COURSE #98160 — 5 CONTACT HOURS/CREDITS Release Date: 01/01/25 Expiration Date: 12/31/27

Alternative Therapies for Depression and Anxiety

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Chelsey McIntyre, PharmD, is a clinical pharmacist who specializes in drug information, literature analysis, and medical writing. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017, after which she spent the next six years as a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She continues to create rigorous professional analysis and patient education materials for various publications while also practicing as a hospital pharmacist. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care.

Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John V. Jurica, MD, MPH
Margaret Donohue, PhD
Alice Yick Flanagan, PhD, MSW
Mary Franks, MSN, APRN, FNP-C

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals whose patients are taking or are interested in using complementary therapies to manage symptoms of depression and/or anxiety.

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

As a Jointly Accredited Organization, NetCE is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. Regulatory boards are the final authority on courses accepted for continuing education credit.

American Psychological Association

Continuing Education (CE) credits for psychologists are provided through the co-sponsorship of the American Psychological Association (APA) Office of Continuing Education in Psychology (CEP). The APA CEP Office maintains responsibility for the content of the programs.

NetCE has been approved by NBCC as an Approved Continuing Education Provider, ACEP No. 6361. Programs that do not qualify for NBCC credit are clearly identified. NetCE is solely responsible for all aspects of the programs.

A complete Works Cited list begins on page 21.

Mention of commercial products does not indicate endorsement.

Designations of Credit

NetCE designates this enduring material for a maximum of 5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

This activity has been approved for the American Board of Anesthesiology's® (ABA) requirements for Part II: Lifelong Learning and Self-Assessment of the American Board of Anesthesiology's (ABA) redesigned Maintenance of Certification in Anesthesiology Program® (MOCA®), known as MOCA 2.0®. Please consult the ABA website, www.theABA.org, for a list of all MOCA 2.0 requirements. Maintenance of Certification in Anesthesiology Program® and MOCA® are registered certification marks of the American Board of Anesthesiology®. MOCA 2.0® is a trademark of the American Board of Anesthesiology®.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

This activity has been designated for 5 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Social workers completing this intermediate-to-advanced course receive 5 Clinical continuing education credits.

NetCE designates this continuing education activity for 1.5 NBCC clock hours.

NetCE designates this continuing education activity for 5 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-25-013-H01-P and JA4008164-0000-25-013-H01-T.

NetCE designates this continuing education activity for 5 CE credits.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

Individual State Behavioral Health Approvals

In addition to states that accept ASWB, NetCE is approved as a provider of continuing education by the following state boards: Alabama State Board of Social Work Examiners, Provider #0515; Florida Board of Clinical Social Work, Marriage and Family Therapy and Mental Health, Provider #50-2405; Illinois Division of Professional Regulation for Social Workers, License #159.001094; Illinois Division of Professional Regulation for Licensed Professional and Clinical Counselors, License #197.000185; Illinois Division of Professional Regulation for Marriage and Family Therapists, License #168.000190.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement
It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective
The purpose of this course is to help healthcare professionals in all practice settings increase their understanding of nutrients, lifestyle changes, complementary modalities, and herbal products that are often used by patients experiencing depression or anxiety.

Learning Objectives
Upon completion of this course, you should be able to:

1. Discuss the prevalence and severity of depression and anxiety in the U.S. adult population.
2. Provide counseling points for the safe and effective use of alternative modalities for anxiety and depression.
3. Review the evidence for herbal supplements commonly used for depression and anxiety.
4. Compare the evidence for vitamins and minerals in the management of mental health.
5. Consider the evidence for safe and appropriate use of alternative therapies during pregnancy and breastfeeding.

Pharmacy Technician Learning Objectives
Upon completion of this course, you should be able to:

1. Describe the prevalence and impact of mental disorders in the United States.
2. Outline alternative or complementary approaches to the treatment of depression and anxiety.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Mental health, which includes emotional, psychological and social well-being, affects the way that a person acts, thinks and feels. Although mental health has traditionally been considered separate from physical health, there has been a large and relatively successful movement toward recognizing mental health as equally important to physical health, and a core component of a person's overall well-being.

In fact, it is now well-established that mental health issues can increase a person's risk of physical health problems, such as diabetes, heart disease and stroke. Conversely, chronic physical health conditions can increase the risk for mental health concerns [1].

PREVALENCE AND IMPACT

In the United States, it is estimated that more than one in five adults (20%) live with a mental illness. This statistic covers what is referred to as "any mental illness," defined as a mental, behavioral or emotional disorder that can vary in its impact from mild to severe. In the United States, women are more likely to have a mental illness than men (27.2% vs. 18.1%) and younger adults are more likely to have a mental illness than older adults. In 2021, 34% of all adults 18 to 25 years of age had a mental illness, compared to 28% of adults 26 to 49 years of age and 15% of all adults 50 years of age and older [2]. The prevalence of mental illness in adolescents (12 to 17 years of age) is also increasing [3].

The majority of mental illnesses are classified as mild to moderate, meaning that they cause mild-to-moderate functional impairment. According to the National Institute of Mental Health, a mental illness is considered serious (or severe) if it "substantially interferes with or limits one or more major life activities" [2]. In 2021, it was estimated that 14 million adults (5.5%) had a serious mental illness. This suggests that about 75% of all mental illnesses in U.S. adults are classified as mild to moderate at any given time [2].

Even mental illness that is not considered severe can have serious long-term impacts if not addressed. Mental illness is known to cause significant disability and can even contribute to premature mortality. The Global Burden of Disease study attributes nearly 15% of years of life lost to mental disorders, making mental illnesses one of the largest causes of disability worldwide [4].

Mental illness is also known to increase the number of "deaths of despair." These deaths from drugs, alcohol, and suicide—which tend to be caused by mental health difficulties, as well as pain and economic distress—more than doubled between the 1960s and 2017 and have continued to rise [5]. Adolescents and younger adults have not been immune to this increase. In the decade prior to 2018, suicide death rates among individuals 10 to 24 years of age increased by 47% [6].

AN OVERVIEW OF COMMON MENTAL HEALTH DISORDERS

DEPRESSION

Depression is one of the most common mental illnesses reported in the United States. In 2021, 21 million U.S. adults (8.3%) had at least one major depressive episode. This rate was highest in those 18 to 25 years of age (18.6%). Major depressive episodes resulting in severe impairment affected 5.7% of all U.S. adults in 2021. That same year, 5 million adolescents—representing about 20% of those 12 to 17 years of age—reported major depressive episodes. This rate was much higher in girls than boys, at 29% and 11.5%, respectively [2].

Major depressive disorder (MDD) is defined in the revised fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) as a period of at least two weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities, and had a majority of specified symptoms, such as problems with sleep, eating, energy, concentration, or self-worth [7].

The prevalence of depression in the general population increased significantly during the COVID-19 pandemic. According to a scientific brief published by the World Health Organization (WHO) in early 2022, the global prevalence of depression increased by 27.6% in the preceding year. Women were more affected than men, and younger adults (especially those 20 to 24 years of age) were most affected [8].

Seasonal Depression

Some forms of depression manifest only at certain times. One such form that affects many adults in the United States, but with a more intermittent impact, is seasonal affective disorder (SAD), also known as seasonal depression or winter depression. This mental illness is identified in the DSM-5-TR as a type of depression (Major Depressive Disorder with a Seasonal Pattern) [9].

People with seasonal depression experience mood changes and symptoms similar to other forms of depression. The symptoms usually occur during the fall and winter months—comprising about 40% of the calendar year—when there is less sunlight. In the United States, the most difficult months tend to be January and February, with the majority of people experiencing improvement with the arrival of spring. This form of depression is estimated to affect 5% of all U.S. adults. As with other forms of depression, it is more common women than in men [9].

Postpartum Depression

Postpartum depression is another important form of depression that manifests only at certain times, in this case, after giving birth. This should not be confused with what is sometimes referred to as the "baby blues," which often resolves within a few days of delivery. Rather, postpartum depression is more intense, lasts much longer, and mirrors the symptoms of MDD. For some patients, this manifests as crying more often, feelings of anger, withdrawing from loved ones, feeling numb or disconnected from the newborn, and feelings of guilt [10].

Some adults are at a higher risk of postpartum depression, including those who have recently experienced stressful life events, experienced pregnancy complications, have low social support, have a previous history (or family history) of depression, delivered preterm, and/or gave birth to multiple newborns at once. However, it can also affect otherwise healthy adults with no apparent risk factors [10].

This form of depression seems to occur in about one of eight adults (13%) who have recently given birth in the United States. This rate is higher (greater than 20%) in those who were 19 years of age or younger at the time of delivery. Due to this high prevalence, experts recommend that all pregnant adults be screened for depression [11].

ANXIETY

Anxiety is another common mental illness in the United States, although it can take many forms. When referred to under the general umbrella of anxiety, this can include generalized anxiety disorder (GAD), panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, and separation anxiety disorder, among others.

Most adults diagnosed with anxiety are considered to have GAD. This is characterized by excessive worry that is difficult to control and is accompanied by physical symptoms like restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and/or sleep disturbance. In 2019, approximately 15% of adults had experienced symptoms of anxiety of some level in the past two weeks, with 9.5%, 3.4%, and 2.7% of adults experiencing mild, moderate, or severe symptoms of anxiety, respectively [12].

Anxiety symptoms were most common in those 18 to 29 years of age. In this age group, about 20% experienced any symptoms, with 12% experiencing mild symptoms, 5% moderate, and 3% severe. More than 19% of women reported symptoms of anxiety in the past two weeks, compared with 12% of men [12].

Symptoms of anxiety are often assessed using the GAD-7 scale, which is a validated brief self-report screening that can assess the severity of symptoms. Adults with GAD-7 scores of 0–4 are considered to have no or minimal symptoms; those with scores of 5–9, 10–14, or 15–21 are considered to have mild, moderate, or severe symptoms, respectively [13].

As with depression, the COVID-19 pandemic led to a notable global increase in the prevalence of anxiety. The same WHO report that identified an increase in symptoms of depression also identified a 25.6% increase in the prevalence of anxiety disorders during the first year of the pandemic. As with depression, women and adults 20 to 24 years of age were most affected [8].

