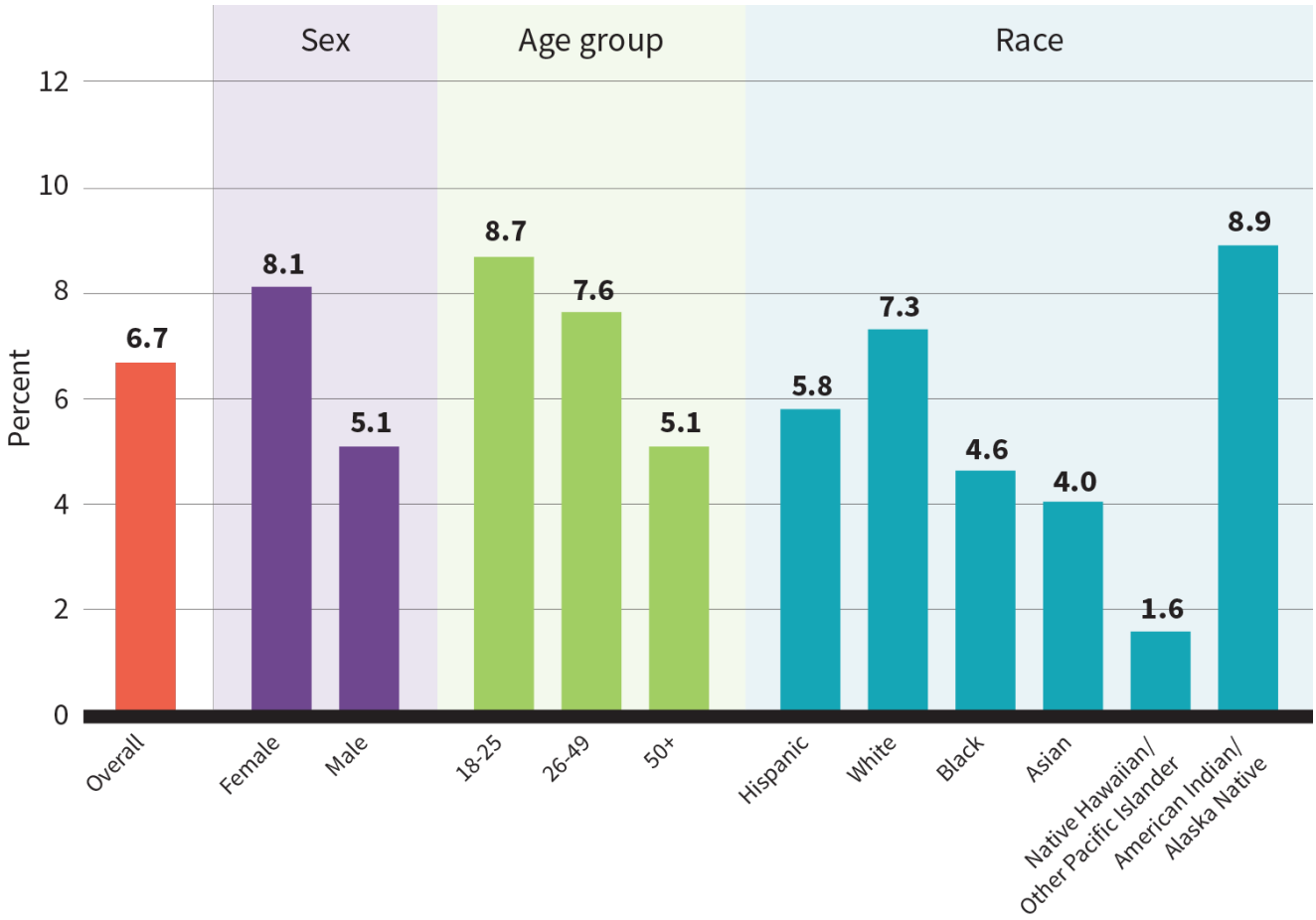
The most common mood disorder is *major depressive disorder* (MDD), a condition that affects nearly 322 million people worldwide[1] and is one of the largest contributors to global disability. The World Health Organization (WHO) estimates that the number of people living with depression increased by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

Despite depression being 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 regarding measurement and diagnoses

Mood disorders are difficult to diagnose, notably because they cannot be assessed *objectively*. To diagnose depression, we have to weigh *subjective* symptoms such as anxiety, fatigue, insomnia, and low 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, while another may suffer from serious anxiety, very little fatigue, and insomnia.

This is especially problematic because questionnaires used to assess depression tend to assign greater weight to the _number _of symptoms than to their *severity*.[6][7] Let's say you answer a 20-item questionnaire and that each item is a symptom you grade 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 (using mathematical models) from observable variables.[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 is about 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-SR$_{*30*}$) is a 30-item questionnaire.[10] Each item is about a specific symptom 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 hard to establish robust, generalizable theories and find treatments that work for everyone. Also, they make it even harder for researchers to take depression seriously. This is worth keeping in mind as we explore theories that have been proposed over the years.

⚠ ***Caution:*** **Don't self-diagnose**

Though diagnosing depression often involves patient-filled questionnaires, it is a much more involved process than our summary suggests, so don't self-diagnose. If you suspect you're depressed, get the opinion of a mental-health clinician or your primary care doctor.

Theories 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 theory was heavily marketed by the pharmaceutical industry, which created several types of antidepressants designed to raise serotonin levels.[14]

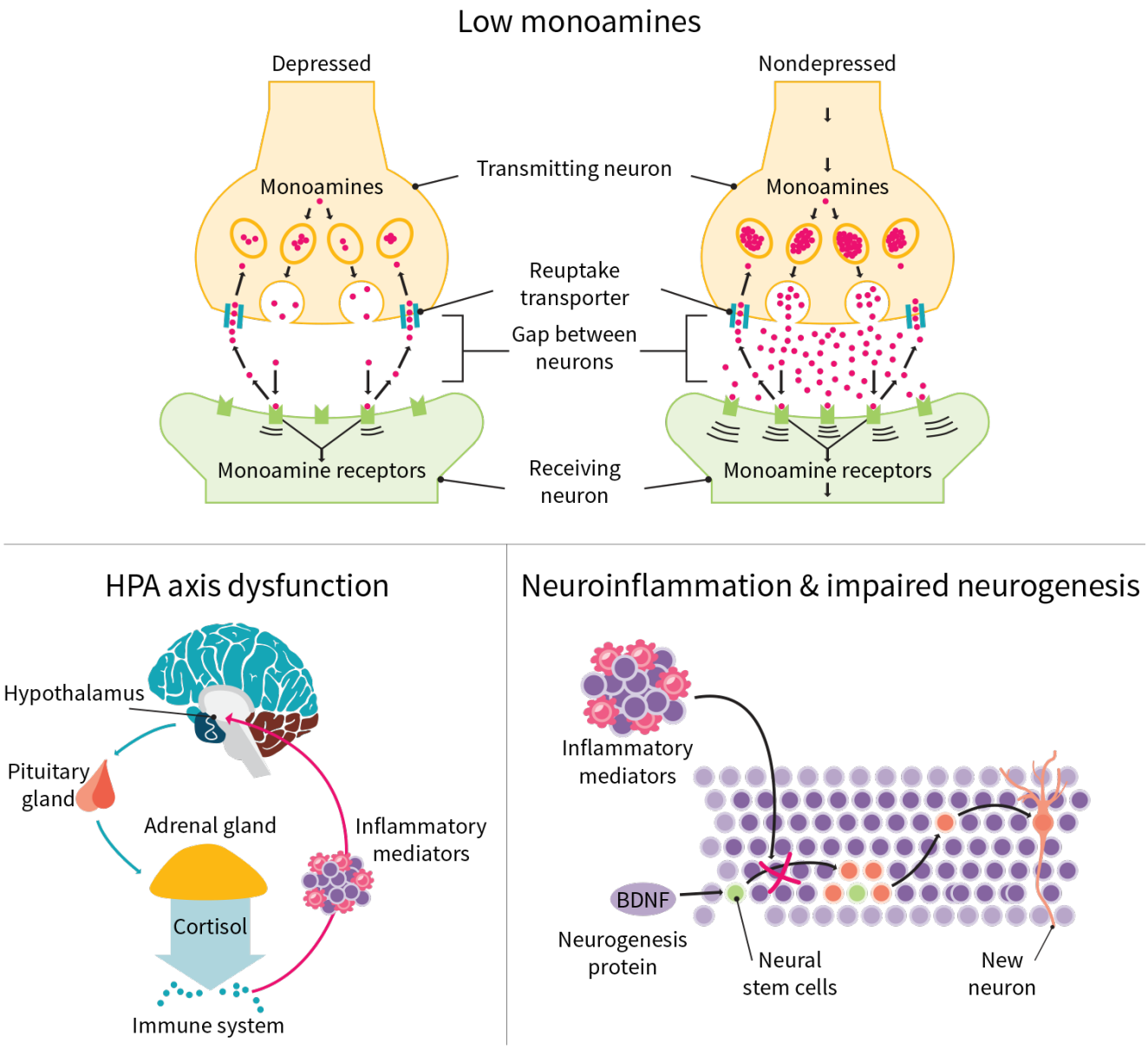
Presynaptic neurons are serotonergic: they produce serotonin, which activates postsynaptic neurons. *Selective serotonin reuptake inhibitors* (SSRIs), by far the most common class of antidepressants, prevent the presynaptic neurons from reabsorbing serotonin, so that more gets absorbed by the postsynaptic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

