Depression

Clinically proven natural alternatives for treating depression

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Evidence-Based Use of Supplements

ABSTRACT

TDepression is a common and growing problem, the interventions for which are less than optimal. Those who suffer from depression are at increased risk of other diseases as well as suicide. Conventional treatment options are plagued by questionable efficacy and adverse side effects, some of which cause safety concerns. Emerging data point to the potential value of a nutrition-based approach to depression. Here we provide a review of depression and commonly deployed interventions and discuss new data that suggest that nutritional supplements could provide an easy, safe, cost-effective way to prevent and reduce symptoms of depression.

What is Depression, and What Causes It?

Depression is a potentially life-threatening disease that can severely disrupt daily activities, mood, and productivity.1 Recent data on depression in the U.S. have shown that in 2017, approximately 11 million adults suffered at least one major depressive episode that included severe impairment. In the same year, 3.2 million U.S. adolescents between the ages of 12 and 17 had at least one major depressive episode.2

Unfortunately, not only is depression and the suffering accompanying it common, but it can also lead to highly adverse outcomes. For instance, depression increases risk for suicide, even more so than other mental health disorders that are associated with suicidal thoughts and behaviors.3,4

Better treatment has been posed as an important way to prevent depression-related suicide.5 Unfortunately, conventional treatments are limited for several reasons. One factor making treatment challenging is the dynamic nature of depression symptoms, which include low mood, fatigue, and anhedonia, with several other symptoms often present.6–13 Feelings of guilt, sleep disturbances, low self-esteem, suicidal thoughts, gastrointestinal and autonomic issues, and psychomotor disturbances are just some of these symptoms. There are several hypotheses about why and how depression develops, some of which are not mutually exclusive.

The Monoamine Hypothesis

The first major hypothesis to explain depression was described about half a century ago and is known as the monoamine hypothesis.14–16 According to thisview, depression results from a functional deficiency in one or a combination of the monoaminergic transmitters of the brain, which include serotonin, dopamine, and norepinephrine.

The monoamine hypothesis has beensupported by preclinical research demonstrating that presynaptic depletion of serotonin, dopamine, and norepinephrine leads to a syndrome that is reminiscent of depression. Studies on postmortem blood, urine, and cerebrospinal fluid have also been conducted with the aim of proving this hypothesis. Data from these studies have shown that those with major depression are more likely to have reduced central serotonergic turnover.1,17

However, the use of an amino acid mixture that is free of tryptophan and leads to rapid depletion of tryptophan and the lowering of serotonin levels has shown that such monoamine depletion does not worsen symptoms in unmedicated depressed patients or induce symptoms of depression in healthy controls.18,19 These observations suggest that what occurs in depression is not simply an overall reduction in serotonin.

The Molecular and Cellular Hypothesis

Scientists have therefore speculated that the monoamine deficiency that appears to occur in depression may instead result from other disruptions to monoamine transmission, such as from changes to receptors or other elements downstream of the signal transduction cascade.1 The molecular and cellular hypothesis of depression is based on this view and posits that abnormalities in the signal transduction pathways underlie depression.

Though some of the specific mechanisms underlying depression are not fully understood, scientists agree that because all the antidepressant drugs available to those suffering from depression act to, in one way or another, promote the neurotransmission of serotonin, the serotonin and norepinephrine systems must play critical roles in the pathophysiology of depression.20

How is Depression Treated, and are Treatments Safe and Effective?

CONVENTIONAL TREATMENTS

Pharmacological Interventions

Though pharmacological interventions are commonly used to treat depression, the U.S. Food and Drug Administration (FDA) requires that antidepressants come with a black box warning, which is the most severe warning for any prescription drug.21 This warning is necessary because antidepressants are associated with an increase in suicidal thoughts and behaviors, particularly in the early weeks of beginning the drugs. People on antidepressants must therefore be closely monitored for behavior that is consistent with thoughts of suicide.

