Complementary & Alternative Medicine for Mental Health

Updated April 8, 2016

TREATMENTS

Click on any item to go directly to the summary

LIST OF CONDITIONS, INCLUDING SIDE EFFECT RISK LEVELS

■ = GENERALLY SAFE

■ = MINOR TO MAJOR SIDE EFFECTS

■ = CAUTION ADVISED

Click on* GO *to go directly to the summary for that item

DEPRESSION

- Chromium for atypical depression GO>
- Cranial Electrical Stimulation for depression GO>
- DHEA and 7-keto DHEA for depression and bipolar disorder GO>
- Folate for depression and to enhance the effectiveness of conventional antidepressants GO>
- Inositol for depression GO>
- Omega-3 polyunsaturated fatty acids (fish oil) for mood stabilization and depression and to enhance the effectiveness of conventional antidepressants GO>
- Rhodiola (*Rhodiola rosea)* for mild to moderate depression GO>
- St. John's wort (*Hypericum perforatum*) for mild to moderate depression GO>
- S-Adenosyl-L-Methionine (SAM-e) for depression and to enhance the effectiveness of conventional anti-depressants GO>
- Transcranial Magnetic Stimulation for depression GO>
- Tryptophan/5-HTP for depression and to enhance the effectiveness of conventional antidepressants GO>
- Wellness GO>
- Yoga for depression and schizophrenia GO>

ANXIETY, STRESS, PANIC DISORDER, AND OTHER CONDITIONS

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- Inositol for panic disorder GO>
- Kava (*Piper methysticum*) for anxiety and stress GO>
- Meditation for all forms of stress GO>
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- Tryptophan/5-HTP for anxiety GO>
- Wellness GO>

- **Yoga for anxiety, PTSD and ADHD GO>**

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- **Melatonin for jet lag and sleep disorders GO>**
- **Valerian (*Valeriana officinalis*) for sleep disorders GO>**
- **Wellness GO>**

NEUROPROTECTION

- **CDP choline as a possible neuroprotectant GO>**
- **Folate as a possible neuroprotectant GO>**
- **Ginkgo (*Ginkgo biloba*) as a possible neuroprotectant GO>**
- **Omega-3 polyunsaturated fatty acids (fish oil) as a possible neuroprotectant GO>**
- **Rhodiola (*Rhodiola rosea)* as a possible neuroprotectant GO>**
- **S-Adenosyl-L-Methionine (SAM-e) as a possible neuroprotectant GO>**
- **Wellness GO>**

MENTAL HEALTH AMERICA

CAM FOR MENTAL HEALTH CONDITIONS (2012)

A COMPARATIVE EVIDENCE-BASED APPROACH TO

COMPLEMENTARY AND ALTERNATIVE TREATMENT

FOR MENTAL HEALTH CONDITIONS

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[1] Although some of the sources are later in time, reflecting publication in 2013, the information in this outline is current as of December, 2012. Mental Health America cannot and does not undertake any obligation to keep the information current after that date.

[2] WIKICITATION: MHA does not have the resources to exhaustively check all citations and cross-references in this outline, and new evidence may make existing citations obsolete at any time. Accordingly, readers are encouraged to correct citations and update information **on the listed treatments** by sending e-mail to jnderaismes@gmail.com.

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- **rhodiola (*Rhodiola rosea)* for mild to moderate depression**
- **S-Adenosyl-L-Methionine (SAM-e) for depression and to enhance the effectiveness of conventional anti-depressants**
- **St. John's wort (*Hypericum perforatum*) for mild to moderate depression**
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ACKNOWLEDGEMENTS

This outline has been developed by Mental Health America (MHA) from the principal available evidence-based sources of information concerning “complementary,” “alternative,” “integrative,” “natural,” and often self-administered treatments for mental health conditions. Mental Health America acknowledges the generous assistance of David Mischoulon, M.D., Ph.D., Associate Professor of Psychiatry at Harvard Medical School, who has reviewed the manuscript, but who bears no responsibility for the information, which is derived mainly from published sources. Syntheses and evaluations of the information by MHA are its responsibility alone. MHA also bears complete responsibility for its decisions to shorten and redraft descriptions of information from the sources. Only quoted text should be presumed to be verbatim.

SOURCES

MHA began with the limited information accepted by the National Center for Complementary and Alternative Medicine (NCCAM) and the Agency for Healthcare Research and Quality

(AHRQ), at the National Institutes of Health[1] and added the information contained in ten recent compilations of "complementary and alternative medicine" (hereinafter CAM) for mental health disorders: (1) Dr. Mischoulon's *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited with Jerrold F. Rosenbaum, M.D. (also of Harvard Medical School) (2002/2008),[2] (2) *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (2009) ("Brown *et al."*) ,[3] preceded in 2004 by Brown, R.P. and Gerbarg, P.L., *The Rhodiola Revolution*[4] and supplemented in 2012 by *Non-drug Treatments for ADHD*, by Brown, R.P. and Gerbarg, P.L.,[5] and *The Healing Power of the Breath*, by Brown, R.P. and Gerbarg, P.L.,[6] and in 2013 by Muskin, Gerbarg and Brown's latest distillation, *Complementary and Integrative Therapies for Psychiatric Disorders* ("Brown *et al.* II")[7] [For the purpose of counting, the foregoing five books are treated as a single source], (3) The seminal article, "Dietary Supplements and Natural Products as Psychotherapeutic Agents," by Adriane Fugh-Berman, M.D. (of Georgetown Medical School) and Jerry M. Cott, Ph.D. (of the National Institutes of Health) (1999),[8] (4) *Complementary and Alternative Treatments in Mental Health Care*, By James H. Lake, M.D. (clinical assistant professor in the department of psychiatry and behavioral science at Stanford and visiting assistant professor of medicine at the Center for Integrative Medicine, University of Arizona School of Medicine) and David Spiegel, M.D.,[9] (5) relevant portions of the *Natural Standard Herb and Supplement Guide* (2010 edition),[10] (6) relevant portions of *Berkeley Wellness Reports – Dietary Supplements* (2010 and 2011 editions, University of California),[11] (7) relevant portions of *Consumer Reports*, "Dangerous Supplements," published by Consumers Union, September, 2010, at p. 16-20 (2010),[12] (8) relevant portions of *The Mayo Clinic Guide to Alternative Medicine 2011,* published by Time Home Entertainment, Inc. (2010),[13] (9) the compendium by Iovieno, N., Dalton, E. D., Fava, M. & Mischoulon, D., "Second-tier Natural Antidepressants: Review and Critique" (2011),[14] and (10) Director of the Center for Integrative Medicine, University of Arizona School of Medicine and bestselling CAM and integral health advocate Andrew Weil, M.D.'s relevant book, *Spontaneous Happiness* (2011).[15]

Although not treated as a source, except for the chapter on yoga and meditation, MHA has benefitted enormously by guidance from James S. Gordon, M.D., a psychiatrist who runs the Center for Mind-Body Medicine in Washington, D.C., and the nuanced approach to recovery from mental health conditions that he advocates in *Unstuck,*[16] which describes recovery as a spiritual path.

The quest for mental wellness and recovery from mental and emotional setbacks is fundamental to everyone's path in life. Any search for insight into one's life purpose, any quest for knowledge of the self, must treat mental adversity as an opportunity for growth and for enlightenment. That is the spiritual core of the recovery concept. And it is in that spirit that this outline is offered, for those on the quest.

INTRODUCTION

When should people interested in mental health and overall wellness consider using CAM treatments?

This outline is a comparative research-based approach to that question. While some activities, like exercise, are good for everyone who is physically able to do them and have no uncontrollable side effects, **most decisions about CAM treatment options, and especially the decisions faced by people coping with serious mental health conditions, involve trade-offs**. Nonetheless, 40% or more of Americans treat themselves with CAM without professional supervision, often without disclosing it to their psychiatrist or primary care provider. Moreover, many patients who use CAM remedies also take prescription antidepressants, risking potentially dangerous adverse herb/drug interactions. **While most natural psychotropics are generally safe, they are not risk free, and the common public misconception that natural products are inherently safe has been refuted by predictions and reports of toxic reactions from these agents, which may be due to intrinsic toxicity, contamination, or interaction with other herbs or drugs.**

People considering using CAM treatments need to make an informed decision, just as they would with any synthetic medication or other treatment**, weighing the evidence about effectiveness, drug interactions, side effects, and less dangerous options, to come up with a risk/benefit assessment.** These are the issues that any physician must consider, and that anyone considering CAM treatment should consider. But the blizzard of competing claims poses a real challenge to getting efficient access to reliable evidence about safety and efficacy. This effort is an attempt to help fill this void. Mental Health America hopes that its new website will fill this void. By putting all of the recommendations not tied to product advertising in one place, side-by-side, Mental Health America hopes to help health care providers and consumers be better informed about the principal non-traditional options available and the evidence that supports them. Mental Health America and other large mental health advocacy groups have never previously taken a positionprovided systematic information on supplements., which have been used extensively by consumers based on word of mouth recommendations, in the

absence of reliable advice about risks or efficacy. With the publication of this website, Mental Health America hopes to remedy this oversight.

Dialogue for Recovery and Thriving Mindset

MHA has another website, Dialogue for Recovery, which may help consumers to navigate the issues that need to be faced to get optimal treatment for mental health conditions. (http://www.mentalhealthamerica.net/go/recovery) If you live with mental illness, you may be struggling to find treatment, manage your medication and cope with life's challenges effectively. **There is ample cause for hope. You are not alone, help is available, mental health conditions are treatable, and you can take practical steps to recover your life.** On this site, you'll find interactive tools and resources to help you better understand your treatment options, work closely with your health care provider, learn about the supports available to you, and start on your recovery journey.

Use the Dialogue for Recovery tools to open up communication with your health care provider. Educate yourself about treatment options, paying for care, and getting the most from your treatment. Get practical advice on handling many challenges you might be facing, like finding the right medication, securing housing, pursuing education and work, and managing money. On this site, you will find information about how to start and maintain your recovery and live your richest, fullest life. **Friends and loved ones will also find information here about how best to support you in your journey to recovery and wellness**. This outline and the more specific treatment options

described on the MHA website should be read in the context of MHA's strong advice to seek a supportive partnership with heath care providers as the best foundation for durable recovery.

