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MANAGING DEPRESSION

NUTRACEUTICAL AND NON-PHARMACOLOGIC INTERVENTIONS FOR THE TREATMENT OF DEPRESSION

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INTRODUCTION

Disclaimer

This review of options is not intended as a stand-alone guide for treating depression. Nothing in this document should be taken as a basis to initiate treatment without guidance from a treating physician. Management of depression should always be supervised by a healthcare provider.

Please note that this is a "living" document that will be continuously updated and refined. Please ensure you are reviewing the most recent version.

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Preface

Depression (also known as major *depression*, major *depressive* disorder, or clinical *depression*) is a common and serious mood disorder. Globally, an estimated 10-15% of adults suffer from depression, with women being affected more commonly than men. Depression appears to be more common in Western nations as opposed to low-income countries.

The field of psychiatry has been entirely captured by the pharmaceutical industry, with effectively ineffective and unsafe drugs dominating the treatment of depression. This monograph outlines a more holistic approach to the treatment of depression, based on scientific evidence and an understanding of pathophysiology, using nutraceuticals and other non-pharmacological interventions,

Patients should review this information, independently validate the reliability of the data, and discuss the treatment options with their family/healthcare advocates. Patients should formulate a treatment plan with their healthcare provider that is compatible with their values and goals.

CHAPTER 1: About Depression

Depression is a mental disorder characterized by sadness, loss of interest in activities, and decreased energy. Other symptoms include loss of confidence and self-esteem, inappropriate guilt, thoughts of death and suicide, diminished concentration, and disturbance of sleep and appetite.

Diagnostic criteria for a major depressive episode (DSM-IV) include a depressed mood, a marked reduction of interest or pleasure in virtually all activities, or both, lasting for at least two weeks. (1, 2) In addition, three or more of the following must be present:

- gain or loss of weight
- increased or decreased sleep
- increased or decreased level of psychomotor activity
- fatigue
- feelings of guilt or worthlessness
- diminished ability to concentrate
- recurring thoughts of death or suicide

Scope and scale of the problem

Major depressive disorder (MDD) is estimated to affect 17% of the general population during their lifetimes, often at tremendous suffering and cost. (3-5) With over 25 million Americans having significant depression every year, this condition represents a major health burden and is considered one of the five most important and costly health problems in the world today. The World Health Organization estimates that more than 300 million people suffer from depressive disorders worldwide. (6)

Depression contributes dramatically to morbidity and poor quality of life. MDD is the leading cause of disability for people ages 15 to 44 years in the United States. (7) Depression in elderly patients is associated with cardiovascular events, including myocardial infarction, stroke, and death. (8) In 2013, there were more than 40,000 deaths by suicide in the United States, making it the tenth leading cause of death. (9)

The diagnosis of depression is almost always delayed, in many instances persisting for years before the diagnosis is made. The initial symptoms of depression are usually dismissed and regarded as an understandable reaction to life stressors and a temporary problem. Many of these patients never receive treatment until their symptoms become so severe that they become a risk to themselves or are simply unable to function any longer.

Causes of depression

Half of patients (50%) have an onset of major depression between the ages of 20 and 50, but this can begin as early as childhood or in old age. Use of alcohol and other substances can result in an early onset of depression. Depression can be triggered by stress, traumatic life events, physical illnesses, and drug and alcohol use.

Major depression occurs most often in people who have been divorced, separated, or those who don't have close interpersonal relationships. Also, there is a significant genetic factor involved in depression. Family studies have repeatedly found a much greater likelihood of a person having depression if one or both parents, or a brother or sister also have a depressive disorder.

Pathophysiology

MDD and anxiety disorders often occur concomitantly, their symptoms frequently overlap, and patients with these two comorbidities often present with a higher severity and duration of symptoms. Several studies suggest that depression may share common pathophysiologic characteristics with cardiovascular diseases and their risk factors, such as the increased production of proinflammatory cytokines, endothelial dysfunction, and elevations in plasma homocysteine levels. (10) Chronic inflammation and obesity are associated with an increased risk of depression. (2, 6) This relationship has been shown to be bidirectional, such that individuals who are overweight/obese have a higher risk of depression (55% increased risk of developing depression) and those with depression have a higher risk of becoming overweight/obese (58% increased risk of obesity). (11)

Among the main biological mechanisms implicated in the pathophysiology of depression (and anxiety disorders), compelling evidence has pointed to neuroinflammation as a key factor in its onset and progression. (12) This inflammatory process may involve inflammation-related signaling molecules, microbiota, as well as immune and brain cells. Mediators released by activated microglia induce astrocyte polarization. This polarization contributes to the impairment of signaling pathways that play a crucial role in neuronal survival and synaptic plasticity. In summary, neuroinflammation results from intrinsic communication among peripheral immune cells, gut microbiota, and immune cells present in the brain, and these interactions culminate in glutamatergic dysregulation, as well as reduced synaptic plasticity and monoamine synthesis. Together, these factors contribute to the atrophy and neuronal loss seen in patients with chronic depression and anxiety disorders. (13) In this regard, compounds with anti-inflammatory, pro-neurogenic, and neuromodulatory properties are of special interest for the treatment of patients with mood disorders. (13)

Mistargeting of traditional treatments

When Selective Serotonin Reuptake Inhibitors (SSRIs) were discovered, the pharmaceutical industry created a myth that they worked by fixing a serotonin deficiency in the brain; with time this theory has been disproven. Prozac (and its successors) were sold on the narrative that depression is caused by a chemical imbalance (of serotonin) in the brain. While this was a catchy marketing slogan, it was actually never proven. As more and more data has emerged that argues against the chemical imbalance theory, the psychiatric field has gradually moved towards identifying the (highly damaging) neural rewiring as the actual mechanism of the drug. (14)

SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) have been utilized for years, and while these medications are considered the gold standard for the treatment of depression the overall efficacy is modest, as evidenced by studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. This showed that antidepressants achieved a remission rate of only 30%, and that more than 70% of patients were unable to maintain remission. (15) While benefits of antidepressants in this study have been overinflated, only 108 of the 4,041 patients had a "sustained remission," which means that only 3% of the patients who entered the trial remitted, stayed well, and stayed in the trial during the year of follow-up; (16) it is believed this is an overestimate of the true long term benefit. (14)

The STAR*D study results show that the practice guideline of the American Psychiatric Association, which advises that "following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse," is likely harmful advice. (14, 17) Indeed, the evidence suggests that antidepressants do not cure depression. (14) They are depressogenic agents when used long term, meaning they can cause depression.

The many STAR*D papers display highly selective reporting of outcomes, numerous false claims, contradictory statements, and even pure fiction. (14) A Cochrane review of nine trials with atropine in the placebo (active placebo) failed to demonstrate an effect of tricyclic antidepressants. (18) A meta-analysis with individual patient-level data from six trials found SSRIs were ineffective for both mild, moderate and severe depression. (19) The FDA found in a meta-analysis of randomized trials with 100,000 patients, half of whom were depressed, that about 50% got better on an antidepressant and 40% on a placebo. (20) A meta-analysis of 37 industry-sponsored trials of fluoxetine and venlafaxine showed that severely depressed patients had improved after four weeks on the drug, while it took eight more days before patients on placebo had improved to the same extent. (21) However as these trials were not adequately blinded, the true difference is likely to be only a few days. (14)

SSRIs may be particularly lethal in the elderly. A UK cohort of 60,746 patients older than 65 demonstrated that SSRIs kill 3.6% of patients treated for one year. (22) Another cohort study of 136,293 American postmenopausal women participating in the Women's Health Initiative

found that antidepressants were associated with a 32% increase in all-cause mortality. (23) Due to underreporting, the actual risk of death in this study may be much higher. (14)

It should be noted that in the United States primary care providers prescribe 79% percent of antidepressant medications, and they do so with little support from specialist services. (24) While most patients prescribed a SSRI do not benefit from this medication, SSRIs help a minority of the patients who are put on them. Since most cases of depression are mild and self-limiting, treatment should be reserved for patients with severe depression that has failed to improve spontaneously. Typically, patients have much better results if they are prescribed SSRIs by a psychiatrist than by a general practitioner. There are psychiatrists with advanced expertise in psychopharmacology who can get excellent results for their patients; unfortunately, doctors like this are quite rare to find. Nevertheless, there are many patients that psychiatrists cannot help, and for those that they do help, it may be necessary for them to utilize integrative modalities.

Side effects of traditional treatments

SSRIs and SNRIs therefore appear to be marginally more efficacious than placebo (in the short term), however, they are associated with horrendous side effects. SSRI antidepressants are among the most harmful medications available. Unfortunately, due to widespread denial in psychiatry about the issues with their drugs, the common SSRI side effects are often misinterpreted as a sign the individual had a pre-existing mental illness and needs more of the drug — which all too often then leads to catastrophic events for the over-medicated patient.

In a survey on antidepressants in New Zealand, 62% reported sexual difficulties, 60% felt emotionally numb, 52% felt not like themselves, 39% cared less about others, 47% experienced agitation, and 39% experienced suicidal ideation. (25) Most importantly, the respondents to this survey reported that their prescribers did not warn them about many of these side effects.

In a review of 29 published and 11 unpublished clinical trials containing 3,704 patients who received paroxetine and 2,687 who received a placebo, an equal proportion of patients in both groups left their study early; compared to placebo, 77% more stopped the drug because of side effects and 155% more stopped because they experienced suicidal tendencies. (26) An international survey of 3,516 people from 14 patient advocacy groups found that 44% had permanently stopped taking a psychiatric drug due to its side effects. (27)

Sexual dysfunction is common in patients taking SSRIs. A Spanish study of five of the most commonly prescribed SSRIs found on average that the drugs caused sexual disturbances in 59% of 1,022 patients (who all had a normal sex life before they started on drug), and 40% of the 1,022 considered that dysfunction unacceptable. (28)

SSRIs may induce a switch to mania or hypomania at a rate two or three times the spontaneous rate. (29) Long-term use may destabilize the illness, leading to an increase in the number of both manic and depressed episodes; induce rapid cycling (at least four episodes a year); and

increase the likelihood of a mixed state. A survey found 60% of bipolar patients only developed their illness after receiving SSRIs for depression. (29) SSRIs increase the risk of birth defects when prescribed to pregnant women. (14) Cardiac birth defects are a class effect of SSRIs. (14)

It should be noted that most SSRI/SNRI agents, but notably sertraline, fluvoxamine, paroxetine, venlafaxine, and duloxetine are associated with severe anxiety that may progress to mania, akathisia (an inability to remain still), self-inflicted harm, suicide, anger outbursts, physical violence, homicidal thoughts, and homicide. (30-34) Akathisia, suicides and homicides, particularly when they involved children, gave rise to the first antidepressant suicide advisories in 2003. (35) This followed the landmark review by Healy entitled "*Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors (SSRIs*)." (36) This paper challenged but did not stop the ongoing denial by the pharmaceutical industry in the US.

