Stress, Anxiety and Cognitive Function

Clinically proven natural alternatives for treating stress & anxiety and declining memory

CURT HENDRIX, M.S., C.C.N., C.N.S.
Evidence-Based Use of Supplements

ABSTRACT

Stress-related anxiety and mild cognitive impairment are common, related, and inadequately treated. Scientific data are increasingly demonstrating the power of nutrition to address these conditions. In addition to effectively preventing and treating anxiety and cognitive dysfunction, nutritional approaches have the added advantage of circumventing serious risks posed by other interventions. Here we discuss the realities of stress-related anxiety and mild cognitive impairment, including the limitations of conventional strategies to combat them. We also provide information on our current understanding of the relevance and potential of specific ingredients to promote mental health as it related to anxiety and cognition.

Rates of chronic stress and cognitive decline are increasing rapidly, and unfortunately the solutions to these issues are not keeping pace.1,2 Complicating and exacerbating the problem is that stress and cognitive decline are inextricably linked. Finding new and better ways to prevent and treat stress, anxiety, and cognitive problems is critical, particularly as our older population, who is at a heightened risk for cognitive decline, is projected to soon outsize children for the first time in U.S. history.3

Anxiety Disorders and Cognitive Deficits are Prevalent and Linked

Anxiety Disorders

According to the National Institute on Mental Health (NIMH), 1 out of every 3 people will suffer from an anxiety disorder in their lifetime.4 Anxiety disorders are the most common mental illness in the U.S, with roughly 40 million Americans suffering from these disorders.5 Among adults, about 1 in 5 people have an anxiety disorder, whereas the prevalence is more than 1 in 4 for children between the ages of 13 and 18. Women are significantly more affected than men, developing certain anxiety disorders twice as frequently as their male counterparts.

Chronic stress and anxiety have detrimental effects on health. According to the American Psychological Association (APA), chronic stress is becoming a public health crisis, as adults are experiencing stress at growing rates. Though often unrecognized, the rise in adult stress has also been shown to be taking an increasing toll on children.1 Not only are children more anxious than they used to be, but they are increasingly debilitated by this anxiety. Of adolescents experiencing anxiety, more than 8% are found to be severely impaired.4 If not treated properly, anxiety is chronic.5

Mild Cognitive Impairment

Stress and anxiety are common in those with mild cognitive impairment (MCI), which exists in 15% to 20% of people who are 65 and older.6 As with anxiety, MCI can be difficult for clinicians to identify and classify.7,8 Unlike anxiety, however, no treatments for MCI have been shown to be effective.9 MCI involves changes in cognition that are not severe enough to disrupt everyday activities but affect functioning enough to be noticed by the person experiencing MCI and those around them. As many as 15% of people with MCI progress to dementia each year, highlighting the importance of identifying and effectively treating MCI.10 Though having MCI increases the risk of developing Alzheimer's disease or another form of dementia, not everyone with MCI will go on to have dementia.11–14 Nonetheless, those who simultaneously suffer from both MCI and anxiety are more likely to develop dementia.15 It is therefore critical that we find ways to adequately address anxiety and cognitive dysfunction, not only to minimize their burden but also to prevent their progression and development into potentially more severe impairments.

The Reciprocal Relationship Between Stress and Cognition

Anxiety Can Derail Cognition

While stress is a part of everyday life, our ability to cope with stress is critical for avoiding maladaptive anxiety and associated health problems. Stress responses are triggered by cues and events that signal threats and occur as a way to promote mechanisms for coping that increase our likelihood for survival.16 Thus, while it is important to experience stress, an overreaction to stress or an inability to cope properly with the perception of stress can lead to pathological anxiety and a variety of mental and physical health problems.

Acute stress has detrimental effects on a variety of cognitive abilities, including executive functioning, the formation of and updating of memories, mental rotation and spatial memory, and hand-eye coordination.17–19 Experiencing anxiety can limit working memory capacity by, for instance, redirecting some of our attentional resources.20 Indeed, if we are distracted by our anxieties, we simply have less brain power to devote to other tasks, especially cognitive tasks that require concentration. It is perhaps therefore not surprising that measurements using the Montreal Cognitive Assessment (MoCA) have found that compared to those without psychological distress, those experiencing such distress display higher levels of cognitive deterioration.21

These cognitive effects of stress are likely mediated by the stress hormone cortisol, the levels of which are inversely correlated with memory.22 When stress and cortisol concentrations are high, structural changes in areas of the brain that are important for memory and cognition – such as the hippocampus – can occur, leading to atrophy and associated memory disorders.23,24

A poignant example of this relationship between stress and brain change-associated memory impairment is what occurs in those with post-traumatic stress disorder (PTSD). Magnetic resonance imaging (MRI) studies on patients with PTSD have revealed reduced hippocampal volume and weaker verbal memory in those with the disorder.25

Research has also shown that a stroke victim undergoing cognitive training is more likely to improve in cognitive performance if the victim has lower levels of anxiety.26 Based on data on neural activation patterns, it appears that those with lower anxiety also have more neural efficiency that accompanies their ability to improve their cognitive performance over time. Indeed, those who experience acute stress seem to require more brain activation in somatosensory cortices to perform as well as those without such stress.27

Similarly, research on those with MCI has shown that between 35% and 85% of adults with the disorder also display neuropsychiatric symptoms, which often occur before cognitive decline.28 In those who suffer from both MCI and anxiety, cognitive decline is more likely to occur at a faster rate.29 In some patients, anxiety also increases with increasing cognitive decline, suggesting a bidirectional relationship between the conditions.28

It should be noted that in cases of mild stress, short-term memory can be improved, as is often the case in high pressure contexts such as academic test taking. However, long-term stress and high intensity stress have the opposite effect, leading to cognitive disorders.30

Cognitive Problems Can Lead to Anxiety

The way we respond to stress not only affects but also likely derives from aspects of our cognition. Our cognitive appraisal of our situation critically contributes to our stress response, as no cue or event is in itself stressful unless it is perceived that way.31,32 Thus, abnormal cognitive processing can lead to anxiety that is out of proportion with the existing threat or potential threat.

Research on both cognitive and neuropsychiatric disturbances suggests that these issues not only influence one another but that there may be common pathological pathways leading to anxiety and MCI.33 Experts posit that in certain cases, anxiety is likely a manifestation of neurodegeneration rather than the cause.34

Given the way that abnormal cognitive processing can lead to anxiety while stress and anxiety can simultaneously disrupt cognitive performance, it is important that we find ways to prevent problems related to both cognition and stress. Unfortunately, difficulties related to anxiety and cognitive continue to grow, with virtually no new effective strategies for prevention or treatment being introduced.

CONVENTIONAL TREATMENTS

Pharmacological Interventions

Drugs for Stress and Anxiety

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are generally considered first line treatments for anxiety disorders, particularly generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, and PTSD. There is also evidence, though, that PTSD is not adequately addressed by current pharmacological or non-pharmacological options.35–40 This particularly troubling given that PTSD is thought to be the most extreme form of stress-induced anxiety.

Second line and other treatments for anxiety disorders include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), benzodiazepines, and anticonvulsants like gabapentin and pregabalin.41

Unfortunately, there are weaknesses and limitations associated with all the currently available drugs for managing stress and anxiety. For instance, a proportion of the population with anxiety is resistant to first line treatments, with some people actually experiencing enhancements in their anxiety upon starting these medications.42

These first line options are also associated with adverse side effects including headache, nausea, stomach pain, sexual dysfunction, and difficulty sleeping.43,44 In addition, data have shown that SSRIs can lead to suicidal thoughts and behaviors, including in children, led the FDA to issue a warning regarding these drugs in October 2004.5,45 Drugs in this class have also been associated with negative outcomes when taken by pregnant women.46–50

SSRIs are also associated with dangerous drug interactions, including interactions with recreational substances like alcohol as well as with drugs used to treat other conditions.51–53 For those who may want to discontinue use of SSRIs in favor of another drug may struggle with withdrawal.54

Other non-first line treatment options are classified as such because they pose significant risks related to safety and tolerability.41 For instance, in addition to their side effects, benzodiazepines also carry risks associated with dependence and withdrawal.55 Current guidelines do not recommend addressing anxiety with benzodiazepines as first-line treatments because of the adverse side effects associated with these drugs.39 In the context of addressing co-existing anxiety and cognitive deficits, it is also important to note that systematic meta-analyses have shown that long-term use of benzodiazepines is associated with cognitive dysfunction that persists even if benzodiazepine use is discontinued.55