Thriving Mindset is a highly interactive Apple iPad application comprising a video course that provides the user with eighteen, 8-10 minute daily lessons designed to teach one how to change their perceptions and emotional behavior to create and nurture a "thriving mindset." Each day, the user is introduced to a new concept about how one develops and sustains a positive outlook on life. Following the short, highly professional video featuring some of the top scientists and academics in the positive psychology field, the user is offered additional information on the daily subject, including a link to one of the ten supporting wellness tracks the on the MHA website, "Live Your Life Well," described in this outline.

Users also have the opportunity at the end of each lesson to experience a recommended iPad wellness application available from the Apple Store that reinforces the lesson of the day that they can then upload into an individually-tailored dashboard for quick daily reference. Finally, at the end of each lesson, users will be shown a featured product of the day that also complements the daily lesson. A portion of the proceeds from the sale of these products will support MHA.

Thriving Mindset was developed through a partnership between MHA and bLife, Inc., a for-profit technology company.

Intent of This Outline

By disseminating MHA's synthesis of the information and analysis gleaned primarily from ten prominent sources, this outline is intended to help you, as consumers, advocates, physicians, and other health care practitioners, to evaluate potential CAM treatments. It is better to evaluate them with the help of a clinician, with a physical examination and a global wellness perspective, to deal with side effects, physical illness challenges, co-occurring conditions and

drug interactions, and to titrate dosages through clinical observation of effects. But even if a clinician is not involved, all of these factors must be considered. That is the daunting task taken on by consumers under the American model of CAM, largely outside our private health care system and our public drug regulatory system, with minimal quality control, without requirements for standardized formulations, and often without professional guidance for appropriate use by consumers.

This outline compiles evaluations of the CAM treatments most studied, recommended and used for mental health conditions, based on the ten principal sources. MHA recognizes that there are significant inconsistencies and methodological limitations in the published evidence, and only a few CAM studies meet rigorous scientific standards. Large, long-term, dose-differential studies are needed, as are comparative effectiveness and patient outcome studies, but few exist for these CAM treatments. This outline will stress the evidence for those CAM treatments that have been proven (to the level of being judged "promising") effective with acceptable risk in credible clinical trials. Whenever possible, it is MHA's intent to compare the findings of the ten sources, making this outline a kind of "meta-review." It will also point to recommended but less well documented treatments. Depending on the risk, these are potential avenues of experimentation if more documented alternatives have failed to provide relief. None of the CAM treatments surveyed in this outline is truly proven as evidence-based to federal government drug-approval standards.

These evaluations will change as new evidence is developed. MHA will try to update the outline with new evidence and corrections as needed, but the outline is current ONLY through the end of 2012 until this sentence is revised to show the change.

Some authors, and notably Drs. Richard Brown, Patricia Gerbarg, and Philip Muskin, authors of *How to Use Herbs, Nutrients and Yoga in Mental Health Care*, ("Brown *et al*.," 2009), and one of the principal sources for this outline, take a comprehensive perspective, providing evidence for CAM treatments, based on supported by well-controlled studies, open trials, and their own clinical observations. This approach, derived from both research literature and extensive clinical experience, is thorough and suggestive, and an invaluable resource for people wanting to go

further in considering less-tested CAM treatments, when better-tested treatments have not worked well enough to promote recovery.

The clinical insights described by Brown *et al*. are an invaluable adjunct to academic studies and point the way to future studies that may expand on the *material medica* described in this outline. However, MHA's focus is on comparative evaluations of those CAM treatments that have been evaluated by multiple sources. Clinical experience is not often documented in the comprehensive way undertaken by Brown *et al*., and is best studied by reading this important book and Brown and Gerbarg's related work directly.

Whenever possible, this outline, unlike a package insert for a prescription drug, will attempt to give a survey of the evidence for and against each proposed CAM treatment. Side effects and drug interactions will be discussed, based on clinical practice and the evidence from the available trials. A long list of potential side effects and potential drug interactions is inevitable, but aside from drug interactions assessed by prescribing physicians, such lists are seldom read and routinely ignored. The challenge for the consumer is the estimation of risk and benefit. This outline will give the sources' evaluations whenever possible, or those of peer reviewers, when the concern is likely more theoretical than real, as is often the case with the potential concerns raised by the *Natural Standard*. This is the information most conspicuously missing from prescription package inserts, driven in part by liability concerns.

CAUTION IS IN ORDER. What is unproven today may be proven tomorrow, and vice-versa. This is an outline of CURRENTLY AVAILABLE EVIDENCE, AS OF THE END OF 2012, and it documents disagreements which should be resolved in time. There are many potentially beneficial CAM treatments for which more evidence is needed. However, when the risks are low, practitioners and consumers may choose to do a trial of such treatments while further information is being developed. WE STILL HAVE A LOT TO LEARN.

It may be helpful to add an observation about **AUTONOMY AND HOPE**. In the American model of CAM, the consumer has complete autonomy in selecting nutritional supplements and can try even dangerous supplements without a prescription. This autonomy means that only the consumer's own knowledge and tolerance for risk informs the decision about which

supplements to choose and which information to trust. This outline is an effort to aid consumers in making those choices and to further educate the professionals who advise them.

If the potential consumer is getting care from a physician or other health care practitioner, it is important to discuss CAM treatments with that person to avoid unintended drug or herb interactions and to tailor the overall treatment to the consumer's individual, evolving needs. But it is also important to realize that as treatment proceeds, the consumer may need to consider alternatives and to experience the hope that comes from trying new treatments that may improve quality of life. One of the worst aspects of mental illness is the fear of losing control over one's own mine, and therefore, one's ability to direct one's own treatment and recovery. One of the functions of CAM in America is to reserve freedom to the "patient" to direct a portion of the treatment spectrum without prior medical authorization. This places the obligation on professionals to engage in candid dialogue with their clients on the subjects covered by this outline. It also places a moral obligation on the person seeking treatment to discuss CAM remedies used or desired.

A successful working relationship is the ultimate goal of the therapeutic alliance. Consumers' experimentation with CAM treatments can be helpful in the recovery process if they successfully harness the inner reserves of strength associated with choosing one's own treatment, ideally in tandem with a trusted clinician. This outline has not been written to encourage innovation and risk-taking, but to recognize that people seek their own remedies when the medical system fails to meet their needs for any reason. MHA's intent is to make the available evidence and analysis known so that consumers and practitioners can work together better and make responsible choices.

THIS OUTLINE CANNOT AND DOES NOT CONSTITUTE MEDICAL ADVICE. MHA is an advocacy organization and does not provide treatment advice. This outline merely assembles the evidence compiled and analyzed by others – principally the ten sources listed above. More importantly, mental health conditions are complex, people differ widely in their conditions and responses, and interactions with other conditions and treatments are best evaluated by a

physical examination and consultation with a qualified clinician. MHA suggests that this outline is a good starting point to discuss potential CAM treatments with your physician or other health care practitioner.

The National Center for Complementary and Alternative Medicine (NCCAM)

CAM treatments for mental health conditions have not been extensively studied in **large, long-term, randomized, double-blind, active-placebo-controlled trials**, and even those that seem promising in meta-analyses (which combine comparable studies to increase the reliability of a set of clinical studies) have not been "proven" to the satisfaction of The National Center for Complementary and Alternative Medicine (NCCAM). Formal review and elaborate research projects are expensive processes. It takes gold to pay for the "gold standard," and the lack of patentable products has discouraged research, except in Germany, where popular reliance on CAM and government-sponsored health care that encourages it have led to recent promising randomized clinical trials sponsored by pharmaceutical companies that market CAM remedies.

So we really don't have much accepted science to go on. As the NCCAM website shows, while most of the CAM treatments discussed in this outline have been acknowledged as promising, **NONE** has yet received federal (FDA, NCCAM or AHRQ) recognition for use as a psychotropic agent. But people have been coping with mental health conditions for a long time without modern medicines, and many consumers are conversant with and use these remedies. So it is important that the evidence that exists be compiled and disseminated.

According to NCCAM, there are five major branches of CAM:

Whole Medical Systems

Whole medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States. Examples of whole medical systems that have developed in Western cultures

include homeopathic medicine and naturopathic medicine. Examples of systems that have developed in non-Western cultures include traditional Chinese medicine and Ayurveda. This outline will not discuss these medical systems but will discuss biologically-based (herbal medicine) practices derived from them which have been studied and found to have an evidence base. People wishing to study or use such medical systems need to consult accomplished practitioners. The sources contain discussions of homeopathy (Mischoulon and Rosenbaum and Lake and Spiegel), Chinese medicine (Lake and Spiegel), acupuncture (Mischoulon and Rosenbaum), and Ayurveda (Lake and Spiegel).

Mind-Body Medicine

Mind-body medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Some techniques that were considered CAM in the past have become mainstream (for example, patient support groups and cognitive-behavioral therapy). Other mind-body techniques are still considered CAM, including relaxation techniques, biofeedback, meditation/mindfulness, prayer, mental healing, yoga, martial arts, and therapies that use creative outlets such as art, music, or dance. These practices are hard to study, and truly randomized trials are impossible. This outline will discuss those treatments that have been studied and found to be promising based on the best evidence that we now have. Brown *et al.* and Brown *et al*. II and Lake and Spiegel (in an article authored by Brown and Gerbarg) discuss these therapies, as does Scott Shannon in his *Handbook of Complementary and Alternative Therapies in Mental Health.*[17]

Biologically-Based Practices

Biologically-based practices use substances found in nature, such as herbs, foods, and vitamins, as remedies. Some examples include dietary supplements, herbal products, and the use of other natural, but as yet scientifically unproven therapies. These treatments are easily available and extensively used in America, now appearing in your neighborhood grocery. The biologically-based practices that have been found to work in alleviating mental health conditions are the focus of this outline.

Manipulative and Body-Based Practices

Manipulative and body-based practices in CAM are based on manipulation or movement of one or more parts of the body. Some examples include chiropractic or osteopathic manipulation, and massage. This outline will not discuss these treatments.

Energy Medicine

Energy therapies (a controversial term little used in the field) involve the use of magnetic and electrical (or electro-magnetic) fields. They are of two types:

Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven. Some forms of energy therapy manipulate biofields by applying pressure or manipulating the body by placing the hands in, or through, these fields. Examples include qigong, Reiki, and Therapeutic Touch. This outline will not discuss these therapies. Lake and Spiegel discuss these therapies, as does Scott Shannon in his *Handbook of Complementary and Alternative Therapies in Mental Health.*[18]

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating-current or direct-current fields.[19] This outline will discuss these therapies.