In addition to increasing the risk of suicide, antidepressants are associated with a variety of other adverse consequences. These outcomes include:

-Potentially fatal interactions with other drugs22–27
-Risk to unborn or nursing babies of mothers using the drugs28–32
-Postpartum risks33
-Difficulty terminating treatment, even when drugs exacerbate depression symptoms34–40

Antidepressants may be used alone or in combination and at a variety of doses. The variability in toxicity is not limited to different classes of antidepressants but it also seen within those classes, which can complicate prescribing strategies.41

The potential benefits and risks of antidepressants vary and are discussed below.

First generation antidepressants

First generation or traditional antidepressants represent the breadth of pharmacological interventions that were available for depression up until the late 1980s.42 First generation antidepressants act to increase concentrations of serotonin, norepinephrine, or both.43 Though they have been widely used, these drugs, which include monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), are also associated with a number of adverse side effects.

Monoamine Oxidase Inhibitors (MAOIs)

The first group of antidepressants that were introduced for the treatment of depression were MAOIs.44–46 Data suggest that these drugs may be particularly effective in treating atypical features of depression, such as overeating and oversleeping. MAOIs include isocarboxazid (also known as Marplan), tranylcypromine (also known as Parnet), and phenelzine (also known as Nardil).47–50

Though in the 1950s, these were the first drugs used for depression, MAOIs are now considered a last resort when no other treatment options have worked.45 The reason for the trend away from MAOIs is their potentially serious side effects. Two consequences of MAOIs are:

Hypertension

MAOIs can cause life-threatening hypertension when they interact with tyramine.43 Commonly referred to as the "cheese effect," these dangerous interactions tend to occur with specific foods and drinks, like cheese, wine, and pickles.51 People taking MAOIs must therefore follow a relatively strict diet.52 These patients also cannot use MAOIs in combination with selective serotonin reuptake inhibitors (SSRIs), another class of antidepressant that is commonly used to combat depression.53

Birth defects

Women who have used MAOIs while pregnant have had children with similar patterns of malformations, which scientists postulate could be due to the drug's vasoactive properties.54

Given the severity of unwanted side effects, newer MAOIs that are used as a skin patch – such as Selegiline (also known as Emsam) – have been developed to attempt to improve MAOI safety.55–63 Nonetheless, MAOIs are not a first line therapy for depression.

Tricyclic Antidepressants (TCAs)

The TCA class of antidepressants tends to be prescribed unless patients' symptoms are resistant to other therapies because these drugs, like MAOIs, are associated with relatively severe side effects. Cognitive impairment is one such risk with TCAs.25 The TCAs on the market include imipramine (also known as Tofranil), protriptyline (also known as Vivactil), desipramine (also known as Norpramin), trimipramine (also known as Surmontil), amitriptyline, and doxepin.64–67

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are a group of drugs that includes sertraline (also known as Zoloft), fluoxetine (also known as Prozac), citalopram (also known as Celexa), paroxetine (also known as Pexeva or Paxil), and vilazodone (also known as Viibryd).68–73 SSRIs are frequently used to treat depression. Though their side effects are generally viewed as more tolerable than those associated with first generation antidepressants, for many patients, they do cause significant undesirable outcomes. These side effects include:

Sexual dysfunction

Data suggest that more than other classes of antidepressants, SSRIs lead to sexual side effects.74 The sexual effects of SSRIs have been shown to extend to fertility, reducing semen quality. Fluoxetine has also been implicated in gonadotoxic effects including reduced sperm concentration and sperm motility.

Some people continue to suffer sexual dysfunction even after discontinuing the use of SSRIs in a condition referred to as post-SSRI sexual dysfunction (PSSD). This condition has been observed to have a severe negative impact on quality of life.75

In addition to sexual dysfunction that may have arisen while taking SSRIs, new side effects can occur even after drug cessation. The most common such effect is a reduction in ability to experience sexual pleasure.76

Risks during pregnancy

There are data that highlight the potential risks of SSRI use during pregnancy, to both the mother and the child.77 Use of SSRIs during pregnancy is associated with miscarriage, premature birth, birth defects, neonatal complications, and neurodevelopmental disorders.78

Some specific issues that may arise in children prenatally exposed to SSRIs include persistent pulmonary hypertension and autism.79,80 Based on evidence that SSRIs cause harm to the fetus, scientists have urged the FDA to reclassify these drugs as Category D drugs (meaning there are data to show adverse effects in humans) rather than Category C drugs (which come with the claim that there are no well-controlled studies in humans) so that the public is more aware of the relevant risks.81