In the United States, as many as 40% of all adults reported symptoms consistent with anxiety and depression during the first year of the pandemic. This declined to about 30% of all adults as the pandemic continued into 2022 and 2023. A full 50% of young adults (18 to 24 years of age) reported anxiety and depression symptoms in 2023, with women reporting symptoms of anxiety and/or depression at a rate of 36% (compared with 28% of men) [14].

OTHER MENTAL ILLNESSES

Many other conditions fall under the umbrella of "mental illness" and affect adults and adolescents in the United States. Some examples of these conditions include attention deficit hyperactivity disorder (ADHD), psychotic disorders, post-traumatic stress disorder (PTSD), bipolar disorder, eating disorders, and more.

Due to the severity and specificity of these conditions, these mental illnesses will not be covered in this course. Similarly, severe depression and anxiety are also not within the scope of this course. The research discussed will instead focus on adults with mild-to-moderate depression and anxiety.

AN IMPORTANT NOTE ABOUT TREATMENT AND DIAGNOSIS

Mental illnesses should always be taken seriously, even in patients who report only mild or moderate impairment. Screening for these conditions should occur consistently, in alignment with national recommendations. Any patients identified as having a mental illness should be provided with referrals for appropriate and evidence-based treatment options.

Unfortunately, due to an ongoing shortage of behavioral health workers, patients may experience difficulties accessing standard treatments, such as counseling and support groups. For patients who are experiencing more modest impairment from a mental health condition, or for those who are waitlisted with a specialized provider, alternative therapies may be considered as a stopgap measure. Additionally, for patients who are currently receiving recommended treatment, alternative therapies may be considered as supplemental treatment options.

Alternative treatment options should never be considered or relied upon as a replacement for evidence-based care in a patient with a serious mental health disorder or in a patient experiencing symptoms of suicidality.

EXERCISE-BASED THERAPIES

Over the years, exercise has become a well-accepted tool for the management of depression and anxiety. In fact, the American Psychiatric Association (APA)'s guideline on the treatment of depression acknowledges exercise as a relevant and beneficial treatment modality for all severities of depression. For mild depression, the guideline indicates that a patient may elect to try exercise as a sole treatment for their symptoms for the first several weeks. As for patients with more severe depression and/or those who are using other treatments, exercise is considered a reasonable addition to any treatment plan [15].

For adults with depression for whom psychotherapy or pharmacotherapy is either ineffective or unacceptable, the American Psychological Association suggests exercise monotherapy.

(https://www.apa.org/depression-guideline/guideline.pdf. Last accessed December 17, 2024.)

Strength of recommendation: Conditional

A 2023 meta-analysis pooled together more than 90 studies to assess the overarching benefits of exercise for the management of depression, anxiety, and stress. The analysis found that physical activity had medium benefits for all three conditions when compared with usual care. Some of the largest benefits were seen in people with depression, certain chronic conditions, and pregnant and postpartum females. Higher intensity interventions were associated with greater improvements, although the benefits of physical activity appeared to wane over time [16].

A separate, large meta-analysis pooled data from more than 200 studies in people with depression. That analysis determined that certain forms of exercise, including walking or jogging, strength training, mixed aerobic exercises, yoga, and tai chi or qi gong, offered the greatest benefits. Here, we will review the evidence for these last three forms of physical activity, all of which contain a meditative component.

YOGA

Yoga is a form of meditative physical activity that originated from a traditional system of medicine in India: Ayurveda. Yoga generally involves controlled breathing, meditation, and body posturing, although there are many subtypes of yoga which involve differing levels of physical activity.

The evidence to date indicates that practicing yoga for one to two months can improve symptoms of depression in people with mild or new-onset depression. Additionally, it appears to be beneficial as an adjunct therapy in people who are taking conven-

tional antidepressants. Importantly, most of these studies evaluated the use of "Western yoga," which tends to entail a greater focus on physical yoga poses [17].

Research on the use of yoga for anxiety is limited to smaller clinical studies. However, that research does suggest that practicing differing styles of yoga can modestly improve symptoms of anxiety when compared with a control or other active treatment [17].

Yoga is generally considered safe, with temporary musculoskeletal pain as the most common adverse effect. For adults with limited prior exercise, mobility concerns, or other serious health issues, encourage a consultation with a trained practitioner prior to participation in yoga.

Pregnancy and Breastfeeding

A number of studies have evaluated the benefits of yoga during pregnancy. Most of these studies suggest that practicing yoga during pregnancy reduces the rate of depression. However, some studies have yielded conflicting findings, which may be associated with whether or not the person already had depression at the start of the study. Some studies have also evaluated yoga for the management of anxiety during pregnancy, finding modest benefits when compared with either baseline or a control group [18; 19; 20; 21].

Importantly, these studies all indicate that yoga is generally safe during pregnancy and does not adversely affect the child's outcomes. However, aggressive or more extreme forms of yoga, such as hot yoga, should likely be avoided during pregnancy.

QI GONG AND TAI CHI

Qi gong is a martial art-like exercise with a focus on meditation and breathing that originated in China. It is intended to regulate the body's qi (vital energy or life force). There are several varieties of qi gong, with some that involve slow movements and exercise and others that involve bodywork conducted by a trained practitioner [22].

Tai chi is one specific form of qi gong that has become relatively popular in North America. This form of exercise involves controlled breathing and slow, rhythmic body movements which are intended to facilitate the flow of qi [23].

Small clinical studies suggest that practicing qi gong for 90 to 350 minutes each week for up to four months can reduce symptoms of depression when compared with various control groups [22]. Tai chi has also been evaluated in people with depression, although these studies have been relatively small. While one study suggests that practicing tai chi for two hours weekly for 10 weeks can improve symptoms when compared with simple health education, a follow-up study in this same group of patients did not ultimately identify additional benefit with tai chi [23; 24].

A meta-analysis of 10 clinical studies in healthy adults, some of which were low-quality and not randomized, shows that practicing tai chi five times weekly for a year can modestly improve anxiety symptoms when compared with a waitlist or control group. However, it did not seem to improve depressive symptoms or stress [25].

Qi gong and tai chi are generally considered safe; temporary musculoskeletal pain is the most common adverse effect of qi gong. However, for adults with limited prior exercise, mobility concerns, or other serious health issues, encourage a consultation with a trained practitioner prior to participation.

Pregnancy and Breastfeeding

There is little to no research evaluating the benefits or safety of qi gong or tai chi while pregnant or breastfeeding. Advise patients to consult with a trained professional before initiating tai chi or any other exercise program when pregnant or breastfeeding.

ALTERNATIVE MODALITIES

For patients who are interested in pursuing alternative treatment options that do not involve the use of an oral supplement, a variety of other modalities have been evaluated for both anxiety and depression. However, it is important to note that many of these modalities have been studied in conjunction with the use of conventional treatment options, including antidepressants and therapy.

ACUPUNCTURE

Acupoint therapies, which utilize concepts based in traditional Chinese medicine, have grown in popularity over recent years. These include acupuncture, acupressure, moxibustion, and acustimulation.

Although there is general interest in the use of these therapies for the management of depression and anxiety, the best evidence is for acupuncture. Most clinical studies suggest that acupuncture can reduce symptoms of depression when used as an adjunct to conventional therapy. These studies suggest that acupuncture can improve the rate of treatment response with conventional antidepressants and may also reduce remission rates [26; 27]. Importantly, most of these studies were of low quality and conducted in a single country (outside of the United States); their relevance to the typical patient with depression in North America remains unclear.

Acupuncture is considered generally safe, so long as it is performed in a hygienic environment with sterilized needles by a licensed practitioner using appropriate techniques. The most common adverse effects include bruising, pain, and swelling at the site of needle entry.

Pregnancy and Breastfeeding

Small clinical studies have evaluated acupuncture for postpartum depression, suggesting that there may be a small benefit when acupuncture is added to conventional antidepressants [28]. Generally, research with traditional acupuncture during pregnancy has not identified any safety concerns for the unborn baby. However, there is one specific acupoint (SP6) which may be unsafe to stimulate during pregnancy, as it has been associated with an increased risk for early contractions and miscarriage [29].

It is unclear if laser acupuncture or electroacupuncture are safe during pregnancy. Additionally, there is little to no research evaluating the safety of acupuncture while breastfeeding. Counsel patients to consult with a licensed practitioner prior to undergoing any form of acupuncture while pregnant or breastfeeding.

ANIMAL-ASSISTED THERAPY

Animal-assisted therapy, as the name implies, involves using a trained animal to help with either recovery from or coping with various health conditions. This form of therapy has been used for the management of both physical and mental illness.

Clinical research has found that single sessions of various types of animal-assisted therapy can improve short-lived situational symptoms of anxiety (often self-reported). These studies mostly involved a dog as part of individual or group therapy and the sessions lasted for 8 to 30 minutes [30; 31]. The benefit is similar to that seen with therapeutic recreation sessions or interactions with social workers, suggesting that animal-assisted therapy may be a reasonable adjunct to various other anxiety treatments. Research on the use of animal-assisted therapy for depression, however, is limited and inconclusive.

Animal-assisted therapy is generally safe for most people, although people who are at increased risk of infection should take appropriate precautions. Additionally, allergies may be an important consideration for some individuals.

EXPRESSIVE THERAPIES (MUSIC AND ART)

Expressive therapies combine some form of artistic expression with some form of therapy. This artistic expression can include art, music, dance, drama, poetry, or creative writing. Two specific forms of expressive therapy—art and music—have shown benefit for symptoms of anxiety and depression.

The best evidence for both forms of expressive therapy is in the management of depression. Various forms of art therapy can improve symptoms of depression, from adolescents to the elderly. Research has shown that art therapy, in the form of regular sessions over 10 to 20 weeks, can offer modest benefit as an adjunct to conventional antidepressants or as monotherapy [32; 33]. Similarly, music therapy has shown benefit for symptoms of depression across various age groups. This therapy may include listening to and/or making music, with or without the presence of a therapist. In most cases, the patients in these studies were already taking a conventional antidepressant [34; 35].