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

This has led some researchers to posit that antidepressants actually work by other mechanisms 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 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 theories 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, since 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, there have been numerous theories of depression (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 meta-analyzed all the published clinical trials and, using the Freedom Act of Information, obtained unpublished data from pharmaceutical companies; he 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, combining 522 controlled trials, found that antidepressants led to a small reduction in symptoms of depression but was also associated with higher study drop-out 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, due to many of the analyzed trials suffering from poor study design and poor choice of method of statistical analysis, and due to the potential of publication bias[37] (meaning that studies with positive results, being 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 no longer monitored (or at least not in the same way), even though the trial is still ongoing. Therefore, we don't always know if recorded adverse effects persist, lessen, or worsen after the patient 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] While this 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 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**

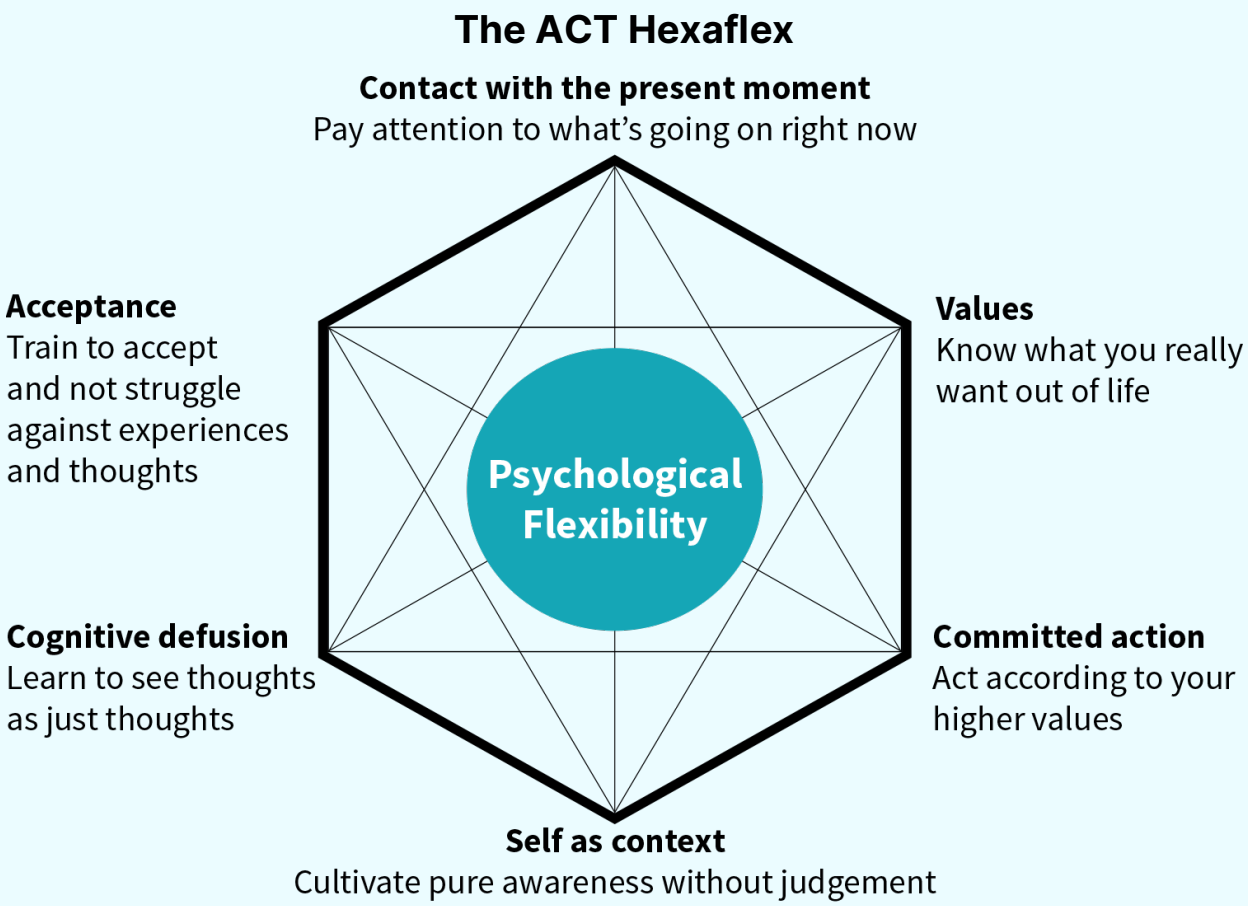
There have been three "waves" of behavioral therapies.

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 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 them 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 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*), in order to emphasize a commitment to action. There are six 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 judgement about trying 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.

Zad Rafi, Researcher
BA in neuroscience

Combos

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

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

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

Core Combo

Three times a day, with or without food, take 400 mg of SAMe (i.e., 1,200 mg/day).

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

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

If your blood plasma zinc levels are adequate or you don't know your levels, 5–20 mg/day of zinc sulfate or gluconate may help maintain your levels in the adequate range, preferably on an empty stomach. If your blood plasma zinc levels are low, 30–40 mg per day of elemental zinc for 2–4 weeks can raise zinc levels to normal, at which point 10–20 mg/day should suffice for maintenance. In case of full-blown deficiency, a medically supervised intervention will be needed.

If these zinc doses cause nausea or discomfort, take the zinc with food that is not rich in phytates (grains, legumes, seeds, and nuts), as they may reduce zinc absorption.

If your blood levels of vitamin D (25(OH)D) are adequate or you don't know your levels, 400 IU (10 mcg) of vitamin D_3 per day may help maintain your levels in the adequate range. If your 25(OH)D levels are low, 800–2,000 IU (20–50 mcg) of D_3 per day is likely to raise them to an adequate level, at which point 400–1,000 IU (20–25 mcg) per day should suffice for maintenance. In case of full-blown deficiency, a medically supervised intervention will be needed.