Drug interactions

Like other antidepressants, SSRIs can lead to dangerous drug interactions. In fact, the majority of fatalities that involve SSRIs also involve the consumption of other substances.26 Alcohol appears particularly problematic when combined with SSRIs.24 Nonetheless, SSRIs can also interact adversely with drugs that are used to treat other conditions. One example of such a drug is tamoxifen, which is a hormone therapy that has been used for decades to treat breast cancer.82

*Withdrawa*l

Ceasing to use SSRIs can lead to withdrawal symptoms. SSRI withdrawal syndrome is common and can prevent or delay people from getting off of SSRIs even when they are compelled to because of other adverse side effects. For those who do commit to terminating SSRI treatment,

the withdrawal period can be quite unpleasant.83

In addition to these significant side effects, SSRIs have also been shown to lead to apathy in some patients and to cause other unwanted side effects such as optic neuropathy.25,84

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Similar to SSRIs are serotonin-norepinephrine reuptake inhibitors (SNRIs), which include duloxetine (also known as Cymbalta), desvenlafaxine (also known as Pristiq or Khedezla), venlafaxine (also known as Effexor XR), and levomilnacipran (also known as Fetzima).85 The extent to which people can tolerate SNRIs varies. There are data to suggest that venlafaxine is the least well-tolerated, leading to cardiovascular troubles like hypertension.86

Atypical Antidepressants

There are some drugs for depression that do not fully comply with the criteria for the other drug groupings and so are referred to as atypical antidepressants. These drugs include bupropion (also known as Wellbutrin), mirtazapine (also known as Remeron), vortioxetine (also known as Trintellix), nefazodone, and trazodone.87–95

The relative efficacy of some of the these drugs compared to other antidepressants is debated.88 While there are some data pointing to the potentially cytotoxic properties of some atypical antidepressants, the more common side effects associated with these drugs involve dry mouth, nausea, vomiting, diarrhea, changes in body weight and appetite, and sedation.89,96,97

Non-Pharmacological Interventions

Given the limitations and adverse side effects associated with drugs for depression, there are also a number of non-pharmacological interventions that are commonly applied instead of, or in combination with, antidepressants.

Lifestyle changes

Diet and exercise appear to affect depression. Physical activity has even been shown to improve symptoms of depression at similar rates as antidepressant drugs.98 Recent research into the potential therapeutic impact of physical exercise showed that those with late life depression who were on the SSRI sertraline were quicker to go into remission when they combined their sertraline therapy with exercise.99 Other research has shown that adding aerobic exercise to antidepressant treatment also provides benefits related to cognitive abilities in older patients.100

In addition to a role for exercise in depression, accumulating evidence also suggests that diet may be critical. Specifically, gut microbiota, which are largely influenced by diet, affect behavior and mood, as there is well-established communication between the gut and the brain.101–106 There is therefore growing interest in how microbiota could contribute to depression, and researchers have pointed to gut microbiota as a potential target for preventing or treating depression.107–110

Sugar and gluten are also known to be associated with the experience of depression. Global data have shown that there is a high correlation between national sugar consumption and the annual depression rate.111 Other research has shown that diets high in sugars and refined carbohydrates or alcohol are common in depression.112,113 While the results are mixed, there are also data showing that sugar-sweetened beverages could specifically elevate the risk for depression.113,114

Similarly, research on the impact of gluten on depression has shown that even short-term exposure to gluten can induce feelings of depression.115 These findings have helped to explain why patients with gluten sensitivity feel better when they consume a gluten-free diet even if their gastrointestinal symptoms persist.