There is also a large body of evidence showing that music therapy can benefit people with symptoms of anxiety. In these studies, music therapy had a small to medium benefit in a variety of patients, including postpartum adults, people with a variety of underlying health conditions, and adolescents. These benefits appear to be short-term, however, and do not seem to continue after the therapy has ended [36]. Some small clinical studies have also shown modest benefit with art therapy, particularly in the elderly or in women with various anxiety disorders. In most of these studies, 10 to 12 art therapy sessions occurred over about three months [37; 38].

Particularly for patients who already enjoy music and/or art, these expressive therapies could be considered as safe adjunctive modalities for managing symptoms of depression and anxiety.

Pregnancy and Breastfeeding

Some small clinical studies suggest that music therapy may be beneficial for postpartum depression, although those same studies did not find benefit for postpartum anxiety [39]. Art therapy has not been adequately evaluated for the management of perinatal or postpartum depression or anxiety.

Although neither modality has been extensively evaluated for safety during pregnancy or breastfeeding, there are no reasons to expect safety concerns so long as adequate precautions (e.g., avoidance of loud noises) are taken.

MINDFULNESS

Mindfulness, a practice derived from Buddhist theory, has also become popular for general well-being and the management of mild to moderate mental health concerns. Mindfulness involves a purposeful attention and awareness of present thoughts, emotions, and sensations without evaluation or judgment of what is occurring.

Mindfulness-based stress reduction (MBSR) is a well-studied and standardized mindfulness practice. It usually includes eight weekly 2.5-hour sessions, as well as daily home recordings of mindfulness exercises and a half-day retreat after the sixth class [40]. It includes three main components:

- Didactic material that explains the concept of mindfulness
- Practicing mindfulness exercises during group sessions and at home
- Discussing and sharing MBSR experiences with a group

In general, mindfulness seems to modestly reduce anxiety, although benefits appear to be short-term. It is unclear how mindfulness or MBSR compares with other nonpharmacologic treatment options. Meta-analyses, small clinical studies, and observational research in patients with various forms of anxiety, or without diagnosed anxiety, show that practicing MBSR or modified MBSR improves anxiety severity

when compared with baseline or no intervention [41; 42; 43]. One large clinical trial shows that practicing MBSR for eight weeks may be as effective as taking escitalopram [44].

Most clinical research also shows that mindfulness can reduce symptoms of depression. These studies evaluated MBSR, as well as another form of mindfulness known as mindfulness-based cognitive therapy (MBCT) [45]. Although most studies have evaluated only the short-term effects of these modalities, MBCT does appear to reduce the risk of depressive relapse within 60 weeks of treatment [46].

Considering that MBSR has also shown benefit for the management of stress, mindfulness may be of particular interest to patients who experience mild and intermittent symptoms of anxiety or depression.

Pregnancy and Breastfeeding

Mindfulness during pregnancy or breastfeeding has not been well-researched. That being said, mindfulness is considered safe in the general population and in people with various chronic conditions, with no reason to expect adverse effects.

RELAXATION THERAPY

Relaxation therapy involves the teaching of various skills and methods to achieve relaxation, including imagery, breathing exercises, focused muscle tensing and relaxing, and cue-controlled relaxation. Patients are instructed to practice these methods on a regular basis.

Clinical research shows that relaxation therapy can improve symptoms of anxiety in people with anxiety disorders or situational anxiety and can also improve symptoms of depression in people with MDD. However, in both cases, it appears to be less effective than cognitive-behavioral therapy (CBT) or certain forms of meditation [47; 48].

Although the benefits of relaxation therapy may be modest at best, it is a generally safe modality that can be integrated into everyday life.

Pregnancy and Breastfeeding

In a small clinical study, relaxation therapy has demonstrated modest benefit for symptoms of depression and anxiety in perinatal adults [49]. Although research in those who are pregnant or breastfeeding has been limited to date, there is no reason to expect safety concerns with the use of relaxation therapy.

LIGHT THERAPY

Also known as phototherapy, light therapy involves exposing the skin to specific wavelengths of light. This modality is of particular interest, and has shown particular benefit, in the management of seasonal depression.

Clinical research shows that light therapy, delivered at a brightness of 3,000–10,000 lux, reduces symptoms of seasonal depression and may be similarly effective to fluoxetine 20 mg daily [50]. Higher intensity light therapy appears to be more effective than dimmer therapy, and blue and green wavelengths appear to be more beneficial than red wavelengths [50; 51]. In most studies, patients have been exposed to a light placed 12–18 inches away from the face for 30 minutes to 3 hours each day.

Light therapy for seasonal depression does not include ultraviolet (UV) wavelengths and is thus considered safe for use. When the appropriate wavelengths and brightness are employed, light therapy has not been associated with adverse effects.

For patients with mild-to-moderate major depressive disorder with or without a seasonal pattern (formerly seasonal affective disorder), the Department of Defense/Veterans Affairs suggest offering light therapy.

(https://www.healthquality.va.gov/guidelines/MH/mdd/VADODMDDCPGFinal508.pdf. Last accessed December 17, 2024.)

Strength of recommendation: Weak for

Pregnancy and Breastfeeding

One very small clinical study suggests that light therapy may be beneficial for untreated perinatal or postpartum depression. In this study, bright light therapy was associated with remission in 42% of patients, compared with 0% of the patients who received placebo (low-light) therapy. This study was too small to determine whether there were any adverse effects to the fetus [52].

Although there is no reason to suspect that light therapy would cause harm to an unborn baby, counsel patients to ensure that light is directed to the face and used at the appropriate wavelength, brightness, and duration.

DIETARY SUPPLEMENTS

A variety of supplements, including herbal products, vitamins, minerals, and other naturally occurring chemicals, have been proposed for use in the treatment of mild-to-moderate depression and anxiety. Unfortunately, the evidence to support the use of these supplements is not typically of the same size and quality as the evidence for prescription medications. Additionally, just like prescription drugs, many supplements have the potential to cause drug interactions. These considerations should be kept in mind while reviewing the options discussed here.

HERBAL SUPPLEMENTS

St. John's Wort

St. John's wort (*Hypericum perforatum*) is a plant with a yellow, star-shaped flower. Extracts of the plant are known to affect the neurotransmitters serotonin, dopamine, and norephinephrine, possibly limiting their reuptake. It has been extensively studied for the treatment of mild or moderate depression, with most studies showing evidence of benefit.

Many individual clinical trials show that St. John's wort extracts are more effective than placebo and may be as effective as selective serotonin reuptake inhibitors (SSRIs) for treating depression. It is important to note that the benefits of St. John's wort are only seen with certain extracts that contain specific amounts of chemicals found in the plant. The extracts that have shown benefit in clinical research contain 0.3% hypericin and 1% to 4% hyperforin. If a patient purchases a St. John's wort product that contains differing quantities of these chemicals, they may have a reduced likelihood of benefit [53].

St. John's wort extracts may have a lower rate of various adverse effects than conventional antidepressants, including gastrointestinal, neurological, and sexual adverse effects [53]. That being said, St. John's wort does seem to cause adverse effects, including gastrointestinal upset, fatigue, sedation, dizziness, headache, and dry mouth. Additionally, it can cause photodermatitis, a risk that appears to increase with the dose of hypericin, with most events reported in people takin hypericin 5–10 mg daily [54].

St. John's wort is notorious for its ability to interact with many prescription drugs. This herb can induce cytochrome P450 (CYP) 3A4, which is responsible for metabolizing many drugs. This can reduce the levels and efficacy of a wide range of medications, including birth control, immunosuppressants, and certain anticoagulants [54]. Also, because St. John's wort has serotonergic activity, it can cause serious interactions with other serotonergic drugs, and even increase the risk for serotonin syndrome [54; 55].

Due to its popularity and the amount of research conducted to date, St. John's wort is discussed in some clinical guidelines, including those from the American College of Physicians (ACP). Although the ACP acknowledges the available evidence, it stops short of recommending this extract for the treatment of depression due to the fact that it may be difficult for patients to obtain a product of adequate quality and with the appropriate amount of hypericin and hyperforin. Conversely, an international guideline

from the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce recommends St. John's wort at doses of 600–1,800 mg daily as monotherapy for mild-to-moderate forms of MDD [54].

Pregnancy and Breastfeeding

St. John's wort extracts may be unsafe for use during pregnancy and should be avoided. An observational study identified an association between the use of St. John's wort and birth defects, including neural tube, urinary, and cardiovascular malformations [57].

The safety of taking St. John's wort extracts while breastfeeding is unclear. Inconclusive reports suggest that infants exposed to St. John's wort via human milk may have a higher chance of colic, drowsiness, and lethargy. Until more is known, recommend that patients avoid St. John's wort while breastfeeding [58; 59].

Saffron

Saffron, derived from the flower of *Crocus sativa*, is perhaps best known for its use as a vibrant red-orange spice. However, it has recently been gaining popularity for use in the treatment of both depression and anxiety.

The most extensive evidence to date is for the use of saffron extract for the treatment of depression, either alone or in combination with conventional antidepressants. Clinical research shows that taking saffron extract 30 mg daily, or taking dried saffron stigma 100 mg daily, for up to three months improves symptoms of depression when compared with a control group. When compared with a variety of antidepressants, including SSRIs, it seems to have a comparable effect [60; 61]. When used in combination with an SSRI, some research suggests that saffron may provide a further modest reduction in depressive symptoms [62].

The evidence for anxiety, on the other hand, is less robust. Only a couple of small clinical studies have evaluated saffron for this purpose. Although both suggest that saffron may modestly improve symptoms of mild-to-moderate anxiety, more research is needed to confirm this finding [63; 64].

Overall, saffron seems to be well tolerated, with the most common adverse effects including gastrointestinal complaints, nausea, vomiting, and sedation. Unlike St. John's wort, saffron has not been associated with major drug interactions to date [60].

The same international guideline that recommends St. John's wort for the treatment of depression (from WFSBP and CANMAT) also provisionally recommends saffron 30 mg daily for either monotherapy or as an adjunct treatment in mild to moderate depression [54].

Anyone who has purchased saffron as a spice knows that it can be quite expensive. In fact, saffron is one of the most expensive spices on the planet. This is because one pound of saffron requires approximately 225,000 hand-picked stigmas or 75,000 flower blossoms [65; 66].

Unfortunately, this means that saffron products are at high risk for adulteration, with some manufacturers using other ingredients (such as red-colored corn, pomegranate fruit peel, red-dyed silk fibers, and more) to replace saffron due to its high price and limited availability [67]. Caution patients to only purchase products with verified ingredients.