If you get plenty of sun, you may not need to supplement vitamin D. Similarly, eating foods rich in zinc and foods rich in vitamin D can render supplementation unnecessary, especially on days you don't work out (i.e., on days you sweat less).

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

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

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

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

Specialized Combos

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

After consultation with your physician, add EPA (500 mg) to the core supplements. Additionally, take twice daily 500 mg or either BCM-95 or curcumin.

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

Take St. John's wort (600 mg of an extract containing 3–6% hyperforin and 0.1–0.3% hypericin).

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

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

For people who want to improve their mood and

reduce agitation and irritability:

Take NAC (2,400 mg).

Primary Supplements

SAMe

What makes *SAMe* a core supplement

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

As a supplement, SAMe can enhance the action of *selective serotonin reuptake inhibitors* (SSRIs), which is usually seen as beneficial, although a high enough dose of both SAMe and SSRIs could cause a negative reaction.

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that helps process amino acids. If you have an MTHFR gene mutation, SAMe can still benefit your mood, but it may also cause a "backlog" of a potentially harmful metabolite known as homocysteine. In this scenario, it would be safer to replace SAMe by L-methylfolate (aka levomefolic acid, 5-methyltetrahydrofolate, and 5-MTHF). L-methylfolate is the biologically active form of vitamin B_9 (aka folate).

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

How to take *SAMe*

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

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

Take 1.5–2 g of *trimethylglycine* (TMG) twice or thrice a day (i.e., 3–6 g/day). TMG can be consumed as a powder or simply through foods, notably wheat bran (1,339 mg of TMG per 100 g), spinach (600–645 mg of TMG per 100 g), and beetroot (114–297 mg of TMG per 100 g).

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

Adequate Intake (AI) for choline (mg)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–6 months	125	125	—	—
7–12 months	150	150	—	—

AGE	MALE	FEMALE	PREGNANT	LACTATING
1–3 years	200	200	—	—
4–8 years	250	250	—	—
9–13 years	375	375	—	—
14–18 years	550	400	450	550
>18 years	550	425	450	550

Reference: Institute of Medicine. Choline (chapter 12 in *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*. The National Academies Press. 1998. DOI:10.17226/6015)

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

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

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

Vitamin D

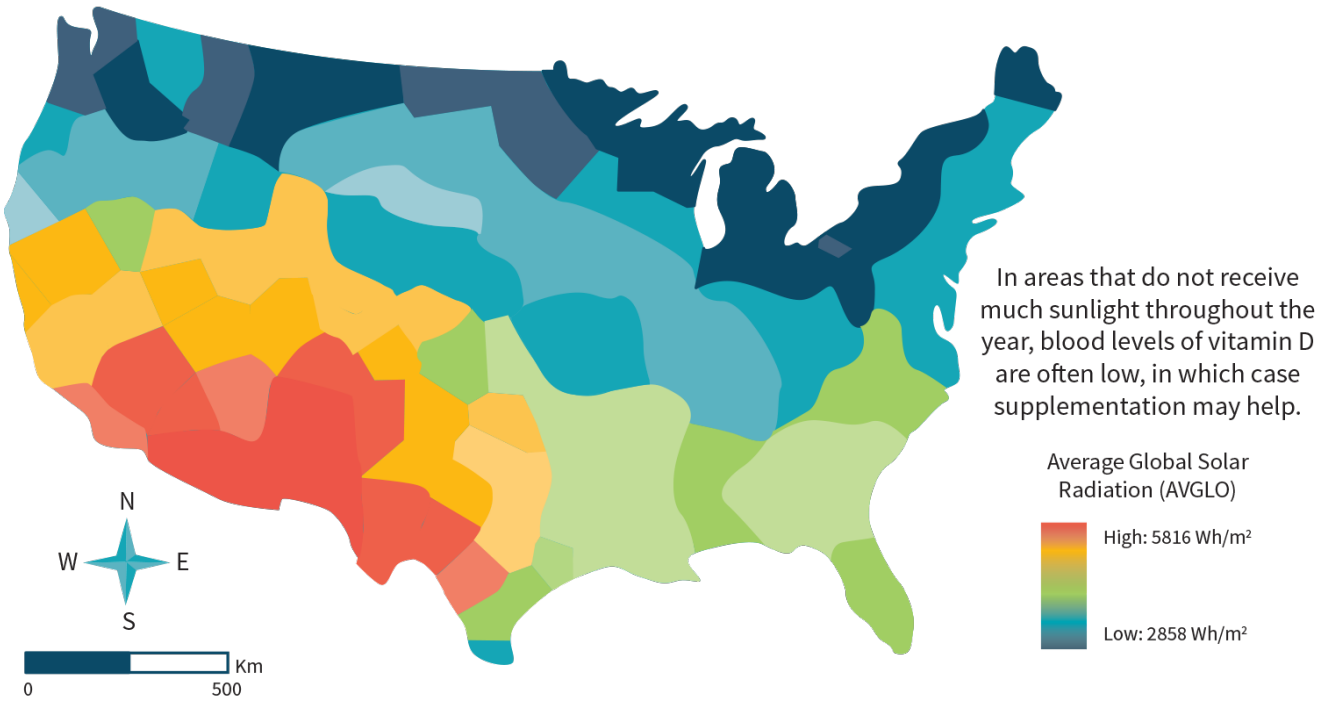
What makes *vitamin D* a core supplement

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 your skin, the longer you need to expose yourself to sunlight to synthesize enough vitamin D, which is why people with darker skin are at an increased risk of suboptimal vitamin D levels.[43]

The situation doesn't improve as you age. The older you get, the less efficient your body becomes at synthesizing vitamin D, the less time you're likely to spend outside, the less vitamin D you're likely to get through food, and the more likely you become to carry extra fat (belly fat has been linked to vitamin D

deficiency).[44][45]

Average yearly sunlight exposure in the US



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

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

Vitamin D is commonly available in two forms. *Ergo*calciferol (D_2) is available in a handful of plants and fungi, whose D_2 content can be increased dramatically when exposed to *ultraviolet B* (UVB) radiation,[46][47] whereas *chole*calciferol (D_3) is synthesized from the cholesterol in your skin when exposed to the sun's UVB rays.[48][49][50]

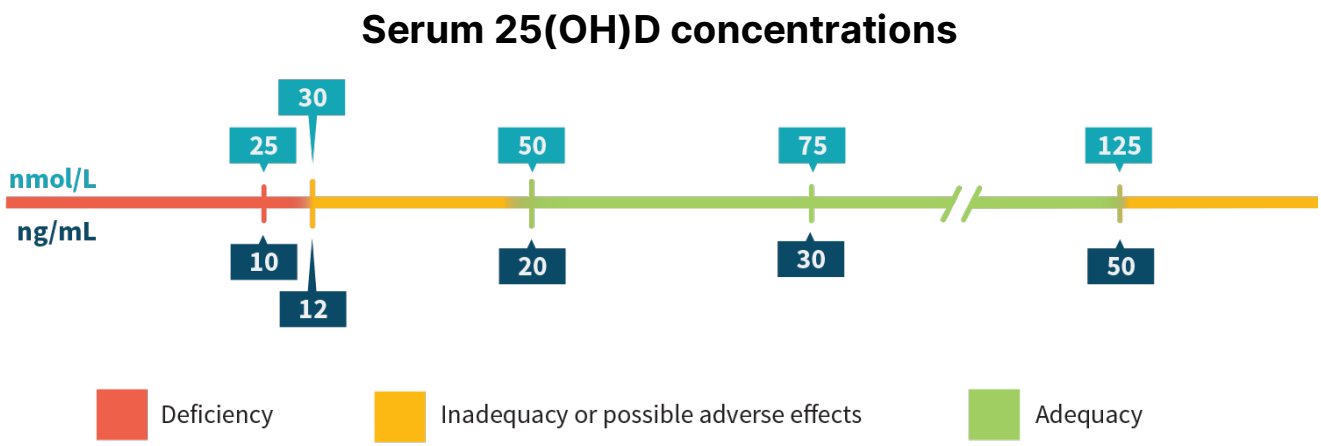
Vitamin D_3 is both more stable and more bioavailable than vitamin D_2. As a supplement, it is usually derived from lanolin, a waxy substance secreted by the skin glands of woolly animals, but a vegan-friendly option (a lichen extract) is also available.