Psychotherapy

Psychotherapy refers to treatment that involves talking about depression with a mental health professional like a psychologist or psychiatrist.116–121 There are different types of psychotherapy,such as cognitive behavioral therapy (CBT) and interpersonal therapy, which can be used not only to treat but also to prevent depression.122 Though psychotherapy is highly cost-effective, there are also challenges with this approach. For instance, the generalizability of evidence-based approaches to all demographics of depressed patients and to all types of depression has been called into question.123 In the case of severe depression, the use of psychotherapy tends only to be advised in combination with medication.124

Electroconvulsive therapy (ECT)

Studies on the efficacy of electroconvulsive therapy (ECT) for depression have emphasized the potential for ECT to blunt depression better than antidepressants can.125 During ECT, electrical currents are passed through the brain to influence neurotransmitter activity associated with depression.126–133 This type of therapy tends to be used in patients who do not improve with drugs or who cannot take antidepressant drugs because of other health conditions. While ECT may reduce symptoms of depression, it is also associated with adverse impacts on memory and cognition.134–140

Transcranial magnetic stimulation (TMS)

Like ECT, transcranial magnetic stimulation (TMS) is usually used in those who do not respond to antidepressants. TMS involves stimulating nerve cells associated with depression with magnetic pulses that are delivered through a coil that is placed on the scalp.141 Though TMS may help to reduce symptoms of depression, it has been observed to lead to potentially dangerous events, such as seizures.142 The risk for TMS-related seizures appears to be similar in adults and children.143

How Can We Improve Depression Prevention and Treatment?

There is no ideal, foolproof way to prevent or treat depression.1 A solution for depression should not only be effective and safe but also improve quality of life rather than introduce new problems or limitations. Unfortunately, these types of solutions have not been historically developed or deployed. As a result, depressed patients have the option of going untreated or trying risky or potentially ineffective interventions. Failing to address depression is associated with its own risks, including an increased likelihood of engaging in risky behavior and suffering improper nutrition and sleep.144

We desperately need a new approach to depression. Changes to nutrition offer a solution.

According to the Mayo Clinic, certain nutritional and dietary supplements are sometimes used to treat depression.145 Given the recognition of the importance of gut microbiota in the pathophysiology of depression, some scientists have postulated that probiotics may reduce the risk of depression. Unfortunately, research into this relationship has found no association between probiotics exposure and rates of depression.146

The key to a nutrition-based approach to depression is therefore likely more complex and may require supplements. However, because nutritional supplements are not subject to tight FDA regulation, it can be difficult to determine the true contents of these products and how effective the products may be in combatting symptoms of depression. Indeed, label

inaccuracies related to ingredient doses are a recognized challenge in the supplement industry.147

A reliable supplemental product that is formulated based on evidence of the impact of the included ingredients on the pathophysiology of depression could thus be transformative in the clinical approach to depression. Here we describe key ingredients that could contribute to an effective formulation.

Saffron

Scientists have a significant interest in the impact of saffron, or Crocus sativus L. on depression. Saffron extract has been shown to improve mood in healthy adults and also to be effective in the treatment of major depressive disorder, as well as in major depressive disorder with anxious distress.148–150

Experts have suggested that safranal, the major component of saffron, could account for the ability of saffron to combat depression, so saffron used to combat depression may need to contain a certain level of safranal to be effective.151–153 Safranal has indeed been shown to have strong antioxidant properties and the ability to scavenge radicals.154

More Effective than Placebo

Research has shown that 30 mg of saffron taken twice weekly over a 6-week period is more effective than placebo in reducing symptoms in those with mild to moderate depression.155 Importantly, these results have been replicated by other researchers.156

The effects of larger doses of saffron have also been investigated. One study evaluated 60 adult patients with depression and anxiety compared the impact of 50 mg of saffron versus placebo taken twice daily over the course of 12 weeks.157 According to scores on the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), the daily supplementation with 100 mg of saffron was more effective than placebo in treating depression and anxiety.