Pregnancy and Breastfeeding

When taken in medicinal doses, saffron may be unsafe for use during pregnancy. Although there has been little to no research conducted on this topic, there is a hypothetical concern that saffron can stimulate the uterus and increase the risk of miscarriage [68].

One small clinical study suggests that taking saffron 30 mg daily may be as effective as fluoxetine in patients with postpartum depression. However, the study lasted only six weeks, and fluoxetine may take up to six weeks to reach its full effect [69]. Additionally, this study did not evaluate whether saffron was safe while breastfeeding.

There is no reliable evidence available regarding the safety of saffron while breastfeeding. It is not known whether saffron transfers into human milk; there is also no research available on the safety of saffron in newborns. Until more is known, caution patients to avoid saffron supplements while breastfeeding.

Lavender

Lavender (*Lavandula angustifolia)*, a popular evergreen herb with a purple flower, is known for its pleasant scent, which is used in a variety of bath products and perfumes. Over the years, lavender has also gained popularity for use in the management of depression and anxiety, both when taken by mouth and when inhaled as aromatherapy.

When it comes to anxiety, the strongest available evidence has evaluated only one specific lavender oil extract (Silexan) that is taken by mouth. This extract has been studied at doses of 80–160 mg orally daily for up to 2.5 months, and research shows that it improves anxiety when compared with placebo [70; 71]. Lavender oil aromatherapy has also been evaluated for the management of both chronic and situational anxiety, for which it seems to moderately reduce symptoms when compared with a control group [70; 72; 73].

Clinical research on the use of oral lavender for depression has also shown benefits when compared with placebo. These studies have evaluated lavender in the form of a tea, a tincture, a powder, or the specific oil product that has also been studied for anxiety (Silexan) [74; 75]. Although the quality of the available research varies, oral lavender seems to modestly improve depression scores. Lavender oil aromatherapy also seems to offer some benefit for reducing symptoms of depression [75].

It is important to note that most of the available research on the use of lavender oil aromatherapy has evaluated a single dose only. Additionally, the control groups in these studies either receive no intervention at all or are asked to inhale water or lemon juice. Thus, it is difficult to ensure adequate blinding when studying the effects of aromatherapy, as patients will likely be aware of which group they have been assigned to based on the scent inhaled.

Oral lavender seems to be generally well-tolerated, although it has been reported to cause some gastrointestinal disturbance, such as constipation, diarrhea, and dyspepsia, as well as headache and breath odor. Inhaled lavender has not been associated with any serious adverse effects, although some patients who have applied lavender oil to the skin have experienced allergic reactions [76].

The international guideline from WFSBP and CANMAT provides a weak recommendation for the use of either oral lavender oil at a dose of 80–160 mg daily, or the use of dried lavender flower at a dose of 500–1,500 mg twice daily, as either monotherapy or as an adjunct for the treatment of MDD [54].

Pregnancy and Breastfeeding

There has been little to no research on the safety of lavender when taken by mouth during pregnancy or while breastfeeding. Until more is known, recommend against the use of oral lavender in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

The safety of inhaled lavender (aromatherapy) is also unclear. Some small studies have evaluated a single inhalation of lavender aromatherapy during labor. However, these studies have not adequately evaluated assessed the newborn for any adverse effects [77].

Turmeric

Turmeric (*Curcuma longa*) is a well-known, yellow-colored spice that has gained increasing popularity over the past decade for a range of medical uses. Most of its medical benefits seem to be related to a specific chemical, curcumin, which is present in varying concentrations in turmeric.

Clinical research shows that curcumin can improve symptoms of depression when taken for at least six weeks and seems most likely to provide benefit for middle-aged patients as compared to older patients. However, the actual extent of the benefit of curcumin remains unclear. Some studies suggest that taking at least 1 gram daily is beneficial; other research suggests that curcumin 1 gram daily is only beneficial when taken along with conventional antidepressants [78; 79; 80].

Overall, turmeric is well-tolerated when taken at the doses studied for depression. The most commonly reported adverse effects are constipation, dyspepsia, diarrhea, and reflux.

Although rare, turmeric has also been associated with reports of serious liver damage. It is not entirely clear whether turmeric was the cause of liver damage in these patients; however, in most cases, the liver damage resolved after discontinuation of the supplement. Turmeric should be used with caution in people with existing liver dysfunction [81].

There are some potential drug interactions with turmeric, which should be given strong consideration in certain populations. For example, turmeric may increase the risk of bleeding in patients that are taking anticoagulants and may alter the effects of a variety of drugs used for the treatment of cancer [82; 83; 84].

The WFSBP and CANMAT international guideline provisionally recommends the use of curcumin extract 500–1,000 mg daily for mild-to-moderate depression, either as monotherapy or as an adjunct to other treatments [54].

Pregnancy and Breastfeeding

When taken in medicinal doses, turmeric may be unsafe for use during pregnancy. Although there has been little to no research conducted on the safety of turmeric supplements during pregnancy, there is a hypothetical concern that it can stimulate the uterus and increase menstrual flow [68].

There is no reliable evidence available regarding the safety of turmeric while breastfeeding. It is not known whether turmeric transfers into human milk; there is also no research available on the safety of turmeric in newborns. Until more is known, caution patients to avoid turmeric supplements while breastfeeding.

Lemon Balm

This lemon-scented herb (*Melissa officinalis)* has been used for relaxation across a variety of cultures over the last few centuries. More recently, clinical research has indicated that it may have some benefit for the treatment of depression, anxiety, and stress.

Clinical research shows that taking lemon balm orally can modestly improve depression. Most of these studies have used 1,200–3,000 mg daily for up to two months. Clinical research in adults with anxiety shows that these doses of lemon balm can also moderately improve anxiety scores when compared with a control group [85]. And in otherwise healthy adults experiencing stress, a single dose of lemon balm extract 300–600 mg seems to increase calm when compared with placebo [86].

Lemon balm is generally well-tolerated, although it has only been studied for up to two months at a time. This may be considered as a short-term, complementary therapy, particularly for patients experiencing intermittent stress or anxiety.

Pregnancy and Breastfeeding

There has been little to no research on the safety of lemon balm when taken by mouth during pregnancy or while breastfeeding. Until more is known, recommend against the use of oral lemon balm in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

Kava

Piper methysticum is a plant that has become relatively popular as both a beverage and extract in the United States. When consumed as a beverage, it is often obtained at a "kava bar," where it is marketed as a relaxing recreational drink. When consumed as an extract, it is sold as a dietary supplement and is typically standardized to a group of chemicals called kavalactones. Most extracts evaluated in clinical research contain anywhere between 30% to 70% kavalactones [87].

The available clinical research suggests that kava extracts 150–400 mg daily, standardized to 70% kavalactones, can modestly improve symptoms of general anxiety when compared with placebo. Any effect of kava on anxiety appears to be dose-dependent; extracts that provide at least 200 mg kavalactones daily tend to be more beneficial than those that provide lower doses. Additionally, research indicates that it takes at least five weeks before benefit is obtained [88; 89].

However, kava does not appear to be beneficial in people with GAD. Some small clinical trials and one larger clinical study show that kava extracts, taken daily for four to eight weeks, are no more effective than placebo [54; 90].

Although kava appears to be generally safe when taken by mouth, it has been associated with multiple reports of hepatotoxicity. It is not entirely clear whether these cases of liver damage have been directly related to kava extracts; however, analyses of the reports suggest that the risk may be higher with higher doses and a prolonged duration of use. Some reports have also suggested that the extraction method for kava, or contamination of the kava plant, may increase the risk of liver damage [87; 91]. In general, patients with liver dysfunction, or patients who are using other medications that can cause liver damage, such as alcohol, should avoid kava.

Kava has been shown to cause central nervous system (CNS) depression and sedation and should be used with caution in patients who are taking other CNS depressants, such as opioids, alcohol, or benzodiazepines [54]. Additionally, there is some concern that kava can cause impairment when driving or operating heavy machinery. However, there is no strong evidence to indicate the level of impairment that kava may cause, and small studies evaluating its effect on reaction time and visual attention have yielded conflicting findings [92; 93]. Until more is known, patients should determine how kava affects them before driving or operating heavy machinery.

The international guideline from WFSBP and CANMAT recommends *against* the use of kava for the treatment of GAD. For practitioners that are still interested in discussing the use of kava with patients that are not at increased risk for liver damage, the group notes that only supplements standardized to a sufficient level of kavalactones should be used [54].

Pregnancy and Breastfeeding

There has been little to no research conducted on the use of kava during pregnancy or while breastfeeding. However, there is a hypothetical concern that kava may cause loss of uterine tone, which could threaten a pregnancy. There is also a hypothetical concern that certain chemicals in kava can pass into human milk [68]. Until more is known, recommend against the use of kava in those who are pregnant or trying to become pregnant, as well as those who are breastfeeding.

Ashwagandha

This shrub (*Withania somniferia*) is native to parts of India, the Middle East, and Africa and has a long history of use in traditional medicine. It has also gained widespread popularity as an adaptogen, which is a class of substances that are believed to increase the body's ability to adapt to and avoid damage from various factors, including physical, environmental, and emotional stress [94]. As a result, ashwagandha has become popular for the management of stress and anxiety.

Some small clinical studies suggest that taking ashwagandha daily for six to eight weeks can reduce the symptoms of anxiety in adults with GAD when compared with placebo. The extracts used in these studies provided 300–600 mg ashwagandha, standardized to contain 5% of a specific class of chemicals called withanolides. As a result, the international guideline from WFSBP and CANMAT provisionally recommends the use of these extracts as either monotherapy or adjunctive therapy in patients with GAD [54]. In patients with anxiety but without GAD, on the other hand, small clinical studies of ashwagandha have shown conflicting results [95; 96].

There is a growing body of research evaluating ashwagandha for the management of chronic stress, with a number of small clinical studies suggesting that taking ashwagandha daily for 8 to 12 weeks can improve stress when compared with placebo [97].

Ashwagandha appears to be generally well tolerated when taken by mouth. High doses have been reported to cause mild gastrointestinal upset, diarrhea, nausea, and vomiting. It has also been reported to cause drowsiness and should initially be used with caution with other medications that can cause CNS depression. Some research suggests that ashwagandha may increase thyroid hormone levels; use with caution in people with thyroid disorders [98].