There is now overwhelming evidence that SSRIs significantly increase the risk of akathisia, suicidal thoughts, suicide, and homicidal behavior and that this risk is not limited to children and adolescents. (14, 37) Suicides occur most frequently soon after initiation of SSRIs, with a change in dosage, or when stopping the drug. Suicidal ideation and suicidal behavior as well as agitation and disturbed behavior has been reported in healthy volunteers treated with an SSRI. (14)

An analysis of a national database in Sweden found that SSRIs increased the rate of violent crimes committed by 43% in those between the ages of 15 and 24 receiving these drugs. (38) Over 160 homicides and over 1500 episodes of aggressive behavior directly related to the use of SSRIs have been reported to the FDA and Health Canada, and these numbers are likely a gross underestimate (https://rxisk.org/antidepressants-and-violence-the-numbers/). Eighty of the homicides were associated with the use of sertraline. Many of the perpetrators of school and mass shootings were under the influence of SSRIs, including the Columbine and Aurora shooters. (14)

SSRIs are extensively metabolized by the CYP450 phase 1 enzymes. Lucire and Crotty studied the alleles of the CYP450 system in patients prescribed SSRIs who had displayed violent, suicidal and/or homicidal behavior. (35) In this study all the subjects had variant alleles and diminished CYP450 metabolism. Furthermore, many were also using, alone or in combination, either other medications, illicit substances, or herbal remedies that had the combined effect of exacerbating the impaired metabolism caused by their variant alleles. This study detailed and substantiated in specific terms how the metabolism of each of the antidepressant drugs used by the subjects would have been seriously impaired both before and at the time they committed or attempted homicide. (35) Since these alleles are genetically determined, such reactions may be more common in first degree relatives. While it is unlikely that pharmacovigilance studies can be performed in all patients prior to treatment with an SSRI, these patients should be cautioned and monitored very closely for the development of these serious adverse reactions.

A Cochrane review investigated the adverse events of antidepressants in healthy volunteer studies. (39, 40) This systematic review of 150 studies showed that about a third of all trials

failed to report adverse event data and the meta-analysis showed that the incidence of adverse events possibly predisposing to suicide is doubled. Analysis of the European Medicine Agency (EMA) trials showed selective publication and inadequate reporting of adverse events. (14)

One of the most serious issues with SSRIs is that they are often extremely difficult to stop and frequently the addiction can start after a very brief course of the SSRI (e.g., a month). Sadly, when patients suffer SSRI withdrawals doctors typically interpret it as relapse of depression and a sign the withdrawn medication was "working" (hence needing to be resumed) or recognize it is in fact a withdrawal, but only know to "treat" it by resuming the addictive drug. A recent meta-analysis found that 56% of patients who stop using SSRIs experience withdrawals, that 46% who stop an SSRI experience severe withdrawal, and that these withdrawals last for weeks to months. (41)

The limited efficacy of SSRIs and SNRIs in the treatment of major depressive disorder and bipolar disease suggests that these agents should not be considered as first line therapies (at least not as mono therapy). Conventional anti-depressants and anxiolytics may have a role in the initial phase of the treatment approach in selected patients. However, long-term SSRI/SNRI medications are generally not recommended due to the long-term effects of these drugs on serotonin receptors, intracellular messenger pathways, as well as genetic and epigenetic effects. (42, 43)

An alternate approach

Since depression is a whole-body illness, solutions to treatment require whole-body response, including changing what you eat, how you exercise, and how you sleep. Antidepressant medication remains the most common method of therapy, yet, compared to medications for nonpsychiatric conditions, antidepressants have a relatively low response rate, high relapse rate, and long time to response, as well as side effects that limit tolerability or contribute to poor compliance.

With more than 70% of patients treated with standard SSRI/SNRI monotherapy unresponsive to treatment, clinicians are left with the challenge of what to consider next. A novel approach to a safe and efficacious alternative for patients with an inadequate response to standard antidepressant is augmentation/replacement with pharmaceutical grade nutrients, known as nutraceuticals, such as: L-Methylfolate, Vitamin D, Ashwagandha (for control of stress and anxiety) and Omega-3 fatty acids, as well as other novel therapeutic interventions. It should be noted that about 85% of patients with depression have significant anxiety, and 90% of patients with anxiety disorder have depression. (44)

CHAPTER 2: Nutraceutical and non-pharmacological interventions

The following lifestyle and dietary interventions are recommended, based on published data and stratified by the strength of the clinical evidence. We suggest that patients with depression and bipolar disease be treated (as a clinical trial) with L-methylfolate (active form of folic acid), high dose vitamin D, Ashwagandha, and an exercise program as first line therapy. Depending on the response, additional interventions, such as omega-3 fatty acids and magnesium supplementation, can be added. We consider traditional antidepressants (SSRI/SNRI) as a second line therapy.

Patients should always consult with their primary care provider (and/or psychiatrist) to develop a personalized approach to the management of depression and concomitant anxiety disorder.

Summary of suggested interventions

1. L-Methylfolate (7.5-15 mg/day)
2. Vitamin D3 (dosage adjusted based on vitamin D3 blood levels, but 10,000 IU/day is recommended; take with Vitamin K2 100 mcg/day and Magnesium 200-500 mg/day if taking more than 8,000 IU/day of Vitamin D3)
3. Lithium Orotate 5-15 mg/day
4. Ashwagandha (300-600 mg/twice daily)
5. Omega-3 fatty acids (1,000 mg/day)
6. Magnesium (100-200 mg/day starting dose)
7. Zinc (20-30 mg/day)
8. Melatonin (.75-1 mg/night to start, up to 5-10 mg/night)
9. Curcumin (500-1,000 mg/day)
10. St. John's wort (600-1,800 mg/day)
11. Saffron (50 mg/twice day)
12. Low insulinemic diet
13. Treatment of gut dysbiosis (e.g., pre/probiotics, glucomannan, chia seeds)
14. Cognitive behavioral therapy and social support
15. Exercise (20 minutes/day, 5 days/week)
16. Sunshine (30 minutes/day)
17. Photobiomodulation
18. Non-invasive brain stimulation
19. Whole body hyperthermia

L-Methylfolate (LMF)

Folate is a water-soluble vitamin (vitamin B9) that is added to some foods, found naturally in others, and can be purchased as a dietary supplement. The main biologically functional form of

folate, known as folic acid, is used by cells to regulate homocysteine, the cysteine cycle, DNA synthesis, and neurotransmitter synthesis (see figure 1). (45-47)

L-methyl folate (LMF) differs from folic acid in that it is the biologically active form of folate that more readily crosses the blood-brain barrier. LMF, in a daily dose of 7.5 to 15 mg, should be considered the primary intervention of choice in patients with depression and bipolar disease and traditional anti-depressants considered second line therapy.

Low folic acid levels correlate with increased risk of depression, severe depressive symptoms, prolonged duration of depressive episodes, and increased risk of relapse. (48-51) Furthermore, depressed patients with folate deficiency demonstrated limited to no response upon receiving antidepressant treatment. (50, 51) Therefore, folate augmentation with standard antidepressant medication may improve treatment outcome in patients with low folate levels. (50-52) LMF increases depression scale scores, patient response, and remission rates, according to results from randomized trials and case and cohort studies.

Vitamins B12 and L-methylfolate act as cofactors in the conversion of homocysteine to methionine, an essential amino acid involved in numerous methylation processes necessary for the synthesis of proteins, lipids, nucleic acids, neurotransmitters, and hormones. The single-carbon groups needed to produce methionine must be carried by the co-enzymatic molecule folate (active form 5' tetrahydrofolate; see figure 2). Following this, the trans-sulfuration process transforms methionine into S-adenosylmethionine (SAM). Methionine can contribute its methyl group in this process to the synthesis of neurotransmitters like norepinephrine, serotonin, and dopamine. (45-47)