Drugs for MCI

Though treating reversible causes of MCI tends to have positive results, many cases of MCI do not emerge due to identifiable and reversible causes.56 There are no pharmacological interventions for MCI that have been approved by the U.S. Food and Drug Administration (FDA).56,57 Given the role of acetylcholine in cognition, 3 cholinesterase inhibitors were developed and later approved by the FDA for the treatment of mild dementia due to Alzheimer's disease. These drugs include donepezil, galantamine, and rivastigmine.58,59

Despite their modest benefits in this Alzheimer's disease population, research into the potential of cholinesterase inhibitors to treat those with MCI has yielded disappointing results.60,61 Given that the drugs do not appear to be effective and yet are associated with adverse side effects like diarrhea, nausea, hypotension, increased risk of falling, fatigue, and bradycardia, experts have concluded that there is no justification for using these drugs in those with MCI.62

Non-Pharmacological Interventions

Cognitive Approaches

While engagement in intellectual and cognitively stimulating activities may help protect against MCI,63 cognitive behavioral therapy (CBT) – a form of psychotherapy - can be an effective way to reduce anxiety and involves strengthening connections between cognitive and affective parts of the brain to improve emotion regulation.64 Over the course of several weeks of CBT, people can learn skills to help them combat their anxiety.5 Though CBT is generally considered the gold standard form of psychotherapy, this status has recently been called into question because of weaknesses in the relevant research, including studies deemed low in quality.65

TMS

Transcranial magnetic stimulation (TMS), more often used to treat depression, was approved by the FDA for use against obsessive-compulsive disorder (OCD) in 2018.66 This technique leverages magnetic fields to influence aberrant activity in brain circuits that may underlie neuropsychiatric conditions. Research into the potential for TMS to effectively and safely treat other forms of anxiety, such as PTSD, is ongoing.

Meditation, Relaxation, and Breathing Techniques

Data have shown that meditation, as well as relaxation and breathing techniques, can counteract detrimental effects of psychological stress. These observations have led experts to suggest that these techniques be used as both first-line and supplemental treatments for stress and anxiety.67,68 Similarly, meditation has been deemed feasible even for older adults, and research has shown that meditation may be able to combat age-related cognitive decline.69

Recent data suggest that mindfulness-based interventions are capable of not only reducing perceived stress and cognitive decline but also of affecting brain physiology. Specifically, researchers have observed increased functional connectivity, cerebral blood flow, and brain volume change following these types of interventions.70 However, more data from stronger study designs are needed to determine the specific ways that meditation could help those suffering from anxiety and stress-related behavior.71

Acupuncture

Acupuncture may be a promising intervention for anxiety.72 Systematic reviews of the literature have shown that acupuncture therapy is effective and also associated with fewer side effects than conventional anxiety treatments.73

Recent research has also shown that acupuncture therapy is a promising non-pharmacological method to treat patients with MCI, successfully improving their cognitive functioning.74 Based on functional magnetic resonance imaging (fMRI) data, this effect may occur due to the ability of acupuncture to activate areas of the brain associated with cognition in those with MCI.75 Based on the positive data collected on the impact of acupuncture, clinical trials aimed at optimizing acupuncture therapy for use in MCI are being pursued.76–79

Exercise

Though the data are limited, there is evidence that exercise can provide a cost-effective way to address both anxiety and cognition.57,80 For instance, data point to a role of physical activity in improving subjective memory impairments and to yoga in relieving stress and anxiety.81,82 A comprehensive meta-analysis covering 15 cohort studies showed that the risk of cognitive decline was 38% greater in sedentary people than in those who were physically active.83 It is thought that these advantages occur because exercise stimulates the blood to take nutrient and oxygen rich blood to the brain, reduce cortisol levels, and protect against cardiovascular disease.84

However, when it comes to anxiety, it is unclear whether exercise can achieve the same impact as psychopharmaceuticals.85 Though exercise appears to confer mental benefits, our understanding of exactly if and how exercise can be preventative or therapeutic is incomplete due to a lack of solid data from randomized controlled trials.80

Diet

Adequate nutrition is known to be critical for optimizing brain function, including for preventing cognitive decline and improving cognitive capacity.86 Cognitive impairments are observed less frequently in those who follow a Mediterranean diet, rich in plant-based foods, whole grains, fish, nuts, and monosaturated fats.87 In addition, consuming and staying on a Mediterranean diet has been shown to reduce the rate of cognitive decline in MCI.88

Combining approaches

Data increasingly suggest that combining different types of strategies to combat MCI may be more effective than using individual interventions alone. A recent meta-analysis found that not only were combined cognitive-physical interventions associated with improvements in the performance of daily activities as well as in mood, but that these benefits occurred at equal levels in those with MCI and in patients with dementia.89

A multicomponent therapy referred to as MAKS, an acronym for Motor, Activities of daily living, Cognitive, Social) has been shown to be effective in improving cognition in a wide range of patients, ranging from those suffering from MCI to those with moderate dementia.90 Specifically, MAKS was associated with improvements in performance on the Mini-Mental State Examination (MMSE) and the Erlangen Test of Activities of Daily Living (ADL) in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM), as well as improvements in neuropsychiatric symptoms.

CLINICALLY DOCUMENTED SUPPLEMENTS

Given that MCI has no pharmacological treatments and accordingly, interventions are shifting to diet and exercise as ways to combat cognitive deficits,56 supplements offer a particularly important opportunity to address MCI. Similarly, nutritional strategy and supplementation have been deemed an effective way to treat anxiety and anxiety-related disorders with the added benefit of avoiding the risks associated with other treatment options.91–96

The challenge is thus to determine the best ingredients and the details of the formulations to optimize treatment for or prevention of these challenges that arise within the brain. Below is information on research into ingredients that hold promise for addressing stress, anxiety, and cognition.

Ashwagandha Extract

The nootropic potential of ashwagandha extract, also known as Withinia Somnifera, and its health benefits as a supplement have been widely demonstrated through

scientific research.97 This compound has been shown to reduce anxiety through its impact on a variety of anxiety tests including the Hamilton Anxiety Scale, the Beck Anxiety Inventory, and the Perceived Stress Scale.98 Research on ashwagandha has helped to clarify its benefits for anxiety in specific contexts as well, including during alcohol withdrawal.99

The extract has been shown not only to substantially reduce cortisol levels but also the stress and weight gain associated with cortisol release.100,101 Studies on the extract have supported ashwagandha as a safe and effective intervention for stress that is not associated with adverse events.100,101

In addition to its beneficial effects in contexts of stress and anxiety, ashwagandha can also enhance memory. It has been shown to improve cognition across different age groups, in those with obesity-induced cognitive impairments, and in those with bipolar disorder. Some of the specific cognitive domains in which ashwagandha has demonstrated benefits include: auditory-verbal working memory, reaction time, and social cognition.102–104

Ashwagandha may also help with information processing, attention, and executive functioning in those with MCI.105 A recent review that included a comprehensive look at the impact of ashwagandha on cognition even argued that the substance should be considered in the development of therapies for Alzheimer's disease.106

In addition to its ability to promote the formation of dendrites on cells of the brain,103 the positive effects of ashwagandha on cognition appear to also occur through its antioxidant properties. Its ability to quench free radicals help ashwagandha to protect the brain against environmental toxins.107 This neuroprotective effect may allow it to play a role in the reversal of pathologies related to Alzheimer's disease and Parkinson's disease.97,108

The modulation of the immune system is another way that ashwagandha may confer benefits to the brain. Ashwagandha fights inflammation and cell death,109 and it has been shown to suppress reactive gliosis and the production of inflammatory cytokines like TNF-α, IL-1β, IL-6.110 It also appears to activate the PI3/AKT pathway and thereby promote cell survival and plasticity.104

Ascorbic Acid

Ascorbic acid, more commonly referred to as vitamin C, is a vital antioxidant and has been implicated in the promotion of healthy brain aging.111,112 For instance, vitamin C supplementation has been deemed safe and effective for reducing anxiety levels in human patients.113 Specifically, it has been shown to be capable of achieving acute anxiolytic effects in people with anxiety as measured through the State-Train Anxiety Inventory (STAI) and the Visual Analogue Mood Scale (VAMS), as well as in animal models.114,115

Its anxiolytic effects have also been demonstrated in specific patient groups, such as in those with type 2 diabetes.113 A study on 42 high school students, given either 500 milligrams (mg) of vitamin C daily or a placebo showed that only those who took vitamin C supplements displayed significantly lower anxiety based on testing with the Beck Anxiety Inventory after 14 days.116

Research suggests that the decrease in anxiety level observed in those treated with vitamin C supplements may occur through a reduction in oxidative damage that vitamin C achieves through its antioxidant properties and by modulating the nitric oxide system113,117,118 It may also attenuate harmful cortisol activity that increases in response To stress, as well as other stress responses.117 For example, high-dose sustained release vitamin C may help to improve anxiety by combatting the increased blood pressure that accompanies stress.119