Pregnancy and Breastfeeding

Ashwagandha extracts may be unsafe for use during pregnancy. Although there has been little to no research conducted on the safety of taking ashwagandha during pregnancy, there is a hypothetical concern that it has miscarriage-causing (abortifacient) activity [68].

There is no reliable evidence available regarding the safety of ashwagandha while breastfeeding. It is not known whether ashwagandha transfers into human milk; there is also no research available on the safety of ashwagandha in newborns. Until more is known, caution patients to avoid ashwagandha while breastfeeding.

Cannabidiol (CBD)

CBD is one of more than 100 cannabinoids found in the *Cannabis sativa* plant. Due to the passage of the 2018 Farm Bill, which legalized the use of CBD from certain types of *Cannabis* plants (known as hemp), this substance has exploded in popularity for a wide variety of indications, including anxiety.

Despite its widespread availability, research on the use of CBD for any non-prescription purpose remains limited. Although some very small studies have evaluated CBD for general anxiety, these studies have not used a placebo control group, limiting the validity of any findings [99; 100].

One small study evaluating CBD 300 mg daily for one month for social anxiety disorder found modest benefit when compared with placebo [101]. However, small studies evaluating single doses or limited doses of CBD for social anxiety or public speaking-associated anxiety have found no benefit when compared with placebo [102; 103].

CBD seems to be generally safe when taken by mouth at doses of 200–1,200 mg daily for up to 13 weeks. Prescription CBD, which is taken in much higher doses of 20 mg/kg daily, has been reported to cause somnolence and diarrhea. These high doses have also been associated with increased liver enzymes, for which the risk is especially high when used in conjunction with valproic acid [104].

Product quality is a particular concern with CBD supplements, which have been found to contain far different quantities of CBD than those listed on the label. CBD supplements have also been found to contain other ingredients which are not listed on the label, including the psychoactive cannabinoid tetrahydrocannabinol (THC). In an analysis of 84 commercially available CBD products in the United States, only 31% of products were accurately labeled and 21% of products contained unlabeled THC [105]. Another assessment of 14 products commercially available in Europe and 25 products available in the United States found that up to 90% of the products were inaccurately labeled and that up to 86% of products contained detectable quantities of THC [106].

Pregnancy and Breastfeeding

The U.S. Food and Drug Administration (FDA) strongly recommends against the use of CBD during pregnancy [107]. Research on the use of CBD during pregnancy is currently limited to animal studies. However, these studies have detected an increased risk of developmental toxicity [104]. Additionally, due to the widespread issues with product quality, there is a risk that taking a CBD supplement may expose the fetus to THC. THC can cause serious adverse effects to the fetus, including low birth weight, birth defects, placental abruption, and an increased risk for requiring intensive care after birth. It can also cause long-term developmental issues [108].

For similar reasons, CBD products should be avoided while breastfeeding. THC passes into human milk and can cause serious adverse effects for the newborn [109].

VITAMIN AND MINERAL SUPPLEMENTS

In a separate segment of the dietary supplement market, there has been quite a bit of interest in recent years related to the use of various vitamins and minerals for the treatment or prevention of depression and anxiety. In some cases, this supplementation is intended to treat a known deficiency. In other cases, these supplements are used regardless of whether the patient is deficient.

VITAMINS

B Vitamins

Various members of this water-soluble vitamin family have garnered attention for use in the treatment of certain mental health issues, including thiamine (B1), pyridoxine (B6), folic acid (B9), and cyanocobalamin (B12). Observational research suggests that higher dietary consumption of these vitamins is associated with a lower risk of developing depression when compared with lower consumption. However, in most cases, it is unclear whether taking supplements containing any of these B vitamins offers benefit [110].

Of these vitamins, folic acid has the most convincing evidence of benefit for the treatment or prevention of depression. Although folic acid alone does not seem to be beneficial in the management of depression, clinical studies have found that taking folic acid 0.2–15 mg daily in conjunction with a conventional antidepressant can improve treatment response in adults with MDD when compared with taking the antidepressant alone [111].

Additionally, some observational research has found that taking a folic acid supplement is associated with a reduced risk for suicidal events when compared with patients that were not taking a folic acid supplement. However, only 12% of the patients within that study were diagnosed with depression, and the cohort included people who were taking folic acid either alone or as part of a multivitamin, in doses of 0.4–5 mg daily. It is unclear if patients with a folic acid deficiency may be more likely to benefit [112].

Folic acid is available in multiple forms, all of which provide different quantities of folate. As a result, recommended daily intakes for folate are expressed in dietary folate equivalents (DFEs). Folic acid, which is found in supplements, is about 85% bioavailable; folate in foods, on the other hand, is about 50% bioavailable. Thus, 1 mcg DFE is equivalent to 1 mcg dietary folate or 0.6 mcg folic acid [113].

Although most supplements contain synthetic folic acid, a growing number of supplements contain an alternative form of folate, L-methylfolate. Some manufacturers claim that L-methylfolate has a higher bioavailability than folic acid, although blood levels appear comparable between people who take both supplements. Some manufacturers also claim that L-methylfolate is beneficial for people who lack the enzymes necessary to convert folic acid to its active form; however, there is currently no reliable evidence to support this claim [114].

Vitamin D

Vitamin D is a fat-soluble vitamin has been extensively evaluated for the prevention of depression, with disappointing results. A variety of studies have found that taking vitamin D 2,000 IU daily for two to five years does not reduce the risk of depression or depressive symptoms when compared with placebo [115; 116].

Vitamin D has also been evaluated for the treatment of depression, with conflicting findings. Some clinical studies have found that vitamin D does not improve depressive symptoms, whereas others have found that it may modestly improve symptoms. It is unclear whether the presence or absence of a vitamin D deficiency is responsible for these conflicting findings [117; 118; 119; 120].

Due to the limited evidence of benefit and lack of clarity as to the impact of vitamin D deficiency, the international guideline from WFSBP and CANMAT provides only a weak recommendation for the use of vitamin D, in doses of 1,500–4,000 IU daily, as an adjunct or monotherapy for adults with MDD. This recommendation also focuses on people who are likely to have a vitamin D deficiency due to inadequate sun exposure and notes that the benefits may be greater in winter months [54].

Miscellaneous Vitamins

Some limited observational research has evaluated the potential role of various other vitamins in the prevention of depression and depressive symptoms. For example, observational research suggests that higher dietary intake of vitamin E and vitamin A (individually) is associated with a reduced risk of depression when compared with lower intake. However, higher intake of vitamin E is not associated with a reduced risk of anxiety [121; 122]. Similarly, a higher dietary intake of vitamin K is associated with reduced odds of depressive symptoms when compared with lower intakes [123].

A secondary analysis of a large clinical study has also evaluated the role of vitamin C in the prevention of depression. This study, which enrolled pre- and perimenopausal adults, identified an inverse association between vitamin C intake and depressive symptoms, which persisted regardless of age, physical activity, antidepressant use, and various other factors [124].

It is important to note that these studies are observational in nature and assess only the dietary intake of each of these vitamins. These findings do not indicate whether a supplement would be beneficial in any of these patients, nor do they assess the relevance of a vitamin deficiency. In general, patients should be counseled to consume a well-rounded, nutritious diet that provides adequate quantities of all macro- and micronutrients.

MINERALS

Magnesium

Magnesium plays an important role in a large number of cellular functions in the body and is a natural component of the diet. In recent years, it has gained popularity for the prevention and treatment of anxiety and depression.

Surprisingly, however, there is currently no reliable evidence exploring the benefits of magnesium supplements for general anxiety. As for depression, the available research is limited to lower quality studies which have yielded mostly negative findings, suggesting little to no benefit with magnesium supplements in depression [125; 126].

Zinc

This mineral has also been evaluated for use in depression, with more promising (although preliminary) findings. Observational research suggests that higher dietary intake of zinc is associated with a lower rate of depression than lower intake [127]. Additionally, some small, lower-quality studies show that taking an oral zinc supplement at doses of 7–25 mg daily for up to 12 weeks in conjunction with a conventional antidepressant may increase the benefits of the antidepressant [128].

ENDOGENOUS CHEMICAL SUPPLEMENTS

Supplements that contain chemicals which are naturally found in the human body are also commonly discussed as potential options for the management of anxiety and depression.

There has been little to no research on the safety of taking any of these endogenous chemicals in supplement form during pregnancy or while breastfeeding. Although these substances do occur naturally in the human body, the large doses found in supplements may have unanticipated effects on an unborn baby or breastfeeding newborn. Until more is known, recommend against their use in people who are pregnant or planning to become pregnant, as well as people who are breastfeeding.

5-HYDROXYTRYPTOPHAN (5-HTP)

5-hydroxytryptophan (5-HTP) is produced in the body from the essential amino acid L-tryptophan and is then converted to serotonin. Dietary supplements contain a form of 5-HTP that is derived from a shrub called *Griffonia simplicifolia.* Clinical research indicates that taking this supplement at a dose of 150–800 mg daily for up to eight weeks can improve some symptoms of depression. Some small studies suggest that it may have similar efficacy as some conventional antidepressants [129].

This supplement is generally well tolerated when taken by mouth, although it can cause gastrointestinal upset, abdominal pain, dizziness, drowsiness, headache, and insomnia. These adverse effects appear to be dose-dependent. Due to its serotonergic activity, 5-HTP should be used with caution in combination with other serotonergic drugs, since it may increase the risk for serotonergic side effects and serotonin syndrome [130].

SAMe

S-adenosyl-L-methionine (SAMe) is naturally formed in the body, where it serves a wide variety of functions. Clinical research shows that taking SAMe 800–1,600 mg daily in divided doses for one to three months can improve symptoms of depression when compared with placebo and may be equally effective to tricyclic antidepressants [131]. Additionally, one clinical trial shows that adding SAMe 400–800 mg twice daily to a conventional antidepressant can modestly improve remission rates when compared with taking the antidepressant alone [132].