Before turning to supplementation, you should try incorporating some foods rich in vitamin D into your diet. Very few foods, alas, contain appreciable amounts of naturally occurring vitamin D, with fatty fish being a notable exception (cod liver oil, in particular). For that reason, milk is commonly fortified with either D_2 or, more recently, D_3. Why milk? Because milk is rich in calcium, which vitamin D helps your intestines absorb. For the same reason, yogurt, cheese, and breakfast cereal are also commonly fortified with 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, vary by country, based on local laws and policies.

How to take *vitamin D*

First, you should determine if you really need to supplement vitamin D by checking your current vitamin D

levels — your blood levels of 25-hydroxyvitamin D (25(OH)D).



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)

In case of *deficiency*, a medically supervised intervention will be needed. *Do not begin any intervention without discussing it with your physician.* Common medical interventions include taking 50,000 IU (1,250 mcg) of D_2 or D_3 at least three times a week for six to eight weeks, though people with a borderline deficiency may not need as high a dose. At the end of this intervention, if vitamin D levels are above 30 nmol/L (12 ng/mL), a daily dose of 400–1,000 IU (20–25 mcg) is commonly used for maintenance.

In case of *inadequacy*, 800–2,000 IU (20–50 mcg) of D_3 per day is likely to raise vitamin D levels to an adequate level, at which point 400–1,000 IU (20–25 mcg) per day should suffice for maintenance.

In case of *adequate* vitamin D levels, a vitamin D supplement may not be necessary, especially if you spend a lot of time outside and live near the equator. However, taking 400–600 IU (10–15 mcg) of D_3 per day may help maintain vitamin D levels in the adequate range, particularly during the colder, darker months, when you are least likely to synthesize enough vitamin D from sun exposure.

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.

If you do not know your vitamin D levels and cannot get them tested but are still intent on taking a vitamin D supplement, it would be prudent to limit yourself to a maintenance dose of 400 IU (10 mcg) of D_3 per day. Alternatively, you could track your food intake for a week to determine your average vitamin D intake, then select a complementary dose to reach your RDA.

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 mcg | ** Adequate intake (AI) *Reference:* Institute of Medicine. 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:10.17226/13050)

If the maintenance doses in the paragraphs above prove insufficient, as could be the case notably if your BMI is over 30[51] or if you suffer from poor vitamin D absorption or processing (due to a problem with your kidneys, liver, or gastrointestinal tract), you could switch to 1,000–2,000 IU (25–50 mcg) of D_3 per day.

Vitamin D being fat-soluble, it is better absorbed when taken with a fat-containing food or supplement (e.g., fish oil).

Zinc

What makes *zinc* a core supplement

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

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

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

Overt zinc deficiency is actually uncommon in the United States, but it isn't entirely unknown. It has notably been documented in people suffering from malabsorption syndromes — including Crohn's disease, celiac disease, and short-bowel. Furthermore, even healthy people can have *suboptimal* levels — especially the elderly. Finally, since zinc is lost through sweat, athletes should take special care of their zinc intake.

Zinc should be taken with food to prevent potential nausea, but studies observing nausea have used large doses, so it's unclear what risk there is when not exceeding the Tolerable Upper Intake Level (UL) (see table below). Since calcium, iron, magnesium, and zinc compete for absorption, it is better to take them at least one hour apart.

Tolerable Upper Intake Levels (ULs) for zinc (mg)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–6 months	4	4	—	—
7–12 months	5	5	—	—
1–3 years	7	7	—	—
4–8 years	12	12	—	—
9–13 years	23	23	—	—
14–18 years	34	34	34	34
>18 years	40	40	40	40

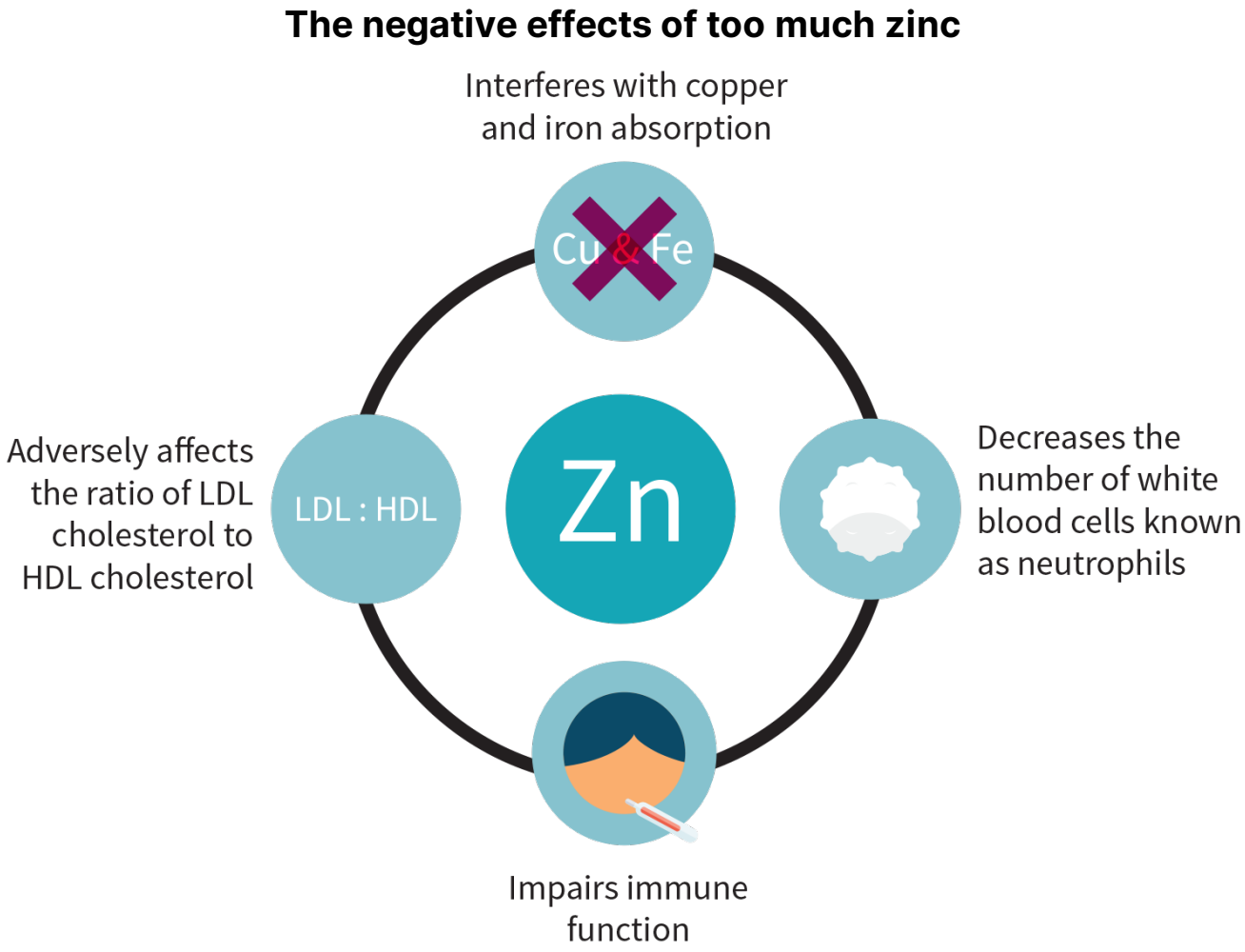
Reference: Institute of Medicine. Zinc (chapter 12 in *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium,*

Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. The National Academies Press. 2001. DOI:10.17226/10026)

Zinc may also impair the absorption of antibiotics, notably the tetracycline (e.g., doxycycline) and quinolone (e.g., ciprofloxacin) classes, so consider taking zinc and antibiotics at least 6 hours apart. Zinc can also impair the absorption of penicillamine, a drug used to treat rheumatoid arthritis, so these should be taken at least 2 hours apart. Thiazide diuretics may increase zinc excretion, thus causing zinc deficiency if taken in the long term.[52]

Excessive intake of zinc can be toxic and cause copper deficiency, and high-dose supplementation increases this risk.[53][54] *Do not exceed the UL for zinc for more than 2 weeks unless under the direction and supervision of a physician.*

Zinc can lower blood sugar and may have additive effects when taken with other supplements or pharmaceuticals that can lower blood sugar, such as antidiabetic drugs.



How to take *zinc*

First, you should determine if you really need to supplement with zinc. This can be done by checking your current blood plasma levels, but this test is not always very accurate,[55] so it can be more practical to track your food intake for a week to determine your average dietary zinc intake.

If, on average, you are getting less than 80% of your Recommended Dietary Allowance (RDA), supplementation becomes an option, though you should first try eating more foods rich in zinc.

If you have high blood sugar or insulin resistance, getting your zinc levels tested may be a better option, as you could have an adequate dietary intake but still have low blood levels.[56]

Blood plasma zinc status

HEALTH STATUS	µmol/L	mcg/dL
Severe deficiency	<4.6	<30
Deficiency	4.6–9.1	30–59
Mild deficiency	9.2–12.7	60–83
Normal	12.8–24.3	84–159
Intoxication	>24.3	>159

Reference: Yanagisawa. *JMAJ.* 2004. Vol:47-9:359–364)

In case of *deficiency or severe deficiency*, a medically supervised intervention will be needed. *Do not begin supplementing without discussing it with your physician first.* Common medical interventions include taking a short-term oral dose of 1–2 mg/kg/day of elemental zinc; for severe deficiency, a short-term oral dose of 3 mg/kg/day may be used.[57][58]

In cases of *mild deficiency*, 30–40 mg per day of elemental zinc for 2–4 weeks may raise zinc levels to normal, at which point 10–20 mg/day may suffice for maintenance.

In people on the *lower end of the normal range* (12.9–16.7 µmol/L, 84–109 mcg/dL), 5–20 mg/day of elemental zinc may help maintain normal levels.

In people on the *higher end of the normal range* (18.6–24.3 µmol/L, 121.5–159 mcg/dL), a zinc supplement may not be necessary, but taking 5 mg/day of elemental zinc may help maintain normal levels.

In cases of *intoxication* (which can cause serious adverse effects), do not supplement with zinc, cease use of any zinc-containing supplements unless specifically instructed to by a medical professional, and consult your physician.

If you do not know your zinc levels and cannot get them tested but are intent on taking a zinc supplement, it would be prudent to limit yourself to a maintenance dose of 5–20 mg/day. If you cannot get your levels tested and have high blood sugar or insulin resistance, take up to 20 mg/day of elemental zinc.

The RDA for zinc for adults ranges from 8–12 mg/day.[59] While the 20–40 mg/day doses discussed here exceed that, they do not exceed zinc's UL of 40 mg/day.[59]

Zinc *sulfate* and *gluconate* are the most researched forms of oral supplementation and are preferred. Zinc *citrate* seems to have comparable absorption to gluconate, whereas zinc *oxide* is less well absorbed.[60] Zinc *picolinate* and *bis-glycinate* may have greater absorption rates than gluconate, but more research is needed.[61][62]

Zinc absorption can be reduced if consumed with foods rich in phytates — namely, grains, legumes, seeds, and nuts.[63][64] If you're unable to take zinc on an empty stomach, the next best way is with some low phytate food.

Greater effects are more likely when baseline zinc levels are lower.

Secondary Supplements

Adaptogens

What makes *adaptogens* a primary option

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

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

Common adaptogens

Panax ginseng | Rhodiola rosea | Withania somnifera (Ashwagandha)

The roots are what is normally used in supplements derived from these plants

How to take *adaptogens*

Rhodiola rosea is commonly taken with food. The usual dosage range for SHR-5 (an extract standardized for 3% rosavins and 1% salidroside) is 80–160 mg.

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

EPA

What makes *EPA* a primary option

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

EPA is a primary option for people suffering from severe (rather than minor) depressive disorders. *Consult with a physician* before using EPA as supporting therapy.

How to take *EPA*

Take 500 mg of EPA.

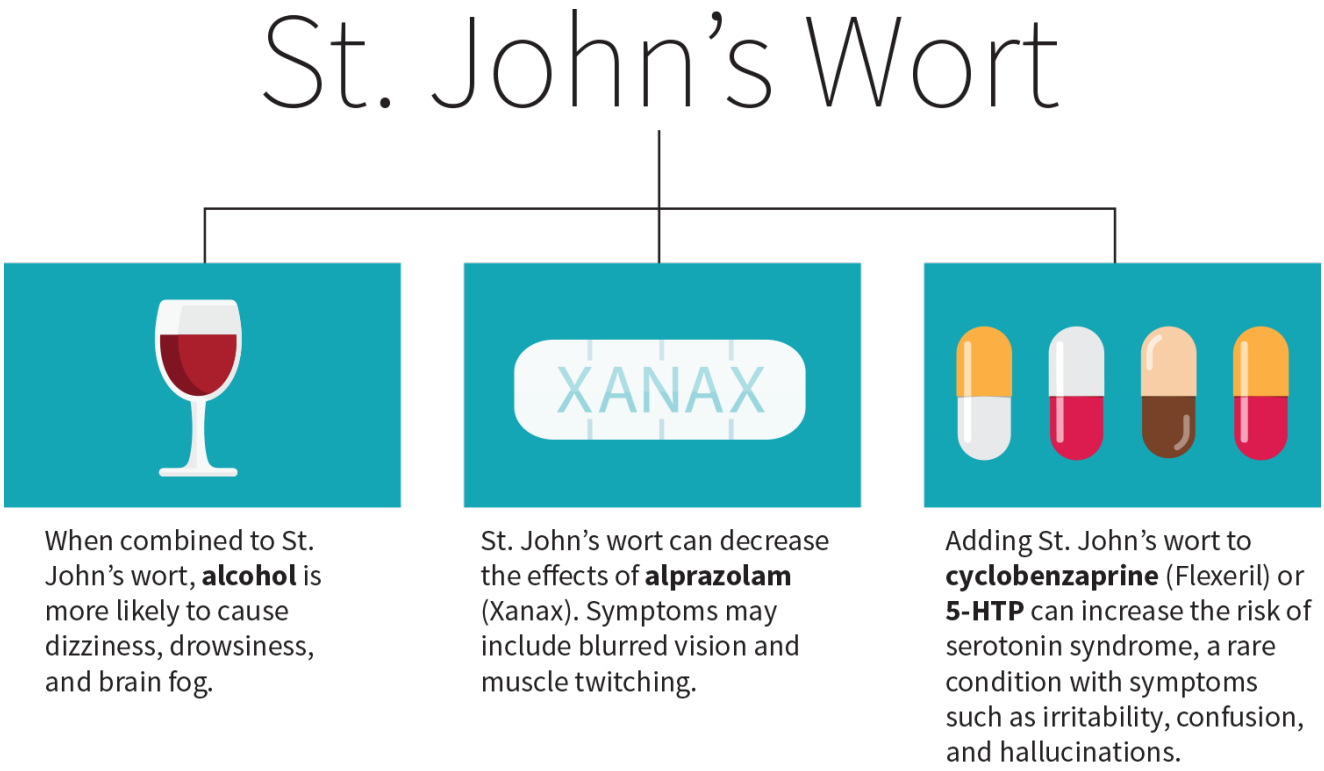
While EPA-only supplements exist, including vegan supplements, EPA is most often consumed as fish oil. Most 1-g fish oil softgels on the markets contain 180 mg of EPA, so 3 such softgels, taken all at once or separately, would make for a daily dose. You can choose to lower your dose on days you consume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