Why do People Use CAM?

People use CAM for good reasons and for bad reasons, and with more or less information. Most importantly, **if a person suffering from a serious mental health condition has not responded well to standard treatments or has been unable to tolerate the side effects, it makes sense to consider less well-proven treatments**. According to Mischoulon and Rosenbaum, one-third of people treated with antidepressants fail to respond,[20] and researchers are discovering CAM treatments that help people with such "refractory" depression, often as "adjunctive treatment," added on to prescription meds, but sometimes as alternatives to standard psychotropic drugs. CAM treatments are more often complements than alternatives, when standard treatments do not fully relieve the symptoms or cause side effects that can be mitigated by CAM. Many – though by no means all – have minimal side effects and drug interactions. And the low cost of some CAM treatments (despite the lack of insurance reimbursement) is an additional appeal for many consumers.

Our bodies have remarkable self-healing as well as self-sickening capacities. The beauty of mind-body and other CAM treatments is that they can enable us to discover ways to turn on and support those self-healing abilities.

Information Needed

MHA is concerned that many consumers are using CAM treatments that are not likely to help their condition, without discussing their use with their health care provider, or in situations where the clinician is unable to help because of inadequate information, and without adequate consideration of the evidence that exists on efficacy, co-occurring conditions, drug interactions, side effects, dosages, and alternatives.

What constitutes an adequate evidence base varies among authors, researchers, clinicians, and government regulatory agencies. Further, within each of these professions, individuals and groups use the existing evidence bases in different ways and for different purposes. Under FDA regulations, while drug companies may not advertize off-label uses, doctors are permitted to use medications to treat conditions even if the medication has not acquired FDA approval for that particular usage, as long as there is a clear rationale documented by the doctor. For example, if a patient has failed to respond to (or cannot tolerate) standard FDA-approved treatments, there is leeway for the physician to use non-FDA approved treatments. This is a common practice because there are many useful treatments for which no company has spent the millions of dollars required to meet the FDA's study requirements. So in these cases, what is the evidence base? Sometimes there are studies, of ascending quality as a promising treatment is studied more, but many times there are only preliminary data and clinical experience.

An academic researcher can refuse to endorse a CAM treatment if, for example it has been shown to be beneficial in open-label studies, but not yet in randomized double-blind placebo-controlled studies. In contrast, the physician's goal is to get the patient/consumer as well as possible. [In accord with current custom, this outline uses the terms "person" or "consumer" for persons with lived experience of mental health conditions.] A clinician responsible for the care of a person who has not responded or has had adverse reactions to standard treatments is justified in offering other options even if the evidence base is not yet as strong, particularly if the risks are low and the clinician knows of other cases (by anecdote or through a preliminary study) in which they have been effective. The physician then can present the evidence for trying a CAM treatment and help the consumer weigh the risks vs. benefits. Some consumers are more conservative and require a higher level of proof, while others are more willing to try new options even if there is only a small chance of success so long as the risks are low. MHA hopes that this outline will help in presenting comparative analyses of the CAM treatments that have been evaluated by multiple sources, so that consumers can participate actively in treatment decisions. But nothing can replace the advice of a skilled practitioner.

The clinician's job is different from the researcher's job. The researcher aims to demonstrate significant, reproducible treatment effects that can be defended as valid. The clinicians' job is to heal the consumer or relieve an adverse condition using every reasonable method without injuring the consumer, and the process requires starting with treatments with the highest likelihood of success, and, if those fail, moving on to other approaches with smaller (but not zero) chance of success without a significant risk of causing harm. Most consumers appreciate the fact that innovative clinicians take the "no stone unturned" approach because in many cases, with a little experimentation, effective CAM treatments can be found.

The uncounseled consumer is in a more difficult position, without the experience of clinical practice, relying on what the studies have shown. Sometimes, the evidence is ambiguous, sometimes clearer. And often the evidence is only promising, based on research rather than anecdote, but open-label, not placebo-controlled, not randomized, with small groups and for short periods. People considering the evidence presented in this outline need to consider all of these shortcomings, but where the risk is truly not significant, a more lenient standard may be appropriate. And only the consumer can set her or his risk tolerance.

Progress in genomics has shown that polymorphisms play a significant role in how an individual will or will not respond to treatments. Ultimately, when scientific studies are repeated using genomic measures so that the polymorphisms for each subject are documented, the research probably will show that there is a significant genetic effect on outcomes that will account for the differences in response rates. Then, by selecting people with the most responsive polymorphisms, we will develop studies showing much higher response rates. This needs to be established for CAM treatments as well.

What Works?

FUGH-BERMAN AND COTT: Among the sources that MHA has found most helpful is the seminal 1999 article by Adriane Fugh-Berman, M.D. and Jerry Cott, Ph.D., “Dietary Supplements and

Natural Products as Psychotherapeutic Agents."[21] The authors used meta-analyses to find persuasive evidence supporting use of:

- **St. John's Wort (*Hypericum perforatum*) for mild to moderate depression,**
- **ginkgo (*Ginkgo biloba*) for mild cognitive impairment/dementia,**
- **kava (*Piper methysticum*) for anxiety and stress** (which Fugh-Berman and others now caution against, in light of more recent information about liver toxicity – CAUTION ADVISED)**,**
- **valerian (*Valeriana officinalis*) for sleep disorders,**
- **S-Adenosyl-L-Methionine (SAM-e) for depression,**
- **folate and tryptophan to enhance the effectiveness of conventional antidepressants, and**
- **omega-3 polyunsaturated fatty acids for mood stabilization.**

The CAM therapies for mental health conditions evaluated by Fugh-Berman and Cott but **not** found to be supported by the available evidence included:

- **ginseng,**
- **passion flower,**
- **skullcap and**
- **vitamins**

But dealing with clinically diagnosed vitamin deficiencies should be differentiated from self-prescribed vitamin therapy, especially mega-vitamin therapy, and the absence of evidence for all of these treatments could change with more targeted studies.

TO THE SUPPLEMENTS VALIDATED BY FUGH-BERMAN AND COTT, THIS OUTLINE ADDS:

MISCHOULON ADDITIONS

- **chromium** for atypical depression
- **folate** for depression and as a possible neuroprotectant
- **inositol** for depression and panic disorder
- **melatonin** for jet lag and sleep disorders
- **omega-3s** for depression and to enhance the effectiveness of conventional anti-depressants
- **tryptophan** and **5-HTP monotherapy** for anxiety and depression

BROWN AND GERBARG ADDITIONS

- **CDP – choline** for cognitive impairment/dementia
- **rhodiola** for stress, mild to moderate depression, and as a possible neuroprotectant
- **S-Adenosyl-L-Methionine (SAM-E)** as a possible neuroprotectant
- **omega-3s** for depression and to enhance the effectiveness of conventional anti-depressants and as a possible neuroprotectant

MHA ADDITIONS

- **5-HTP** as a modern substitute for tryptophan
- **energy medicine,** FDA-approved or FDA-grandfathered
- **yoga and meditation,** in tribute to Brown's, Gerbarg's and Gordon's work in responding to mass disasters
- **Dehydroepiandrosterone** (**DHEA)** and **7-keto DHEA** - CAUTION ADVISED

Following Mischoulon's recommendation, MHA cautions that consumers need to exercise extra care in considering the risks and the alternatives before using DHEA, or any other hormone, as a CAM treatment for mental health conditions. Although Mischoulon and Rosenbaum agree that DHEA is **generally** well tolerated and free of major side effects, they still find the risk-benefit ratio too uncertain in the current state of the evidence. People taking DHEA or considering it should read about the evidence and make their own decision. People considering using DHEA should also consider its modern variant, 7-keto DHEA, which may avoid or minimize the negative hormonal side effects of DHEA.

OTHER SOURCES: James Lake, M.D. and David Spiegel, M.D.'s 2007 compendium of *CAM Treatments in Mental Health Care*, CAM advocate Andrew Weil, M.D.'s book on *Spontaneous Happiness*, the *Natural Standard – An Evidence-based Herb and Supplement Guide*, The (University of CA) *Berkeley Wellness Reports*, *The Mayo Clinic Guide to Alternative Medicine 2011,* the recent (2011) Iovieno *et al.* compendium of "second-tier antidepressants," and, for its few interventions, *Consumer Reports*, round out this outline. The *Natural Standard* always has the longest list of possible drug interactions, often with no notation about the prevalence of the interaction and many warnings of potential interactions and side effects that have not yet been observed in clinical practice. Nonetheless, this outline will report the listed possible interactions and side effects, in truncated form, giving information from the other sources as much as possible to put concerns in perspective. Consumers are advised to discuss any concerns with a health care practitioner.

The U.S. Food and Drug Administration

The U.S. Food and Drug Administration issued a 2003 Final Task Force Report on its "Consumer Health Information for Better Nutrition Initiative," which proposed that more and better information be made available about dietary supplements.[22] As part of the 1990 Nutrition Labeling and Education Act,[23] Congress empowered the FDA to authorize health claims based

on “significant scientific agreement” that a claim is supported by evidence including “well-designed” studies. However, the data examined in this outline have yet to be submitted to this process, in part because of cost considerations and in part due to the paucity of well-designed studies and the gaps noted in this outline. Thus, to some extent, this outline substitutes for the lack of an expeditious FDA process **giving the public access to less-than-perfect scientific evidence and less-than-complete scientific consensus about dietary supplements that are already in wide use for mental health conditions.** MHA believes that the current FDA process, while a good-faith response to First Amendment concerns about the FDA stifling free expression of ideas,[24] still makes perfection the enemy of the good.