SAMe is generally well-tolerated when taken by mouth, although it has been reported to cause gastrointestinal upset, constipation, diarrhea, dizziness, dry mouth, headache, insomnia, sweating, and nervousness. It is not clear if these adverse effects are dose-dependent or how often they occur when compared with placebo. As with 5-HTP, SAMe should be used with caution in patients taking serotonergic medications.

ACETYL-L-CARNITINE

Acetyl-L-carnitine is an ester of L-carnitine, both of which occur naturally in the body, particularly in the brain, liver, and kidneys. Clinical research shows that taking acetyl-L-carnitine supplements 1-4 grams daily for up to six months may moderately reduce depressive symptoms when compared with placebo. Most of these studies have included elderly adults [133].

This supplement is generally well-tolerated and has been reported to cause agitation, dry mouth, headache, insomnia, and reduced appetite. Some people have reported a fishy odor in the urine, breath, and sweat after taking L-carnitine, to which acetyl-L-carnitine is related [134].

GABA

Gamma-aminobutyric acid (GABA) is a well-known neurotransmitter that plays a role in a variety of bodily functions. The GABA receptors in the human body are the target of prescription benzodiazepines. The known sedative and anxiolytic effects of GABA agonists has led to interest in the use of GABA supplements for the management of anxiety and/or depression. However, clinical research on this use is lacking. Additionally, it is unclear whether GABA crosses the blood-brain barrier after oral intake, which would be necessary to induce any relevant effects [135].

SUMMARY

The prevalence of mental illness continues to increase across the world and in North America, with depression and anxiety representing the most common forms of mental illness. Although the symptoms of depression and anxiety experienced by many people may not be regarded as severe, even mild to moderate symptoms can be debilitating and difficult to manage.

Many patients may be interested in pursuing alternative therapies for the management of their mild or moderate symptoms. These alternative therapies can span a wide range of options, from exercise to acupuncture, and from herbs to vitamins. They may be used in conjunction with established, evidence-based treatments or on their own.

For non-pharmacologic modalities (those that do not involve taking an oral dietary supplement), the major concerns relate to ensuring safe use, which is often guided by a trained or licensed practitioner.

Some of these options, such as exercise, yoga, and mindfulness, have relatively strong evidence of efficacy and should be considered as a primary or adjunctive treatment option for most patients.

When discussing dietary supplements, on the other hand, the major concerns relate to ensuring both efficacy and safety. Although some supplements are widely discussed for these indications, the evidence does not necessarily support their use. Additionally, many of these products may carry side effects and the risk for serious drug interactions, and should always be evaluated on an individual basis, with consideration for each person's unique health situation. If a dietary supplement is recommended for a patient (or chosen by a patient), special care should be taken to ensure that a high-quality supplement is selected. This will increase the risk of efficacy by ensuring that the active chemicals are present in the right quantities and that the product is not adulterated. It will also reduce the risk of safety concerns that can be caused by unexpectedly high doses or the presence of contaminants.

Understanding the reasons that these products are used, as well as their actual risks and benefits, will allow healthcare professionals to help patients sift through the hype, avoid dangerous products, and select treatment options that are most likely to offer benefit.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Centers for Disease Control and Prevention. About Mental Health. Available at https://www.cdc.gov/mentalhealth/learn/index.htm. Last accessed December 13, 2024.
2. National Institutes of Mental Health. Mental Illness: Statistics. Available at https://www.nimh.nih.gov/health/statistics/mental-illness. Last accessed December 13, 2024.
3. Substance Abuse and Mental Health Services Administration (SAMHSA). Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health. Available at https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf. Last accessed December 13, 2024.
4. Arias D, Saxena S, Verguet S. Quantifying the global burden of mental disorders and their economic value. *eClinicalMedicine*. 2022;54:101675.
5. U.S. Congress, Joint Economic Committee. Long-Term Trends in Deaths of Despair. Available at https://www.jec.senate.gov/public/index.cfm/republicans/2019/9/long-term-trends-in-deaths-of-despair. Last accessed December 13, 2024.
6. Curtin SC. State Suicide Rates Among Adolescents and Young Adults Aged 10-24: United States, 2000–2018. *Natl Vital Stat Rep*. 2020;69(11):1-10.
7. Substance Abuse and Mental Health Services Administration. Table 9, DSM-IV to DSM-5 Major Depressive Episode/Disorder Comparison. Available at https://www.ncbi.nlm.nih.gov/books/NBK519712/table/ch3.t5. Last accessed December 13, 2024.
8. World Health Organization. Mental Health and COVID-19: Early Evidence of the Pandemic's Impact. Available at https://iris.who.int/bitstream/handle/10665/352189/WHO-2019-nCoV-Sci-Brief-Mental-health-2022.1-eng.pdf?sequence=1. Last accessed December 13, 2024.
9. American Psychiatric Association. Seasonal Affective Disorder (SAD). Available at https://www.psychiatry.org/patients-families/seasonal-affective-disorder. Last accessed December 13, 2024.
10. Centers for Disease Control and Prevention. Depression Among Women. Available at https://www.cdc.gov/reproductivehealth/depression/index.htm. Last accessed December 13, 2024.
11. Bauman BL, Ko JY, Cox S, et al. Vital Signs: postpartum depressive symptoms and provider discussions about perinatal depression—United States, 2018. *MMWR*. 2020;69(19):575-581.
12. Centers for Disease Control and Prevention. Symptoms of Generalized Anxiety Disorder Among Adults: United States, 2019. Available at https://www.cdc.gov/nchs/data/databriefs/db378-H.pdf. Last accessed December 13, 2024.
13. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.
14. Panchal N, Saunders H, Rudowitz R, Cox C. The Implications of COVID-19 for Mental Health and Substance Use. Available at https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use. Last accessed December 13, 2024.
15. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. Available at https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-1410197717630.pdf. Last accessed December 13, 2024.
16. Singh B, Olds T, Curtis R, et al. Effectiveness of physical activity interventions for improving depression, anxiety and distress: an overview of systematic reviews. *Br J Sports Med*. 2023;57(18):1203-1209.
17. Cramer H, Lauche R, Langhorst J, Dobos G. Yoga for depression: a systematic review and meta-analysis. *Depress Anxiety*. 2013;30(11):1068-1083.
18. Lin IH, Huang CY, Chou SH, Shih CL. Efficacy of prenatal yoga in the treatment of depression and anxiety during pregnancy: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022;19(9):5368.
19. Jiang X, Li H, Wang D, Shan L, Wang F, Kang Y. Efficacy of nondrug interventions in perinatal depression: a meta-analysis. *Psychiatry Res*. 2022;317:114916.
20. Wang G, Liang C, Sun G. Yoga's therapeutic effect on perinatal depression: a systematic review and meta-analysis. *Psychiatr Danub*. 2022;34(2):195-204.
21. Liu L, Liu C, Liu X, Yang Y. Summary of the effect of an exercise intervention on antenatal depression and the optimal program: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2023;23(1):293.
22. Guo L, Kong Z, Zhang Y. Qigong-based therapy for treating adults with major depressive disorder: a meta-analysis of randomized controlled trials. *Int J Environ Res Public Health*. 2019;16(5):826.
23. Lavretsky H, Alstein LL, Olmstead RE, et al. Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. *Am J Geriatr Psychiatry*. 2011;19(10):839-850.
24. Lavretsky H, Milillo MM, Kilpatrick L, et al. A randomized controlled trial of tai chi chih or health education for geriatric depression. *Am J Geriatr Psychiatry*. 2022;30(3):392-403.