Figure 1. Methionine-Folate Cycle

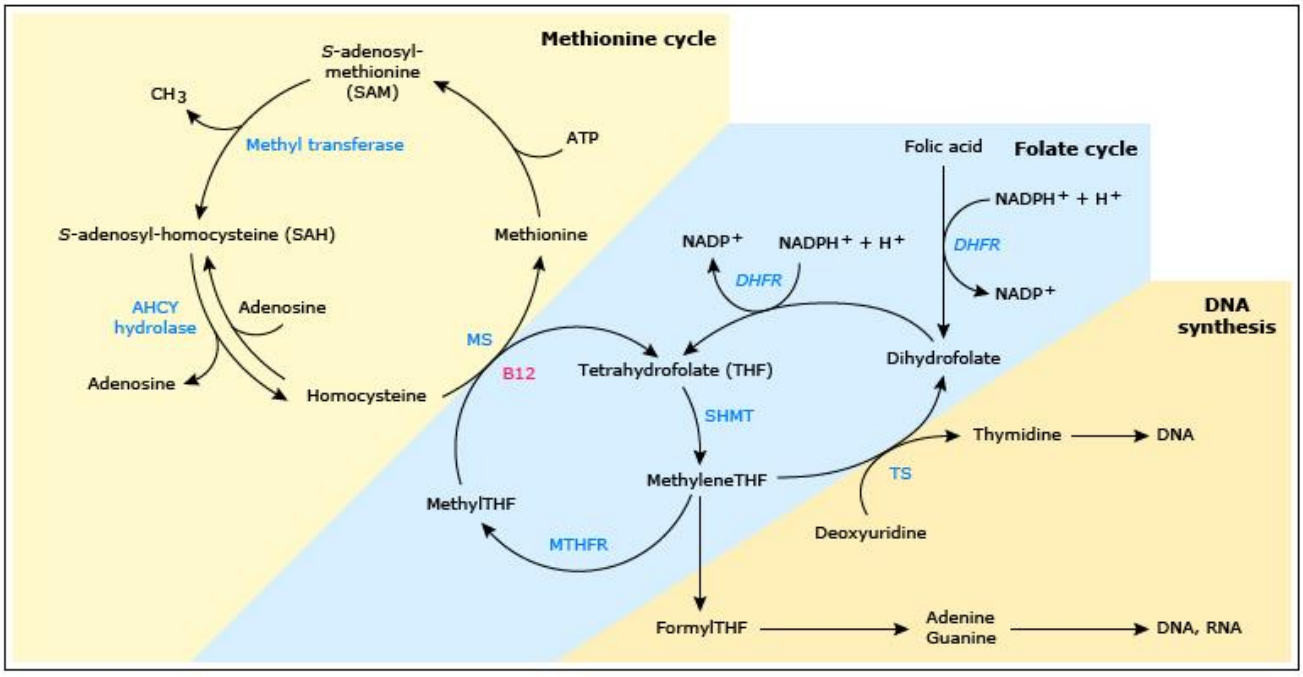

Figure 2. The Folate-Methionine Cycle

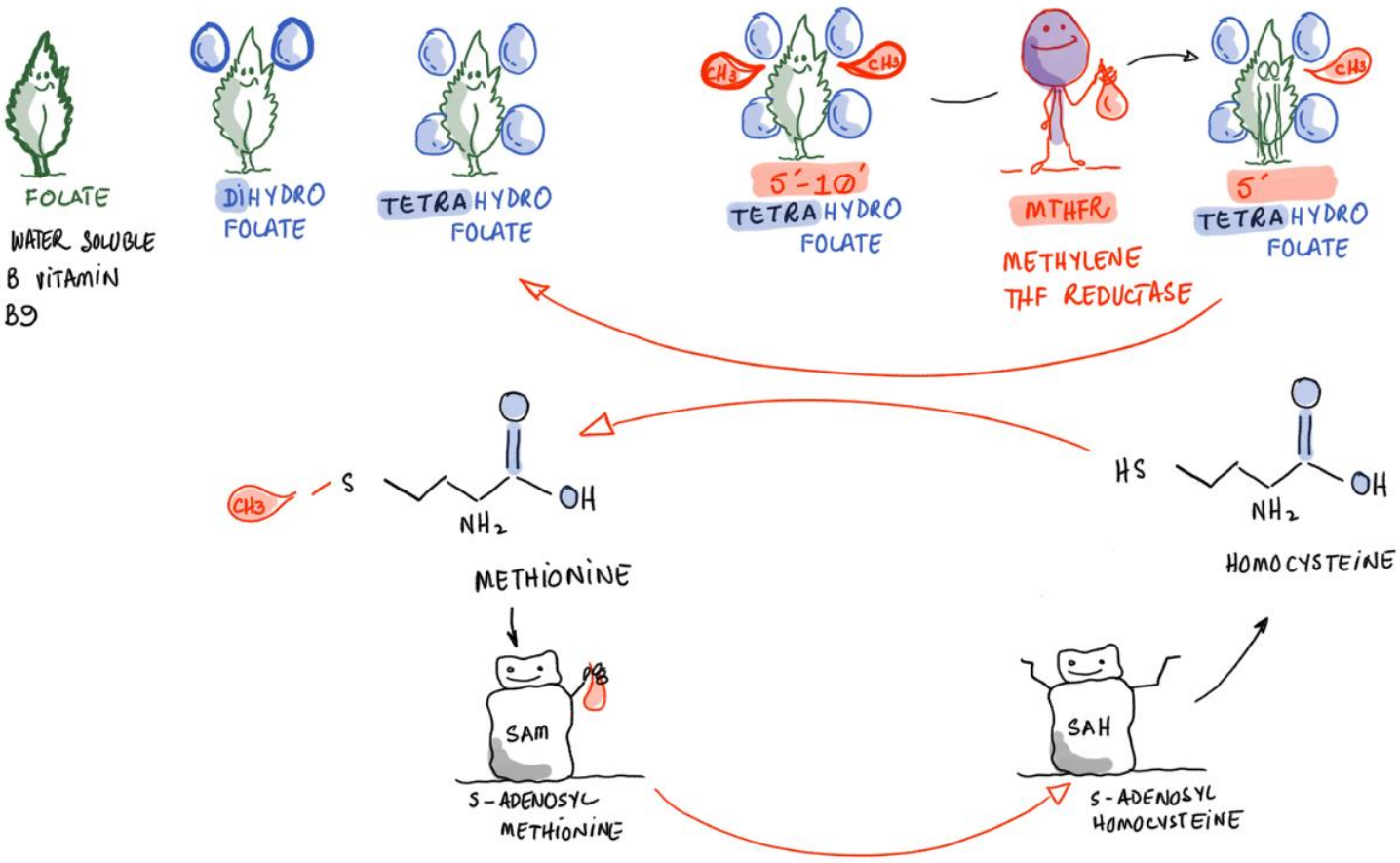

Figure Courtesy of Dr. Mobeen Syed

Folic acid plays an essential role in one carbon metabolism and has been linked with the synthesis of monoamines such as serotonin, epinephrine, and norepinephrine. Folic acid is converted into L-Methylfolate (5' methyl tetra hydro folate) by the enzyme methylene tetrahydrofolate reductase, also known as MTHFR. It is important to stress that L-Methylfolate is the active form of the vitamin. After its conversion to L-Methylfolate, it crosses the blood brain barrier. L-Methylfolate is known to aid in the formation of BH4, or tetrahydrobiopterin, which activates tyrosine hydroxylase and tryptophan hydroxylase and aid in the synthesis of monoamines. MTHFR gene mutation results in low levels of L-Methylfolate in the central nervous system, leading to a depletion of monoamines. This explains the benefit patients may experience with supplementation with L-methylfolate.

The 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme plays a central role in folate metabolism by irreversibly converting 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, the predominant circulating form of folate (active form of folate). 5-methylenetetrahydrofolate donates a methyl group to homocysteine in the generation of S-adenosylmethionine, a major source of methyl groups in the brain. Two common single

nucleotide polymorphisms in MTHFR have been reported, a C/T transition at nucleotide 677 and an A/C transversion at position 1298. (53-56) Both polymorphisms are functional and result in diminished enzyme activity. For the C677T polymorphism, homozygote variants have 30% enzyme activity in comparison with homozygotes for the wild-type C allele, while heterozygotes retain 65% of wild-type MTHFR enzyme activity.

The consequences of the C677T polymorphism have been demonstrated in population studies, where lower levels of red blood cell folate, plasma folate, and vitamin B12 have been reported among non-diseased persons with the 677 TT genotype in comparison with persons with other genotypes. The 1298 polymorphism has been less extensively studied; however, it is known that persons with the 1298 CC genotype have approximately 60% of the enzyme activity of those with the common AA genotype.

The frequency of the C677T allele is subject to considerable ethnic and geographic variation, with a high allele frequency being reported in California Hispanics and a low allele frequency in US African Americans. (53-56) Among White populations in Europe, North America, and Australia, the frequency of homozygotes ranges from 8-20%. The prevalence of the A1298C homozygote variant genotype ranges from 7-12% in White populations from North America and Europe.

A meta-analysis by Gilbody et al demonstrated an association between the MTHFR C677T variant and depression and bipolar disorder. (56) A study from Egypt reported an association between the MTHFR C677T and the risk of schizophrenia and bipolar disorders, of which the polymorphism may contribute to the age of onset for bipolar disorders. (57) However, a more recent meta-analysis concluded the association of the MTHFR C677T with risk of schizophrenia, MDD and bipolar disorders in the Asian and Africans and not in the Caucasian population. (58) Supplementation with L-methylfolate may overcome the folate metabolism problems seen in individuals with disadvantageous genetic polymorphisms. (59)

Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme in folate and homocysteine metabolism. Despite normal levels of folate, some patients may not be able to methylate appropriately. MTHFR polymorphisms are implicated in the development of depressive symptoms and reduce the ability to adequately synthesize monoaminergic neurotransmitters; thus, the effectiveness of SSRIs and SNRIs may be limited in these patients. (60, 61) Hence, patients with high homocysteine levels and normal vitamin B12 and methylmalonic acid (MMA) levels will particularly benefit from L-methylfolate augmentation.

A meta-analysis by Bender et al which included 43 studies demonstrated that patients with depression have lower serum levels of folate and dietary folate intake than individuals without depression. (48) In a study of 46 patients with MDD 52% had raised total plasma homocysteine (an indicator of reduced active folic acid). (62) In this study, depressed patients with raised total plasma homocysteine had significantly lower serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls.

Kim et al reported that reduced serum folate levels (<6.0 ng/mL) were independently associated with suicidal behavior. (63) Yan et al reported that prolonged folic acid supplementation during pregnancy was associated with a decreased risk of post-partum depression. (64)

Pan et al conducted a case-control, targeted, metabolomic evaluation of 33 adolescent and young adult patients with well-characterized histories of treatment refractory depression. (65) In this study cerebral folate deficiency was most common abnormality detected (36%), with these patients having normal serum folate levels but low CSF 5-methyltetrahydrofolate (5-MTHF) levels. All patients with cerebral folate deficiency showed improvement in depression symptom inventories after treatment with folinic acid.

The effect of LMF in patients with depression has been linked to multiple mechanisms, including monoamine synthesis, neurogenesis, and antioxidant effects. LMF is thought to enhance the response to antidepressant therapy due to its role in the production of tetrahydrobiopterin (BH4) and subsequent increase in monoamine synthesis. (11) BH4 is a critical cofactor in the metabolic pathway for neurotransmitter synthesis and is highly labile and sensitive to oxidation. BH4 regulates several methylation reactions, some of which involve S-adenosylmethionine (SAMe) as a key factor, such as the metabolism of serotonin using SAMe as a methyl donor. (11) Therefore, reduced levels of BH4 can alter the bioavailability of neurotransmitters relevant to depression, such as serotonin and dopamine.

LMF can increase clinical response when used adjunctively in patients with MDD who are SSRI-resistant. The results of two randomized controlled clinical trials support the use of adjunctive LMF in this patient population. (66) These trials were conducted in patients with MDD who did not respond to adequate antidepressant therapy. Pooled results from both studies found that patients receiving 15 mg/day of adjunctive LMF therapy showed significantly greater response rates than those receiving an SSRI with placebo (32.3 vs. 14.6%; P = 0.04). A 12-month open-label extension of the randomized controlled trials (N=68) found that 38% of patients receiving 15 mg/day of adjunctive LMF achieved full recovery and no fully recovered patients experienced MDD recurrence. (67)

LMF has demonstrated effectiveness in real-world studies, with 67.9% of patients responding to therapy. (51) A retrospective analysis comparing patients with SSRI or SNRI monotherapy versus those treated with a combination of an SSRI/SNRI antidepressant and L-Methylfolate (7.5 mg or 15 mg) found adjunct therapy with L-Methylfolate in patients with MDD was more efficient, led to symptom improvement, and had fewer patients discontinue medications. (51, 68)

Lam et al performed a meta-analysis on the use of folate supplements in the treatment of various psychiatric diseases. (45) These authors identified 23 studies of folate, 9 of which investigated the efficacy of folate supplements in major depressive disorders. In this study, oral folic acid or 5-methylfolate was associated with an improvement in clinical outcomes especially in major depressive disorder including postpartum and post-menopausal depression.

Altaf et al performed a meta-analysis comparing adjunctive therapy with folate (L-Methylfolate or folic acid) compared to selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor (SSRI or SNRI) monotherapy. (69) In this meta-analysis, which included 6 studies, adjunctive therapy with L-Methylfolate or folic acid significantly improved depression scale scores, patient response, and remission rates. Furthermore, patients on adjunct therapy with folic acid had a 39% increase in achieving remission compared to patients on SSRI/SNRI alone.

This data provides convincing evidence that L-methyl folate (LMF) at a dose of 7.5 to 15 mg day should be considered first line intervention in patients with depression and bipolar disorder. Genetic evaluation for the presence of the C677T and A1298C mutations of the MTHFR gene is recommended, as this may provide additional evidence for treatment with LMF.

Vitamin D3

It is likely that almost all patients with depression are vitamin D deficient. Therefore, unless contraindicated, all patients with depression should be treated with vitamin D3. Doses should be adjusted based on vitamin D3 blood levels, but a dose of at least 10,000 IU/day is recommended, as this is the highest dose that can be used safely without extensive monitoring. When taking more than 8,000 IU of vitamin D3 daily, it is best to include both Vitamin K2 (Menaquinone [MK4/MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day).

Vitamin D is synthesized in human skin after the photoisomerization of 7-dehydrocholesterol to pre-vitamin D3 under the influence of UV B radiation (wavelength, 280-315 nm). (70) The major factors influencing this process are either environmental (latitude, season, time of day, ozone and clouds, reflectivity of the surface) or personal (skin type, age, clothing, use of sunscreen, genetics). (71) From the skin, vitamin D3 (*cholecalciferol*) finds its way into the general circulation, and it is then metabolized in the liver to 25-hydroxyvitamin D3 [25(OH)D3] (*calcifediol*). 25(OH)D3 is an immediate precursor metabolite to the active form of vitamin D3, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] (*calcitriol*), that is the product of the mitochondrial CYP27B1-hydroxylase confined primarily but not entirely to the proximal tubular epithelial cell of the kidney. (71, 72)

Vitamin D is a unique neurosteroid hormone that may have an important role in the development of depression. Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been implicated in the pathophysiology of depression. (73, 74) Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity, and brain development, (75) making it biologically plausible that this vitamin might be associated with depression and that its supplementation might play an important part in the treatment of depression.