In addition to stress and anxiety, vitamin C deficiency has also been linked to age-related cognitive decline and cognitive deficits that occur in patients with schizophrenia.120,121 Consistent with these findings are data that suggest that vitamin C supplementation can improve cognitive abilities like memory.122 Research in this area has suggested that vitamin C supplementation may help to mitigate the cognitive impairments that can accompany menopause.123

The specific mechanisms by which vitamin C may improve memory are not well understood, but the vitamin has a variety of beneficial effects on the central nervous system that could help explain the cognitive improvements that are observed with vitamin C supplementation. For instance, in addition to its ability to scavenge reactive oxygen species, vitamin C contributes to neuronal maturation and differentiation, angiogenesis, proper neurotransmission, and the formation of myelin.111,120

Bacopa Monnieri

Bacopa monnieri, commonly referred to as bacopa, has long been used in formulations aimed at treating anxiety, memory loss, poor cognition, and loss of concentration.124,125 Some of the anxiolytic effects that have been demonstrated with bacopa include improvements in mood and reduced cortisol levels.126 Reductions in anxiety and heart rate have been observed in people taking 300 mg per day of bacopa orally.127 Bacopa supplementation has been shown to be well-tolerated.125

Bacopa, however, is perhaps even better known for its cognitive benefits. One meta-analysis of 9 studies covering over 500 subjects supported the idea that bacopa improves cognition, particularly in the area of attention.128 Another meta-analysis pointed to the potential of bacopa to help with free recall memory.129

It has been suggested that bacopa's safe improvement of cognition may be particularly pronounced in older individuals.130 Indeed, in a study where older adults were provided with 300 mg per day of oral bacopa supplementation for 12 weeks, those taking the supplements were found to display greater cognitive improvements than those taking placebo, including enhanced performance on the Rey Auditory Verbal Learning Test (AVLT).130

The cognitive benefits of bacopa, however, appear to extend beyond the elderly. For instance, a study on middle-aged adults, aged 40 to 65 years, showed that bacopa improved retention of new information in this population.131 Research has also demonstrated cognitive benefits of bacopa in specific patient groups, such as those with schizophrenia and hypoxia-induced memory impairments.132,133

Other studies have shown that 320 mg of bacopa is sufficient for improving cognitive performance.126,127 One of these studies showed that improvements in multitasking tests like the Letter Search and Stroop tasks occurred within just 1 hour of bacopa consumption.127

Bacopa is neuroprotective, mitigating brain oxidative stress and combatting inflammation, and also capable of inhibiting the release of cytokines like TNF-α and IL-6.124,132,134,135 In schizophrenia, bacopa appears able to improve cognition by attenuating the enhanced N-methyl-D-aspartate (NMDA) density that may occur in the prefrontal cortex of the brain in this group of patients.136

Huperzine A

Huperzine A has been shown to safely improve performance on memory tasks in animal models, as well as in clinical trials.137–140 Based on preclinical and clinical research, huperzine A appears capable of improving cognition in specific patient sets, including those with schizophrenia, dementia, amnesia, diabetes, acute hyperbaric hypoxia, and hypoxic-ischemic encephalopathy.141–146

Huperzine A has been widely implicated in the treatment of Alzheimer's disease, based largely on its ability to improve cognitive performance in those with mild to moderate Alzheimer's disease.140,147,148 A new study specifically showed that Huperzine A helps to reduce cognitive and task switching deficits in Alzheimer's patients.149

Research has demonstrated that Alzheimer's disease patients who took huperzine A medication for 8 weeks showed cognitive improvements in task switching, whereas another study found that 8 to 12 weeks of huperzine A improved Mini-Mental State Examination results in Alzheimer's disease patients.149,150 Yet another study, conducted on 50 Alzheimer's disease patients taking 0.2 mg of huperzine A daily for 8 weeks, showed that huperzine A led to improvements in the patients' performance on several tasks related to cognition and memory.151

The cognitive benefits of huperzine A may be at least partly due to its ability to suppress the overexpression of inflammatory factors like tumor necrosis factor-alpha (TNF-alpha) and the overphosphorylation of JNK and p38 mitogen-activated protein kinases MAPKs).138,152 In addition to reducing neuroinflammation, huperzine A is also capable of combatting oxidative stress.137,145 It also inhibits acetylcholinesterase.139,150 It has been suggested that huperzine A may protect against the death of brain cells that results from actions of the neurochemical glutamate.139

Investigation into the effects of huperzine A in specific patients helps to clarify the mechanisms by which it provides cognitive benefits and the different ways it may achieve these effects in distinct contexts. Its improvement of cognitive symptoms in dementia, for instance, may be due to its ability to affect cholinergic dysfunction and cerebral blood flow.153

Following ischemia, huperzine A has been shown not only to improve memory, but also to reduce neuronal degeneration and partially restore hippocampal choline acetyltransferase.154 Studies on diabetes-induced cognitive decline suggest that huperzine A improves cognition by reducing oxidative stress, inflammation, and cell death, and by modulating BDNF.144,155

Pyridoxal-5-Phosphate

Pyridoxal-5-phosphate, more commonly referred to as vitamin B6, contributes to a variety of neural processes by acting as a cofactor for several enzymes.156 The production of serotonin, a chemical implicated in anxiety, is one process for which vitamin B6 acts as a cofactor, and low serum concentrations of vitamin B6 have been implicated in higher levels of anxiety, panic attacks, and hyperventilation attacks.157,158

Vitamin B6 is also implicated in cognition. Studies have shown that older adults with lower levels of vitamin B display faster rates of cognitive decline than those with higher levels of vitamin B.159 The adverse effects of low vitamin B levels on cognition appear worse in certain contexts, such as in older people or in those who smoke.160 Vitamin B has also been shown to combat memory impairment in animal models of specific illnesses, such as in tmpneumococcal meningitis.161

The glutamatergic neurotransmitter system contributes critically to learning and memory,162 and NMDA receptors for glutamate appear to be functionally altered by vitamin B deficiency. These observations suggest that vitamin B could contribute to the integrity of the brain's cognitive systems.162

Pantothenic Acid

Oral pantothenic acid, also known as pantothenate or vitamin B5, appears to protect against both anxiety and cognitive decline.163,164 As such, diets rich in pantothenic acid have been suggested to improve psychological disorders.165

The benefits that vitamin B has for the brain may be related to its role in the synthesis of acetylcholine, which is used by the brain for cognitive processes including memory encoding and concentration.164 Acetylcholine appears to be important for brain plasticity, which allows for the formation of new connections between brain cells. Without these new connections, we cannot make new memories or learn new skills. Vitamin B5 appears to be particularly important in the link between brain plasticity and age-related memory loss.

Vitamin B5 likely confers its benefits through mechanisms other than those related to acetylcholine as well. For instance, according to experts, those who consume less vitamin B5 also have more inflammatory biomarkers, so vitamin B5 may help to combat problematic inflammation that inhibits healthy brain functioning.166 U.S. Food and Drug Administration (FDA) guidelines recommend 5 mg daily of vitamin B5, which has been determined to be a safe dose.164

Gingko Biloba

Gingko biloba is thought to act a cognitive enhancer and appears to be specifically involved in improving cognition in stressful contexts, or in other words, acting as an anti-stress buffer for cognition. 167,168 Consistent with this notion, preclinical research has shown that the extract can reduce stress-induced memory deficits.169 This protective effect applies to different types of memory, including spatial memory and recall.170,171

There is also evidence for the cognitive benefits of Gingko biloba when anxiety is not considered. For instance, though MCI and dementia are likely associated with stress-related anxiety, studies focused on MCI and dementia patients – but not specifically on their anxiety – have found benefits of Gingko biloba.

A recent meta-analysis of eight randomized controlled trials on the effects of Gingko biloba in dementia patients found that the substance improved cognitive functioning as well as daily life activities in these patients.172 According to a recent systematic review, the benefits of Ginkgo biloba extract in people with dementia occur when the extract is taken at doses of 200 mg per day for 5 months or more.173

A 2016 review and meta-analysis covering 21 trials involving the use of Ginkgo biloba in MCI and Alzheimer's disease found that compared to Alzheimer's disease and MCI patients taking medicine for their cognitive challenges, those taking Ginkgo biloba in combination with their medicine saw greater improvements in their performance on the MMSE and in ADL scores.174 These differences were apparent 24 weeks into using Gingko biloba.