New guidelines issued by the FDA in 2009 as *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final*[25] have given additional guidance in the determination of “significant scientific agreement,” and the disclaimers that are needed to allow less-than-perfect claims, but retained the restrictive criteria enunciated in the 2003 Report:

> whether the food or dietary supplement that is the subject of the petition is likely to have a significant impact on a serious or life-threatening illness; the strength of the evidence; whether consumer research has been provided to show the claim is not misleading; whether the substance that is the subject of the claim has undergone an FDA safety review (i.e., is an authorized food additive, has been Generally Recognized as Safe (GRAS) affirmed, listed, or has received a letter of "no objection" to a GRAS notification); whether the substance that is the subject of the claim has been adequately characterized so that the relevance of available studies can be evaluated; whether the disease is defined and evaluated in accordance with generally accepted criteria established by a recognized body of qualified experts; and whether there has been prior review of the evidence or the claim by a recognized body of qualified experts.[26]

This formulation leaves out the central First Amendment consideration, which is clarification of the disclaimer language needed to make a less-than-perfect claim not misleading, in order to get the existing information out to the public. In fact, the new Guidance goes so far as to eliminate separate review of "qualified" health care claims based on its conclusion that the standard is essentially the same as for any health care claim.

The impact of this regulatory change remains to be seen as new petitions are reviewed, but it assures that **for now, data about CAM treatments for mental health conditions will not become widely available because the FDA review process itself will curtail availability of information from product labels. This situation underlies the need for this outline.**

According to *Berkeley Wellness*, there have been numerous reports of dietary supplements containing much less, or much more, than what's listed on the labels. To address these concerns, the FDA issued final rules in 2007 that require dietary supplement makers to follow more extensive "good manufacturing practices" (GMPs) to ensure the identity, purity, strength and composition of their products.

The 2007 GMPs are specific for dietary supplements and impose higher standards on these products than food GMPs do. For example, companies are supposed to test all raw materials, set expiration dates based on documented science, ensure that workers are appropriately trained and follow proper procedures, and keep more extensive records, subject to FDA inspection. But the final rules were watered down from the original proposals. Not surprisingly, manufacturers fought against measures that would increase costs. What's more, the FDA, despite increased funding and a pledge to substantially increase inspections, still lacks the resources to fully monitor compliance, which is done primarily through inspection of paperwork, not facilities.

In particular, the provision to test finished products was dropped in the final rule. Though the GMPs for dietary supplements are supposed to ensure that products contain what their labels say, manufacturers are required only to test raw ingredients—and they can still cut corners and make poor-quality products. The FDA has also been criticized for allowing some companies to

be exempt from testing all their ingredients, for not setting lead or pesticide limits in supplements, and for a range of other holes and loopholes.

GMPs for dietary supplements don't guarantee safety. Ingredients can still have side effects and unknown long-term effects, interact with drugs and be dangerous if you have certain medical conditions. They have nothing to do with whether a product "works." And the GMPs do not change how dietary supplements are labeled. **Unlike labels on drugs, those on supplements still need not list any precautions, contraindications or possible interactions -- another reason for this outline.**

MHA AND CAM

MHA has long advocated a recovery and wellness approach to mental health conditions. In June of 2007 the National Mental Health Association was renamed Mental Health America (MHA), reflecting an intention to develop and implement new strategies to engage the general public in a holistic approach to health, which fully embraces the centrality of mental health to overall health.

The concept of wellness recognized by the 2007 changes to the MHA mission statement represents a new policy direction for MHA, which broadens the organization's role to advocacy of the health promoting measures that American society desperately needs to respond to the challenges of modern life and its multiple threats to our health and well-being. MHA believes that the concept of wellness is closely tied to the concept of recovery from mental health conditions, and that many of the strategies and tactics that are used to maintain good health also are useful in negotiating recovery from the disability associated with a chronic illness - including mental health and substance use conditions.

These recovery and wellness approaches are documented in MHA's policies[27] and form the core of MHA's overall effort to reframe mental health as an issue of central concern to all of

American society. We must never relax our vigilance in reaching out to protect the stigmatized, marginalized people who, abandoned by lack of government funding of both institutional and community-based treatment, roam our streets and sleep under our bridges. But we must do more to help the broader group of people who want to make their lives better and need basic scientific information about alternatives.

Thus, in 2008, MHA adopted Operation Policy O-18, committing itself to address that unmet need:

a. **Development of Balanced Information**: It is in the interest of persons with mental health and substance use conditions that research and education be dedicated to investigating and disseminating reliable scientific information concerning behavioral health medications and other treatments, services and supports. MHA will seek to assure the availability of balanced information that does not overstate the advantages of any single intervention or class of interventions, nor cause MHA to be perceived as endorsing any provider or providers of treatments, services and supports.

b. **Dissemination of Balanced Information.** Thus, among other initiatives, and consistent with its policy promoting recovery and self-directed treatment, **MHA will seek to make information and data concerning alternative, complementary and integrative treatments for mental health and substance use conditions more available.** Similarly, MHA will advocate wide dissemination of clinical trial data, including data concerning side effects and data that question the safety or effectiveness of any medication or other treatment, service or support as well as research on design and delivery of exemplary treatments, services and supports across the full range of treatment options.

This outline is MHA's effort to keep that promise.

CAM FOR MENTAL HEALTH CONDITIONS

GLOSSARY

This outline uses the general glossary of SAMHSA's National Registry of Evidence-based Programs and Practices

http://nrepp.samhsa.gov/AboutGlossary.aspx

ADDITIONAL GLOSSARY:

Adjunctive use means use of multiple psychotropic drugs. Use of one psychotropic drug alone is called **monotherapy**.

Psychotropic drug means any drug that significantly affects mental processes

MAOI, SSRI, and Tricyclic Antidepressants, see the NIMH's website on treatment of depression,

http://www.nimh.nih.gov/health/publications/depression/how-is-depression-diagnosed-and-treated.shtml

Mood stabilizers are medications used to even out the mood swings experienced by a person with bipolar disorder. All mood stabilizers treat mania and hypomania, and some have been found to be effective in treating depression as well. See the NIMH's website on treatment of bipolar disorder:

http://www.nimh.nih.gov/health/publications/bipolar-disorder/how-is-bipolar-disorder-treated.shtml

The first mood stabilizer discovered was lithium, a naturally occurring substance. Other mood stabilizers currently used were originally developed to treat seizure disorders, such as epilepsy, and are thus called anticonvulsants. Acute episodes of mania result in psychosis in as many as two-thirds of those with this disorder. Thus, antipsychotics are used frequently in treating

bipolar symptoms. They are also often used to decrease symptoms of mania until mood stabilizers such as those listed above can take full effect. In some cases, these may be used for long-term maintenance of stability.

Anti-anxiety drugs in a class called benzodiazepines are sometimes used to gain rapid control of manic symptoms so that mood stabilizers have time to take effect. The benzodiazepines are central nervous system (CNS) depressants. These medications are primarily used to produce sedation, induce sleep, relieve anxiety and muscle spasms, and prevent seizures. They may also be used to help restore a normal sleep schedule.

MIND-BODY MEDICINE

WELLNESS:

LIVE YOUR LIFE WELL

In 2009, MHA launched a website called "Live Your Life Well," intended to promote mental wellness through ten straightforward steps:

1) Connect with Others. People who feel connected are happier and healthier--and may even live longer.

2) Stay Positive. People who regularly focus on the positive in their lives are less upset by painful memories.

3) Get Physically Active. Exercise can help relieve insomnia and reduce depression.

4) Help Others. People who consistently help others experience less depression, greater calm and fewer pains.

5) Get Enough Sleep. Not getting enough rest increases risks of weight gain, accidents, reduced memory and heart problems.

6) Create Joy and Satisfaction. Positive emotions can boost your ability to bounce back from stress.

7) Eat Well. Eating healthy food and regular meals can increase your energy, lower the risk of developing certain diseases and influence your mood.

8) Take Care of Your Spirit. People who have strong spiritual lives may be healthier and live longer. Spirituality seems to cut the stress that can contribute to disease.

9) Deal Better with Hard Times. People who can tackle problems or get support in a tough situation tend to feel less depressed.

10) Get Professional Help if You Need It. More than 80 percent of people who are treated for depression improve.

These steps, and concrete suggestions for achieving mental wellness, are summarized on the MHA wellness website, http://www.liveyourlifewell.org/go/you-can-live-life-well-more.

The Evidence

The concrete steps suggested by the website are not based on guesses, fads or advice from grandma (though she probably got a lot right). They represent hundreds of research studies with thousands of participants, cited on the website.

This research shows that there are several evidence based approaches to help individuals handle stressful situations effectively and protect their wellbeing. No matter how stressful your situation, you can take steps to promote your well-being.

We're not talking about huge changes to your lifestyle, either. We're talking about reasonable steps that if used consistently can increase your comfort and boost your ability to build a rewarding life.

About the Live Your Life Well Campaign

MHA launched the Live Your Life Well campaign to provide tools to people like you who are stressed by the many demands of modern life.

We want you to know that you can thrive even in the face of stress. We want you to know that you can build more of the life you want.

We also want you to know that your mental health is one of your greatest assets. It helps you focus at work, overcome obstacles, get along with the people around you and even fight off illness. There are simple, effective tools you can use to support this vital asset.

You can find the tools on this website. You also can get more information from your local MHA affiliate.

We at MHA believe...

You can feel better--more vibrant, alert and gratified.

You can feel stronger--more comfortable, confident and productive.

You can Live Your Life Well.

[1] National Center for Complementary and Alternative Medicine (NCCAM) Clearinghouse
National Institutes of Health, DHHS, P.O. Box 7923 Silver Spring, MD 20907-7923 email: info@nccam.nih.gov; http://nccam.nih.gov

[2] Second Edition Copyright Lippincott Williams & Wilkins, Philadelphia (2008).

[3] Copyright W. W. Norton & Company, New York (2009).

[4] Copyright Rodale, Inc., Emmaus, PA (2004).

[5] Copyright W.W. Norton & Company, New York (2009).

[6] Copyright Shambhala, Boston (2012)

[7] Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013).

[8] *Psychosomatic Medicine* 61:712-728 (1999).

[9] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007)

[10] *Natural Standard Herb and Supplement Guide: An Evidence-based Reference*, Ulbricht, Catherine, Ed. and founder, copyright Mosby, Inc., an affiliate of Elsevier, Inc., Maryland Heights, MO (2010).

[11] http://www.berkeleywellnessalerts.com/catalogs/supplements.html

[12] Copyright Consumers Union, Yonkers, New York (2010).

[13] Copyright 2010.

[14] *Journal of Affective Disorders* 130(3):343-57 (2011).

[15] Little, Brown and Company, New York (2011).