Indeed, the benefits of vitamin D go beyond its effects on calcium-phosphorus metabolism, particularly, its antioxidant, anti-inflammatory, pro-neurogenic, and neuromodulatory properties, which contribute to its antidepressant and anxiolytic effects. (76) The biological plausibility of the association between vitamin D and depressive illness has been strengthened by the identification of vitamin D receptors in areas of the brain implicated in depression, (73, 74) the detection of vitamin D response elements in the promoter regions of serotonin genes, (77) and demonstration of interactions between vitamin D receptors and glucocorticoid receptors in the hippocampus. (78)

Vitamin D deficiency is strongly associated with the risk of depression. In a meta-analysis that included one case-control study, ten cross-sectional studies and three cohort studies with a total of 31 424 participants, lower vitamin D levels (25(OH)D or 25(OH)D3) were found in people with depression compared with controls (SMD = 0.60, 95% CI 0.23–0.97) and there was an increased odds ratio of depression for the lowest v. highest vitamin D categories in the cross-sectional studies (OR = 1.31, 95% CI 1.0–1.71). (73)

In an analysis of 11,471 participants enrolled in the National Health and Nutrition Examination Survey (NHNES), those who had a 25(OH)D_3 deficiency were more likely by 54% to report depression symptoms (OR = 1.54,95%CI:1.14-2.07). (79) In a meta-analysis that included 13 independent reports involving 10,317 pregnant patients, vitamin D deficiency was associated with increased risk of post-partum depression (OR 0·49; 95 % CI 0·35, 0·63). (80) In this study, the dose-response analysis indicated that the lowest pooled OR was at blood 25(OH)D concentrations of 90–110 nmol/l. Similarly, the metaanalysis by Aghajafari et al demonstrated a strong association between vitamin D status and antepartum and post-partum depression. (81) Vitamin D levels are associated with the prevalence of depression in perimenopausal women. (82)

Głabska et al evaluated the association of vitamin D status and mental health in children. (83) This metanalysis supported potential positive influence of vitamin D on mental health of children including mood, quality of life, well-being, anxiety disorder and sleep patterns.

Multiple RCTs have been performed investigating the effect of vitamin D supplementation on depression. Alavi et al randomized elderly patients (over the age of 60 years) with depression to high dose vitamin D (50,000 IU vitamin D3 weekly for 8 weeks) or placebo. (84) These authors demonstrated a significant reduction in depression scores in the treatment group. At least 5 meta-analyses have been published investigating the role of vitamin D supplementation and depression. (85-89) An “Umbrella meta-analysis” that included 10 RCTs demonstrated a significant reduction in depression symptoms comparing participants on vitamin D supplements to those on placebo (SMD - 0.40; 95 % CI: - 0.60, -0.21, $p < 0.01$. (87) A recent study demonstrated that vitamin D supplements were significantly superior to placebo in reducing depression (SMD = –0.49; 95% CI, –0.75 to –0.23). (90) In this study, patients with more severe depression tended to respond better than those with less severity depression.

Four meta-analyses of cohort studies revealed that participants with lower levels of serum vitamin D were at increased odds of depression than those with higher levels of serum vitamin D (OR 1.60; 95 % CI: 1.08, 2.36, $p < 0.01$).

The results of these meta-analyses provide convincing evidence that unless contraindicated all patients with depression should be treated with vitamin D3. It is important to recognize that the dose of Vitamin D3 in the RCTs was relatively low, being between 3,000 IU to 6,000 IU/day. A dose of at least 10,000 IU/day is recommended, this is the highest dose that can be used safely without extensive monitoring. It is best to include both Vitamin K2 (Menaquinone [MK4/MK7] 100 mcg/day, or 800 mcg/week) and magnesium (250-500 mg/day) when doses of vitamin D > 8,000 IU/day are taken. (91, 92)

A high loading dose of vitamin D is suggested (100,000 IU) followed by dose titration according to vitamin D blood levels, aiming for a 25-OH D3 level of > 50 ng/ml (target 55-90 ng/ml). Patients with severe/resistant depression may have vitamin D resistance and in these patients it may be preferable to target a level of 100 ng/ml. Vitamin D intoxication is observed when serum levels of 25-OH D3 are greater than 150 ng per milliliter (374 nmol per liter). (71, 93) Hypercalcemia will usually not occur until levels exceed over 250 ng/ml. (93) In patients with resistant depression, we suggest a daily dose of 20,000 – 30,000 IU/day until a vitamin D level is obtained. If measuring vitamin D levels is not feasible/possible, we would suggest a loading dose of 100,000 IU followed by 10,000 IU/day.

Doses of 10,000 IU of vitamin D3 per day for up to 5 months were reported to be safe and without toxicity. (71, 94) It should be noted that dosages of vitamin D between 50,000 to 80,000 IU/day have been reported to be safe. (95-97)

We recommended vitamin D3 over D2 as vitamin D2 is approximately 30% as effective as vitamin D3 in maintaining serum 25-OH D3 levels. (98) Furthermore, vitamin D3 should be dosed daily rather than large intermittent bolus dosing.

Patients taking coumadin need to be closely monitored and need to consult with their PCP before taking vitamin K2. Further, in patients with resistant depression we suggest measuring PTH (parathyroid) levels and calcium levels and titrating the dose of Vitamin D according to the PTH levels as follows (Coimbra Protocol): (99, 100)

i) if the PTH level is below the lower end of the reference range, reduce the dose of Vitamin D
ii) if the PTH level is at (or close to) the lower end of the reference range, maintain dose
iii) if PTH is within the reference range but not near to the low end of the reference range increase the dose of vitamin D

Lithium Orotate

The growing evidence from epidemiological studies and cellular studies suggests lithium is a crucial trace element necessary for optimum brain functioning. (101) High concentrations of lithium are found in the earth's crust with the major source of intake being drinking water.(102) While lithium is not traditionally considered an essential trace element, a daily dose of approximately 1mg lithium has been suggested to prevent lithium deficiency.(102, 103) Lithium appears to be neuroprotective while inadequate lithium intake (especially in vulnerable individuals) may predispose and/or perpetuate a range of psychiatric and neurodegenerative conditions. (104) Due to the uneven distribution of lithium in the Earth's crust, its estimated consumption in populations of various regions of the world is highly diverse.(102) There is an impressive body of evidence that people who live in areas where the land or water supply is relatively lithium rich have lower rates of mental illness (and suicide) compared to areas where the land or water supply is relatively lithium poor. (104-109) In addition, a recent, large, population-based Danish study concluded that long-term exposure to higher lithium levels in drinking water may be associated with a lower incidence of dementia. (110) It should be noted that the use of filtered and bottled water may reduce lithium intake.

Lithium penetrates the interior of the cell mainly by simple diffusion through voltage-dependent sodium channels according to the concentration gradient. (102) The biochemical mechanism of lithium action seems to be multifactorial and interdependent with the function of various enzymes, hormones, and vitamins.(102, 103) Lithium modulates the activity of glutamate, dopamine, serotonin, gamma-aminobutyric acid, acetylcholine, and glycine. (102) Lithium inhibits the activity of glycogen synthase kinases (GSK3), associated with cell proliferation, metabolism, inflammation and apoptosis. In addition, lithium enhances the expression of protection factors, such as the brain-derived neurotrophic factor (BDNF) and its receptor. By modulating the expression of clock genes lithium can resynchronize circadian rhythms. Therapy with lithium has also been shown to increase density of the gray matter and increase the size of the amygdala and hippocampus. Lithium is also known to stimulate the production of neural stem cells and has protective effects against oxidative stress and its consequences. (102, 111)

Lithium carbonate has been used for decades for the treatment of bipolar depression. Lithium carbonate has a very narrow therapeutic index with a wide range of side effects, which has limited its use.(112) Lithium orotate (LO), however, has a very wide therapeutic index and is associated with minimal toxicity even at high doses. Due to the differences in pharmacokinetics, LO is more potent with reduced adverse effects as compared to lithium carbonate. (113, 114) Orotic acid is a mineral carrier that can readily transport inorganic ions – such as lithium, magnesium, or calcium – across biological membranes. (113, 114) In contrast to Lithium carbonate, LO shows no effect on water intake or kidney and thyroid function. (113, 114) In a murine model, doses of LO up to 400 mg/kg failed to demonstrate toxicity or target organ dysfunction. (115) LO has been used worldwide, mainly by non-medical health practitioners for over 30 years. (104) LO can be purchased through a number of sources and does not require a doctor's prescription. Furthermore, as LO is considered a mineral supplement it does not require approval from the Food and Drug Administration. (104)

The reported benefits of taking LO include feeling calmer; experiencing fewer or less intense depressive hypomanic or mixed affective symptoms; being less impulsive; experiencing less frequent and less intense suicidal thoughts or aggressive impulses and stress reduction. (104) The reported benefits of LO are similar to the known benefits of lithium carbonate, albeit in an attenuated form. LO has been demonstrated to be effective, safe and well tolerated. (104, 116) In an experimental model microdose lithium has been demonstrated to reduce cellular senescence in human astrocytes. Lithium, a potent inhibitor of glycogen synthase-kinase 3-α and β enzymes that may play an important role in the pathogenesis of Alzheimers disease. Microdose Lithium (300 ug LO) has been demonstrated to stabilize cognitive impairment in patients with Alzheimer's Disease. (117) long-term low-dose exposure to lithium appears to exert antiaging capabilities and unambiguously decreases mortality in evolutionary distinct species.(118)

There are no established guidelines for the daily dose of LO. However, the standard dose prescribed by alternative health practitioners is a dose equivalent to 5 mg of elemental lithium.(104) This is only 10% of the dose of elemental lithium that you would find in a single 250 mg tablet of lithium carbonate, which would have about *50 mg* of elemental lithium. The standard dose of lithium carbonate is 600–1200 mg per day containing 113–226 mg of elemental lithium. (112) The dose of LO (elemental lithium) can be increased to 10 -15 mg daily. As LO has a long half-life once daily administration is suggested. (113, 114)

Ashwagandha

Despite being different disorders, symptoms of depression and anxiety frequently overlap in individuals, making them difficult to diagnose and treat adequately. Adaptogens are herbs that help in combating stress and anxiety. These herbs normalize physiological processes and help the body adapt to stress.

In Ayurvedic medicine (traditional medicine native to India) *Ashwagandha*, also known as *Withania somnifera,* has proven to be a safe and effective adaptogen. It is an evergreen, straight, branching shrub that originates in Western India and Mediterranean regions.

Ashwagandha has been used for centuries to treat many chronic diseases like high blood pressure, arthritis, diabetes, Alzheimer's disease, and depression. As with many botanical drugs, Ashwagandha possesses anti-inflammatory, antioxidant, anticarcinogenic, and anti-diabetic properties. (119)

We recommend a dosage of 300- 600 mg twice daily.

The roots of the plant are considered the most important part of the whole plant, as they are rich in bioactive molecules, especially withanolides, which are responsible for their medicinal property. (120)

Large numbers of withanolides have been isolated from the roots and leaves, which contribute to the medicinal property of this plant; 12 alkaloids, 35 withanolides, and several sitoindosides have been isolated from the root and leaves of the plant. (119, 120)

Ashwagandha is often compared to the ginseng plant due to its ability to reduce stress, improve cognitive functions (e.g., memory), and promote a healthy immune system. It promotes immunomodulatory effects whose function is to balance the humoral and cellular responses of the adaptive immune system. Ashwagandha has been shown to play a significant role in immunological diseases by modulating several cytokines, increasing T-cell proliferation, and enhancing macrophage function.

Randomized controlled trials have shown a significant benefit in terms of stress reduction, improved cognition and mood (reduction of depression) and quality of sleep. (121-123) In a double-blind, placebo-controlled randomized controlled trial, participants who had chronic stress were randomized to ashwagandha extract (300 mg twice daily) or placebo for 60 days. (124) At the end of 60 days, participants in the active treatment group had a 44% ($p< 0.001$) reduction in stress scores and a 28% ($p< 0.001$) reduction in cortisol levels.

Similarly, Remenapp et al reported that one month of Ashwagandha supplementation had a positive effect on the participants' cortisol levels, cognitive ability, and self-reported stress, anxiety, depression, and food cravings, and was devoid of serious adverse events. (125) A randomized-placebo controlled trial demonstrated that Ashwagandha improved cognitive function (auditory-verbal working memory and social cognition) in patients with bipolar disorder. (126)

A metaanalysis of 12 RCTs demonstrated that Ashwagandha supplementation significantly reduced anxiety ($p = .005$) and stress level ($p = .005$) compared to placebo. (127) In this study, the non-linear dose-response analysis indicated a favorable effect of Ashwagandha supplementation on anxiety until 1 200 mg/day and stress at a dose of 300-600 mg/day.