Gingko biloba appears to confer its protective benefits by improving the survival of relevant neurons,175 and its

benefits appear to extend beyond the cognitive to the psychiatric as well. A randomized, double-blind, controlled trial also showed that a Ginkgo biloba extract reduced anxiety in elderly patients who were suffering from cognitive decline.176 Other studies corroborate the anxiolytic-like effect of Ginkgo biloba extract.177

Phosphatidylserene

Phosphatidylserine is critical for proper neuronal functioning,178 and it has been shown to reduce stress, to improve memory, and to preserve cognition in older adults.179–181A study that provided people with 400 mg of soy-derived phosphatidylserine demonstrated that this phosphatidylserine supplementation led to improvements in cognitive performance in just 14 days, as measured by the Serial Subtraction Test (SST).179

Another study found that 300 mg of soy-derived phosphatidylserine taken for 6 months improved cognitive functions in elderly patients who had complained of memory deficits.180 Many of these improvements were seen in the domain of verbal recall. A study on almost 60 patients with Alzheimer's disease showed that phosphatidylserine improved vocabulary and picture matching scores.151

Preclinical studies have shown that phosphatidylserine improves hippocampal inflammation injury and decreases cholinesterase,151 which could help explain its beneficial effects on the brain. According to the Natural Medicine Comprehensive Database, 100 mg taken 2 to 3 times each day represents the therapeutic dose for phosphatidylserine when used for failing memory.178 A recent review found that humans can efficiently absorb 300 to 800 mg of this substance daily.182

Alpha glycerylphosphorylcholine

Alpha glycerylphosphorylcholine, also referred to as choline alfoscerate, has been implicated in anxiety and cognition. Specifically, research has revealed an inverse relationship between choline alfoscerate concentration and anxiety levels,183 suggesting that choline alfoscerate deficiency can cause or exacerbate anxiety, whereas choline alfoscerate supplementation may alleviate anxiety symptoms.

Choline alfoscerate has also been shown to be effective in improving cognitive functioning, including memory in dementia and stroke patients.184 A study on patients with mild to moderate dementia who were given 400 mg of choline alfoscerate 3 times each day for 180 days showed that the intervention improved cognitive symptoms, as measured with the MMSE, Alzheimer's Disease Assessment Scale (ADAS-Total), and Clinical Global Impression (CGI).185

This supplement has demonstrated good tolerability among patients and is currently being studied in clinical trials funded by the National Institutes of Health for its potential benefits on the brain and cognition.185,186 Like vitamin B5, choline alfoscerate appears to provide neural benefits through its interaction with acetylcholine systems of the brain. Specifically, it appears able to increase brain levels of acetylcholine, particularly in the hippocampus, which is vital for memory and cognition.187

CONCLUSION

Given that stress-related anxiety and cognitive dysfunction are on the rise and often co-exist, there is an urgent need to address each condition and any overlapping underlying mechanisms. Current therapeutic interventions are limited by efficacy and safety concerns, and emerging data are pointing to the critical role of nutrition in these disorders. Supplemental formulations that leverage what we know about how nutritional ingredients can prevent or combat anxiety and cognitive impairment offer new opportunities for people to boost their mental health in a safe, noninvasive, and cost-effective way.

References

1. Stressed in America. American Psychological Association. https://www.apa.org/monitor/2011/01/stressed-america. Published 2011. Accessed September 7, 2019.
2. 2019 Alzheimer's Disease Facts and Figures. Alzheimer's Association. https://www.alz.org/media/Documents/alzheimers-facts-and-figures-2019-r.pdf. Published 2019. Accessed August 31, 2019.
3. Older people projected to outnumber children for first time in U.S. history. United States Census Bureau. https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html. Published 2018. Accessed September 18, 2019.
4. Any Anxiety Disorder. National Institute on Mental Health. https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml. Accessed September 6, 2019.
5. Facts & Statistics. Anxiety and Depression Association of America. https://adaa.org/about-adaa/press-room/facts-statistics. Accessed September 16, 2019.
6. Chen C, Hu Z, Jiang Z, Zhou F. Prevalence of anxiety in patients with mild cognitive impairment: A systematic review and meta-analysis. J Affect Disord. 2018;236:211-221. doi:10.1016/j.jad.2018.04.110
7. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Hofler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry. 2002;63 Suppl 8:24-34.
8. Lopez O. Mild cognitive impairment. Continuum (Minneap Minn). 2013;19(2):411-424.
9. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551-2561. doi:10.1001/jama.2014.13806
10. Petersen R.Mild cognitive impairment. Continuum (Minneap Minn). 2016;22(2):408-418.
11. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. Arch Neurol. 2011;68(6):761-767. doi:10.1001/archneurol.2011.101
12. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009;66(12):1447-1455. doi:10.1001/archneurol.2009.266
13. Aretouli E, Okonkwo OC, Samek J, Brandt J. The fate of the 0.5s: predictors of 2-year outcome in mild cognitive impairment. J Int Neuropsychol Soc. 2011;17(2):277-288. doi:10.1017/S1355617710001621
14. achdev PS, Lipnicki DM, Crawford J, et al. Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. PLoS One. 2013;8(3):e59649. doi:10.1371/journal.pone.0059649
15. Li X-X, Li Z. The impact of anxiety on the progression of mild cognitive impairment to dementia in Chinese and English data bases: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2018;33(1):131-140. doi:10.1002/gps.4694
16. Koolhaas JM, Bartolomucci A, Buwalda B, et al. Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev. 2011;35(5):1291-1301. doi:10.1016/j.neubiorev.2011.02.003
17. Starcke K, Wiesen C, Trotzke P, Brand M. Effects of Acute Laboratory Stress on Executive Functions. Front Psychol. 2016;7:461. doi:10.3389/fpsyg.2016.00461
18. Hou G, Zhang Y, Zhao N, et al. Mental abilities and performance efficacy under a simulated 480-m helium-oxygen saturation diving. Front Psychol. 2015;6:979. doi:10.3389/fpsyg.2015.00979
19. de Kloet ER, Oitzl MS, Joels M. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci. 1999;22(10):422-426. doi:10.1016/s0166-2236(99)01438-1
20. Moran TP. Anxiety and working memory capacity: A meta-analysis and narrative review. Psychol Bull. 2016;142(8):831-864. doi:10.1037/bul0000051
21. Freire ACC, Ponde MP, Liu A, Caron J. Anxiety and Depression as Longitudinal Predictors of Mild Cognitive Impairment in Older Adults. Can J Psychiatry. 2017;62(5):343-350. doi:10.1177/0706743717699175
22.nLing MH, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy. Psychiatric aspects. Arch Gen Psychiatry. 1981;38(4):471-477. doi:10.1001/archpsyc.1981.01780290105011
23. McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci. 1999;22:105-122. doi:10.1146/annurev.neuro.22.1.105
24. Lupien SJ, Lepage M. Stress, memory, and the hippocampus: can't live with it, can't live without it. Behav Brain Res. 2001;127(1-2):137-158. doi:10.1016/s0166-4328(01)00361-8
25. Bremner JD. Does stress damage the brain? Biol Psychiatry. 1999;45(7):797-805. doi:10.1016/s0006-3223(99)00009-8
26. Leung AWS, Barrett LM, Butterworth D, Werther K, Dawson DR, Brintnell ES. Neural Plastic Effects of Working Memory Training Influenced by Self-perceived Stress in Stroke: A Case Illustration. Front Psychol. 2016;7:1266. doi:10.3389/fpsyg.2016.01266
27. Bierzynska M, Bielecki M, Marchewka A, et al. Effect of Frustration on Brain Activation Pattern in Subjects with Different Temperament. Front Psychol. 2015;6:1989. doi:10.3389/fpsyg.2015.01989
28. Gallagher D, Fischer CE, Iaboni A. Neuropsychiatric Symptoms in Mild Cognitive Impairment. Can J Psychiatry. 2017;62(3):161-169. doi:10.1177/0706743716648296
29. Gallagher D, Coen R, Kilroy D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2011;26(2):166-172. doi:10.1002/gps.2509
30. Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A. The impact of stress on body function: A review. EXCLI J. 2017;16:1057-1072. doi:10.17179/excli2017-480
31. Kleim B, Ehlers A, Glucksman E. Investigating Cognitive Pathways to Psychopathology: Predicting Depression and Posttraumatic Stress Disorder From Early Responses After Assault. Psychol Trauma. 2012;4(5):527-537. doi:10.1037/a0027006
32. Sun M-K, Alkon DL. Stress: perspectives on its impact on cognition and pharmacological treatment. Behav Pharmacol. 2014;25(5-6):410-424.