[16] The Penguin Press, New York (2008)

[17] Academic Press, San Diego (2002)

[18] *Id.*

[19] http://nccam.nih.gov/health/whatiscam/overview.htm

[20] Mischoulon and Rosenbaum, *op. cit*. at 108.

[21] *Psychosomatic Medicine* 61:712-728 (1999).

[22] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/QualifiedHealthClaimsPetitions/ucm096010.htm

[23] Pub. L. 101-553

[24] See *Pearson v. Shalala*, 164 F.3d. 650 (D.C. Cir. 1999). In that case, the plaintiffs challenged FDA's decision not to authorize health claims for four specific substance-disease relationships in the labeling of dietary supplements. Although the district court ruled for FDA (14 F. Supp. 2d 10 (D.D.C. 1998), the U.S. Court of Appeals for the D.C. Circuit reversed the lower court's decision (164 F.3d 650 (D.C. Cir.1999)). The appeals court held that the First

Amendment does not permit FDA to reject health claims that the agency determines to be potentially misleading unless the agency also reasonably determines that a disclaimer would not eliminate the potential deception. The appeals court also held that the Administrative Procedure Act (APA) required the FDA to clarify the "significant scientific agreement" (SSA) standard for authorizing health claims.

[25] http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm

[26] *Id.*

[27] Position Statement 17, Promotion of Mental Wellness, http://www.nmha.org/go/position-statements/17 and Position Statement 11, In Support of Recovery-based Systems Transformation, http://www.nmha.org/go/position-statements/11

CDP CHOLINE AS A POSSIBLE NEUROPROTECTANT

SUMMARY

WHAT WE KNOW

Citicoline, also known as cytidine diphosphate-choline (**CDP Choline**) and cytidine 5'-diphosphocholine, is a psychostimulant/nootropic. It is a natural constituent of brain chemistry. It has been used for several years outside the United States to treat cerebrovascular disorders (those that affect the blood in the brain), including stroke, and has been studied for use in cognitive impairment and dementia.

MENTAL HEALTH IMPLICATIONS

The studied mental health uses of CDP Choline are almost exclusively for neuroprotection. One source and one meta-analysis (by the Cochrane Stroke Review Group), have found evidence that supports CDP Choline's effectiveness as a neuroprotectant. A recent well-designed Italian study confirms its effectiveness in treating vascular dementia. The other sources do not mention it. One study looked for an effect on attention but couldn't find one.

SIDE EFFECTS & DRUG INTERACTIONS

There are no reported side effects or drug interactions with CDP Choline. The risk is minimal.

CONCLUSION

CDP choline may be effective only in treating vascular dementia, but it is a promising neuroprotectant for that purpose.

OUTLINE

1. Citicoline, also known as **cytidine diphosphate**-choline (CDP Choline) and cytidine 5'-diphosphocholine, is a naturally occurring intermediate involved in the synthesis of phosphatidylcholine, a major constituent of the grey matter of brain tissue (30%). CDP choline consumption promotes brain metabolism by enhancing the synthesis of acetyl-choline, restoring phospholipid content in the brain and affecting neuronal membrane excitability and concentration. CDP Choline is mainly used in the treatment of disorders of a cerebrovascular nature. The many years of use have caused an evolution in dosage, method of administration, and selection criteria.

2. **EFFICACY: NEUROPROTECTION**
   - Brown *et al*. state that CDP choline has been used to treat stroke, **dementia, and brain injury** in Europe and Japan,[1] is well absorbed, crosses the blood- brain barrier, and breaks down into components useful for brain health. Choline is incorporated into the membrane phospholipid structure, improves mitochondrial metabolism and synthesis of phospholipids and elevates norepinephrine, dopamine, and serotonin. Thus, it has long been thought of as a sort of "brain tonic."[2]
   - A 2005 meta-analysis of controlled trials of CDP choline by the Cochrane Stroke Review Group concluded that "**there is some evidence that the CDP choline has positive effects on memory and behavior in the short to medium term in cerebral disorders in the elderly**. **The evidence of benefit from global impression was stronger, but is still limited by the duration of the studies.**[3]
   - Fourteen studies were included in this review. Participants varied over the years and by type of disorders and severity, and ranged from aged individuals with subjective memory disorders to patients with Vascular Cognitive Impairment (mild to moderate),

Vascular Dementia or Senile Dementia (mild to moderate). Seven of the included studies observed the subjects for a period between 20 to 30 days, one study was of 6 weeks duration, four studies used periods extending over 2 and 3 months, one study observed continuous administration over 3 months and one study was prolonged, with 12 months of observation. The studies were heterogeneous in dose, modalities of administration, inclusion criteria for subjects and outcome measures. Results were reported for the domains of attention, memory testing, behavioral rating scales, global clinical impression and tolerability.

- The Cochrane Stroke Review Group further concluded that **there was no evidence of a beneficial effect of CDP Choline on attention. There was evidence of benefit of CDP Choline on memory function and behavior.**
- **A well-designed nine-month 2013 Italian study of 349 subjects validated the use of CDP Choline for treatment of mild vascular dementia.**[4] Alzheimer's dementia was excluded from the study. The main outcomes were an improvement in Mini-Mental State Examination, Activities of Daily Living, and Instrumental Activities of Daily Living scores in the study group compared with the control group. The study group was administered oral CDP Choline 500 mg twice a day throughout the study.

3. Thus, Brown and Gerbarg recommend, "more long-term studies, particularly for vascular cognitive impairment, vascular dementia, and age-related memory decline."[5]

4. **DRUG INTERACTIONS:** Not covered by the *Natural Standard*. None noted by others.

5. **SIDE EFFECTS:** The Cochrane Stroke Review Group concluded that the drug was well tolerated. Brown *et al.* assert that CDP choline is "quite safe and causes virtually no side-effects."

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[1] Alvarez, X.A., Mouzo, R., Pichel, V., Pérez, P., Laredo, M., Fernández-Novoa, L., Corzo, L., Zas, R., Alcaraz, M., Secades, J.J., Lozano, R. & Cacabelos, R., "Double-blind, Placebo-controlled Study with Citicoline in APOE Genotyped Alzheimer's Disease Patients: Effects on Cognitive Performance, Brain Bioelectrical Activity and Cerebral Perfusion," *Methods Find Exp Clin Pharmacol.* 21(9):633-44 (1999).

[2] Brown *et al*, *op. cit*. at 155-156.

[3] Fioravanti, M. & Yanagi, M., "Cytidinediphosphocholine (CDP Choline) for Cognitive and Behavioural Disturbances Associated with Chronic Cerebral Disorders in the Elderly," *Cochrane Database Syst. Rev.* 18(2):CD000269 (2005).

[4] Cotroneo, A.M., Castagna, A., Putignano, S., Lacava, R., Fantò, F., Monteleone, F., Rocca, F., Malara, A., & Gareri, P., "Effectiveness and Safety of Citicoline in Mild Vascular Cognitive Impairment: The IDEALE Study *Clin Interv Aging.* 8:131-7 (2013). doi: 10.2147/CIA.S38420. Epub 2013 Feb 5.

[5] Brown *et al*, *op. cit*.

CHROMIUM FOR ATYPICAL DEPRESSION

SUMMARY

WHAT WE KNOW

Although the studies are mixed, two of the three sources that mention **chromium** affirm its antidepressant activity in atypical depression, a condition characterized by increased appetite, hyperphagia (excessive hunger and abnormally large intake of solids by mouth), and carbohydrate craving, among other clinical features. The third source judges chromium treatment to be promising. No source dissents. Leading researchers (Lake and Spiegel) posit a therapeutic effect in other kinds of depression as well, but the studies are not yet adequate to fully credit this suggestion.

The risk is minimal.

DRUG INTERACTIONS

- Chromium use should be coordinated with the prescribing physician of any immunosuppressive drug.
- Since chromium may lower insulin resistance, people taking oral drugs for diabetes or using insulin should closely monitor their insulin levels while using chromium.
- People taking beta-blockers may experience higher HDL cholesterol levels and increases in blood pressure while using chromium.

SIDE EFFECTS

According to the *Natural Standard*, chromium "appears to be well tolerated with rare or uncommon adverse effects."

- The most commonly reported side effects with chromium supplementation include initial insomnia, increased and vivid dreams, tremor, mild psychomotor activation, stomach discomfort, nausea, and vomiting.
- Given the risk of “cycling,” caution should be used in people who have (or may develop) bipolar disorder.
- Chromium is safe in children, pregnancy and lactation.

OUTLINE

1. Chromium is a widely used nutritional supplement marketed for a wide range of applications. Estimated sales of chromium supplements in U.S. amounted to $85 million in 2002, representing 5.6% of the total mineral-supplement market. Chromium is sold as a single-ingredient supplement as well as in combination formulas, particularly those marketed for weight loss and performance enhancement. Clinical studies have focused on chromium picolinate, but chromium is sold in many forms.

2. **EFFICACY**: **ATYPICAL DEPRESSION**
   - **Recent clinical and experimental studies have reported antidepressant activity of chromium, particularly in atypical depression,** characterized by increased appetite, hyperphagia (excessive hunger and abnormally large intake of solids by mouth), and carbohydrate craving, among other clinical features. **A compound such as chromium that exerts a normalizing effect on insulin sensitivity and appetite while having antidepressant activity may be a promising therapeutic option in people with atypical depression, a subtype of depression typically associated with overeating and weight gain.**
   - **Lake and Spiegel conclude that, "although, to date, there have been [few] … controlled studies, the available data from open [label] trials and observational**

studies are compelling…. The available evidence suggests that chromium supplementation can be used as a monotherapy [for depression and other mood disorders] or as an adjunct therapy with conventional antidepressants."[1]

- **A 2011 review co-authored by Mischoulon (Iovieno, N., Dalton E. D., Fava, M. & Mischoulon, D., "Second-tier Natural Antidepressants: Review and Critique," *Journal of Affective Disorders* 130(3):343-57 (2011)) describes chromium as part of the "next wave of natural antidepressants.**" The group reported on the evidence, focusing on the Davidson *et al*.'s (2003)[2] placebo-controlled, double-blind pilot study in 15 subjects with atypical major depression. Ten persons received chromium picolinate (initial dose of 400 mcg per day, increased to 600 mcg per day after 2 weeks) and 5 persons received placebo for 8 weeks. **Response rates were 70% for chromium vs. 0% for placebo (p=.02), and remission rates were 60% for chromium vs. 0% for placebo (p=.04).** A 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score was evident as early as week 2 in the patients receiving chromium. Treatment was well tolerated, although two subjects reported insomnia.
- The *Natural Standard* rates use of chromium for both depression and bipolar disorder as "C," "Unclear scientific evidence for this use." But the *Natural Standard* acknowledges that "**early studies show that [chromium picolinate] may improve symptoms of depression in people with atypical depression."**

3. **DRUG INTERACTIONS:**
    - According to the *Natural Standard*, chromium may change the way the body processes certain drugs and herbs using the liver's cytochrome P450 enzyme system. As a result, the level of these drugs may be increased in the blood and may cause increased effects or adverse reactions. This concern seems more theoretical than real, at least with the use that has been made of chromium in clinical practice. Brown and Gerbarg and Iovieno have not observed any such interactions in extensive experience with chromium picolinate.