Healthy sleep is essential for neural development, learning, memory, cardiovascular and metabolic regulation. Sufficient sleep is needed to provide recovery after preceding waking activities and ensure optimal functioning during subsequent wakefulness. (128) As recommended by the National Sleep Foundation, in a healthy individual, the recommended sleep duration for younger adults is seven to nine hours, and for older adults is seven to eight hours. (129) Other than adequate duration, healthy sleep comprises good quality. The National Sleep Foundation endorses the following sleep quality indicators: 1) sleep latency of 15 minutes and less, 2) one or fewer awakening of more than five minutes per night, 3) wake time after sleep onset of 20 minutes and less, and 4) sleep efficiency of 85% and more. (130) Insomnia is defined by the complaints of difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings and is associated with one or more daytime symptom such as fatigue, cognitive impairment, or mood disturbance (depression). (131) A systematic review demonstrated that short sleep duration, defined as less than six hours of sleep per 24 hours, is associated with a significant mortality increase. (132)

A metaanalysis of 5 RCTs demonstrated that Ashwagandha supplementation significantly improved sleep, particularly in subgroup of adults diagnosed with insomnia; the treatment dosage > 600 mg/day and treatment duration was > 8 weeks. (131) Ashwagandha showed improvement in sleep compared to the placebo for the Sleep Quality Scale, sleep onset latency, total sleep time, wake time after sleep onset, and sleep efficiency.

Omega 3 fatty acids

The changing of omega-6/omega-3 polyunsaturated fatty acids (PUFA) in the food supply of Western societies over the last 150 years is thought to have promoted the pathogenesis of many inflammatory-related diseases, including depressive disorders. (10)

PUFA can be classified into various groups by their chemical structure into omega-3 fatty acids (omega-3 FA) and omega-6 fatty acids (omega-6 FA). Omega-3 FA refers to a group of PUFA in which the first double bond is 3 carbons from the end (omega) carbon atom of the molecule; the omega-6 FA are a family of PUFA that have in common a final carbon-carbon double bond in the n-6 position. (10)

Alpha-linolenic acid (ALA, 18-carbon PUFA obtained from plant sources), eicosapentaenoic acid (EPA, 20-carbon PUFA from fish) and docosahexaenoic acid (DHA, 22-carbon PUFA obtained from marine source) are the most common omega-3 FAs. (133) Omega-6 fatty acids are found in processed vegetable oils including sunflower, safflower, soy, sesame, and corn oils as well as meat, poultry, and eggs.

Due to changes in lifestyle over the last 150 years the omega-6/omega-3 in the food supply of Western societies has changed from 1:1 to about 15.1. (10, 134) This pattern of fatty acids intake is thought to promote the pathogenesis of many inflammatory-related diseases, including cardiovascular disease, cancer, and autoimmune diseases, whereas increased levels of omega-3 PUFA and a low omega-6/omega-3 ratio may exert suppressive effects. (135)

Omega-6 PUFA is converted into arachidonic acid and then metabolized into the omega-6 eicosanoids, which have proinflammatory activity. On the other hand, omega-3 FA increase EPA in the cell membrane. This competes with AA for enzymatic conversion into its own metabolites, the omega-3 derived eicosanoids. These are less active and can partly oppose or antagonize the proinflammatory actions of the omega-6 eicosanoids.

Among the biological properties of omega-3 fatty acids, their anti-inflammatory effects and their role on the structural changing of the brain may explain the pathway through which they can be effective both in preventing or treating depression. (10) The membrane changing induced by omega-3 FA intake may affect different neurotransmitter system altering the regulation of dopaminergic and serotonergic neurotransmission. (10)

Depression has been associated with a high level of cortisol in the blood due to the hyperactivity of the HPA axis (endocrine pathways involving the hypothalamus, anterior pituitary gland, and adrenal gland), largely due to a hypersecretion of corticotropin releasing hormone (CRH). EPA may regulate the HPA axis dysfunction associated with depression by reducing corticotrophin releasing factor expression and corticosterone secretion. (10)

Several epidemiological studies reported a significant inverse correlation between intake of oily fish and depression or bipolar disorders. (136-138) Prospective studies suggest that omega-3 fatty acids appear to have a role as adjunctive therapy in patients with depression. A meta-analysis published in 2015, which included 19 trials, demonstrated a significant clinical benefit of omega-3 FA compared to placebo (0.38 SD; 95% CI: 0.18, 0.59). (139) Use of mainly EPA within the preparation, rather than DHA, influenced final clinical efficacy. Furthermore, significant clinical efficacy had the use of omega-3 PUFA as adjuvant rather than monotherapy.

A more recent Cochrane meta-analysis, published in 2021, evaluated 35 studies. Of these 35 studies, 34 studies (involving a total of 1924 participants) investigated the impact of omega-3 FA supplementation compared to placebo, while one study involving 60 participants investigated the impact of omega-3 FA supplementation compared to antidepressant treatment and the combination of both interventions. (140) For the placebo comparison, omega-3 FA supplementation resulted in a small benefit for depressive symptomology compared to placebo. Due to heterogeneity between studies, the confidence interval included both a possible clinically important effect and a possible negligible effect. The study comparing omega-FA to treatment with antidepressant comparison found no difference between the treatment groups in depressive symptomology, however the combination was superior to either intervention alone. (141) In an additional report, the authors of the latter study demonstrated that plasma cortisol decreased significantly after 8 weeks of intervention. (142)

A meta-analysis of omega-3 FA in depressed elderly patients demonstrated a benefit only in the elderly patients with mild to moderate depression. A study in adolescents with MDD demonstrated that monotherapy with omega-3 FA was no better than placebo. (143) The treatment efficacy of supplementation with omega-3 FA in depression is influenced by the proportion and dosage of EPA or DHA. A meta-analysis performed by Liao et al showed an overall beneficial effect of omega-3 FA on depression symptoms (SMD = −0.28, P = 0.004). (144) However, this benefit appeared to be restricted to the intake of EPA. Compared with placebo, EPA-pure and EPA-major formulations ($\geq$ 60% EPA) demonstrated clinical benefits, whereas DHA-pure and DHA-major formulations did not exhibit such benefits. This finding is consistent with that of a review by Song et al., which found that the ratio of EPA to DHA that would be most effective for depression was 2:1 or 3:1. (145) The study by Liao et al suggests that the optimal dose of EPA for the treatment of depression was a range of 720 mg/day to 1,000 mg/day. (144)

Current evidence supports the findings that omega-3 FA with EPA $\geq$ 60% at a dosage of approximately 1,000 mg/day (of active EPA and DHA) would have beneficial effects on depression and should be considered as adjunctive treatment in patients with MDD.

Magnesium

Magnesium (Mg) is the second-most abundant intracellular mineral, and it is required as a cofactor for over 300 enzymatic reactions. Thus, it is necessary for the biochemical functioning of numerous metabolic pathways. Magnesium participates in all reactions that involve the formation and utilization of adenosine-triphosphate (ATP) in energy metabolism. (146)

Magnesium-threonate or magnesium taurate at starting dose of 100 to 200 mg daily is suggested, increasing the dose as tolerated up to 300 mg (females) to 400 mg (males) daily.

Whenever neurons cannot generate sufficient ATP to keep their ion pumps working properly, membranes depolarize and excessive Ca2+ leaks into cells, triggering the synaptic release of glutamate, which further depolarizes neurons, further raising intracellular Ca2+, which causes even more glutamate to be released. This repeats in endless cycles, resulting in neuronal dysfunction and depression. (146)

Magnesium plays a key role in the regulation of N-methyl-D-aspartate (NMDA) receptor excitability in the brain. Mg is a naturally occurring NMDA-receptor antagonist and has effects in concentrations, which are physiologically occurring in the extrasynaptic space. (147)

Magnesium-deficiency causes NMDA coupled calcium channels to be biased towards opening, causing neuronal injury and neurological dysfunction, which may appear to humans as major depression. (146, 148) Ketamine is a NMDA receptor blocker and this may in part explain its antidepressant effect and its overlapping and synergistic clinical efficacy with magnesium supplementation. (148, 149) Additionally, magnesium deficiency has been shown to increase inflammatory mediators leading to neuroinflammation, which is said to enhance progression of cognitive impairment and dementia. (150, 151) Magnesium leads to synaptic strengthening, as measured by an increase in slow wave sleep in humans. (148) Patients with therapy refractory depression appear to have lower CNS Mg levels in comparison to health controls. (148) Experimental Mg depletion leads to depression- and anxiety like behavior in animal models. (148)

Intracellular concentrations of Mg are about four times extracellular and are regulated by several systems, including ion pumps and intracellular binding sites. (152) The blood–brain barrier and choroid plexus regulate CSF and brain Mg against acute changes in Mg concentrations, however during extended periods of Mg deficiency brain levels of Mg decrease. (153) Inadequate central nervous system concentration of Mg has a critical level below which neurological dysfunction occurs. (146)

Higher intake of Mg has been associated with lower depression symptoms. (154) Although serum magnesium concentration (rather than RBC magnesium) is a poor indicator of total magnesium stores, a systemic review by Yeo et al reported an association between decreased Mg levels and depression (WMD-.088, 95% CI -.164 to -.012). (155) Tarlton et al performed a cross-sectional analysis of medical records from 3,604 adults (mean age 62 years; 42% men)

seen in primary care clinics between 2015 and 2018. (156) Using univariate and multivariate analysis these authors reported a strong relationship between serum magnesium and depression. Cerebral spinal fluid magnesium has been found low in treatment-resistant suicidal depression and in patients who have attempted suicide. (146, 157)

A study based on data from the National Health and Nutrition Survey (NHANES) between 2011 and 2014, which included 2,508 participants aged 60 years and older, found that intake of total magnesium was independently associated with significantly higher global cognitive scores. (158) Similarly, Sun et al reported that dietary magnesium intake was inversely associated with the risk of depression in a linear manner. (159)

Wang et al performed a meta-analysis evaluating the role of “antioxidants” in the treatment of depression. (160) Eight studies evaluated the role of magnesium in the treatment of depression. In this study, treatment with magnesium was highly effective in the management of depression (SMD = 0.16, p = 0.03). Tarlton et al performed an open label, randomized, crossover trial in 126 adults (mean age 52; 38% male) diagnosed with mild-to-moderate symptoms of depression. (161) In this study, the active group received 248 mg of elemental magnesium per day for 6 weeks. Consumption of magnesium chloride for 6 weeks resulted in a clinically significant net improvement in depression scores and net improvement in Generalized Anxiety Disorders-7 scores (P<0.001). Afsharfar et al demonstrated that the daily intake of 500 mg magnesium oxide for at least 8 weeks improved Beck's test score and serum magnesium in depressed patients, but had no significant effect on brain derived neurotrophic factor (BDNF) levels between the two groups. (162) Saba performed an RCT evaluating the risk of depression in patients undergoing cardiac surgery. (163) Patients in the intervention group received two 250-mg magnesium oxide tablets for five days. At the end of the study, the mean level of anxiety and depression was significantly lower in the intervention group than the control group (p=0.007). Barragán-Rodríguez et al randomized 23 elderly patients with newly diagnosed depression, associated with type 2 diabetes and hypomagnesemia (serum magnesium levels < 1.8 mg/dL) to treatment with magnesium chloride (450 mg/day elemental magnesium) vs imipramine (50mg/day). (164) In this study, both treatments were equally efficacious in improving depression scores. Mehdi et al randomized patients with treatment resistant depression into a double-blind crossover trial to receive an infusion of 4 g of magnesium sulfate in 5% dextrose or placebo infusion of 5% dextrose with a 5-day washout in between the 8-day intervention period. (165) In this study, as serum magnesium increased from baseline to day 7, the depression score decreased significantly to day 7 (P = 0.02). Ryszewska-Pokrasniewicz et al performed a randomized, placebo-controlled study comparing fluoxetine and magnesium compared to fluoxetine and placebo in patients with refractory depression. (166) The magnesium group received low dose magnesium (120 mg/day as magnesium aspartate). The authors reported no significant differences in either Hamilton Depression Rating Scale scores or serum magnesium levels between the groups at any stage of treatment. This study emphasizes that the dose of magnesium should be sufficient to increase the serum/RBC magnesium level.