St. John's Wort

What makes *St. John's wort* a primary option

St. John's wort (*Hypericum perforatum*), is one of the best-researched herbal antidepressants. It may be comparable to pharmaceutical alternatives, such as *selective serotonin reuptake inhibitors* (SSRIs), *tricyclic antidepressants* (TCAs) and *monoamine oxidase inhibitors* (MAOIs). St. John's wort is recommended for people suffering from depressive symptoms but not taking medication.

If you take any medication, talk to your physician before supplementing St. John's wort, as it can interact with several pharmaceuticals. Since it can increase serotonin signaling in the brain, it especially should not be taken with serotonin-related medication, such as SSRIs, *serotonin-norepinephrine reuptake inhibitors* (SNRIs), and MAOIs, so as to avoid the risk of overdose. Also, *St. John's wort can render birth control pills ineffective*.



How to take *St. John’s wort*

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

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

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

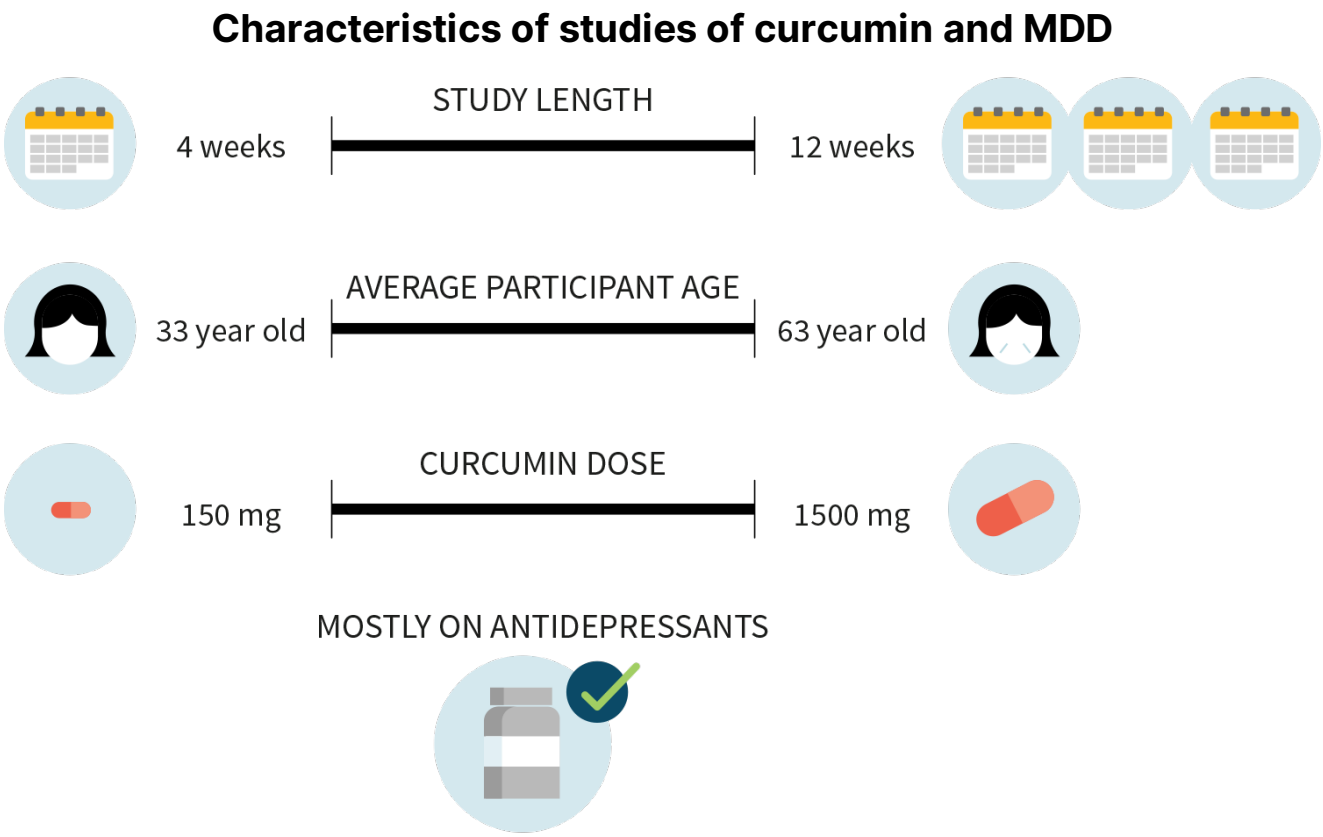
Promising Supplements

Curcumin

What makes *curcumin* a secondary option

Curcumin is a component of turmeric (*Curcuma longa*). It can inhibit the *cyclooxygenase* (COX) enzymes and thus reduce inflammation in the body, so its action is similar to that of *nonsteroidal anti-inflammatory drugs* (NSAIDs).[65] It also may protect neurons from excessive glutaminergic neurotransmission.[66][67][68][69] Both of those are likely influenced on depression.[70]

Curcumin is being studied for use in *major depressive disorder* (MDD), and so far a number of studies generally support its use for reducing symptoms.[71][72][73][74][75][76][77] However, when considering only the best quality trials, the effect is small, and there isn't a great deal of evidence yet.[78]



How to take *curcumin*

For either *BCM-95* (Biocurcumax™) or *curcumin*, take 500 mg twice daily.