- The *Natural Standard* warns that since chromium may modify serotonin function in the brain, it may interact with prescription antidepressants such as sertraline (Zoloft) and fluoxetine (Prozac). The *Natural Standard* makes no reference to clinical evidence, and Brown and Gerbarg have never observed such an interaction.
- Immunosuppressive drugs are also warned against as a potential harmful interaction by the *Natural Standard*, based on "some evidence" that chromium, in combination with copper, may suppress the immune system. The *Natural Standard* urges caution to people with compromised immune systems, while acknowledging that, "the evidence thus far has not been conclusive." Chromium use should be coordinated with the prescribing physician of any immunosuppressive drug.
- Since chromium may lower insulin-resistance, people taking oral drugs for diabetes or using insulin should monitor themselves carefully while using chromium.
- People taking beta-blockers may experience higher HDL cholesterol levels and increases in blood pressure while using chromium.
- Drugs that may decrease chromium levels include esomeprazole (Nexium/Prilosec), ranitidine (Zantac), antacids, corticosteroids, aspirin and NSAIDs.

4. **SIDE EFFECTS**:
    - According to the *Natural Standard*, chromium "appears to be **well tolerated with rare or uncommon adverse effects**." This position applies only to the trivalent form of chromium, as the hexavalent form appears to be toxic. The principal side effects cited by the *Natural Standard* are stomach discomfort, nausea and vomiting. "Very rarely," skin rashes, insomnia, headache, mood changes, muscle damage, or anemia may occur. The *Natural Standard* says only that "it is possible" that chromium may lower blood sugar, and this concern is only relevant if the person is taking diabetes medicine. The *Natural Standard* details less likely side effects, including adverse effects on the heart, blood, kidneys, or liver, and cognitive, perceptual and motor effects.
    - **Iovieno *et al*. found chromium supplements to be well tolerated and safe.** However, they reported different "commonly reported side effects" with chromium

supplementation including initial insomnia, increased and vivid dreams, tremor, and mild psychomotor activation.

- Lake and Spiegel refer to chromium as "one of the least toxic nutrients," "well-tolerated" so long as bedtime dosing is avoided if insomnia becomes a problem. Vivid dreaming is reported to remit after 2 weeks.
- **Given the risk of cycling, caution should be used in people who have (or may develop) bipolar disorder.**
- Preclinical studies have shown that the addition of chromium picolinate to the diet of rats is not associated with toxicity even at doses greater than a thousand times the usual human intake.[3]
- The **Institute of Medicine** reviewed the safety information on chromium in 2001 and concluded that **up to 160 mcg per day of trivalent chromium picolinate (or 200 mcg per day of trivalent chromium) is safe when used consistent with published clinical data for up to three to six months.**[4]
- The Natural Medicines Comprehensive Database states that chromium is "probably safe" in children, pregnancy and lactation.

5. **PREPARATION: TRIVALENT CHROMIUM PICOLINATE**: Supplements are available as chromium chloride, chromium nicotinate, polynicotinate, chromium picolinate, high chromium brewer's yeast, and chromium citrate. **Trivalent chromium picolinate seems to be the best tolerated form and is easily absorbed by humans.** Over the past three decades, there have been no reports of chromium toxicity in any chromium supplementation studies that used trivalent chromium picolinate.

6. **DOSAGE:**
   - The *Natural Standard* reports that studies have used **200-1000 mcg per day**, but asserts that the recommended chromium picolinate doses are lower, at **200-250 mcg per day.**
   - Lake and Spiegel cite **therapeutic study dosages of from 200-600 mcg per day in divided doses** and a recommended daily intake of **50-200 mcg.**

- Iovieno *et al.* recommend doses of chromium picolinate in the range of **400 to 600 mcg per day (twice those reported by the *Natural Standard*)**, and add that chromium should be taken in the morning because of possible interference with sleep. According to Iovieno *et al*., the dose of **400 mcg** was sufficient to alter brain serotonin activity in an experimental study on healthy volunteers who received chromium picolinate for seven days, and is considered **the biologically active daily dose in well-nourished individuals**.
- Chromium is **often found in multi-vitamin and multi-mineral dietary supplements, in doses ranging from 50 to 400 mcg per day**, and some dietary supplements may include forms of chromium other than chromium picolinate.

7. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with chromium and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects. In particular, studies should examine the efficacy of chromium in treating other forms of depression.

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[1] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 144.

[2] Davidson, J.R., Abraham, K., Connor, K.M. & McLeod, M.N., "Effectiveness of Chromium in Atypical Depression: A Placebo-controlled Trial," *Biological Psychiatry* 53:261-264 (2003).

[3] Anderson, R.A., Bryden, N.A. & Polansky, M.M., "Lack of Toxicity of Chromium Chloride and Chromium Picolinate in Rats," *Journal Am. Coll. Nutr*.16:273-279(1997).

[4] Institute of Medicine, Food and Nutrition Board (2001). http://www.iom.edu/Reports/2001/Dietary-Reference-Intakes-for-Vitamin-A-Vitamin-K-Arsenic-Boron-Chromium-Copper-Iodine-Iron-Manganese-Molybdenum-Nickel-Silicon-Vanadium-and-Zinc.aspx

DHEA AND 7-KETO DHEA FOR DEPRESSION AND BIPOLAR DISORDER

SUMMARY

DHEA (5-Dehydroepiandrosterone) is a natural steroid produced in the adrenal glands, the gonads and the brain. It is the most abundant circulating steroid in humans. A form of DHEA, **7-keto DHEA (3-acetyl-7-oxodehydroepiandosterone),** is claimed to have fewer side effects.

WHAT WE KNOW

- DHEA is involved in a range of biological effects and may cause some problematic hormonal side effects. The newer form (7-keto DHEA) may be safer, but research on its effectiveness and its side effects is extremely limited.
- DHEA supplementation may help with depression, but it has a long list of potential side effects and drug interactions. MHA cautions against use of DHEA, cautiously recommends 7-keto DHEA as an alternative to DHEA pending further testing, and counsels getting the help of a skilled health care practitioner, especially if using any other drugs or herbs.

MENTAL HEALTH IMPLICATIONS

Mood Disorders

Only two of the four sources that discuss DHEA are unambiguous in supporting its use for treatment of depression. Most sources do not mention DHEA for depression. All sources advise caution because of the risks.

Bipolar Disorder

DHEA should be used with caution and in lower doses in people with bipolar disorder. DHEA may exacerbate mania, irritability and aggression. Leading researchers (Mischoulon and Rosenbaum) recommend that people taking DHEA should be regularly monitored for occasional development of aggressive or disinhibited behavior.

PTSD

Case reports showed promising possibilities for the effects of 7-keto DHEA on PTSD; however, there are still inadequate clinical studies supporting this use.

Schizophrenia

Two trials of DHEA treatment in people with schizophrenia showed a reduction in negative symptoms, and experts theorize that there may be a deeper connection. But there isn't enough research to show that DHEA is particularly promising or effective for this use.

Cognition

Recent trials do not support the use of DHEA for neuroprotection.

7-KETO DHEA

7-keto-DHEA is a byproduct of DHEA. But unlike DHEA, 7-keto-DHEA is not converted to steroid hormones such as androgen and estrogen. Taking 7-keto-DHEA by mouth or applying it to the skin does not increase the level of steroid hormones in the blood. Thus, 7-keto DHEA deserves study to determine whether it has the same efficacy as DHEA without the hormonal side effects.

DRUG INTERACTIONS AND SIDE EFFECTS

Drug Interactions: If you are considering taking or continuing to take DHEA or 7-keto DHEA, you should definitely consult with a skilled health care practitioner. It is critical to consult with your prescribing physician if you are taking any psychotropic medication.

DHEA may interfere with a wide variety of prescription medications, over-the-counter medications, and other herbal supplements. DHEA may also interact with a recent flu vaccination or with alcohol consumption. As a result, great care should be taken before supplementing DHEA levels. No prescription medication should be taken with DHEA without consulting with the prescribing physician. The following list is illustrative only.

Interactions include potential interference with:

- Other steroids;
- Psychotropic drugs such as clozapine (Clorazil);
- Medications and herbs that affect blood sugar levels;
- Anticoagulant or anti-platelet drugs (those that thin the blood), such as warfarin Coumadin), hepadrin or clopidogrel, or herbs with similar effects, such as ginseng;
- Hormone replacement therapy and birth control pills, as well as herbs that have hormonal effects, such as alfalfa and blood root;
- Heart medications or herbs that alter heart rhythms;
- Any medication that may increase DHEA levels in the body, including growth hormones and aprazolem (Xanax), antipsychotics, and pain killers, as well as supplements like chromium.

Studies have not yet been conducted to determine whether the same interactions exist with 7-keto DHEA.

Side Effects

- May increase the risk of developing prostate, breast, ovarian, uterine, or cervical cancer and malignant melanoma or other hormonally-affected cancers.
- Hormonal side effects can be significant, including acne, skin changes, excess hair or hair loss, increased sweating, and weight gain.
- Men may develop more prominent breasts, breast tenderness, increased blood pressure, testicular wasting, and significant elevations in testosterone levels with potential effects on the prostate and increased aggressiveness.
- In women, the most common side effects are abnormal menses, emotional changes, headache, and insomnia.
- Additional hormonal side effects may include increases in blood sugar levels, insulin resistance, altered cholesterol levels, altered thyroid hormone levels, and altered adrenal function. .

