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Millions Led Astray by These Pills, No Better Than a Placebo

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STORY AT-A-GLANCE

- In the U.S. in 2017, an estimated 17.3 million American adults, or 7.1% of the adult population, experienced at least one major depressive episode. The highest rates were reported among those aged between 18 and 25
- In the period of March 30, 2022, to April 11, 2022, 22% of U.S. adults reported symptoms of depression, although it was even higher in 2021: Early in the pandemic depression tripled, from 8.5% just before to 27.8%, then skyrocketed to 32.8% in 2021
- Research suggests major depression may be vastly overdiagnosed and overtreated with antidepressants, and that a majority of those who take these drugs stay on them long-term, which may compromise their health
- Antidepressants double the risk of harm from suicide and violence in healthy adults, increase aggression two- to threefold in children and adolescents, increase risk of suicide and violence by four to five times in middle-aged women with stress urinary incontinence, and double women's risk of a core psychotic or potential psychotic event
- There's a solid and ever-growing body of scientific evidence showing physical exercise is a major key in the successful treatment of depression. Several studies investigating this oft-ignored prescription are reviewed
- A review that examined randomized controlled trials published between 1999 and 2016, and meta-analyses/systematic reviews published between 2009 and 2016, concluded that "exercise is an evidenced-based medicine for depression"

This article was previously published June 20, 2019, and has been updated with new information.

In 2017 the World Health Organization declared that depression was the leading cause of ill health and disability worldwide, and had increased 18% between 2005 and 2015.[1] In the U.S., an estimated 17.3 million American adults, or 7.1% of the adult population, experienced at least one major depressive episode in 2017.[2] The highest rates were reported among those aged between 18 and 25.[3]

In 2021 those numbers changed drastically in the wake of the COVID-19 pandemic, with approximately 280 million people worldwide suffering from depression.[4] In the U.S. in the early months of the pandemic, depression tripled from 8.5% to 27.8%, and then skyrocketed to 32.8% in 2021.[5] It dropped to 22% in the period between March 30, 2021, and April 11, 2022.[6]

Although the confinement of quarantines and the restrictiveness of mandatory masking and vaccination, coupled with job and income losses, admittedly played a part in the sharp rise in depression during the pandemic, questions still abound over whether people are being inappropriately diagnosed, and even more importantly, what the best treatment might be.

With regard to treatment, my review will focus primarily on exercise which, rather overwhelmingly, appears to have a solid scientific basis of support.

Many Are Needlessly Taking Antidepressants

According to one 2013 study,[7] major depression may be vastly overdiagnosed and overtreated. When Dr. Ramin Mojtabai, associate professor at the Johns Hopkins Bloomberg School of Public Health, evaluated the diagnostics of 5,639 participants with clinician-identified depression, he found only 38.4% of them actually met the DSM-4 criteria for a major depressive episode (MDE).[8] Among seniors over the age of 65, only 14.3% met the criteria. Furthermore:[9]

> *"[P]articipants with more education and those with poorer overall health were more likely to meet the criteria. Participants who did not meet the 12-month MDE criteria reported less distress and impairment in role functioning and used fewer services. A majority of both groups, however, were prescribed and used psychiatric medications."*

Mojtabai told The New York Times:[10]

> *"It's not only that physicians are prescribing more, the population is demanding more. Feelings of sadness, the stresses of daily life and relationship problems can all cause feelings of upset or sadness that may be passing and not last long. But Americans have become more and more willing to use medication to address them."*

An earlier 2009 meta-analysis[11] of 41 studies that assessed the accuracy of diagnoses of depression by general practitioners found "GPs correctly identified depression in 47.3% of cases." So, over the years, it appears overdiagnosis is becoming more prevalent and not less.

According to this review, findings suggest "that for every 100 unselected cases seen in primary care, there are more false positives (n=15) than either missed (n=10) or identified cases (n=10)," and that "Accuracy was improved with prospective examination over an extended period (three to 12 months) rather than relying on a one-off assessment or case-note records."