doi:10.1097/FBP.0000000000000045
33. Mirza SS, Ikram MA, Bos D, Mihaescu R, Hofman A, Tiemeier H. Mild cognitive impairment and risk of depression and anxiety: A population-based study. Alzheimers Dement. 2017;13(2):130-139. doi:10.1016/j.jalz.2016.06.2361
34. Kassem AM, Ganguli M, Yaffe K, et al. Anxiety symptoms and risk of cognitive decline in older community-dwelling men. Int psychogeriatrics. 2017;29(7):1137-1145. doi:10.1017/S104161021700045X
35. Stein MB, Stein DJ. Social anxiety disorder. Lancet (London, England). 2008;371(9618):1115-1125. doi:10.1016/S0140-6736(08)60488-2
36. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2011;14(5):697-710. doi:10.1017/S1461145710001434
37. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF 3rd. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry. 2013;12(2):137-148. doi:10.1002/wps.20038
38. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane database Syst Rev. 2006;(1):CD002795. doi:10.1002/14651858.CD002795.pub2
39. Thibaut F. Anxiety disorders: a review of current literature. Dialogues Clin Neurosci. 2017;19(2):87-88.
40. Birk JL, Sumner JA, Haerizadeh M, et al. Early interventions to prevent posttraumatic stress disorder symptoms in survivors of life-threatening medical events: A systematic review. J Anxiety Disord. 2019;64:24-39. doi:10.1016/j.janxdis.2019.03.003
41. Murrough JW, Yaqubi S, Sayed S, Charney DS. Emerging drugs for the treatment of anxiety. Expert Opin Emerg Drugs. 2015;20(3):393-406. doi:10.1517/14728214.2015.1049996
42. Naslund J, Hieronymus F, Emilsson JF, Lisinski A, Nilsson S, Eriksson E. Incidence of early anxiety aggravation in trials of selective serotonin reuptake inhibitors in depression. Acta Psychiatr Scand. 2017;136(4):343-351. doi:10.1111/acps.12784
43. Ammar G, Naja WJ, Pelissolo A. [Treatment-resistant anxiety disorders: A literature review of drug therapy strategies]. Encephale. 2015;41(3):260-265. doi:10.1016/j.encep.2013.11.002
44. Beeder LA, Samplaski MK. Effect of antidepressant medications on semen parameters and male fertility. Int J Urol. September 2019. doi:10.1111/iju.14111
45. Amitai M, Kronenberg S, Carmel M, et al. Pharmacogenetics of citalopram-related side effects in children with depression and/or anxiety disorders. J Neural Transm. 2016;123(11):1347-1354. doi:10.1007/s00702-016-1585-7
46. Womersley K, Ripullone K, Agius M. What are the risks associated with different Selective Serotonin Re-uptake Inhibitors (SSRIs) to treat depression and anxiety in pregnancy? An evaluation of current evidence. Psychiatr Danub. 2017;29(Suppl 3):629-644.
47. Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence - an update. Expert Opin Drug Saf. 2019;18(10):949-963. doi:10.1080/14740338.2019.1658740
48. Alwan S, Friedman JM, Chambers C. Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy: A Review of Current Evidence. CNS Drugs. 2016;30(6):499-515. doi:10.1007/s40263-016-0338-3
49. Berard A, Sheehy O, Zhao J-P, Vinet E, Bernatsky S, Abrahamowicz M. SSRI and SNRI use during pregnancy and the risk of persistent pulmonary hypertension of the newborn. Br J Clin Pharmacol. 2017;83(5):1126-1133. doi:10.1111/bcp.13194
50. Andalib S, Emamhadi MR, Yousefzadeh-Chabok S, et al. Maternal SSRI exposure increases the risk of autistic offspring: A meta-analysis and systematic review. Eur Psychiatry. 2017;45:161-166. doi:10.1016/j.eurpsy.2017.06.001
51. Barbey JT, Roose SP. SSRI safety in overdose. J Clin Psychiatry. 1998;59 Suppl 1:42-48.
52. Dalfen AK, Stewart DE. Who develops severe or fatal adverse drug reactions to selective serotonin reuptake inhibitors? Can J Psychiatry. 2001;46(3):258-263. doi:10.1177/070674370104600306
53. Juurlink D. Revisiting the drug interaction between tamoxifen and SSRI antidepressants. BMJ. 2016;354:i5309. doi:10.1136/bmj.i5309
54. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. The lancet Psychiatry. 2019;6(6):538-546. doi:10.1016/S2215-0366(19)30032-X
55. Stewart SA. The effects of benzodiazepines on cognition. J Clin Psychiatry. 2005;66 Suppl 2:9-13.
56. Sanford AM. Mild Cognitive Impairment. Clin Geriatr Med. 2017;33(3):325-337. doi:10.1016/j.cger.2017.02.005
57. Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: a clinical perspective. Mayo Clin Proc. 2014;89(10):1452-1459. doi:10.1016/j.mayocp.2014.06.019
58. Bond M, Rogers G, Peters J, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. Health Technol Assess. 2012;16(21):1-470. doi:10.3310/hta16210
59. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008;148(5):379-397. doi:10.7326/0003-4819-148-5-200803040-00009
60. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005;352(23):2379-2388. doi:10.1056/NEJMoa050151
61. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology. 2009;72(18):1555-1561. doi:10.1212/01.wnl.0000344650.95823.03
62. Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS Med. 2007;4(11):e338. doi:10.1371/journal.pmed.0040338
63. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology. 2009;73(5):356-361. doi:10.1212/WNL.0b013e3181b04ae3
64. Brooks SJ, Stein DJ. A systematic review of the neural bases of psychotherapy for anxiety and related disorders. Dialogues Clin Neurosci. 2015;17(3):261-279.
65. David D, Cristea I, Hofmann SG. Why Cognitive Behavioral Therapy Is the Current Gold Standard of Psychotherapy. Front psychiatry. 2018;9:4. doi:10.3389/fpsyt.2018.00004
66. Cirillo P, GoldAK, Nardi AE, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. Brain Behav. 2019;9(6):e01284. doi:10.1002/brb3.1284
67. Jerath R, Crawford MW, Barnes VA, Harden K. Self-regulation of breathing as a primary treatment for anxiety. Appl Psychophysiol Biofeedback. 2015;40(2):107-115. doi:10.1007/s10484-015-9279-8
68. Chen KW, Berger CC, Manheimer E, et al. Meditative therapies for reducing anxiety: a systematic review and meta-analysis of randomized controlled trials. Depress Anxiety. 2012;29(7):545-562. doi:10.1002/da.21964
69. Gard T, Holzel BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. Ann N Y Acad Sci. 2014;1307:89-103. doi:10.1111/nyas.12348
70. Russell-Williams J, Jaroudi W, Perich T, Hoscheidt S, El Haj M, Moustafa AA. Mindfulness and meditation: treating cognitive impairment and reducing stress in dementia. Rev Neurosci. 2018;29(7):791-804. doi:10.1515/revneuro-2017-0066
71. Goyal M, Singh S, Sibinga EMS, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014;174(3):357-368. doi:10.1001/jamainternmed.2013.13018
72. Goyata SLT, Avelino CCV, Santos SVM Dos, Souza Junior DI de, Gurgel MDSL, Terra F de S. Effects from acupuncture in treating anxiety: integrative review. Rev Bras Enferm. 2016;69(3):602-609. doi:10.1590/0034-7167.2016690325i
73. Amorim D, Amado J, Brito I, et al. Acupuncture and electroacupuncture for anxiety disorders: A systematic review of the clinical research. Complement Ther Clin Pract. 2018;31:31-37. doi:10.1016/j.ctcp.2018.01.008
74. Ghafoor U, Lee J-H, Hong K-S, Park S-S, Kim J, Yoo H-R. Effects of Acupuncture Therapy on MCI Patients Using Functional Near-Infrared Spectroscopy. Front Aging Neurosci. 2019;11:237. doi:10.3389/fnagi.2019.00237
75. Wang Z, Nie B, Li D, et al. Effect of acupuncture in mild cognitive impairment and Alzheimer disease: a functional MRI study. PLoS One. 2012;7(8):e42730. doi:10.1371/journal.pone.0042730
76. Kim J-H, Cho M-R, Park G-C, Lee J-S. Effects of different acupuncture treatment methods on mild cognitive impairment: a study protocol for a randomized controlled trial. Trials. 2019;20(1):551. doi:10.1186/s13063-019-3670-3
77. Suh H-W, Kim J, Kwon O, et al. Neurocircuitry of acupuncture effect on cognitive improvement in patients with mild cognitive impairment using magnetic resonance imaging: a study protocol for a randomized controlled trial. Trials. 2019;20(1):310. doi:10.1186/s13063-019-3446-9
78. Chen Y, Zhang W, Wu H, Lao L, Xu J, Xu S. Combination of acupuncture and Chinese herbal formula for elderly adults with mild cognitive impairment: protocol for a randomized controlled trial. Trials. 2019;20(1):117. doi:10.1186/s13063-019-3212-z
79. Eun-Sun J, Jun-Hwan L, Hyun-Tae K, et al. Effect of acupuncture on patients with mild cognitive impairment assessed using functional near-infrared spectroscopy on week 12 (close-out): a pilot study protocol. Integr Med Res. 2018;7(3):287-295. doi:10.1016/j.imr.2018.06.002
80. Stonerock GL, Hoffman BM, Smith PJ, Blumenthal JA. Exercise as Treatment for Anxiety: Systematic Review and Analysis. Ann Behav Med. 2015;49(4):542-556. doi:10.1007/s12160-014-9685-9
81. Li AW, Goldsmith C-AW. The effects of yoga on anxiety and stress. Altern Med Rev. 2012;17(1):21-35.
82. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008;300(9):1027-1037. doi:10.1001/jama.300.9.1027
83. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med. 2011;269(1):107-117. doi:10.1111/j.1365-2796.2010.02281.x
84. Gomez-Pinilla F, So V, Kesslak JP. Spatial learning induces neurotrophin receptor and synapsin I in the hippocampus. Brain Res. 2001;904(1):13-19. doi:10.1016/s0006-8993(01)02394-0
85. Carek PJ,Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med. 2011;41(1):15-28. doi:10.2190/PM.41.1.c
86. Martinez Garcia RM, Jimenez Ortega AI, Lopez Sobaler AM, Ortega RM. [Nutrition strategies that improve cognitive function]. Nutr Hosp. 2018;35(Spec No6):16-19. doi:10.20960/nh.2281
87. Solfrizzi V, Panza F, Capurso A. The role of diet in cognitive decline. J Neural Transm. 2003;110(1):95-110. doi:10.1007/s00702-002-0766-8
88. Singh B, Parsaik AK, Mielke MM, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;39(2):271-282. doi:10.3233/JAD-130830
89. Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing Res Rev. 2017;40:75-83. doi:10.1016/j.arr.2017.09.003
90. Straubmeier M, Behrndt E-M, Seidl H, Ozbe D, Luttenberger K, Graessel E. Non-Pharmacological Treatment in People With Cognitive Impairment. Dtsch Arztebl Int. 2017;114(48):815-821. doi:10.3238/arztebl.2017.0815
91. Lakhan SE, Vieira KF. Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review. Nutr J. 2010;9:42. doi:10.1186/1475-2891-9-42
92. Fernandez-Rodriguez M, Rodriguez-Legorburu I, Lopez-Ibor Alcocer MI. Nutritional supplements in Anxiety Disorder. Actas Esp Psiquiatr. 2017;45(Supplement):1-7.
93. Murphy M, Mercer JG. Diet-regulated anxiety. Int J Endocrinol.