A meta-analysis on the effects of saffron on adults with mild to moderate depression demonstrated that saffron is more impactful than placebo in reducing symptoms of depression.158 Similar results were obtained from a meta-analysis on the benefits of saffron in those with major depressive disorder, suggesting that saffron is more valuable than placebo in treating a range of degrees of depression severity.159

Therapeutically Comparable to Antidepressants

Saffron has not only been shown to be superior to placebo in treating depression, but its effects have also been shown to be comparable to those of several pharmaceutical antidepressants.158 Saffron has, for instance, been shown to have effects that are comparable to those of SSRIs such as fluoxetine, citalopram, and sertraline in people with depression.149,160,161

In one study, where adult patients with major depression were given either 15 mg of saffron or 10 mg of fluoxetine twice each day for 8 weeks, results showed that both treatments reduced symptoms of depression to a similar extent.162 The remission rate in both cases was also 25%. Another double-blind randomized trial found that the effects of 30 mg of saffron taken twice daily were similar to the effects of 20 mg of fluoxetine taken twice a day over 6 weeks on those with mild to moderate depression.163

When patients with major depressive disorder have been given either 30 mg of saffron or 40 mg of citalopram daily for 6 weeks, the outcomes have been roughly equivalent.149 Similarly, older people with major depressive disorder experienced a similar reduction in depressive symptoms whether they took 60 mg of saffron or 100 mg of sertraline daily for 6 weeks.161

Valuable for Specific Depression Populations

Certain patient populations are more likely to suffer from mental disorders like depression than others. For instance, the metabolic changes that occur in those with type 2 diabetes can aggravate depression. Research has indicated that saffron can benefit type 2 diabetic patients who suffer from Comorbid Depression-Anxiety (CDA).164

One study on 54 outpatients who had been diagnosed with mild to moderate CDA demonstrated that the symptoms of those who took 30 mg of saffron each day for 8 weeks improved significantly more than those taking a placebo, based on Hamilton Depression and Anxiety measurements, the Pittsburgh Sleep Quality Index, and the Satisfaction with Life Scale.164

Similarly, saffron has been shown to improve depressive symptoms as well as hot flashes in postmenopausal women.165 In women with postpartum depression, saffron has also been shown to improve symptoms more so than placebo based on scores on the Beck Depression Inventory-Second Edition (BDI-II) and the Hamilton Depression Rating Scale (HDRS).165,166 The effects of saffron on postpartum depression have been shown to be comparable to those of fluoxetine.

Works Across Age Groups

Much of the work to elucidate the role of saffron in addressing depression has been conducted in adults. However, a recent study was undertaken to address the question of whether saffron can also help with depression in adolescents.167 Over 8 weeks, researchers treated 12 to16 year-olds with mild to moderate depression or anxiety symptoms with 14 mg of saffron extract twice a day. According to scores on the Revised Child Anxiety and Depression Scale (RCADS), saffron extract improved symptoms from the perspective of the adolescents.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone that is released in response to stress and has been shown to have several health benefits, including helping with mood regulation.168,169 Higher levels of the hormone are associated with lower risk for depression in both men and women,170 and higher serum concentrations of DHEA are associated with a higher likelihood of major depression remission.171 Clinical practice guidelines already recommend the use of DHEA as a third-line depression treatment.172

More Effective than Placebo

For decades, research has been providing data that show that DHEA administration can reduce symptoms of depression. Before the year 2000, it had been shown that 90 mg of DHEA per day over a 6-week period led to a greater decrease in HDRS than did administration of placebo.173 Based on these findings of a double-blind study, researchers suggested that DHEA may provide therapeutic benefits to some patients suffering from major depression.

These results showing the potential value of DHEA in depression have been replicated in different contexts. For instance, one study on midlife-onset major and minor depression found that 3 weeks of 90 mg per day followed by 3 weeks of 450 mg per day improved depression on the HDRS in patients taking no other antidepressant medications, regardless of depression severity.174 Further, a meta-analysis on the influence of DHEA on depressive symptoms has corroborated that the cumulative data on DHEA in depression suggest that DHEA is more effective than placebo in reducing

signs of depression.175

Valuable in Specific Contexts

Interestingly, though ECT can have an anti-depressive effect, preclinical studies have shown that combining this therapy with DHEA abolishes the anti-depressive effect of ECT. This observation suggests that those who are resistant to ECT may have higher basal levels of DHEA and highlights the individual differences in variability in manifestations of depression.176 As such, it is not surprising that specific interventions may provide differential value to specific populations of patients.