There's a Fine Line Between Depression and Normal

While we must not downplay the seriousness of major depression, we must also not lose sight of the fact that the experience of a wide range of human emotions is normal and healthy.

In a controversial move, the bereavement exclusion[12] — where "clinicians were advised to refrain from diagnosing major depression in individuals within the first two months following the death of a loved one" — which was included in DSM-4, was removed in

DSM-5 in 2013. As noted in the paper, "The bereavement exclusion and DSM-5: An update and commentary:"[13]

> *"The removal of the bereavement exclusion in the diagnosis of major depression was perhaps the most controversial change from DSM-IV to DSM-5. Critics have argued that removal of the bereavement exclusion will "medicalize" ordinary grief and encourage over-prescription of antidepressants.*
>
> *Supporters of the DSM-5's decision argue that there is no clinical or scientific basis for 'excluding' patients from a diagnosis of major depression simply because the condition occurs shortly after the death of a loved one (bereavement). Though bereavement-related grief and major depression share some features, they are distinct and distinguishable conditions.*
>
> *Bereavement does not 'immunize' the patient against a major depressive episode, and is in fact a common precipitant of clinical depression. Recognizing major depression in the context of recent bereavement takes careful clinical judgment, and by no means implies that antidepressant treatment is warranted.*
>
> *But given the serious risks of unrecognized major depression — including suicide — eliminating the bereavement exclusion from DSM-5 was, on balance, a reasonable decision."*

1 in 5 Americans Is on a Psychiatric Drug

The problem with taking an antidepressant to maneuver through difficult emotional territory is that many end up taking them long-term, and many find they can't get off them without suffering debilitating withdrawal symptoms. As noted by Pharmacy Today in April 2018:[14]

> *"Initially, the drugs were cleared for short-term use; but even today, with millions of long-term users, there is little data about their effects on individuals who take them for years …*

> *And yet, it is not clear that everyone who is taking an open-ended prescription should stop. Most physicians agree that a subset of users may benefit from a lifetime prescription, though they disagree on the size of that group."*

According to a 2017 study,[15] 1 in 6 Americans between the ages of 18 and 85 were on psychiatric drugs, most of them antidepressants, and 84.3% reported long-term use (three years or more). Out of 242 million U.S. adults, 12% were found to have filled one or more prescriptions for an antidepressant, specifically, in 2013. In 2021 the U.S. Centers for Disease Control and Prevention reported that 1 in 5 Americans is now on mental health prescription drugs.[16]

"Mental health doctors in South Carolina say they have been treating two main types of mental health disorders during the pandemic: situational depression and neuropsychiatric sequelae," WRXF reported. What's worse, according to WXRF TV in Horry County, South Carolina, a record number of children are also experiencing mental health issues.

Long-term Use Places Life and Limb at Risk

No matter what your diagnosis is, research does show there may be a price to pay for the long-term use of antidepressants. For example, one 2015 study[17,18] found that, compared to perimenopausal women treated with H2 antagonists or proton pump inhibitors (indigestion drugs), selective serotonin reuptake inhibitors (SSRI, a class of antidepressants) raised bone fracture rates by 76% in the first year of use.

After two years of treatment, the fracture rate was 73% higher. In 2017, Canadian researchers warned SSRIs might increase patients' risk of cardiovascular events by 14% and all-cause mortality by 33%,[19] likely due to their anticlotting properties. As noted in the abstract:[20]

> *"We conducted a meta-analysis assessing the effects of ADs on all-cause mortality and cardiovascular events in general-population and cardiovascular-*

patient samples … Seventeen studies met our search criteria. Sample type consistently moderated health risks.

In general-population samples, AD [antidepressant] use increased the risks of mortality (HR = 1.33, 95% CI: 1.14-1.55) and new cardiovascular events (HR = 1.14, 95% CI: 1.08-1.21). In cardiovascular patients, AD use did not significantly affect risks.