Hypomagnesemia may therefore play a role in depression with magnesium supplementation having a therapeutic role. There are however, at least 11 different types of magnesium that can be taken in supplement form with varying bioavailability. Generally, organic salts of Mg have a higher solubility than inorganic salts and have greater bioavailability. (167) Magnesium citrate is a widely used type of magnesium in salt form and is often recommended to treat constipation; high doses may cause diarrhea and prolonged use should be avoided.

Most magnesium compounds available on the market have low bioavailability and do not lead to increased magnesium levels in the brain because they cannot cross the blood–brain barrier. (168, 169) McKee et al demonstrated that hypermagnesemia induced by magnesium sulphate did not increase CSF magnesium levels. (168) Magnesium oxide and magnesium citrate compounds, commonly prescribed by physicians, have poor bioavailability (less than 5%). (170) Magnesium Malate, Taurate, Glycinate, and L-threonate have good bioavailability and will readily increase RBC magnesium levels. Magnesium taurate and magnesium L-threonate significantly increase magnesium levels in brain cells; hence they are used in the treatment of depression and Alzheimer's disease. (170, 171)

In experimental models, magnesium L-threonate has greater bioavailability, cerebral intraneural concentration and neurological benefits when compared to other magnesium supplements. (172-174) In addition, magnesium L-threonate was demonstrated to significantly elevate magnesium concentrations in cerebrospinal fluid in rats when administered orally, while other magnesium compounds could not. (172) Zhang et al performed a double-blind, placebo-controlled study, in which magnesium L-threonate was tested for its cognitive benefits in 109 healthy Chinese adults aged 18–65 years. (175) In this study, subjects receiving magnesium threonate showed significant improvements over the control group in all five subcategories of "The Clinical Memory Test" as well as the overall memory quotient scores. A randomized, double-blind, placebo-controlled study in older American adults demonstrated that supplementation with magnesium L-threonate significantly improved overall cognitive scores as compared to placebo ($p = 0.003$). (176)

Magnesium-threonate or magnesium taurate at starting dose of 100 to 200 mg daily is suggested, increasing the dose as tolerated up to 300 mg (females) to 400 mg daily. Endpoints of treatment include an RBC-Mag at the higher end of the normal range (between 4.2 and 6.8 mg/dL to be about 6.0 ng/dL).

Zinc

Zinc is an essential trace element important for many biochemical and physiological processes related to brain growth and function, as well as cellular metabolism. More than 300 enzymes require zinc for their activity. An antagonist of the glutamate/N-methyl-D-aspartate (NMDA) receptor, zinc has antidepressant activity in models of depression. Similarly to antidepressants, zinc induces brain derived neurotrophic factor (BDNF) gene expression. (177) In the hippocampus and cortex, zinc ions regulate synaptic transmission and act as neurotransmitters modulating many ligand- and voltage-gated ion channels. (177) Another possible reason for the

antidepressant effects of zinc may be the anti-inflammatory and antioxidant properties of zinc supplementation.

Empirical evidence supports a positive association between zinc deficiency and the risk of depression, and an inverse association between zinc supplementation and depressive symptoms. A meta-analysis of 17 observational studies found that blood zinc concentrations were approximately 0.12 μg/mL lower in depressed subjects than in control subjects. (178) High copper levels and a high copper/zinc ratio have been reported in women with post-partum depression. (179)

Intervention studies in both humans and rodents involving dietary or supplemental zinc have reported antidepressant-like and mood-enhancing activities of zinc. Randomized controlled trials among individuals with depression have demonstrated decreases in depressive symptoms when supplementing antidepressant drug treatments with zinc compared to antidepressants alone. A meta-analysis that included 4 studies of zinc supplementation as an adjunct to antidepressants drug treatment, demonstrated that zinc significantly lowered depressive symptom scores of depressed patients. (180)

Zinc supplements come in various forms, including zinc sulfate, zinc citrate, zinc gluconate, and zinc oxide. A daily dose of 20-30 mg is suggested. Due to competitive binding with the same gut transporter, prolonged high-dose zinc (> 50mg day) should be avoided, as this is associated with copper deficiency. (181)

Melatonin and Circadian Rhythm Resynchronization

Circulating melatonin (N-acetyl-5-methoxytryptamine) originates mainly from the pineal gland in all mammals. In humans, the circadian rhythm of pineal melatonin release is highly synchronized with the habitual hours of sleep, and the daily onset of melatonin secretion is well correlated with the onset of the steepest increase in nocturnal sleepiness. (182)

Melatonin is important for both the initiation and for maintenance of sleep. In all diurnal animals and in human beings, the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity. (182) Serum melatonin levels were reported to be significantly lower (and the time of peak melatonin values was delayed) in elderly subjects with insomnia compared with age-matched normal controls. (182-184)

Melatonin is colloquially referred to as the “hormone of darkness” since it is produced in response to darkness, as perceived by the eye’s retina. (185) Its synthesis is reduced by exposure to light, with artificial light reducing a person’s melatonin production. In the evening, the pineal gland begins to produce melatonin as light diminishes. Melatonin levels peak (about 80 pg/ml) during the mid-sleep cycle (3-4 am) and decrease with daylight (to about 20 mg/ml). It should be noted that melatonin production gradually declines as people age, starting in the late 20s to the 50s; over the age of 50, production of melatonin by the pineal gland is negligible.

(185) In addition to regulating the circadian rhythm melatonin is a pleotropic molecule known to be a potent antioxidant and anti-inflammatory agent.

Altered nocturnal melatonin production, abnormal circadian rhythm, and sleep disturbances are characteristic of depression. (186, 187) Studies have demonstrated a relationship between misalignment of circadian rhythm and severity of depression: the more delayed the more severe the symptoms of illness. (188, 189) Early morning insomnia and improvement in symptoms towards the end of the day are common symptoms of depression and point to a disturbance of the circadian rhythm. (186, 189) The amplitude of the nocturnal melatonin rhythm is frequently reported as blunted in major depression. However, it should be noted that melatonin secretion is markedly inhibited by benzodiazepines and β-blockers commonly used in patients with depression and insomnia. (190, 191)

Neuroinflammation and impaired autophagy are postulated to play a role in the pathogenesis of depression. In a lipopolysaccharide (LPS) depression model, melatonin was demonstrated to improve depressive-like behaviors, normalized autophagy related gene expression, and reduce the levels of proinflammatory cytokines. (192)

The use of agomelatine, a melatonin receptor agonist, as an antidepressant agent supports the concept that melatonin deficiency plays a pathogenetic role in depression. (193, 194) Furthermore, early evening melatonin combined with early morning bright light (blue light) therapy normalizes the circadian rhythm and improves depressive symptoms. (195-197)

Exposure to blue wavelength light in the morning suppresses melatonin and phase advances the circadian rhythm (i.e., sleep onset occurs earlier in the next period) while similar exposure in the evening leads to a phase delay (i.e., sleep onset will be pushed back later in the next period). This modifiability of the circadian rhythm by light exposure has led to efforts to use targeted phototherapy to treat circadian-related sleep problems. (198) A double-blind RCT in patients with mild traumatic brain injury demonstrated that morning blue light led to phase-advanced sleep timing, reduced daytime sleepiness, and improved executive functioning, and was associated with increased volume of the posterior thalamus, greater thalamo-cortical functional connectivity, and increased axonal integrity of these pathways. (198) Morning blue light therapy has been shown to be effective in the treatment of both seasonal affective disorder (SAD) and non-SAD depression. (196, 199, 200)

There are similarities between the widespread concern about vitamin D deficiency as a “sunlight deficiency” and reduced melatonin secretion because of “darkness deficiency” from overexposure to artificial blue light. (185) Blue-blocking glasses, also known as amber glasses, are plastic glasses that primarily block blue light. Blue-blocking glasses have also been studied as a treatment for insomnia, bipolar disorder, major depression, and postpartum depression. (197) Blue-blocking glasses improve sleep by inducing dim-light melatonin onset by reducing activation of intrinsically photosensitive retinal ganglion cells, which are most sensitive to blue light and are a major input for circadian regulation. Clinical research shows that blue-blocking glasses are effective for inducing sleep; they are a viable intervention to recommend to patients

with insomnia or a delayed sleep phase. (201) They should be used for a number of hours prior to going to bed.

We recommend melatonin starting at a dose of 0.75 – 1.0 mg taken an hour before going to bed; the dose should be increased as tolerated up to 5-10 mg. Some patients are intolerant to melatonin, having very disturbing and vivid dreams (hyper-REM sleep); hence we recommend a slow increase in the dose. Melatonin undergoes significant first pass metabolism in the liver with marked individual variation; this explains the wide dosing requirement. Furthermore, as melatonin has a short half-life (< 30 minutes) and to mimic the normal circadian pattern of endogenous melatonin release (blood profile) we suggest a slow release/extended-release formulation.

Curcumin

Curcumin is the main active component in the spice turmeric, which has been used for centuries in Ayurvedic medicine to treat a variety of conditions, including anxiety and depressive disorders. Curcumin has displayed effectiveness in modulating neurotransmitter concentrations, inflammatory pathways, excitotoxicity, neuroplasticity, hypothalamic–pituitary–adrenal disturbances, insulin resistance, oxidative and nitrosative stress, and endocannabinoid system, all of which can be involved in major depressive disease pathophysiology. (202) Curcumin has also been demonstrated to have NMDA receptor blocking activity.

Two meta-analyses have demonstrated the effectiveness of curcumin for the treatment of depression. The first one was in 2017 by Ng et al, which included six studies with a total of 377 patients comparing the use of curcumin to placebo, supporting a significant clinical efficacy in depression. (203) The second meta-analysis was conducted by Fusar-Poli et al, in which curcumin was evaluated as an add-on therapeutic; it included 10 studies with a total of 531 patients, and supported the efficacy of curcumin as an add-on. (204)

The use of curcumin has been limited by its poor solubility, absorption, and bioavailability. The manipulation and encapsulation of curcumin into a nanocarrier formulation can overcome these major drawbacks and potentially may lead to a far superior therapeutic efficacy. Nano-curcumin preparations or formulations designed to enhance absorption are recommended. A dose of nano-curcumin of 500 mg to 1,000 mg /day is generally recommended.

St. John's Wort

Extracts of the herb St. John's wort (botanical name *Hypericum perforatum*) have been used for hundreds of years to treat various conditions, including depressive disorders. The exact mechanism of action of the antidepressant effects of hypericum extracts is still unclear. Hypericum extracts contain at least five groups of components that may contribute to the pharmacological effects. These include naphthodianthrons, flavonoids, bioflavonoids, xanthons, and phloroglucinol derivatives.