2013;2013:701967. doi:10.1155/2013/701967
94. Masana MF, Tyrovolas S, Kolia N, et al. Dietary Patterns and Their Association with Anxiety Symptoms among Older Adults: The ATTICA Study. Nutrients. 2019;11(6). doi:10.3390/nu11061250
95. Forsyth AK, Williams PG, Deane FP. Nutrition status of primary care patients with depression and anxiety. Aust J Prim Health. 2012;18(2):172-176. doi:10.1071/PY11023
96. Firth J, Marx W, Dash S, et al. The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials. Psychosom Med. 2019;81(3):265-280. doi:10.1097/PSY.0000000000000673
97. Wadhwa R, Konar A, Kaul SC. Nootropic potential of Ashwagandha leaves: Beyond traditional root extracts. Neurochem Int. 2016;95:109-118. doi:10.1016/j.neuint.2015.09.001
98. Pratte MA, Nanavati KB, Young V, Morley CP. An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera). J Altern Complement Med. 2014;20(12):901-908. doi:10.1089/acm.2014.0177
99. Bansal P, Banerjee S. Effect of Withinia Somnifera and Shilajit on Alcohol Addiction in Mice. Pharmacogn Mag. 2016;12(Suppl 2):S121-8. doi:10.4103/0973-1296.182170
100. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012;34(3):255-262. doi:10.4103/0253-7176.106022
101. Choudhary D, Bhattacharyya S, Joshi K. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial. J Evid Based Complementary Altern Med. 2017;22(1):96-106. doi:10.1177/2156587216641830
102. Chengappa KNR, Bowie CR, Schlicht PJ, Fleet D, Brar JS, Jindal R. Randomized placebo-controlled adjunctive study of an extract of withania somnifera for cognitive dysfunction in bipolar disorder. J Clin Psychiatry. 2013;74(11):1076-1083. doi:10.4088/JCP.13m08413
103. Singh N, Bhalla M, de Jager P, Gilca M. An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda. African J Tradit Complement Altern Med AJTCAM. 2011;8(5 Suppl):208-213. doi:10.4314/ajtcam.v8i5S.9
104. Manchanda S, Kaur G. Withania somnifera leaf alleviates cognitive dysfunction by enhancing hippocampal plasticity in high fat diet induced obesity model. BMC Complement Altern Med. 2017;17(1):136. doi:10.1186/s12906-017-1652-0
105. Choudhary D, Bhattacharyya S, Bose S. Efficacy and Safety of Ashwagandha (Withania somnifera (L.) Dunal) Root Extract in Improving Memory and Cognitive Functions. J Diet Suppl. 2017;14(6):599-612. doi:10.1080/19390211.2017.1284970
106. Vegh C, Stokes K, Ma D, et al. A Bird's-Eye View of the Multiple Biochemical Mechanisms that Propel Pathology of Alzheimer's Disease: Recent Advances and Mechanistic Perspectives on How to Halt the Disease Progression Targeting Multiple Pathways. J Alzheimers Dis. 2019;69(3):631-649. doi:10.3233/JAD-181230
107. Ahmed ME, Javed H, Khan MM, et al. Attenuation of oxidative damage-associated cognitive decline by Withania somnifera in rat model of streptozotocin-induced cognitive impairment. Protoplasma. 2013;250(5):1067-1078. doi:10.1007/s00709-013-0482-2
108. Shah N, Singh R, Sarangi U, et al. Combinations of Ashwagandha leaf extracts protect brain-derived cells against oxidative stress and induce differentiation. PLoS One. 2015;10(3):e0120554. doi:10.1371/journal.pone.0120554
109. Kaur T, Singh H, Mishra R, et al. Withania somnifera as a potential anxiolytic and immunomodulatory agent in acute sleep deprived female Wistar rats. Mol Cell Biochem. 2017;427(1-2):91-101. doi:10.1007/s11010-016-2900-1
110. Gupta M, Kaur G. Withania somnifera as a Potential Anxiolytic and Anti-inflammatory Candidate Against Systemic Lipopolysaccharide-Induced Neuroinflammation. Neuromolecular Med. 2018;20(3):343-362. doi:10.1007/s12017-018-8497-7
111. Kocot J, Luchowska-Kocot D, Kielczykowska M, Musik I, Kurzepa J. Does Vitamin C Influence Neurodegenerative Diseases and Psychiatric Disorders? Nutrients. 2017;9(7). doi:10.3390/nu9070659
112. Harrison FE, Bowman GL, Polidori MC. Ascorbic acid and the brain: rationale for the use against cognitive decline. Nutrients. 2014;6(4):1752-1781. doi:10.3390/nu6041752
113. Mazloom Z, Ekramzadeh M, Hejazi N. Efficacy of supplementary vitamins C and E on anxiety, depression and stress in type 2 diabetic patients: a randomized, single-blind, placebo-controlled trial. Pakistan J Biol Sci PJBS. 2013;16(22):1597-1600.
114. Moritz B, Schwarzbold ML, Guarnieri R, Diaz AP, S Rodrigues AL, Dafre AL. Effects of ascorbic acid on anxiety state and affect in a non-clinical sample. Acta Neurobiol Exp (Wars). 2017;77(4):362-372.
115. Fraga DB, Olescowicz G, Moretti M, et al. Anxiolytic effects of ascorbic acid and ketamine in mice. J Psychiatr Res. 2018;100:16-23. doi:10.1016/j.jpsychires.2018.02.006
116. de Oliveira IJL, de Souza VV, Motta V, Da-Silva SL. Effects of Oral Vitamin C Supplementation on Anxiety in Students: A Double-Blind, Randomized, Placebo-Controlled Trial. Pakistan J Biol Sci PJBS. 2015;18(1):11-18.
117. Hughes RN, Lowther CL, van Nobelen M. Prolonged treatment with vitamins C and E separately and together decreases anxiety-related open-field behavior and acoustic startle in hooded rats. Pharmacol Biochem Behav. 2011;97(3):494-499. doi:10.1016/j.pbb.2010.10.010
118. Walia V, Garg C, Garg M. Nitrergic signaling modulation by ascorbic acid treatment is responsible for anxiolysis in mouse model of anxiety. Behav Brain Res. 2019;364:85-98. doi:10.1016/j.bbr.2019.02.007
119. McCabe D, Lisy K, Lockwood C, Colbeck M. The impact of essential fatty acid, B vitamins, vitamin C, magnesium and zinc supplementation on stress levels in women: a systematic review. JBI database Syst Rev Implement reports. 2017;15(2):402-453. doi:10.11124/JBISRIR-2016-002965
120. Hansen SN, Tveden-Nyborg P, Lykkesfeldt J. Does vitamin C deficiency affect cognitive development and function? Nutrients. 2014;6(9):3818-3846. doi:10.3390/nu6093818