Depression Types

A comprehensive review has shown that DHEA may be particularly valuable in mild depression and depression that is resistant to conventional therapies.168 Results supporting this view have been replicated not only in Western populations of patients but also Eastern populations.177

Patient Age

DHEA tends to decline with age, and research that has involved the administration of DHEA to middle-aged and elderly patients with major depression and low plasma levels of DHEA has demonstrated the power of DHEA as an antidepressant.178 Specifically, patients taking 30 mg to 90 mg per day of DHEA over a 4-week period experienced improvements in depression ratings and memory performance that were directly related to their enhanced levels of DHEA.

Clarified Mechanisms

In addition to the observations related to the impact of DHEA on depression, there are also data to help elucidate the mechanisms by which DHEA could confer its benefits. At the cellular level, DHEA appears to provide neuroprotection, promote neurite growth, and act as an antioxidant.179 A recent chapter written on the hormone points to the role of DHEA in neural plasticity and protection against depression and negative emotions. This chapter also highlights the value of DHEA in increasing cognitive abilities like attention and memory.180

Given the compelling evidence for the antidepressant effect of DHEA, neuroscientific studies have been undertaken to elucidate the brain mechanisms that mediate the impact that DHEA has on depressive symptoms. One such study involved administering patients with 400 mg of DHEA or placebo and monitoring resulting brain changes using functional magnetic resonance imaging (fMRI).

Compared to patients taking placebo, those who took DHEA displayed lower activity in the amygdala and hippocampus and enhanced connectivity between these two regions during a test of emotion processing and emotional regulation. These brain changes were associated with lower levels of depressive symptoms. Thus it appears that DHEA may combat depression by inhibiting emotional memory and the generation of negative emotion.169

Rhodiola

Rhodiola, or Rhodiola rosea, is a substance of interest for combating age-related diseases,181 and it has been suggested that rhodiola may be effective in both preventing and treating depression.182,183 Rhodiola has been shown to affect transcription related to mood and behavior, which may account for its potential influence on depression symptoms.184

Reduces Symptoms of Depression

Adult patients with mild to moderate depression have been shown to benefit from 340 mg to 680 mg of rhodiola extract daily when studied over a 6-week period and evaluated with the BDI and Hamilton Rating Scale for Depression (HAMD).185 Similarly, mildly anxious patients taking 200 mg of rhodiola extract twice a day for 14 days reported significant reductions in depression, anxiety, stress, and anger compared to patients receiving placebo.186

Is Well-Tolerated

A study aimed to compare the effects of rhodiola on the selective serotonin reuptake inhibitor (SSRI) sertraline on depression found that rhodiola was slightly less effective than sertraline but also led to fewer adverse side effects.187 A recent review of the relevant literature found that rhodiola may have an antidepressant action in adult humans and that unlike conventional antidepressants, rhodiola extract is well-tolerated and has demonstrated a favorable safety profile in short-term studies.186,188

Saffron and Rhodiola Combination

Based on data showing that both rhodiola and saffron can affect depression, a recent study was designed to test the impact of a fixed combination of these substances in mild to moderate depression.189 Depression was assessed in 45 adults taking a tablet containing 154 mg of rhodiola and 15 mg of saffron twice each day for 6 weeks. The results of this double-blind placebo-controlled study showed that the intervention improved symptoms of depression and anxiety according to the HAMD and the Hospital Anxiety and Depression scale. Perhaps not surprisingly, saffron and rhodiola have also been shown to influence gut microbiota.190,191

Folate

Folate is a naturally occurring B vitamin that is required for the synthesis of chemicals that are implicated in depression, including serotonin, norepinephrine, and dopamine.192 Experts have suggested that an 800 microgram (mg) daily dose of folic acid can be useful in managing symptoms of depression, evidence for which has been collected following observations that people with depression are more likely than those without depression to have low levels of folate.193

Low in People with Depression

A meta-analysis on the relationship between folate and depression showed that people with depression have lower serum levels of folate as well as lower dietary consumption of folate than those without depression.194 Other research has revealed that older people with depression often have low folate levels.195 Research into the prevalence of folate deficiency in those with depression has shown that roughly one-third of people with depression are clinically deficient in folate.196

These findings beg the question of how folate supplementation may benefit these patients. Though studies that address the question of whether supplementing with folate may improve symptoms of depression have led to mixed results, meta-analyses have revealed that the duration of supplementation may contribute to these inconsistent findings.197 Specifically, it appears that short-term supplementation of folate may not significantly reduce symptoms of depression, but long-term use may confer real benefits.