A Cochrane review of St. John's wort for depression published in 2008 found a beneficial effect of St. John's wort compared to both placebo and other antidepressant therapies across 29 double-blind randomized controlled trials. (205) Apaydin et al performed an updated meta-analysis evaluating the role of St. John's wort in the treatment of depression. (206) Thirty-five studies examining 6,993 patients were included in this meta-analysis. St. John's wort was associated with more treatment responders than placebo (RR 1.53; 95 % CI 1.19, 1.97). The average response rate to treatment was 56% for St. John's wort compared to a response rate in patients treated with a placebo of 35%. Patients taking St. John's wort were not more likely to experience adverse events than patients receiving a placebo. However, in the included RCTs comparing St. John's wort to standard antidepressant medications, there was evidence that more patients taking antidepressants experienced adverse events (OR 0.67; CI 0.56, 0.81). Specifically, St John's wort was associated with fewer gastrointestinal, neurologic, and sexual adverse events. This study suggests that St. John's wort monotherapy for mild and moderate depression is superior to placebo in improving depression symptoms and not significantly different from antidepressant medication. (206) However, as for all the interventions listed in this monograph, we suggest a combination of multiple interventions that appear to act synergistically. St John's wort at a dose between 600 mg to 1,800 mg/day is recommended.

Saffron

Crocus sativus L. (saffron), belonging to the Iridaceae family, is one of the most expensive spices in the world, and it has been used as a medicinal plant in traditional Arabic and Islamic medicine for hundreds of years. Its major bioactive secondary metabolites, possessing a significant antioxidant activity, include crocin, picrocrocin, safranal, and crocetin. Several studies have demonstrated the antidepressant effects of crocin and crocetin. Toth performed a meta-analysis that included 11 studies evaluating the role of saffron in depressed patients. This study demonstrated that saffron was significantly more effective than placebo (g = 0.891; 95% CI: 0.369‑1.412, p = 0.001) and non-inferior to antidepressant drugs.

Saffron is usually dosed at 50 mg twice daily. (207)

A low insulinemic diet

A healthy diet is the cornerstone of physical, mental, and emotional well-being. Adherence to a healthy diet is associated with a lower risk of major chronic diseases (HR 0.58–0.80) including type 2 diabetes, cancer, cardiovascular disease, depression, and Alzheimer's disease. (208)

Low insulinemic (HR = 0.58, 95% CI = 0.57, 0.60), low inflammatory (HR = 0.61, 95% CI = 0.60, 0.63) or diabetes risk-reducing (HR = 0.70, 95% CI = 0.69, 0.72) diets have the largest risk reduction for these chronic disease as a composite and individually. (208)

We suggest a low insulinemic diet consisting of real food with the avoidance of processed foods combined with intermittent fasting/time restricted eating (see the IMA Eat Well Guide to healthy eating https://imahealth.org/protocol/eat-well-guide-to-fasting-and-healthy-eating/

Mental illness is a complex pathophysiological disease with heterogenous etiology. Convergent evidence suggests mental illness may be caused by a disruption in normal insulin signalling in the brain. (209) Individuals with Type 2 Diabetes Mellitus (T2DM), a disease characterized by impaired insulin sensitivity, have an increased risk of depression. In addition, individuals with metabolic risk factors for insulin resistance have a greater risk of suffering from depression. Clinical reports and meta-analyses indicate a correlation between T2D and depression with a bi-directional increased risk between both conditions. (210) Evidence of the involvement of insulin signaling on brain mechanisms related to depression indicate that insulin resistance, a hallmark of type 2 diabetes, could develop in the brains of depressive patients. (209, 210) Insulin signaling play a role in neuronal dysfunction and cognitive decline in Alzheimer's disease and it emerged as a possible mechanism underlying alterations in the brain and in behavior in mood disorders. (209-211)

Previously, the brain was considered an "insulin-insensitive organ" because, unlike in the periphery, insulin is not needed for glucose transport into the central nervous system. (212) However, insulin is a critically important neuropeptide needed for cognitive functioning as well as other neurotrophic, neuromodulatory and neuroprotective processes. (209, 212) Furthermore, insulin receptors are expressed throughout the brain, including regions classically involved with mood regulation, such as the nucleus accumbens, the ventral tegmental area, the amygdala, and the raphe nuclei. (210) The knockdown of insulin receptors in the hypothalamus of rats triggered depressive and anxiety-like behaviors in mice. Defective brain insulin signaling in T2D patients has been associated with impaired transport of the hormone across the blood-brain barrier. (213) Hippocampal neurogenesis, a process in which neural progenitors from the subgranular zone differentiate into new neurons at the dentate gyrus, is proposed to be involved with depression and to be impaired in diabetes. (214)

Brain insulin resistance is a shared metabolic abnormality amongst many individuals with T2DM and depression. Patients with T2DM with high glycemic control have reduced cognitive and depressive symptom burden. Based on this evidence, it is likely that the treatment of insulin resistance (by diet) may be useful in treating the symptoms of depression. (209) A ketogenic

diet may prove to be beneficial in the management of depression. (215) A recent report demonstrated that adherence to a Mediterranean diet is associated with lower depressive symptoms among U.S. adults. (216) Furthermore, a meta-analysis of 54 studies demonstrated that a Western dietary pattern was associated with increased risk of both depression (1.19; 95% CI: 1.06‑1.32) and depressive symptoms (1.20; 95% CI: 1.08‑1.34). (217)

Treatment of gut dysbiosis

Altered gut flora/dysbiosis has been linked to anxiety and depression and the use of probiotics has been associated with an improvement in mood. (218-222) Sanada et al performed a meta-analysis evaluating the change in the microbiome with depression and the clinical benefit of probiotics. (223) These authors reported that in the observational studies, significant reductions in several taxa at the family and genus levels were observed in patients with major depression compared to non-depressed controls. In the interventional studies with probiotics, a significant improvement was found in depressive symptomatology compared to controls (SMD = -1.62, 95% CI = -2.73 to -0.51, $p < 0.01$)

Unsweetened Greek yogurt with pre and probiotics is recommended. Suggested probiotics include Megasporebiotic (Microbiome labs) and TrueBifidoPro (US Enzymes) and yourgutplus+. (224) In addition, the use of Glucomannan (from Konjac root) and/or Chia seeds provide soluble and insoluble fiber required for the normalization of the microbiome. (225-227)

The consumption of fermented foods may be particularly important in restoring/maintaining a normal microbiome. Large cohort studies as well as limited interventional studies have linked the consumption of fermented foods with weight maintenance and decreased diabetes, cancer, and cardiovascular disease risks. (228)

Cognitive behavioral therapy and social support

Cognitive behavioral therapy (CBT) plays an important role in the management of depression. (229) CBT is based on a combination of basic behavioral and cognitive principles. CBT helps patients to understand and examine how their thoughts, moods, and behaviors interact in a way that can result in or worsen depression. Patients are taught how to replace dysfunctional thoughts and behaviors with more adaptive ones, which can reduce distress and improve mood.

Mindfulness-based cognitive therapy is a therapy that combines mindfulness meditation techniques with elements of cognitive-behavioral therapy. (230, 231) A metanalysis published in the British Medical Journal in 2015 which reviewed 11 studies found no statistically significant difference in effectiveness between second generation antidepressants (SSRI, SNIR, etc) and CBT for response, remission, or change the depression score. (232) However, Spielmans and colleagues found that bona fide CBT (by trained CBT therapists) resulted in

better outcomes that second generation antidepressants. (233) Furthermore, patients with pharmacotherapy-resistant depression may benefit from supplementing usual medication management with CBT. (234) In addition, traditional psychotherapy has a role in the treatment of depression, particularly in adults. (235)

Patients with depression are often socially isolated and going through life-changing stressor situations. The association between loneliness and depression is well documented. Cacioppo et al evidenced a strong association between loneliness and depression among older adults. (236) They also observed that loneliness and depressive symptomatology can act in a synergistic way to diminish well-being in middle-aged and older adults. In depressed people, feelings of loneliness are associated with having a small social network. (237) Further it should be recognized that older adults frequently have smaller social networks in comparison to younger adults. (238) Interventions should aim to increase social connections but also focus on maladaptive subjective feelings of loneliness. (239)

Exercise

There is growing recognition that lifestyle behaviors such as physical activity and exercise can be useful strategies for treating depression, reducing depressive symptoms, improving quality of life, and improving physical health outcomes. Cross-sectional studies have shown that people with higher levels of physical activity present decreased depressive symptoms, and these results are consistent across different countries and cultures. For example, recent evidence using data from the Brazilian National Health Survey, accounting for 59,399 individuals, demonstrated that a lack of physical activity for leisure was associated with depression in young males, middle age, and older adults. (240)

A study across 36 countries demonstrated that lower levels of physical activity (defined as less than 150 minutes of moderate-vigorous physical activity per week) were consistently associated with elevated depression (OR, 1.42; 95%CI, 1.24–1.63). (241) However, mental health benefits have been noted from being physically active, even at levels below the public health recommendations. (242) In The Irish Longitudinal Study on Ageing, participants performing 400 to less than 600 MET-min/wk had a 16% lower rate of depressive symptoms (adjusted incidence rate ratio [AIRR], 0.84; 95%CI, 0.81-0.86) and 43% lower odds of depression compared with 0 MET-min/wk. (243) These findings are consistent with recent meta-analytic data suggesting that salutary mental health benefits among adults can be achieved with physical activity below public health recommendations; specifically, an activity volume equivalent to 2.5 hours per week of brisk walking was associated with a 25% lower risk of depression, and half that activity volume was associated with an 18% lower risk compared with no activity. (242) The findings of The Irish Longitudinal Study on Ageing suggest that accumulating as little as 100 minutes per week or 20 minutes per day for 5 days per week of moderate-intensity activity (eg, brisk walking; 4 METs) may be sufficient to significantly lower the risk of depressive symptoms and odds of major depression over time among older adults.

A large body of trials has been performed over the last 40 years evaluating the role of exercise as a therapy for depression. These results have been summarized in several meta-analyses. A Cochrane analysis of 35 trials (1356 participants) comparing exercise with no treatment or a control intervention, the pooled outcome for the primary outcome of depression at the end of treatment was standardized mean difference (SMD) -0.62; 95% CI-0.81 to -0.42, indicating a moderate clinical effect. Schuch et al performed a meta-analysis that included 25 RCTs comparing exercise versus control comparison groups. (244) Overall, exercise had a large and significant effect on depression. Similarly, Krogh et al performed a meta-analysis that included 35 trials enrolling 2,498 participants. (245) The effect of exercise versus control on depression severity was −0.66 SMD (95% CI −0.86 to −0.46; p<0.001).

Exercise can improve depressive symptoms in people with depression. However, like other treatments, exercise is not a panacea and may not work equally for all. A seminal study by Dunn et al., the Depression Outcomes Study of Exercise, found a response rate of about 40% in depressed people free from other treatments. (246) However, it is likely that when combined with other interventions (i.e., vitamin D, L-methyl-folate, etc.) the response rate and degree of response will be much greater. In essence, exercise has multiple benefits to several domains of physical and mental health and should be promoted to everyone. To ensure compliance, adapting exercise prescription for people with depression should account for personal preferences and previous experiences in terms of making it the most enjoyable experience possible. Acute exercise should be used as a symptom management tool to improve mood in depression, with even light exercise an effective recommendation. (247) These data suggest that physical activity is beneficial for the depressed patient regardless of the intensity of the exercise.