121. Castagne V, Rougemont M, Cuenod M, Do KQ. Low brain glutathione and ascorbic acid associated with dopamine uptake inhibition during rat's development induce long-term cognitive deficit: relevance to schizophrenia. Neurobiol Dis. 2004;15(1):93-105.
122. Parle M, Dhingra D. Ascorbic Acid: a promising memory-enhancer in mice. J Pharmacol Sci. 2003;93(2):129-135.
123. Delrobaei F, Fatemi I, Shamsizadeh A, Allahtavakoli M. Ascorbic acid attenuates cognitive impairment and brain oxidative stress in ovariectomized mice. Pharmacol Rep. 2019;71(1):133-138. doi:10.1016/j.pharep.2018.10.001
124. Nemetchek MD, Stierle AA, Stierle DB, Lurie DI. The Ayurvedic plant Bacopa monnieri inhibits inflammatory pathways in the brain. J Ethnopharmacol. 2017;197:92-100. doi:10.1016/j.jep.2016.07.073
125. Sokolowska L, Bylka W. [Bacopa Monnieri - activity and applications in medicine]. Wiad Lek. 2015;68(3 pt 2):358-362.
126. Downey LA, Kean J, Nemeh F, et al. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of Bacopa monnieri (CDRI 08) on sustained cognitive performance. Phytother Res. 2013;27(9):1407-1413. doi:10.1002/ptr.4864
127. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood. Phytother Res. 2014;28(4):551-559. doi:10.1002/ptr.5029
128. Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, Limpeanchob N, Norman Scholfield C. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. J Ethnopharmacol. 2014;151(1):528-535. doi:10.1016/j.jep.2013.11.008
129. Pase MP, Kean J, Sarris J, Neale C, Scholey AB, Stough C. The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. J Altern Complement Med. 2012;18(7):647-652. doi:10.1089/acm.2011.0367
130. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. J Altern Complement Med. 2008;14(6):707-713. doi:10.1089/acm.2008.0018
131. Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi Bacopa monnieri) on human memory. Neuropsychopharmacology. 2002;27(2):279-281. doi:10.1016/S0893-133X(01)00419-5
132. Piyabhan P, Wetchateng T. Bacopa monnieri (Brahmi) Enhanced Cognitive Function and Prevented Cognitive Impairment by Increasing VGLUT2 Immunodensity in Prefrontal Cortex of Sub-Chronic Phencyclidine Rat Model of Schizophrenia. J Med Assoc Thai. 2015;98 Suppl 3:S7-15.
133. Rani A, Prasad S. A Special Extract of Bacopa monnieri (CDRI-08)-Restored Memory in CoCl2-Hypoxia Mimetic Mice Is Associated with Upregulation of Fmr-1 Gene Expression in Hippocampus. Evid Based Complement Alternat Med. 2015;2015:347978. doi:10.1155/2015/347978
134. Krishna G, Hosamani R, Muralidhara. Bacopa monnieri Supplements Offset Paraquat-Induced Behavioral Phenotype and Brain Oxidative Pathways in Mice. Cent Nerv Syst Agents Med Chem. 2019;19(1):57-66. doi:10.2174/1871524919666190115125900
135. Sekhar VC, Viswanathan G, Baby S. Insights Into the Molecular Aspects of Neuroprotective Bacoside A and Bacopaside I. Curr Neuropharmacol. 2019;17(5):438-446. doi:10.2174/1570159X16666180419123022
136. Piyabhan P, Wetchateng T, Sireeratawong S. Cognitive enhancement effects of Bacopa monnieri Brahmi) on novel object recognition and NMDA receptor immunodensity in the prefrontal cortex and hippocampus of sub-chronic phencyclidine rat model of schizophrenia. J Med Assoc Thai. 2013;96(2):231-238.
137. Mei Z, Zheng P, Tan X, Wang Y, Situ B. Huperzine A alleviates neuroinflammation, oxidative stress and improves cognitive function after repetitive traumatic brain injury. Metab Brain Dis. 2017;32(6):1861-1869. doi:10.1007/s11011-017-0075-4
138. Ratia M, Gimenez-Llort L, Camps P, et al. Huprine X and huperzine A improve cognition and regulate some neurochemical processes related with Alzheimer's disease in triple transgenic mice (3xTg-AD). Neurodegener Dis. 2013;11(3):129-140. doi:10.1159/000336427
139. Bai DL, Tang XC, He XC. Huperzine A, a potential therapeutic agent for treatment of Alzheimer's disease. Curr Med Chem. 2000;7(3):355-374.
140. Damar U, Gersner R, Johnstone JT, Schachter S, Rotenberg A. Huperzine A: A promising anticonvulsant, disease modifying, and memory enhancing treatment option in Alzheimer's disease. Med Hypotheses. 2017;99:57-62. doi:10.1016/j.mehy.2016.12.006
141. Zheng W, Xiang Y-Q, Li X-B, et al. Adjunctive huperzine A for cognitive deficits in schizophrenia: a systematic review and meta-analysis. Hum Psychopharmacol. 2016;31(4):286-295. doi:10.1002/hup.2537
142. Wang LS, Zhou J, Shao XM, Tang XC. Huperzine A attenuates cognitive deficits and brain injury in neonatal rats after hypoxia-ischemia. Brain Res. 2002;949(1-2):162-170.
143. Xu Z-Q, Liang X-M, Juan-Wu, Zhang Y-F, Zhu C-X, Jiang X-J. Treatment with Huperzine A improves cognition in vascular dementia patients. Cell Biochem Biophys. 2012;62(1):55-58. doi:10.1007/s12013-011-9258-5
144. Mao X-Y, Cao D-F, Li X, et al. Huperzine A ameliorates cognitive deficits in streptozotocin-induced diabetic rats. Int J Mol Sci. 2014;15(5):7667-7683. doi:10.3390/ijms15057667
145. Shi Q, Fu J, Ge D, et al. Huperzine A ameliorates cognitive deficits and oxidative stress in the hippocampus of rats exposed to acute hypobaric hypoxia. Neurochem Res. 2012;37(9):2042-2052. doi:10.1007/s11064-012-0826-x
146. Ye JW, Cai JX, Wang LM, Tang XC. Improving effects of huperzine A on spatial working memory in aged monkeys and young adult monkeys with experimental cognitive impairment. J Pharmacol Exp Ther. 1999;288(2):814-819.
147. Malkova L, Kozikowski AP, Gale K. The effects of huperzine A and IDRA 21 on visual recognition memory in young macaques. Neuropharmacology. 2011;60(7-8):1262-1268. doi:10.1016/j.neuropharm.2010.12.018
148. Cui C-C, Sun Y, Wang X-Y, Zhang Y, Xing Y. The effect of anti-dementia drugs on Alzheimer disease-induced cognitive impairment: A network meta-analysis. Medicine Baltimore). 2019;98(27):e16091.