25. Liu X, Li R, Cui J, et al. The effects of tai chi and qigong exercise on psychological status in adolescents: a systematic review and meta-analysis. *Front Psychol*. 2021;12:746975.
26. Xu MM, Guo P, Ma QY, et al. Can acupuncture enhance therapeutic effectiveness of antidepressants and reduce adverse drug reactions in patients with depression? A systematic review and meta-analysis. *J Integr Med*. 2022;20(4):305-320.
27. Xu G, Xiao Q, Huang B, et al. Clinical evidence for association of acupuncture with improved major depressive disorder: a systematic review and meta-analysis of randomized control trials. *Neuropsychobiology*. 2023;82(1):1-13.
28. Li W, Yin P, Lao L, Xu S. Effectiveness of acupuncture used for the management of postpartum depression: a systematic review and meta-analysis. *BioMed Res Int*. 2019;2019:6597503.
29. Pakravan F, Salehabad NH, Karimi F, Isfahani MN. Comparative study of the effect of licorice muco-adhesive film on radiotherapy induced oral mucositis, a randomized controlled clinical trial. *Gulf J Oncolog*. 2021;1(37):42-47.
30. Kline JA, Fisher MA, Pettit KL, Linville CT, Beck AM. Controlled clinical trial of canine therapy versus usual care to reduce patient anxiety in the emergency department. *PloS One*. 2019;14(1):e0209232.
31. Ein N, Li L, Vickers K. The effect of pet therapy on the physiological and subjective stress response: a meta-analysis. *Stress Health J Int Soc Investig Stress*. 2018;34(4):477-489.
32. Blomdahl C, Guregård S, Rusner M, Wijk H. A manual-based phenomenological art therapy for individuals diagnosed with moderate to severe depression (PATd): a randomized controlled study. *Psychiatr Rehabil J*. 2018;41(3):169-182.
33. Ciasca EC, Ferreira RC, Santana CLA, et al. Art therapy as an adjuvant treatment for depression in elderly women: a randomized controlled trial. *Rev Bras Psiquiatr Sao Paulo Braz 1999*. 2018;40(3):256-263.
34. Tang Q, Huang Z, Zhou H, Ye P. Effects of music therapy on depression: a meta-analysis of randomized controlled trials. *PloS One*. 2020;15(11):e0240862.
35. Zhao K, Bai ZG, Bo A, Chi I. A systematic review and meta-analysis of music therapy for the older adults with depression. *Int J Geriatr Psychiatry*. 2016;31(11):1188-1198.
36. Lu G, Jia R, Liang D, Yu J, Wu Z, Chen C. Effects of music therapy on anxiety: a meta-analysis of randomized controlled trials. *Psychiatry Res*. 2021;304:114137.
37. Masika GM, Yu DSF, Li PWC. Visual art therapy as a treatment option for cognitive decline among older adults: a systematic review and meta-analysis. *J Adv Nurs*. 2020;76(8):1892-1910.
38. Abbing A, Baars EW, de Sonneville L, Ponstein AS, Swaab H. The effectiveness of art therapy for anxiety in adult women: a randomized controlled trial. *Front Psychol*. 2019;10:1203.
39. Yang W jiao, Bai Y mei, Qin L, et al. The effectiveness of music therapy for postpartum depression: A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2019;37:93-101.
40. Goldin PR, Morrison A, Jazaieri H, Brozovich F, Heimberg R, Gross JJ. Group CBT versus MBSR for social anxiety disorder: a randomized controlled trial. *J Consult Clin Psychol*. 2016;84(5):427-437.
41. Arch JJ, Ayers CR, Baker A, Almklov E, Dean DJ, Craske MG. Randomized clinical trial of adapted mindfulness-based stress reduction versus group cognitive behavioral therapy for heterogeneous anxiety disorders. *Behav Res Ther*. 2013;51(4-5):185-196.
42. Vøllestad J, Sivertsen B, Nielsen GH. Mindfulness-based stress reduction for patients with anxiety disorders: evaluation in a randomized controlled trial. *Behav Res Ther*. 2011;49(4):281-288.
43. Zhou X, Guo J, Lu G, et al. Effects of mindfulness-based stress reduction on anxiety symptoms in young people: a systematic review and meta-analysis. *Psychiatry Res*. 2020;289:113002.
44. Hoge EA, Bui E, Mete M, Dutton MA, Baker AW, Simon NM. Mindfulness-based stress reduction vs escitalopram for the treatment of adults with anxiety disorders: a randomized clinical trial. *JAMA Psychiatry*. 2023;80(1):13-21.
45. Reangsing C, Lauderman C, Schneider JK. Effects of mindfulness meditation intervention on depressive symptoms in emerging adults: a systematic review and meta-analysis. *J Integr Complement Med*. 2022;28(1):6-24.
46. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. *JAMA Psychiatry*. 2016;73(6):565-574.
47. Jorm AF, Morgan AJ, Hetrick SE. Relaxation for depression. *Cochrane Database Syst Rev*. 2008;(4):CD007142.
48. Kim HS, Kim EJ. Effects of relaxation therapy on anxiety disorders: a systematic review and meta-analysis. *Arch Psychiatr Nurs*. 2018;32(2):278-284.
49. Zenouzi A, Moghadam ZB, Babayanzad S, Asghari M, Rezaei E. The effect of Benson relaxation technique on stress, anxiety, and depression in pregnant women. *Holist Nurs Pract*. 2024;38(4):227-237.
50. Nussbaumer-Streit B, Thaler K, Chapman A, et al. Second-generation antidepressants for treatment of seasonal affective disorder. *Cochrane Database Syst Rev*. 2021;3(3):CD008591.
51. Lee TM, Chan CC, Paterson JG, Janzen HL, Blashko CA. Spectral properties of phototherapy for seasonal affective disorder: a meta-analysis. *Acta Psychiatr Scand*. 1997;96(2):117-121.
52. Donmez M, Yorguner N, Kora K, Topcuoglu V. Efficacy of bright light therapy in perinatal depression: a randomized, double-blind, placebo-controlled study. *J Psychiatr Res*. 2022;149:315-322.

53. Apaydin EA, Maher AR, Shanman R, et al. A systematic review of St. John's wort for major depressive disorder. *Syst Rev*. 2016;5(1):148.
54. Sarris J, Ravindran A, Yatham LN, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry*. 2022;23(6):424-455.
55. Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. *Phytomedicine Int J Phytother Phytopharm*. 2001;8(2):152-160.
56. Qaseem A, Barry MJ, Kansagara D, Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the american college of physicians. *Ann Intern Med*. 2016;164(5):350-359.
57. Schäfer W, Wentzell N, Schink T, Haug U. Characterization of pregnancies exposed to St. John's wort and their outcomes: a claims data analysis. *Reprod Toxicol Elmsford N*. 2021;102:90-97.
58. Lee A, Minhas R, Matsuda N, Lam M, Ito S. The safety of St. John's wort (Hypericum perforatum) during breastfeeding. *J Clin Psychiatry*. 2003;64(8):966-968.
59. Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of St. John's wort (Hypericum) during pregnancy and lactation. *Can J Clin Pharmacol J Can Pharmacol Clin*. 2006;13(3):e268-e276.
60. Tóth B, Hegyi P, Lantos T, et al. The efficacy of saffron in the treatment of mild to moderate depression: a meta-analysis. *Planta Med*. 2019;85(1):24-31.
61. Dai L, Chen L, Wang W. Safety and efficacy of saffron (Crocus sativus L.) for treating mild to moderate depression: a systematic review and meta-analysis. *J Nerv Ment Dis*. 2020;208(4):269-276.
62. Lopresti AL, Smith SJ, Hood SD, Drummond PD. Efficacy of a standardised saffron extract (Affron) as an add-on to antidepressant medication for the treatment of persistent depressive symptoms in adults: a randomised, double-blind, placebo-controlled study. *J Psychopharmacol Oxf Engl*. 2019;33(11):1415-1427.
63. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870-2879.
64. Kianbakht S, Ghazavi A. Immunomodulatory effects of saffron: a randomized double-blind placebo-controlled clinical trial. *Phytother Res PTR*. 2011;25(12):1801-1805.
65. Mohammadzadeh-Moghadam H, Nazari SM, Shamsa A, et al. Effects of a topical saffron (Crocus sativus L) gel on erectile dysfunction in diabetics: a randomized, parallel-group, double-blind, placebo-controlled trial. *J Evid-Based Complement Altern Med*. 2015;20(4):283-286.
66. Modabbernia A, Sohrabi H, Nasehi AA, et al. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. *Psychopharmacology (Berl)*. 2012;223(4):381-388.
67. Gafner S, Blumenthal M, Foster S, Cardellina JH, Khan IA, Upton R. Botanical ingredient forensics: detection of attempts to deceive commonly used analytical methods for authenticating herbal dietary and food ingredients and supplements. *J Nat Prod*. 2023;86(2):460-472.
68. McGuffin M, Hobbs C, Upton R, Goldberg A. American Herbal Products Association's Botanical Safety Handbook. 2nd ed. New York, NY: CRC Press, LLC; 2013.
69. Kashani L, Eslatmanesh S, Saedi N, et al. Comparison of saffron versus fluoxetine in treatment of mild to moderate postpartum depression: a double-blind, randomized clinical trial. *Pharmacopsychiatry*. 2017;50(2):64-68.
70. Donelli D, Antonelli M, Bellinazzi C, Gensini GF, Firenzuoli F. Effects of lavender on anxiety: a systematic review and meta-analysis. *Phytomedicine Int J Phytother Phytopharm*. 2019;65:153099.
71. Yap WS, Dolzhenko AV, Jalal Z, Hadi MA, Khan TM. Efficacy and safety of lavender essential oil (Silexan) capsules among patients suffering from anxiety disorders: a network meta-analysis. *Sci Rep*. 2019;9(1):18042.
72. Kang HJ, Nam ES, Lee Y, Kim M. How strong is the evidence for the anxiolytic efficacy of lavender?: systematic review and meta-analysis of randomized controlled trials. *Asian Nurs Res*. 2019;13(5):295-305.
73. Li D, Li Y, Bai X, Wang M, Yan J, Cao Y. The effects of aromatherapy on anxiety and depression in people with cancer: a systematic review and meta-analysis. *Front Public Health*. 2022;10:853056.
74. Araj-Khodaei M, Noorbala AA, Yarani R, et al. A double-blind, randomized pilot study for comparison of Melissa officinalis L. and Lavandula angustifolia Mill. with fluoxetine for the treatment of depression. *BMC Complement Med Ther*. 2020;20(1):207.
75. Firoozeei TS, Feizi A, Rezaeizadeh H, Zargaran A, Roohafza HR, Karimi M. The antidepressant effects of lavender (Lavandula angustifolia Mill.): a systematic review and meta-analysis of randomized controlled clinical trials. *Complement Ther Med*. 2021;59:102679.
76. Bingham LJ, Tam MM, Palmer AM, Cahill JL, Nixon RL. Contact allergy and allergic contact dermatitis caused by lavender: a retrospective study from an Australian clinic. *Contact Dermatitis*. 2019;81(1):37-42.
77. Yazdkhasti M, Pirak A. The effect of aromatherapy with lavender essence on severity of labor pain and duration of labor in primiparous women. *Complement Ther Clin Pract*. 2016;25:81-86.