Improves Response to Antidepressants

As low folate levels are not only associated with the presence of depression but also with poor response rates to antidepressants, some research efforts have focused on how folate could be used in combination with antidepressant therapy to combat depressive symptoms.193,196 Studies on the effects of folinic

acid – a form of folate - as an adjunctive therapy in depressed patients who were either nonresponsive or only partially responsive to SSRIs has shown that folinic acid reduces symptoms of depression.192 Indeed, increasing folate levels in those taking SSRIs improves antidepressant response.196

While there are several forms of folate, certain single nucleotide polymorphisms can predispose people to fail to convert folic acid to its active form - methylfolate – due to changes in the activity of the enzyme that catalyzes this conversion.198 To achieve the benefits of higher folate levels in those with depression, it is therefore likely safest and most advantageous to provide the active form – methylfolate – rather than an inactive form. Studies on patients' experiences with methylfolate have found that patients on methylfolate supplements reported improvements in their depressive symptoms as well as greater satisfaction with their treatment than when they were on pharmaceutical antidepressants.199

Oxitriptan

Oxitriptan, also known as 5-hydroxytryptophan (5-HTP), has been shown to improve symptoms in patients with depression.200 Its potential role in depression is perhaps not surprising given that 5-HTP is a precursor for serotonin, which is heavily implicated in depression and whose activity is modulated by antidepressants like SSRIs.

Reduces Symptoms of Depression

One study on the specific role of 5-HTP supplementation on those with depression investigated the impact of 150 mg to 300 mg of 5-HTP taken daily for 3 weeks. Nearly 68% of the patients taking the supplements showed improvements in depressive symptoms as indicated by their Analysis of General Improvement Ratings scores.201

*Therapeutically Comparable to Antidepressant*s

Other studies using measures like the HDRS to evaluate depressive symptoms have found that 5-HTP leads to similar outcomes as drugs like fluoxetine and imipramine.202,203 One of these studies found that the effects of 5-HTP could be observed in depression patients within 2 weeks of starting 5-HTP supplementation.202 Another double-blind clinical trial on hospitalized depressed patients on 50 mg per day of clomipramine were additionally administered daily with 300 mg of 5-HTP or placebo.204 Results showed that those who received 5-HTP over the 28-day study period had better outcomes than did those who received placebo.

Saint John's Wort

Though there have been studies to suggest that Saint John's wort may provide therapeutic value in depression, subsequent reviews of the literature have concluded that the evidence that Saint John's wort is effective in combatting depression is not strong and that, critically, there is a lack of data on the long-term impact of this substance on depression.205,206 Researchers from RAND have pointed to heterogeneity between studies on the impact of Saint John's wort in depression and a lack of data showing any influence of Saint John's wort as an adjunct therapy to other antidepressant therapies.207

The lack of reliability of the effects of Saint John's wort likely stems from the many constituents contained within Saint John's wort and the variety of extraction processes that manufacturers use to obtain Saint John's wort.208,209 The effects of commercially available Saint John's wort products may depend on the amount a given constituent is present within the product and the corresponding dose. It should also be noted that in addition to challenges regarding the efficacy of Saint John's wort, experts have also advised caution regarding how the use of Saint John's wort could interact with other medications.210

Conclusion

There are critical limitations and risks associated with our current approaches to depression. The pharmaceutical interventions that are commonly deployed are plagued by unwanted side effects, as well as issues related to efficacy and toxicity.65,211–214 In addition, these therapeutic strategies can be incredibly laborious. For instance, initiating a drug therapy involves phases that can require years of drug and dose iteration, and discontinuing drugs is associated with adverse withdrawal effects124,215,216

Given the ease, cost-effectiveness, and evidence for efficacy related to a nutritional approach to depression, it is reasonable for depressed patients at any part of their journey to try an evidence-based formulation and observe its effects on their symptoms. Whether a patient is drug naïve or years into treatment, nutritional alterations may provide a simple and long overlooked solution.

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