doi:10.1097/MD.0000000000016091
149. Gul A, Bakht J, Mehmood F. Huperzine-A response to cognitive impairment and task switching deficits in patients with Alzheimer's disease. J Chin Med Assoc. September 2018. doi:10.1016/j.jcma.2018.07.004
150. Desilets AR, Gickas JJ, Dunican KC. Role of huperzine a in the treatment of Alzheimer's disease. Ann Pharmacother. 2009;43(3):514-518. doi:10.1345/aph.1L402
151. Xu SS, Gao ZX, Weng Z, et al. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li Xue Bao. 1995;16(5):391-395.
152. Wang J, Zhang HY, Tang XC. Huperzine a improves chronic inflammation and cognitive decline in rats with cerebral hypoperfusion. J Neurosci Res. 2010;88(4):807-815. doi:10.1002/jnr.22237
153. Wang LM, Han YF, Tang XC. Huperzine A improves cognitive deficits caused by chronic cerebral hypoperfusion in rats. Eur J Pharmacol. 2000;398(1):65-72.
154. Zhou J, Zhang HY, Tang XC. Huperzine A attenuates cognitive deficits and hippocampal neuronal damage after transient global ischemia in gerbils. Neurosci Lett. 2001;313(3):137-140.
155. Wang R, Zhang HY, Tang XC. Huperzine A attenuates cognitive dysfunction and neuronal degeneration caused by beta-amyloid protein-(1-40) in rat. Eur J Pharmacol. 2001;421(3):149-156.
156. Mesripour A, Hajhashemi V, Kuchak A. Effect of concomitant administration of three different antidepressants with vitamin B6 on depression and obsessive compulsive disorder in mice models. Res Pharm Sci. 2017;12(1):46-52. doi:10.4103/1735-5362.199046
157. Mikawa Y, Mizobuchi S, Egi M, Morita K. Low serum concentrations of vitamin B6 and iron are related to panic attack and hyperventilation attack. Acta Med Okayama. 2013;67(2):99-104. doi:10.18926/AMO/49668
158. Moore K, Hughes CF, Hoey L, et al. B-vitamins in Relation to Depression in Older Adults Over 60 Years of Age: The Trinity Ulster Department of Agriculture (TUDA) Cohort Study. J Am Med Dir Assoc. 2019;20(5):551-557.e1. doi:10.1016/j.jamda.2018.11.031
159. Hughes CF, Ward M, Tracey F, et al. B-Vitamin Intake and Biomarker Status in Relation to Cognitive Decline in Healthy Older Adults in a 4-Year Follow-Up Study. Nutrients. 2017;9(1). doi:10.3390/nu9010053
160. Palacios N, Scott T, Sahasrabudhe N, Gao X, Tucker KL. Lower Plasma Vitamin B-6 is Associated with 2-Year Cognitive Decline in the Boston Puerto Rican Health Study. J Nutr. 2019;149(4):635-641. doi:10.1093/jn/nxy268
161. Barichello T, Generoso JS, Simoes LR, et al. Vitamin B6 prevents cognitive impairment in experimental pneumococcal meningitis. Exp Biol Med (Maywood). 2014;239(10):1360-1365. doi:10.1177/1535370214535896
162. Guilarte TR. Vitamin B6 and cognitive development: recent research findings from human and animal studies. Nutr Rev. 1993;51(7):193-198. doi:10.1111/j.1753-4887.1993.tb03102.x
163. Pantothenic acid (vitamin B5). WebMD. https://www.webmd.com/vitamins/ai/ingredientmono-853/pantothenic-acid-vitamin-b5. Accessed March 6, 2019.
164. The connection between vitamin B5 and memory. Medicalopedia. https://www.medicalopedia.org/4835/the-connection-between-vitamin-b5-and-memory. Published 2014. Accessed March 6, 2019.
165. Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L, et al. Do patterns of nutrient intake predict self-reported anxiety, depression and psychological distress in adults? SEPAHAN study. Clin Nutr. February 2018. doi:10.1016/j.clnu.2018.02.002
166. Anderson P. Inflammatory dietary pattern linked to brain aging. Medscape. https://www.medscape.com/viewarticle/883038. Published 2017. Accessed March 6, 2019.
167. Singh SK, Barreto GE, Aliev G, Echeverria V. Ginkgo biloba as an Alternative Medicine in the Treatment of Anxiety in Dementia and other Psychiatric Disorders. Curr Drug Metab. 2017;18(2):112-119. doi:10.2174/1389200217666161201112206
168. Ward CP, Redd K, Williams BM, Caler JR, Luo Y, McCoy JG. Ginkgo biloba extract: cognitive enhancer or antistress buffer. Pharmacol Biochem Behav. 2002;72(4):913-922. doi:10.1016/s0091-3057(02)00768-2
169. Walesiuk A, Trofimiuk E, Braszko JJ. Gingko biloba extract diminishes stress-induced memory deficits in rats. Pharmacol Rep. 2005;57(2):176-187.
170. Walesiuk A, Braszko JJ. Preventive action of Ginkgo biloba in stress- and corticosterone-induced impairment of spatial memory in rats. Phytomedicine. 2009;16(1):40-46. doi:10.1016/j.phymed.2007.04.012
171. Walesiuk A, Trofimiuk E, Braszko JJ. Ginkgo biloba normalizes stress- and corticosterone-induced impairment of recall in rats. Pharmacol Res. 2006;53(2):123-128. doi:10.1016/j.phrs.2005.09.007
172. Brondino N, De Silvestri A, Re S, et al. A Systematic Review and Meta-Analysis of Ginkgo biloba in Neuropsychiatric Disorders: From Ancient Tradition to Modern-Day Medicine. Evid Based Complement Alternat Med. 2013;2013:915691. doi:10.1155/2013/915691
173. Yuan Q, Wang C-W, Shi J, Lin Z-X. Effects of Ginkgo biloba on dementia: An overview of systematic reviews. J Ethnopharmacol. 2017;195:1-9. doi:10.1016/j.jep.2016.12.005
174. Yang G, Wang Y, Sun J, Zhang K, Liu J. Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Curr Top Med Chem. 2016;16(5):520-528. doi:10.2174/1568026615666150813143520
175. Ribeiro ML, Moreira LM, Arcari DP, et al. Protective effects of chronic treatment with a standardized extract of Ginkgo biloba L. in the prefrontal cortex and dorsal hippocampus of middle-aged rats. Behav Brain Res. 2016;313:144-150. doi:10.1016/j.bbr.2016.06.029
176. Woelk H, Arnoldt KH, Kieser M, Hoerr R. Ginkgo biloba special extract EGb 761 in generalized anxiety disorder and adjustment disorder with anxious mood: a randomized, double-blind, placebo-controlled trial. J Psychiatr Res. 2007;41(6):472-480. doi:10.1016/j.jpsychires.2006.05.004
177. Kuribara H, Weintraub ST, Yoshihama T, Maruyama Y. An anxiolytic-like effect of Ginkgo biloba extract and its constituent, ginkgolide-A, in mice. J Nat Prod. 2003;66(10):1333-1337. doi:10.1021/np030122f
89 178. Wong C. The health benefits of phosphatidylserine. Very Well Mind. https://www.verywellmind.com/the-benefits-of-phosphatidylserine-89496. Published 2019. Accessed March 7, 2019.
179. Parker AG, Gordon J, Thornton A, et al. The effects of IQPLUS Focus on cognitive function, mood and endocrine response before and following acute exercise. J Int Soc Sports Nutr. 2011;8:16. doi:10.1186/1550-2783-8-16
180. Kato-Kataoka A, Sakai M, Ebina R, Nonaka C, Asano T, Miyamori T. Soybean-derived phosphatidylserine improves memory function of the elderly Japanese subjects with memory complaints. J Clin Biochem Nutr. 2010;47(3):246-255. doi:10.3164/jcbn.10-62
181. Fairbairn P, Tsofliou F, Johnson A, Dyall SC. Combining a high DHA multi-nutrient supplement with aerobic exercise: Protocol for a randomised controlled study assessing mobility and cognitive function in older women. Prostaglandins Leukot Essent Fatty Acids. 2019;143:21-30. doi:10.1016/j.plefa.2019.04.001
182. Glade MJ, Smith K. Phosphatidylserine and the human brain. Nutrition. 2015;31(6):781-786. doi:10.1016/j.nut.2014.10.014
183. Bjelland I, Tell GS, Vollset SE, Konstantinova S, Ueland PM. Choline in anxiety and depression: the Hordaland Health Study. Am J Clin Nutr. 2009;90(4):1056-1060. doi:10.3945/ajcn.2009.27493
184. Lee SH, Choi BY, Kim JH, et al. Late treatment with choline alfoscerate (l-alpha glycerylphosphorylcholine, alpha-GPC) increases hippocampal neurogenesis and provides protection against seizure-induced neuronal death and cognitive impairment. Brain Res. 2017;1654(Pt A):66-76. doi:10.1016/j.brainres.2016.10.011
185. De Jesus Moreno Moreno M. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. Clin Ther. 2003;25(1):178-193.
186. Alpha-GPC and physical and cognitive performances in volleyball players. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02886130. Accessed March 7, 2019.
187. Lopez CM, Govoni S, Battaini F, et al. Effect of a new cognition enhancer, alpha-glycerylphosphorylcholine, on scopolamine-induced amnesia and brain acetylcholine. Pharmacol Biochem Behav. 1991;39(4):835-840.