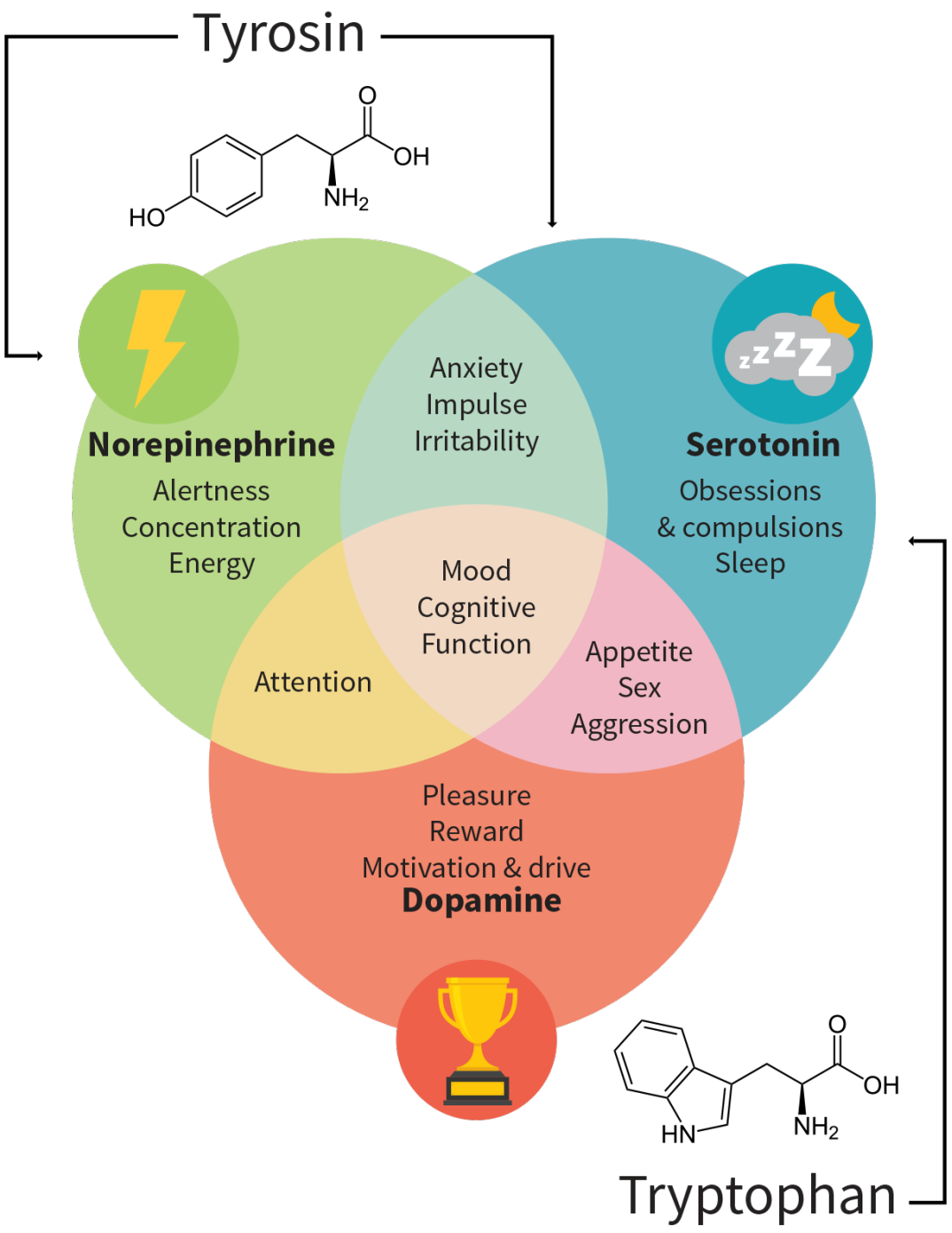
NAC

What makes *NAC* a secondary option

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

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

Select roles of mood-related neurotransmitters



However, NAC has not been directly tested for its effects on people with clinically diagnosed depression, nor for its effects on the mood of people who are not depressed. In addition, it may interact adversely with nitroglycerin, which is used in the treatment of chest pain associated with cardiovascular disease. This

makes two reasons why, as a mood-enhancer, NAC should only be considered a secondary option.

How to take *NAC*

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

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

Unproven Supplements

Uridine

What makes *uridine* a secondary option

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

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

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

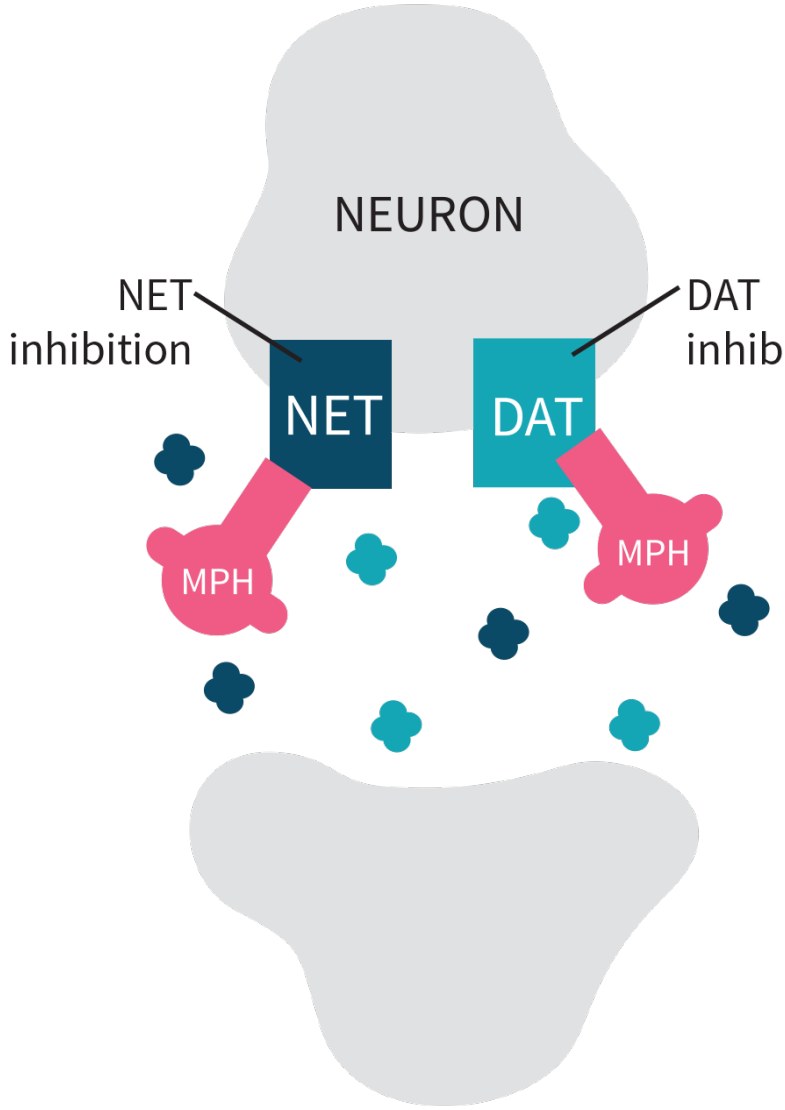
Inadvisable Supplements

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, 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.[79]

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, but also for synergies. If two supplements are synergistic or additive in their effects, you might want to use lower doses of each.

Q. Can I modify the recommended doses?

If a supplement has a recommended dose range, stay within that range. If a supplement has a precise recommended dose, stay within 10% of that dose. Taking more than recommended could be counterproductive or even dangerous. Taking less could render the supplement ineffective, yet starting with half the regular dose could be prudent — especially if you know you tend to react strongly to supplements or pharmaceuticals.

Q. At what time should I take my supplements?

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

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

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

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

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

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

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

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

Q. What's the difference between elemental 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.[80] Typically, a compound found in black pepper, known as piperine, is supplemented alongside curcumin to increase this bioavailability.[81] Other products increase bioavailability by using specialized formulations, such as the use of nanotechnology or a blend of essential oils.

It is unlikely, though, 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.[82]

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

While 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,[83] and therefore, may mislead researchers into producing false hypotheses.