- Can lead to insomnia.
- May affect blood sugar levels. People with severe diabetes should not use DHEA; others should monitor blood sugar levels carefully.
- May increase the risk of bleeding or blood clotting.
- May alter heart rate or rhythms.
- May cause fatigue, nasal congestion, headache, acne, and rapid and irregular heartbeat.
- May cause agitation, delusions, nervousness, irritability, or psychosis and may induce hypomanic, aggressive, psychotic, or disinhibited behavior.
- In people with bipolar disorder, DHEA should be used with caution and only in low doses because it can exacerbate mania, irritability, and aggression.
- People with a history of abnormal heart rhythms, blood clots or problems with clotting, or a history of liver disease, serious diabetes or hyperglycemia, high cholesterol, thyroid disorders, or other serious endocrine (hormonal) abnormalities should avoid DHEA
- Children should not use DHEA, nor should it be used during pregnancy or breast feeding.

While 7-keto DHEA may not cause the same hormonal side effects, there isn't enough research to prove its efficacy or side effects.

CONCLUSION

Each consumer needs to make a risk-versus-reward decision about DHEA. MHA urges caution because the evidence of efficacy is weak and the potential side effects and drug interactions are significant. More study is needed before 7-keto DHEA can be recommended as an alternative, but it may be prudent to consider it prior to studies substantiating the claims being made, in order to reduce risk.

OUTLINE

1. **5-Dehydroepiandrosterone** (**DHEA**) is a 19-carbon endogenous natural steroid hormone. It is the major secretory steroidal product of the adrenal glands and is also produced by the gonads and the brain. DHEA is the most abundant circulating steroid in humans.

2. DHEA has been implicated in a broad range of biological effects in humans and other mammals. It acts on the androgen receptor both directly and through its metabolites, which include androstenediol and androstenedione, which can undergo further conversion to produce the androgen testosterone and the estrogens estrone and estradiol. DHEA is also a potent sigma-1 agonist. It is considered a neurosteroid.

3. DHEA levels in the blood correlate with mood, memory and functional abilities, but causation cannot be inferred.

4. 7-keto DHEA (3-acetyl-7-oxodehydroepiandrosterone) is marketed as a form of DHEA that presents less risk of side effects. While 7-keto DHEA does not increase the level of steroid hormones in the blood, no clinical studies to demonstrate either its efficacy or its safety have yet been completed. PubMed reports only three published studies of 3-acetyl-7-oxo-dehydroepiandrosterone, of which only one deals with a mental health use.

5. **EFFICACY: DEPRESSION AND BIPOLAR DISORDER:**
   - **Brown *et al*. refer to DHEA and 7-keto DHEA as promising CAM therapies for relief of depression and bipolar disorder.** Despite the potential for hormonal effects, Brown *et al.* state that DHEA is "generally well tolerated." 7-keto DHEA is being used as an alternative to reduce the risk of side effects, but there is only one randomized study of its efficacy or safety.
   - Brown *et al.* cite three studies and give a clinical anecdote to support the use of DHEA for depression and bipolar disorder.[1] They cite evidence for the use of DHEA in bipolar disorder but caution that: "**DHEA should be used with caution and only in low doses in bipolar patients because it can exacerbate mania, irritability, and aggression**." Until it is proven safe, this caution applies to 7-keto DHEA as well.
   - Brown *et al.* conclude that: **"Although the evidence for 7-keto DHEA treatment is preliminary, considering the severity of these conditions and low risk of side effects, it is worthwhile to obtain DHEA and DHEA sulfate levels in patients with bipolar disorder … or mid- to late-life depression. While laboratory reports indicate a normal range of 20 to 200 mg/dl, if the DHEA sulfate is below 200, it may still be worth a trial of 7-keto DHEA using 25 to 50 mg per day. If symptoms persist, the dose may be gradually raised up to 200 mg per day."**[2]
   - Mischoulon and Rosenbaum explore all of the trials of DHEA since 1952, focusing on depression, schizophrenia and dementia, showing the trials to be too short, too small and too poorly controlled to serve as an evidence base for clinical use of DHEA. Dosage and the means of administration proved also to be controversial. DHEA and DHEA-S (for sulfate) levels in the blood often correlate with mood, memory and functional abilities,

but the studies are inconsistent, and causation cannot be inferred. A chart of the 17 most prominent hypotheses serves to illustrate the disagreement.[3]

- **Results from the criticized trials were mixed, and some cast doubt on the efficacy of DHEA. A "well-controlled" 2006 trial examined the effects of DHEA on well-being and found no discernible effect over placebo in women or in men over a two-year trial period.[4]**
- **Nonetheless, Mischoulon and Rosenbaum summarize that "beneficial effects on mood are consistently reported" in people with depression using DHEA.**
- **On balance, Mischoulon and Rosenbaum conclude that: "…DHEA administration CANNOT BE RECOMMENDED for clinical use at this time….[T]he full risk-benefit ratio, especially with high-dose treatment or with treatment for extended periods of time, remains uncertain."[5]**
- **The *Natural Standard* states there is "sufficient evidence" supporting use of DHEA, but only for depression, ranking the evidence as "B," "good scientific evidence for this use," and adding that the "majority" of clinical studies support this use.**
- **DISSENT:** The Mayo Clinic takes a strong position against use of DHEA, giving it a **red rating, but its discussion is less absolute**: "Studies suggest that DHEA may be effective in treating mild depression….[but**] long-term use and high levels may cause serious side effects." "DHEA may be useful in treating depression …, but strictly under the guidance of a specialist."**
- DHEA is not recommended for children or during pregnancy or breast-feeding.

6. **SUGGESTED BUT UNPROVEN USES: PTSD:** The five case reports by Brown and Sageman are the only published reports concerning use of 7-keto DHEA for PTSD, but the results are very promising.[6] Clinical studies on 7-keto DHEA are rare, and a follow-up study is needed to substantiate the work of Sageman and Brown.

7. **SUGGESTED BUT UNPROVEN USES: SCHIZOPHRENIA:** Brown *et al*. suggest that because lower DHEA levels correlate with higher psychopathology, DHEA supplementation could

improve symptoms of schizophrenia.[7] Brown *et al.* cite one six-week trial of DHEA with 30 patients with schizophrenia which resulted in significant reductions in negative symptoms. They also cite a larger 12-week study of 40 patients that found that DHEA of up to 150 mg per day reduced negative symptoms. From this, they suggest that: "The effects of DHEA in reducing negative symptoms and medication side effects may be due to several mechanisms. DHEA potentiates N-methyl-D-aspertate (NMDA)-receptor activity, suppresses GABA inhibition, enhances frontal dopamine release, and enhances sigma- receptor activity."[8]

8. **SUGGESTED BUT UNPROVEN USES: COGNITION:** Although DHEA improves memory and brain activation in EEG studies, a three month study of normal older men found no change in cognition or well-being.[9] Recent studies have not supported the use of DHEA for neuroprotection.

9. **CAUTION**: Because of its substantial side-effects and the significant constraints of past studies, DHEA use requires CAUTION until more is known about its effectiveness and about the potential that 7-keto DHEA may be equally effective while reducing or eliminating hormonal side effects.

10. **DRUG INTERACTIONS:**
    - DHEA may increase blood sugar levels and thus affect people with diabetes. This means that people with severe diabetes should not consider DHEA supplementation. Medication adjustments may be necessary, since many medicines affect blood sugar levels. The same is true of herbs. Thus, doses of arginine, cocoa, ephedra or melatonin (which raise sugar levels) should be adjusted when taking DHEA. Serum glucose levels should be monitored while using DHEA.
    - DHEA may increase the risk of bleeding or blood clotting. Thus, persons who take anticoagulants or anti-platelet drugs to prevent blood clots should discuss the use of DHEA with a healthcare professional. These drugs include warfarin (Coumadin), heparin,

and clopidogrel (Plavix). Similarly, coenzyme Q10 or ginseng may increase the risk of clotting when used with DHEA

- According to the *Natural Standard*, **hormone replacement therapy and birth control pills** "should not be combined with DHEA unless under medical supervision." For the same reason, people taking herbs that have hormonal effects such as alfalfa, black cohosh and blood root should be careful about potential additive effects.
- DHEA may alter heart rate or rhythms and should be used cautiously with heart medications or drugs that may also affect heart rhythms. For the same reason, caution is advised in the use of herbs that may alter heart rhythms, including adonis, balloon cotton, and foxglove (digitalis). Alcohol may increase these effects of DHEA.
- There are some reports that drugs such as canrenoate, anastrozole (Arimidex), growth hormones, methyephenidale, amlodipine, nicardipine and other calcium channel blockers such as diltiazem (Cardizem) and aprazolem (Xanax) may increase DHEA levels within the body, which could lead to increased side effects when combined with DHEA supplements. Chromium may have the same effect.
- **DHEA may interact with psychotropic drugs** such as clozapine (Clozaril). Other psychotropic drugs are not mentioned, but DHEA use should be discussed with the prescribing physician.
- DHEA **may interact with GABA-receptor drugs** used for seizures or pain. DHEA may increase the effectiveness of methadone. DHEA may add to the effects of clofibrate or contribute to tamoxifen resistance in breast cancer.
- DHEA use may result in decreased rate of development of antibodies after influenza vaccination.
- Drugs that reduce normal levels of DHEA produced by the body include dopamine, insulin, corticosteroids, drugs used to treat endometriosis such as danazol, opiate painkillers, antipsychotics, and drugs containing estrogen. Many other interactions are possible.
- Since no source including the *Natural Standard* discusses 7-keto DHEA, there is no scientific assessment of any differential drug interaction. This requires more study.