AD class also moderated mortality, but the serotonin reuptake inhibitors were not significantly different from tricyclic Ads … The results support the hypothesis that ADs are harmful in the general population but less harmful in cardiovascular patients."

Low Serotonin Theory Demolished, but Antidepressants Go On

Research[21,22] published in 2009 also strengthened the evidence indicating the low serotonin idea is incorrect, finding strong indications that depression actually begins further up in the chain of events in the brain. Essentially, SSRIs focus on an effect of depression, not the cause.

As noted by investigative health journalist Robert Whitaker,[23,24] as early as the 1980s the National Institutes of Mental Health investigated whether or not depressed individuals had low serotonin.

At that time, they concluded there was no evidence that there is anything wrong in the serotonergic system of depressed patients. Drug companies kept running with the low serotonin theory, though, as it justified the aggressive use of antidepressants to correct this alleged "imbalance."

Most interesting is that diagnoses of mental illness seemed to suddenly spike the same year that the Selective Serotonin Reuptake Inhibitor Prozac debuted. In a paper he wrote on the topic, Whitaker said:[25]

"Prozac was touted as the first of a second generation of psychiatric medications said to be so much better than the old. Prozac and the other SSRIs the tricyclics, while the atypical antipsychotics (Risperidone, Zyprexa, etc.) replaced Thorazine and the other standard neoroleptics.

The combined sales of antidepressants and antipsychotics jumped from around $500 million in 1986 to nearly $20 billion in 2004 (from September 2003 to August 2004), a 40-fold increase … [and] the number of disabled mentally ill in the United States … increased from 3.331 million people to 5.726 million … [equal to] 410 people newly disabled by mental illness every day."

The Placebo Response in Depression

According to the 2015 paper,[26] "Depression: How Effective Are Antidepressants?" studies suggest antidepressants may, on average, improve symptoms in 20 people out of 100. (Studies comparing the drugs to placebo found 20 to 40 out of 100 found relief from placebo alone, while 40 to 60 out of 100 reported improvement on an antidepressant after six to eight weeks.)

Several studies have addressed the surprisingly robust placebo response seen in those with depression.[27] For example, a 2002 paper[28] in the journal Dialogues in Clinical Neuroscience noted that, "With its naturally fluctuating course, depression is a highly placebo-responsive condition: Mean placebo response rates in antidepressant clinical trials are 30% to 40%."

In those with mild depression, the likelihood of a positive response to placebo is even higher — as high as 70%.[29] This paper also notes that when a placebo effect is at play, the patient will be more likely to experience a relapse, compared to when a true drug response is responsible for the improvement.

It also cites studies showing the placebo response rate tends to be highest "for women with a single episode of depression (66.7%) and lowest for women with recurrent depressive episodes (13.3%)."

Antidepressants May Do More Harm Than Good

In a 2019 article,[30] Dr. Peter C. Gotzsche, cofounder of the Cochrane Collaboration and the Institute for Scientific Freedom, also points out other factors that can influence study results, falsely making antidepressants appear better than placebo in some studies. He writes:

> *"[V]irtually all trials are flawed, exaggerate the benefits of the drugs, and underestimate their harms … Virtually all patients in the trials are already on a drug similar to the one being tested against placebo.*
>
> *Therefore, as the drugs are addictive, some of the patients will get abstinence symptoms (usually called withdrawal symptoms) when randomized to placebo, even if a wash-out period before randomization is introduced.*
>
> *These abstinence symptoms are very similar to those patients experience when they try to stop benzodiazepines. It is no wonder that new drugs outperform the placebo in patients who have experienced harm as a result of cold turkey effects.*
>
> *To find out how long patients need to continue taking drugs, so-called maintenance (withdrawal) studies have been carried out, but such studies also are compromised by cold turkey effects. Leading psychiatrists don't understand this, or they pretend they don't.*
>
> *Most interpret the maintenance studies of depression pills to mean that these drugs are very effective at preventing new episodes of depression and that patients should therefore continue taking the drugs for years or even for life …*
>
> *The smallest effect that can be perceived as an improvement on the Hamilton Depression Rating Scale is 5 to 6, but flawed trials attain only approximately 3. Several meta-analyses[31] have found that the effect is larger if the patients are severely depressed, but the reported effects are small and below what is clinically relevant for all severities of depression."*