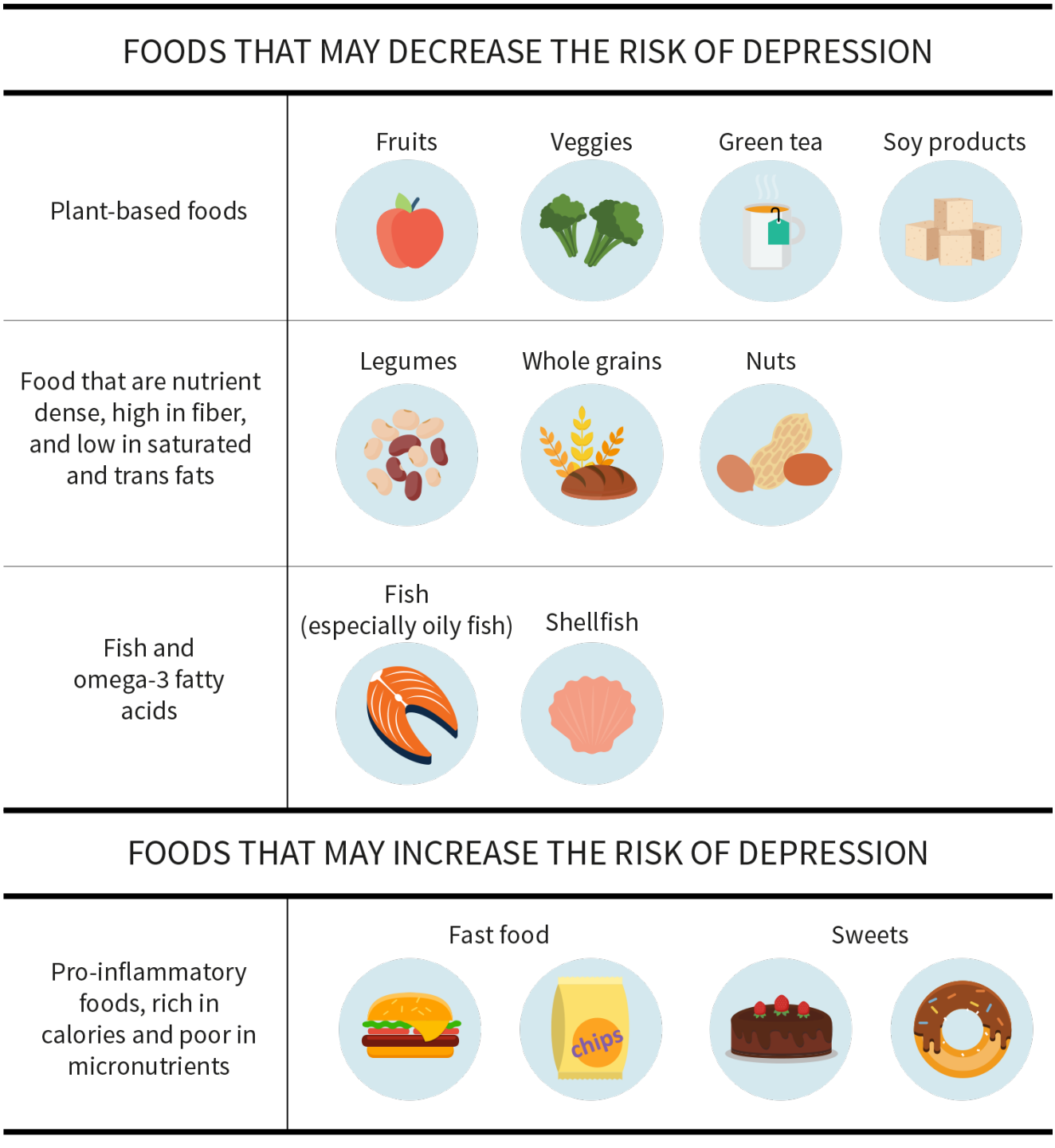
Q. Is there a best diet for depression?

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.[84] 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.[85]

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.[86] ● Phillips et al. *Clin Nutr.* 2018.[85]

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.[87][88] In one clinical trial, researchers randomly assigned 156 moderately depressed males and females to an exercise intervention, medication, or a combined exercise and medication group.[89]

- The *exercise* group walked or jogged on a treadmill for thirty minutes, three times per week for sixteen weeks.

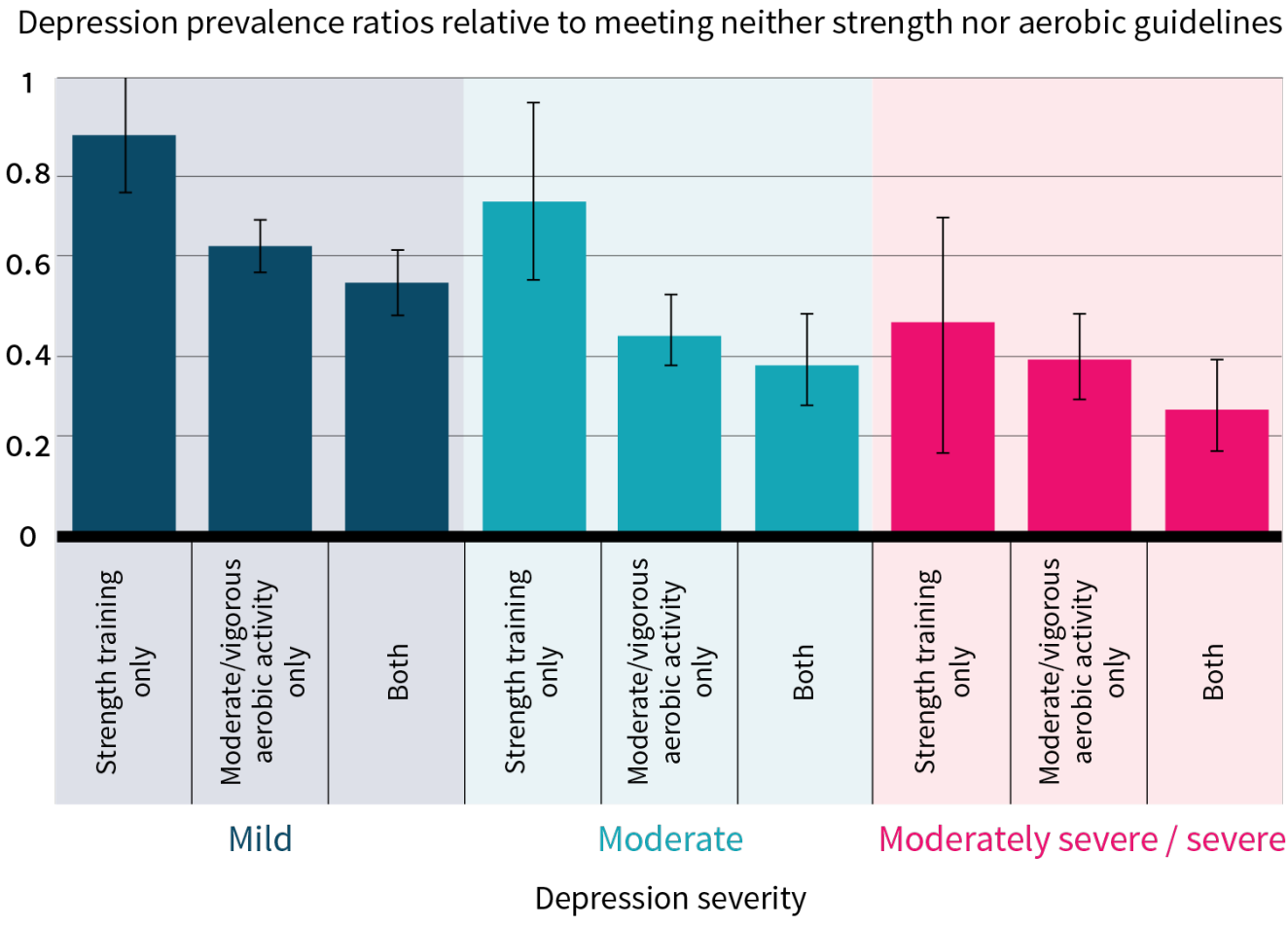
- The *medication* group received the common *selective serotonin reuptake inhibitor* (SSRI) sertraline (Zoloft)
- The *combination* group received the medication and performed the exercise program concurrently.

Results showed that the medication worked more quickly to reduce symptoms of depression, but exercise was equally effective at the end of the sixteen-week program and created more lasting alleviation of depression at a ten-month follow-up.[90]

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.[91] The researchers observed that individuals who met Centers for Disease Control and Prevention (CDC) guidelines for both aerobic and muscle-strengthening exercise[92] 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.[91]

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
- The type(s) of physical activity that may confer the greatest benefit
- Differences between males and females

- Differences across age groups
- The 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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