The neurobiological mechanisms underpinning the antidepressant effects of exercise are largely unclear. However, some hypotheses involving inflammation, oxidative stress, and neuronal regeneration are speculated. Exercise training can promote increases in anti-inflammatory and antioxidant enzymes, referred to as a hormesis response and subsequently decrease IL-6 levels. This effect was demonstrated in the REGASSA trial, where decreases in IL-6 serum levels were associated with reductions in depressive symptoms. (248)

Sunshine

Sunlight is likely an essential human nutrient and humans may not survive healthily without sunlight. Sunlight has great therapeutic powers. Our forefathers roamed the earth and were exposed to sunlight on a daily basis, likely with profoundly important health benefits. (249) UV-B is essential for the synthesis of vitamin D in the skin. However, it is likely that the benefits of solar irradiation extend beyond UV-B. Near infra-red (NIR) radiation makes up about 40% of the solar radiation and likely has important health benefits (see photobiomodulation). There is strong evidence that with decreased sun exposure, the use of LED lights and E coating on glass human exposure to NIR has decreased significantly over the last century. NIR energizes mitochondria increasing ATP production. In addition, NIR increases daytime production of melatonin by mitochondria.(250, 251) Furthermore, NIR Increases HSP, activates cell stress

response, increases autophagy, increases microvascular blood flow, has anti-inflammatory properties and improves sleep. (250, 251)

During the 1918 influenza pandemic, "open-air treatment of influenzae" appeared to be the most effective treatment for seriously ill patients. (252) The Surgeon-General of Massachusetts at that time reported that "*plenty of air and sunshine*" was highly effective for the treatment of influenzae pneumonia. He reported that *"very little medicine was given after the value of plenty of air and sunshine had been demonstrated*."

A recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (253) In this study, the mortality rate amongst avoiders of sun exposure was approximately two-fold higher compared with the highest sun exposure group. Apart from UV radiation stimulating vitamin D synthesis, near-infrared (NIR) radiation has a profound effect on human physiology (as discussed above). (254)

A meta-analysis published in 2005, which included 8 studies evaluating the effect of "white light therapy" on depression, demonstrated a significant reduction in depression symptom severity (effect size of 0.84; 95% CI of 0.60 to 1.08). (255) Benedetti et al reported that hospitalized patients with bipolar depression who had exposure to morning sunlight had a significantly reduced length of hospital stay. (256) Wang et al interviewed 787 operating room nurses (ORNs) who work long hours in operating rooms and have limited sunlight exposure.(257) Mental health, sunlight exposure duration, sociodemographic and work-related variables, and chronic diseases were evaluated. In this study poor mental health was negatively associated with greater sunlight exposure hours per day. Furthermore, as the duration of sunlight exposure increased, survey respondents' mental health status improved. Using data from the Taiwan National Health Insurance Research Database Luo et al demonstrated that moderate levels of UVB lowered the risk of depression, while very high levels of UVB gradually increased the risk. (258) An association between lack of sunlight and schizophrenia relapse has been suggested. It was reported that people living in areas with longer and higher sunlight exposure levels exhibit fewer depressive symptoms and were less likely to report suicidal thought.(259) Additionally, seasonal increases in sunlight duration are associated with decreases in mental health distress. (260) It should be noted that decreased sunlight exposure is usually accompanied by a decrease in physical activity, which can cause neuroplasticity, inflammation, oxidative stress, and changes in the endocrine system.(257)

We suggest that patients expose themselves to about 30 minutes of midday sunshine whenever possible (at least 3 times a week). A brisk midday walk has a doubly beneficial effect, the exposure to sunlight and the health benefits of walking. (261, 262)

Photobiomodulation

Photobiomodulation (PBM) is referred to in the literature as low-level light therapy, red light therapy, and near-infrared (NIR) light therapy. The spectral radiance of solar radiation extends from 10 nm to about 3000 nm i.e., the spectrum from ultraviolet (10-400 nm), visible (400-700 nm with red light 600-700 nm), near-infrared radiation (750-1500 nm (NIR-A) and mid-infrared radiation (1500- 3000 nm (NIR-B). Of all the wavelengths of sunlight, NIR-A radiation has the

deepest penetration into tissues, being up to 23 cm. NIR-A in the range of 1000 to 1500 nm is optimal for heating tissues.

Transcranial photobiomodulation (t-PBM) with near-infrared light (NIR) penetrates the cerebral cortex, stimulating the mitochondrial respiratory chain, and significantly increases cerebral blood flow. Animal and human studies, using a variety of t-PBM settings and experimental models, suggest that t-PBM may have significant efficacy and good tolerability in MDD. It is important to consider whether t-PBM can even reach the brain. The light must pass through various layers of tissue and the skull, before reaching the cortex. This issue has been investigated in cadaveric studies which demonstrate that about 3% of the irradiation penetrates the skull and this is dependent on the energy (Watts) and wavelength with a wavelength of 810nm being optimal. (263-266) T-PBM with NIR light is often applied to the forehead because of the better penetration (no hair, longer wavelength).

Depression is associated with brain hypometabolism and cerebral as well as systemic mitochondrial dysfunction. (267-269) Several studies have demonstrated abnormalities in mitochondrial function in patients with depression. Multiple animal and human studies have found mitochondrial dysfunction in depression, with specific changes seen in respiration and generation of ATP. In a rat model of depression, complexes I, III, and IV of the electro transport chain (ETC) were inhibited in the cerebral cortex and cerebellum. (270) Changes in cytochrome oxidase activity have also been implicated in depression. (271) Changes in mitochondrial respiration in depression have been found outside of the central nervous system as well. Peripheral blood mononuclear cells of depressed patients were shown to have significantly impaired mitochondrial function. (272, 273) Greater mitochondrial dysfunction correlated with severity of neuro-vegetative symptoms, including fatigue and poor concentration. (272) Muscle biopsy samples from depressed patients with physical symptoms had a decreased rate of ATP production and more frequent mitochondrial DNA deletions than controls. (269)

Mitochondria are the main site of physiologic changes related to t-PBM. The primary mode of action of PBM is to enhance mitochondrial electron transport and the generation of ATP. The most well-studied mechanism of action of PBM centers around enhancing the activity of cytochrome C oxidase (CCO), which is unit four of the mitochondrial respiratory chain, responsible for the final reduction of oxygen to water. (274) The theory is that CCO enzyme activity may be inhibited by nitric oxide (NO). This inhibitory NO can be dissociated by photons of light that are absorbed by CCO. These absorption peaks are mainly in the red (600–700 nm) and near-infrared (760–940 nm) spectral regions. When NO is dissociated, the mitochondrial membrane potential is increased, more oxygen is consumed, more glucose is metabolized and more ATP is produced by the mitochondria. (275) t-PBM has been found to specifically increase CCO activity and expression. (274, 276, 277) Studies have also shown increases in complex II, III, and IV activity, as well as upregulation of gene coding for subunits of complex I, complex IV, and ATP synthase. (274) Low-level laser therapy has been shown to increase levels of ATP, the rate of oxygen consumption, and cerebral oxygenation. (274) Though t-PBM with red and NIR light can include wavelengths from 600 to 1070nm, specific wavelengths have been directly

linked to mitochondrial activity. 810 nm NIR activates CCO, increases mitochondrial oxygen consumption, and leads to higher levels of ATP. (278-280)

Ferraresi et al suggested that the ATP levels are highest about six hours following treatment. (281) There are however reports that a brief exposure to light can have effects lasting days, weeks or even months. (282) This long-lasting effect of light can only be explained by activation of signaling pathways and transcription factors that cause changes in protein expression that last for some considerable time. (275) The effects of PBM on stimulating mitochondrial activity and blood flow is of itself, unlikely to explain long-lasting effects.

While t-PBM is a relatively simple, safe, and inexpensive technology, clinical data is limited. In an open study, 10 patients with treatment resistant depression were treated with a single session of NIR t-PBM at two sites on the forehead. (283) At week 2 and 4 post-treatment, a significant decrease in symptoms of depression and anxiety were observed. The response rate of major depressive symptoms at week 2 was 40%. The ELATED-2 Pilot aimed to test the therapeutic benefit of t-PBM in patients with unipolar depression. (284) Twenty-one patients were randomized to twice weekly session of 20 mins of t-PBM (or sham) at a wavelength of 823nm directed at the dorsolateral prefrontal cortex. Compared to the sham group, those who underwent treatment with t-PBM had a significantly greater mean change in HAM-D_{17} score. Response and remission occurred in 50% of the subjects in the NIR arm. Comparatively, 27% of the sham group achieved response and 18% achieved remission. PBM is extremely safe with multiple studies demonstrating no significant difference in adverse effects between treatment and control groups. (274)

There is some evidence that PBM applied peripherally, not just transcranially, may have an effect in attenuating depressive symptoms. (274) There is no clear mechanism proposed explaining this effect. In a recent study, 5 outpatients with low-back pain and concurrent self-reported depression were treated over five weeks with physical therapy (PT) (5-sessions) and concurrent PBM (3-sessions) and matched to five control patients treated with PT alone (5-sessions). (285) Participants receiving s-PBM reported a larger decrease in their depression score. Oron and co-workers have shown that delivering NIR light to the mouse tibia resulted in improvement in a transgenic mouse model of Alzheimer's disease. (286)

Non-invasive brain stimulation

Non-invasive brain stimulation (NIBS) using transcranial direct current stimulation or transcranial magnetic stimulation has been demonstrated to be highly effective in the treatment of depression. (287-291) The Fisher Wallace Stimulator® is FDA approved for the treatment of depression, anxiety, and insomnia. NIBS is painless, extremely safe, and easy to administer. NIBS is a recognized therapy offered by many Physical Medicine and Rehabilitation Centers. Patients may also purchase an FDA-approved device for home use (https://www.fisherwallace.com/).

Whole-Body Hyperthermia

Historically and prior to pharmacological discoveries, depressive symptoms were commonly treated with hyperthermia interventions. In fact, evidence for the use of hyperthermia dates back as far as the times of Galen of Pergamon (129–198 C.E.) who reportedly treated melancholia successfully by bathing his patients in hot tubs and massaging their skin. (292)

Regular sauna bathing has been proven to reduce all-cause and cardiovascular mortality, prolong the lifespan and improve exercise performance. (293-296) Induced hyperthermia increases the expression of heat shock proteins, which activates autophagy. In addition, heat therapy increases the expression of cell stress pathways, has antioxidant and anti-inflammatory effects, and improves mitochondrial function. (297) Sauna bathing has very similar physiologic effects to that of aerobic exercise (increase heart rate, stroke volume, and cardiac output). (298, 299) Whole body hyperthermia (WBH) has been demonstrated to selectively increase IL-6 levels. (300) Waon therapy (infrared dry sauna) has shown promising results in patients with chronic fatigue syndrome. (301, 302)

Animal studies demonstrate that WBH activated subdivisions of the dorsal raphe nucleus implicated in mood regulation with antidepressant like responses. (303) In a pilot study conducted in 16 adults with MDD, a single session of WBH was significantly associated with a reduction in depressive symptoms when measured 5 days after treatment. (304) Janssen et al performed a randomized, double-blind study in 30 depressed patients where they compared whole-body hyperthermia (sauna like conditions) with a sham condition. (305) Patients received a single session of active whole-body hyperthermia (WBH) vs a sham condition matched for length of WBH that mimicked all aspects of WBH except intense heat. Remarkably, the active WBH group showed significantly reduced Depression Rating Scale scores across the 6-week postintervention study.

Hanusch et al performed a meta-analysis on the effect of WBH on indices of depression. (292) A total of 7 studies and 148 subjects were identified. Three out of seven studies utilized hot baths and 4/7 near infrared heating. Study duration ranged from 1 to 6 weeks with one or multiple interventions and an average treatment time of 66.37 min. Six out of seven studies found statistically significant reductions in depressive symptomology between 1- and 6-weeks post-intervention. In this meta-analysis the treatment effect was independent of total number of WBH sessions. Target temperatures between 38^{o}C and 39^{o}C and slower increase in core body temperature during the intervention resulted in larger treatment effects. This finding may explain the benefit of NIR sauna over regular sauna since the ambient temperature in a sauna is set at the beginning of the intervention and higher body temperatures may be reached. Furthermore, as discussed above NIR sauna may have additional benefits due to photobiomodulation. Patients interested in NIR sauna bathing should determine their tolerance to short sessions (5-10 mins) and increase the duration as tolerated (up to 20 minutes) two to three times a week (for maximal cardiovascular benefit). NIR sauna should be combined to the other interventions reviewed in this monograph.

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