More Health Risks Linked to Antidepressants

Gotzsche also summarizes some of the known harms of these drugs, citing research showing antidepressants:

- Double the risk of harm from suicide and violence in healthy adults. According to this study,[32] the number needed to treat to harm one healthy person was 16
- Increase suicidality and aggression two- to threefold in children and adolescents[33] — "an important finding considering the many school shootings where the killers were on depression pills," Gotzsche says
- Increase risk of suicide and violence by four to five times in middle-aged women with stress urinary incontinence[34]
- Double the risk of a core psychotic or potential psychotic event in women[35]

> *"I have described the dirty tricks and scientific dishonesty involved when drug companies and leading psychiatrists try convincing us that these drugs protect against suicide and other forms of violence,"* Gotzsche writes,[36] pointing out that *"Even the FDA was forced to give in when it admitted in 2007, at least indirectly, that depression pills can cause suicide and madness at any age."*[37]

Whitaker takes it a step further in a commentary he wrote in 2005:

> *"A review of the scientific literature reveals that it is our drug-based paradigm of care that is fueling this epidemic. The drugs increase the likelihood that a person will become chronically ill, and induce new and more severe psychiatric symptoms in a significant percentage of patients …*
>
> *… As with any epidemic, one would suspect that an outside agent of some type — a virus, a bacterial infection, or an environmental toxin — was causing the rise in illness. That is indeed the case here. There is an outside agent fueling this epidemic of mental illness, only it is found in the medicine cabinet."*[38]

Criteria for Major Depression

According to DSM-5 criteria,[39] to receive a diagnosis of major depression, you must:

- Experience five or more of the following symptoms (see symptom list below) during a single two-week period
- At least one of the symptoms must include depressed mood and/or loss of interest or pleasure
- The symptoms must cause you "clinically significant distress or impairment in social, occupational or other important areas of functioning"
- The symptoms must not be related to substance abuse or another medical condition

Major depression symptom list:

Depressed mood most of the day, nearly every day
Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down)
Fatigue or loss of energy nearly every day
Feelings of worthlessness or excessive or inappropriate guilt nearly every day
Diminished ability to think or concentrate, or indecisiveness, nearly every day
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Keep in mind that major depression is typically associated with thoughts of suicide and feelings of deep hopelessness or helplessness, making it critical to recognize and address such symptoms.

If you are feeling desperate or have any thoughts of suicide, please call the National Suicide Prevention Lifeline,[40] a toll-free number 1-800-273-TALK (8255), or call 911, or simply go to your nearest Hospital Emergency Department.

Please note that number may change to a simple 988 in some states very soon, as in April 2022 the U.S. Substance Abuse and Mental Health Administration (SAMSHA) announced a $105 million project to help states and territories switch to the three-digit help number.[41]

What Science Says About Exercise as Treatment for Depression

If antidepressants are not the answer in most cases of depression, what is? There's a solid and ever-growing body of scientific evidence showing physical exercise is a major key in the successful treatment of depression. Here's a short-list of studies and scientific review articles that have investigated this oft-ignored prescription, starting with the most recent:

JAMA Psychiatry 2018[42,43] (a study funded in part by the National Institute of Mental Health) concluded exercise "may have greater efficacy than current approaches that target depressed mood."

Contrary to popular belief, they found that while physical activity affected the participants' mood afterward, their mood did not affect the amount of physical activity they engaged in. This defies the common assumption that depression causes physical inactivity. In fact, the results suggest it's largely the other way around.