78. Al-Karawi D, Al Mamoori DA, Tayyar Y. The role of curcumin administration in patients with major depressive disorder: mini meta-analysis of clinical trials. *Phytother Res PTR*. 2016;30(2):175-183.
79. Wang Z, Zhang Q, Huang H, Liu Z. The efficacy and acceptability of curcumin for the treatment of depression or depressive symptoms: a systematic review and meta-analysis. *J Affect Disord*. 2021;282:242-251.
80. Yu JJ, Pei LB, Zhang Y, Wen ZY, Yang JL. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol*. 2015;35(4):406-410.
81. Halegoua-DeMarzio D, Navarro V, Ahmad J, et al. Liver injury associated with turmeric: a growing problem: ten cases from the Drug-Induced Liver Injury Network [DILIN]. *Am J Med*. 2023;136(2):200-206.
82. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res*. 2002;62(13):3868-3875.
83. Mitchell TM. Correspondence re: Somasundaram et al., Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res.*, 62: 3868-3875, 2002. Cancer Res. 2003;63(16):5165-5166; author reply 5166-5167.
84. MEDSAFE: New Zealand Medicines and Medical Devices Safety Authority. Monitoring Communication: Beware Turmeric/Curcumin Containing Products Can Interact with Warfarin. Available at https://medsafe.govt.nz/safety/EWS/2018/Turmeric.asp. Last accessed December 13, 2024.
85. Ghazizadeh J, Sadigh-Eteghad S, Marx W, et al. The effects of lemon balm (*Melissa officinalis L.*) on depression and anxiety in clinical trials: a systematic review and meta-analysis. *Phytother Res PTR*. 2021;35(12):6690-6705.
86. Scholey A, Gibbs A, Neale C, et al. Anti-stress effects of lemon balm-containing foods. *Nutrients*. 2014;6(11):4805-4821.
87. Bian T, Corral P, Wang Y, et al. Kava as a clinical nutrient: promises and challenges. *Nutrients*. 2020;12(10):3044.
88. Zhang W, Yan Y, Wu Y, et al. Medicinal herbs for the treatment of anxiety: a systematic review and network meta-analysis. *Pharmacol Res*. 2022;179:106204.
89. Smith K, Leiras C. The effectiveness and safety of Kava Kava for treating anxiety symptoms: a systematic review and analysis of randomized clinical trials. *Complement Ther Clin Pract*. 2018;33:107-117.
90. Connor KM, Payne V, Davidson JRT. Kava in generalized anxiety disorder: three placebo-controlled trials. *Int Clin Psychopharmacol*. 2006;21(5):249-253.
91. Li XZ, Ramzan I. Role of ethanol in kava hepatotoxicity. *Phytother Res PTR*. 2010;24(4):475-480.
92. Wainiqolo I, Kool B, Nosa V, Ameratunga S. Is driving under the influence of kava associated with motor vehicle crashes? A systematic review of the epidemiological literature. *Aust N Z J Public Health*. 2015;39(5):495-499.
93. Aporosa AS, Atkins M, Brunton R. Kava drinking in traditional settings: towards understanding effects on cognitive function. *Hum Psychopharmacol*. 2020;35(2):e2725.
94. Panossian A, Wikman G, Wagner H. Plant adaptogens. III. Earlier and more recent aspects and concepts on their mode of action. *Phytomedicine Int J Phytother Phytopharm*. 1999;6(4):287-300.
95. Remenapp A, Coyle K, Orange T, et al. Efficacy of Withania somnifera supplementation on adult's cognition and mood. *J Ayurveda Integr Med*. 2022;13(2):100510.
96. Cooley K, Szczurko O, Perri D, et al. Naturopathic care for anxiety: a randomized controlled trial ISRCTN78958974. *PloS One*. 2009;4(8):e6628.
97. Akhgarjand C, Asoudeh F, Bagheri A, et al. Does Ashwagandha supplementation have a beneficial effect on the management of anxiety and stress? A systematic review and meta-analysis of randomized controlled trials. *Phytother Res PTR*. 2022;36(11):4115-4124.
98. Sharma AK, Basu I, Singh S. Efficacy and safety of ashwagandha root extract in subclinical hypothyroid patients: a double-blind, randomized placebo-controlled trial. *J Altern Complement Med N Y N*. 2018;24(3):243-248.
99. Stanley TB, Ferretti ML, Bonn-Miller MO, Irons JG. A double-blind, randomized, placebo-controlled test of the effects of cannabidiol on experiences of test anxiety among college students. *Cannabis Cannabinoid Res*. 2023;8(6):1090-1099.
100. Berger M, Li E, Rice S, et al. Cannabidiol for treatment-resistant anxiety disorders in young people: an open-label trial. *J Clin Psychiatry*. 2022;83(5):21m14130.
101. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Front Psychol*. 2019;10:2466.
102. Appiah-Kusi E, Petros N, Wilson R, et al. Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. *Psychopharmacology (Berl)*. 2020;237(4):1121-1130.
103. Kwee CM, Baas JM, van der Flier FE, et al. Cannabidiol enhancement of exposure therapy in treatment refractory patients with social anxiety disorder and panic disorder with agoraphobia: a randomised controlled trial. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2022;59:58-67.
104. Epidiolex (Cannabidiol) [Package Insert]. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210365Orig1s011lbl.pdf. Last accessed December 13, 2024.
105. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. *JAMA*. 2017;318(17):1708-1709.

106. Gurley BJ, Murphy TP, Gul W, Walker LA, ElSohly M. Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the state of Mississippi. *J Diet Suppl*. 2020;17(5):599-607.

107. U.S. Food and Drug Administration. What You Should Know About Using Cannabis, Including CBD, When Pregnant or Breastfeeding. Available at https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding. Last accessed December 13, 2024.

108. Marchand G, Masoud AT, Govindan M, et al. Birth outcomes of neonates exposed to marijuana in utero: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(1):e2145653.

109. Wymore EM, Palmer C, Wang GS, et al. Persistence of Δ-9-tetrahydrocannabinol in human breast milk. *JAMA Pediatr*. 2021;175(6):632-634.

110. Wu Y, Zhang L, Li S, Zhang D. Associations of dietary vitamin B1, vitamin B2, vitamin B6, and vitamin B12 with the risk of depression: a systematic review and meta-analysis. *Nutr Rev*. 2022;80(3):351-366.

111. Altaf R, Gonzalez I, Rubino K, Nemec EC. Folate as adjunct therapy to SSRI/SNRI for major depressive disorder: systematic review and meta-analysis. *Complement Ther Med*. 2021;61:102770.

112. Gibbons RD, Hur K, Lavigne JE, Mann JJ. Association between folic acid prescription fills and suicide attempts and intentional self-harm among privately insured US adults. *JAMA Psychiatry*. 2022;79(11):1118-1123.

113. Centers for Disease Control and Prevention . General Information About NTDs, Folic Acid, and Folate. Available at https://www.cdc.gov/ncbddd/folicacid/faqs/faqs-general-info.html. Last accessed December 13, 2024.

114. Willems FF, Boers GHJ, Blom HJ, Aengevaeren WRM, Verheugt FWA. Pharmacokinetic study on the utilisation of 5-methyltetrahydrofolate and folic acid in patients with coronary artery disease. *Br J Pharmacol*. 2004;141(5):825-830.

115. Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of long-term vitamin D3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. *JAMA*. 2020;324(5):471-480.

116. Vyas CM, Mischoulon D, Chang G, et al. Effects of vitamin D3 and marine omega-3 fatty acids supplementation on indicated and selective prevention of depression in older adults: results from the Clinical Center Sub-Cohort of the VITamin D and OmegA-3 TriaL (VITAL). *J Clin Psychiatry*. 2023;84(4):22m14629.

117. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients*. 2014;6(4):1501-1518.

118. Srifuengfung M, Srifuengfung S, Pummangura C, Pattanaseri K, Oon-Arom A, Srisurapanont M. Efficacy and acceptability of vitamin D supplements for depressed patients: a systematic review and meta-analysis of randomized controlled trials. *Nutr Burbank Los Angel Cty Calif*. 2023;108:111968.

119. Shaffer JA, Edmondson D, Wasson LT, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med*. 2014;76(3):190-196.

120. Wang R, Xu F, Xia X, et al. The effect of vitamin D supplementation on primary depression: a meta-analysis. *J Affect Disord*. 2024;344:653-661.

121. Lee ARYB, Tariq A, Lau G, Tok NWK, Tam WWS, Ho CSH. Vitamin E, alpha-tocopherol, and its effects on depression and anxiety: a systematic review and meta-analysis. *Nutrients*. 2022;14(3):656.

122. Zhang Y, Ding J, Liang J. Associations of dietary vitamin A and beta-carotene intake with depression. a meta-analysis of observational studies. *Front Nutr*. 2022;9:881139.

123. Bolzetta F, Veronese N, Stubbs B, et al. The relationship between dietary vitamin k and depressive symptoms in late adulthood: a cross-sectional analysis from a large cohort study. *Nutrients*. 2019;11(4):787.

124. Li D, Xu W, Wu Q, Zheng H, Li Y. Ascorbic acid intake is inversely associated with prevalence of depressive symptoms in U.S. midlife women: a cross-sectional study. *J Affect Disord*. 2022;299:498-503.

125. Ryszewska-Pokraśniewicz B, Mach A, Skalski M, et al. Effects of magnesium supplementation on unipolar depression: a placebo-controlled study and review of the importance of dosing and magnesium status in the therapeutic response. *Nutrients*. 2018;10(8):1014.

126. Tarleton EK, Littenberg B, MacLean CD, Kennedy AG, Daley C. Role of magnesium supplementation in the treatment of depression: a randomized clinical trial. *PloS One*. 2017;12(6):e0180067.

127. Yosaee S, Clark CCT, Keshtkaran Z, Ashourpour M, Keshani P, Soltani S. Zinc in depression: from development to treatment: a comparative/ dose response meta-analysis of observational studies and randomized controlled trials. *Gen Hosp Psychiatry*. 2022;74:110-117.

128. da Silva LEM, de Santana MLP, Costa PR de F, et al. Zinc supplementation combined with antidepressant drugs for treatment of patients with depression: a systematic review and meta-analysis. *Nutr Rev*. 2021;79(1):1-12.

129. Javelle F, Lampit A, Bloch W, Häussermann P, Johnson SL, Zimmer P. Effects of 5-hydroxytryptophan on distinct types of depression: a systematic review and meta-analysis. *Nutr Rev*. 2020;78(1):77-88.

130. Maffei ME. 5-Hydroxytryptophan (5-HTP): natural occurrence, analysis, biosynthesis, biotechnology, physiology and toxicology. *Int J Mol Sci*. 2020;22(1):181.

131. Galizia I, Oldani L, Macritchie K, et al. S-adenosyl methionine (SAMe) for depression in adults. *Cochrane Database Syst Rev*. 2016;10(10):CD011286.

132. Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *Am J Psychiatry*. 2010;167(8):942-948.

133. Veronese N, Stubbs B, Solmi M, Ajnakina O, Carvalho AF, Maggi S. Acetyl-L-carnitine supplementation and the treatment of depressive symptoms: a systematic review and meta-analysis. *Psychosom Med*. 2018;80(2):154-159.

134. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. *Clin Pharmacokinet*. 2003;42(11):941-967.

135. Boonstra E, De Kleijn R, Colzato LS, Alkemade A, Forstmann BU, Nieuwenhuis S. Neurotransmitters as food supplements: the effects of GABA on brain and behavior. *Front Psychol*. 2015;6.

Evidence-Based Practice Recommendations Citations

APA Panel for the Treatment of Depressive Disorder. *APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts*. Washington, DC: American Psychological Association; 2019. Available at https://www.apa.org/depression-guideline/guideline.pdf. Last accessed December 17, 2024.

Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder*. Washington, DC: Department of Defense; 2022. Available at https://www.healthquality.va.gov/guidelines/MH/mdd/VADODMDDCPGFinal508.pdf. Last accessed December 17, 2024.