Frontiers in Pharmacology 2017[44] addressed the question of whether a comparison between exercise and drug treatment is evidence based, noting that:

> *"The literature on the benefits of exercise for depression is extensive. Nevertheless, two recent reviews focusing on antidepressants vs. other therapies as a basis for clinical practice guidelines recommended mainly antidepressants, excluding exercise as a viable choice for treatment of depression. The aim of this perspective is to analyze the literature exploring the reasons for this discrepancy …*
>
> *[I]t is possible that academics and health care practitioners are skeptical of viewing exercise as medicine. Maybe, there is a reluctance to accept that changes in lifestyle as opposed to pharmacological treatment can alter biological mechanisms."*

In conclusion, they found three randomized controlled trials comparing four months of exercise to the use of antidepressants (two of which involved patients with major depression and one recruited those with minor depression). All of them found that exercise and antidepressant treatment were equally effective.

Of 11 randomized controlled trials comparing exercise as an adjunctive treatment to antidepressants (combination comparisons) against a wide variety of controls, 10 of them found "a significant depressive improvement after the exercise period, and/or that the proportion of patients with a clinical response was larger for the exercise group than the control."

The paper reviews a variety of biological mechanisms by which exercise can benefit those with depression, including boosting BDNF and serotonin and lowering inflammation biomarkers. The authors also point out that:

> *"Two meta-analyses examining the efficacy of exercise as a treatment for major depression concluded that exercise as a treatment for depression can be recommended as a stand-alone treatment or as an adjunct to antidepressant medication, and that exercise can be considered an evidence-based treatment for the management of depression …*

Almost all reviews examining exercise vs. other treatments of depression, including antidepressants, support the use of exercise in the treatment of depression, at least as an add-on therapy …

Based on the present review, which examined most or all RCTs published in 1999-2016, and most or all meta-analyses/systematic reviews published in 2009-2016, it can be stated that exercise is an evidenced-based medicine for depression — at least as an add-on to antidepressants."

Current Opinion in Psychology 2015[45] highlighted the role of inflammation in depression, and how biological markers can help explain how exercise reduces depressive symptoms. As explained in this review:

"There is growing support for the efficacy of exercise interventions for the treatment of individuals who present with mild-to-moderate depression … The present article reviews contemporary theoretical accounts and recent empirical data pointing to neuroinflammatory states and neurotrophin production as possible biomarkers of the antidepressant response to exercise …

Recent research suggests that depressed patients have elevated levels of pro-inflammatory cytokines, with the most reliably observed elevations in Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha) …

Along with the elevated levels of pro-inflammatory cytokines among depressed individuals, several studies show lower than average levels of anti-inflammatory cytokines such as Interleukin-10 (IL-10) and a lack of correlation between IL-10 and IL-6 that typically is present, suggesting there is a dysregulation of the inflammatory system among depressed patients …

Exercise has emerged as an effective strategy to target inflammatory deregulation … For example, acting as a stressor, acute bouts of exercise result in the release of the pro-inflammatory cytokine IL-6 from muscles.

This release of IL-6, in turn, activates the synthesis of anti-inflammatory cytokines such as IL-10 and inhibits release of pro-inflammatory cytokines such as TNF-alpha, suggesting that exercise promotes, in this way, an anti-inflammatory environment.

Similarly, when occurring chronically, exercise (training) reduces the production of pro-inflammatory cytokines such as IL-6 and TNF-alpha and increases the production of the anti-inflammatory cytokine IL-10."

Many other studies support the view that depression is mediated, and perhaps directly caused,[46] by inflammation, especially gastrointestinal inflammation.[47] Cytokines[48] in your blood, and/or inflammatory messengers such as CRP, interleukin-1, interleukin-6 and TNF-alpha are all predictive of[49] and correlate[50] to depression.

In melancholic depression, bipolar disorder and postpartum depression, white blood cells called monocytes express proinflammatory genes that provoke secretion of cytokines.[51]

At the same time, cortisol sensitivity goes down, and cortisol is a stress hormone that buffers against inflammation. Together, these inflammatory agents transfer information to your nervous system, typically by stimulating your vagus nerve, which connects your gut and brain.[52]

In one study,[53] the researchers suggested "depression may be a neuropsychiatric manifestation of a chronic inflammatory syndrome," and that "these findings justify an assumption that treating gastrointestinal inflammations may improve the efficacy of the currently used treatment modalities of depression …"

In this model, depression is the result of your body's attempts to protect itself from an inflammatory response, and involves hormones and neurotransmitters. Depressive symptoms most strongly associated with chronic inflammation include:[54]

- Fatigue
- Psychomotor slowing

- Mild cognitive confusion
- Memory impairment
- Anxiety
- Deterioration in mood that mirrors features of depression

Asian Journal of Sports Medicine 2015[55] looked at "systematic reviews, meta-analyses and large-scale randomized control trials on effects of exercise on depression" to devise recommendations for doctors "who plan to use exercise protocols in depression."

Here, they highlighted 10 different biological effects of exercise known to have a beneficial effect on people with depression. These effects include[56] upregulation or increase in the levels of norepinephrine, serotonin, BDNF, endorphins and endocannabinoids, and a downregulation or decrease in the levels of cortisol, TNF-alpha, IL-1beta, IL-6 and ACTH.

They also note psychosocial effects that have a beneficial impact, such as self-mastery, social interaction and distraction from rumination. According to this evaluation, depressed patients most likely to benefit from exercise are: Under 20 or over 40 years old, have higher education status, untrained, and have mild to moderate depression.

Characteristics of an exercise program most likely to benefit people with depression include: Supervised and/or structured exercise; individually tailored exercise consisting of aerobic exercise and resistance training (or a mix); low to moderate intensity; 45 to 60 minutes per session at least three to four times per week for a minimum of 10 weeks. The authors also encourage physicians to employ a multidisciplinary team, noting that:

> *"It is very beneficial to encourage physicians and exercise specialists to work in collaboration on depression and exercise treatments. It seems that most medical professionals have little or no training in exercise programs*

and exercise specialists are not familiar with the clinical population particularly depressed patients.

Physicians' recommendation is often limited to 'get more exercise' while the exercise specialist may advise physical activities that are not actually useful for patients with depression.

However with a multidisciplinary team, it is possible to prescribe an exercise program more safely, efficiently, operatively, objectively and realistic. Such a multidisciplinary team may include a psychiatrist or clinical psychologist, sports medicine specialist and exercise trainer."

Journal of Clinical Psychiatry 2011[57] concluded 12 weeks of high-intensity exercise led to a 28.3% remission rate in patients who had previously failed to get any relief from SSRIs.

Clinical Psychology: Science and Practice 2006[58] **—** This meta-analysis of 11 studies concluded doctors would be well advised to recommend exercise to patients suffering from depression, anxiety and eating disorders, as the evidence showed "substantial benefit."

Archives of Internal Medicine 1999[59] reported 16 weeks of aerobic exercise was just as effective as Zoloft for the treatment of major depression in older patients.

Consider Nondrug Solutions First

Addressing your nutrition is perhaps the best place to start if you're feeling depressed. Foods have an immense impact on your brain, and eating whole foods will best support your mental and physical health.

Avoiding processed foods, sugar (particularly fructose) and grains is particularly important as it will help normalize your insulin and leptin levels, which is an important

contributing factor to depression. Certain nutrients are also known to cause symptoms of depression when lacking, and specific herbs and nutritional supplements may also help counteract symptoms.

To suggest that depression is rooted in nutrient deficiencies and other lifestyle related factors does not detract from the fact that it's a serious problem that needs to be addressed with compassion and nonjudgment. It simply shifts the conversation about what the most appropriate answers and remedies are.

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