11. **SIDE EFFECTS**:

- **HORMONAL SIDE EFFECTS of DHEA can be significant.** Examples of hormonal side effects include acne, greasy skin, hirsutism (excess body hair), facial hair, hair loss, increased sweating, weight gain around the waist, or a deeper voice in women. Men may develop more prominent breasts, breast tenderness, increased blood pressure, testicular wasting, or increased aggressiveness. Increases in blood sugar levels, insulin resistance, altered cholesterol levels, altered thyroid hormone levels, and altered adrenal function are additional hormonal side effects.
- According to Brown *et al*., additional side effects include significant elevations in testosterone levels with potential effects on the prostate, elevation of estrogen with increased risk of uterine or breast cancer, vaginal bleeding, endometrial hyperplasia, or venous thrombosis, plus insomnia, irritability, "slight" increases in estrogen, and potential interactions with steroids. Cancer is a contraindication.
- In theory, DHEA may increase the risk of developing prostate, breast, ovarian, uterine, or cervical cancer and malignant melanoma or other **hormonally-affected cancers**. DHEA may contribute to tamoxifen resistance in the treatment of breast cancer. Other side effects may include insomnia, agitation, delusions, mania, nervousness, irritability, or psychosis. The *Natural Standard* does not quantify the risk of these additional hormonal side effects, but all of these side effects should be qualified by statements from all sources that DHEA is generally well tolerated when taken by mouth in prescribed dosages.
- Brown *et al.* add, significantly: "**In contrast, 7-keto DHEA does not convert to testosterone, estrogen, or progesterone and is not associated with these side effects."**[10] According to WebMD, "7-keto-DHEA is a by-product of DHEA. But unlike DHEA, 7-keto-DHEA is not converted to steroid hormones such as androgen and estrogen. Taking 7-keto-DHEA by mouth or applying it to the skin does not increase the level of steroid hormones in the blood."[11] Thus, 7-keto DHEA deserves study to

determine whether it has the same efficacy as DHEA without the hormonal side effects. Since 7-keto DHEA has not been tested in pregnancy and lactation, all DHEA drugs are inappropriate at this time.

- According to the *Natural Standard*, **few side effects are reported when DHEA (or, by extension, 7-keto DHEA) supplements are taken by mouth in recommended doses.** Side effects may include fatigue, nasal congestion, headache, acne, and rapid and irregular heartbeat. In women, the most common side effects are abnormal menses, emotional changes, headache, and insomnia.
- **The *Natural Standard* cautions that people with a history of abnormal heart rhythms, blood clots or problems with clotting, or a history of liver disease, serious diabetes or hyperglycemia, high cholesterol, thyroid disorders, or other serious endocrine (hormonal) abnormalities should avoid DHEA supplements.** At a minimum, serum glucose, cholesterol and thyroid levels may need to be monitored, and medication adjustments may be necessary. This caution applies equally to 7-keto DHEA and to DHEA.
- **Brown *et al*. caution that DHEA should be used with caution and only in low doses in people with bipolar disorder because it can exacerbate mania, irritability, and aggression**. Mischoulon and Rosenbaum suggest that all people taking DHEA should be monitored for occasional development of hypomanic, aggressive, psychotic, or disinhibited behavior.

12. **CHECKLIST**: Mischoulon and Rosenbaum advise the following checklist of concerns:

- The consumer needs to know the state of knowledge about the effects and potential side effects of DHEA, with particular emphasis on diminishing any unrealistic expectations about its "antiaging" effects, and the preliminary nature of most of the positive results reported,
- persons at increased risk for hormonally sensitive tumors (e.g., cancer of the breast, ovary, uterus, cervix, or prostate, or malignant melanoma) should not take DHEA and anyone concerned about cancer risk should be monitored if they do,

- DHEA levels should be checked through blood tests and dosage adjusted to maintain the high-normal range for healthy adults.
- periodic assays of serum testosterone and estradiol levels should be performed and DHEA dosage adjusted to preclude excessive increases in either hormone, and
- treatment should be discontinued if no benefit is observed after approximately three months.
- Of all the sources consulted, only Brown *et al.* discuss 7-keto DHEA and the possibility that it could limit the hormonal side effects of DHEA.

13. **DOSAGE**:
    - Brown *et al.* conclude, from their clinical experience: "**In most patients, energy improves on 25 to 50 mg per day. For the treatment of depression, 75 to 100 mg per day and occasionally higher doses may be needed."**
    - According to Mischoulon and Rosenbaum, doses have generally been in the range of **25 to 100 mg per day**, or higher, with clinical trials using doses **as low as 5 mg a day up to as high as 7 g per day** and very little dosage comparison in the literature. Existing research supports **an average dose of 50 mg in order to maintain the high-normal range for healthy adults.** The *Natural Standard* states that commonly used doses range from **25 to 200 mg per day**.
    - Generally, these doses are divided into two or three doses, with the larger dose given in the morning to mimic the circadian rhythm. Doses late in the evening (after six to eight p.m., depending on bed time) may cause insomnia.
    - Topical (on the skin) application and intravenous (into the veins) injections have also been studied, but safety and effectiveness have not been proven.

14. **RESEARCH:** There is widespread concern about long-term use of DHEA absent better evidence of safety and effectiveness. Research needs to consider long-term as well as short-term effects and needs to catch up with consumer use. There is a particularly great need for study of 7-keto DHEA.

[1] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009), at 52-55.

[2] *Id*. at 124.

[3] Wolkowitz, O.M., Reus, V.I., Maninger, N. & Mellon, S., "Dehydroepiandrosterone in the Treatment of Neuropsychiatric Conditions," in Mischoulon and Rosenbaum*, Natural Medications for Psychiatric Disorders: Considering the Alternatives* (2002/2008), Second Edition Copyright 2008 by Lippincott Williams & Wilkins (Philadelphia), at 84.

[4] Nair, K.S., Rizza, R.A.,O'Brian, P*, et al.* "DHEA in Elderly Women and DHEA or Testosterone in Elderly Men," *New England Journal of Medicine* 355 :1647-1659 (2006).

[5] Mischoulon and Rosenbaum*, op. cit*. at 95-96 (emphasis supplied).

[6] Sageman, S. & Brown, R.P., "3-acetyl-7-oxo-dehydroepiandrosterone for healing treatment-resistant posttraumatic stress disorder in women: 5 case reports," *J Clin Psychiatry* 67(3):493-6 (2006).

[7] Brown *et al, op. cit*. at 273

[8] *Id.* at 273-274.

[9] Wolkowitz, O.M., Reus, V.I., Keebler, A., Nelson, N., Friedland, M., Brizendine, L. & Roberts, E., "Double-blind Treatment of Major Depression with Dehydroepiandrosterone," *Am J Psychiatry* 156(4):646-9 (1999);

[10] Brown *et al., op. cit*. at 53-54.

[11] http://www.webmd.com/vitamins-supplements/ingredientmono-835-7-KETO-DHEA.aspx?activeIngredientId=835&activeIngredientName=7-KETO-DHEA

ELECTRICAL AND MAGNETIC FIELD TREATMENTS

CRANIAL ELECTROTHERAPY STIMULATION ("CES") FOR SUBSTANCE USE REHABILITATION, DEPRESSION, ANXIETY, AND SLEEP DISORDERS

SUMMARY

WHAT WE KNOW

Cranial Electrotherapy Stimulation (CES) uses a cellphone-sized device that stimulates the cranium and brain with a current that cannot usually be sensed by the consumer (below four milliamps). No serious side effects have been reported. The FDA has recognized CES as a Class III device for treatment of:

- depression,
- anxiety, and
- sleep disorders.

A proceeding is pending for Class II status, focused on its use in people recovering from substance use conditions.

Studies and clinical experience also suggest benefits for:

- attention deficit hyperactivity disorder (ADHD),
- obsessive-compulsive disorder,
- post-traumatic stress disorder (PTSD),
- cognitive dysfunction,
- traumatic brain injury,
- pain,
- enhancing attention and concentration, and

- decreasing assaultive behavior.

PRESCRIPTION REQUIRED

Although a prescription is required, CES can be used safely and conveniently in the home, without professional supervision. It can be used adjunctively with most other treatments.

SIDE EFFECTS

Experts (Brown *et al* II) caution against the use of CES in pregnancy. Lactation seems not to be an issue. Differential effects on children remain to be tested. Persons with bipolar disorder need to be cautious, since use of CES could worsen the condition, as can also occur with other antidepressants. At a minimum, a mood stabilizer should be considered.

The lack of drug interactions, low incidence of side effects and suggestive findings in small studies require additional research attention and counsel responsible consumer use as the data are being developed.

RESEARCH NEEDED

MHA encourages additional research to determine whether the promise of CES can be fulfilled, without the serious side effects of large-current ECT, Transcranial Electrostimulation ("TES") or deep brain stimulation (higher-intensity forms of brain stimulation, not discussed in this outline). Future studies should target an understanding of the mechanisms or neurophysiology of both DC and AC methods of neuromodulation, as well as results for a broad range of mental health conditions, particularly depression, since most past studies of depression have been small and generally not double-blind. Efficacy with bipolar disorder has not been studied at all, although the anecdotal evidence is positive. A large number of suggested uses remain to be explored.

CONCLUSION

Promising, but not yet proven. But given minimal side effects, experimentation with CES is a reasonable choice if other treatments prove ineffective or are poorly tolerated.

Photo Gallery:

Fisher Wallace Stimualtor

AlphaStim

Oasis Pro

CESta

OUTLINE

1. Aldini[1] had experimented with galvanic head current as early as 1794 (upon himself) and reported the successful treatment of patients suffering from melancholia using direct low-intensity currents in 1804.

2. FDA approval of Transcranial Magnetic Stimulation in 2008 (see below) led to interest in other forms of non-invasive brain stimulation. This includes, in particular, contrasting the demonstrated polarizing effect of DC stimulation on brain tissue, which has long-term, site-specific effects on the activity of the cortical nervous system, with the mechanism of AC stimulation, which, while it can be shown to induce changes in central nervous system activation, indexed by changes in EEG, neurotransmitter release, and cortical excitability, cannot be explained by polarization.

3. At least eleven competing CES devices are on the market, of which four are pictured above. The fifth picture is of a Transcranial Magnetic Stimulation device, which will be compared to CES. According to Brown and Gerbarg, the most extensively studied CES devices are the Alpha-Stim and the LISS Cranial Stimulator (now marketed by Fisher Wallace as the Fisher Wallace Stimulator). The photo gallery depicts the two listed brands, plus the Oasis Pro and CESta, from internet sources. MHA makes no representation about brand quality.

4. Of the consulted sources, only Brown *et al.* and Brown *et al.* II (the latter through Kirsch, D.L. and Nichols, F., who are both associated with the manufacturer of the Alpha-Stim device) discuss the use of Cranial Electrotherapy Stimulation ("CES"), a.k.a. Cranial Electrical Stimulation or Cranial Electrostimulation, the alternating current version of this over fifty-year-old therapy, grandfathered by the FDA as a Class III device for treatment of **depression, anxiety and sleep disorders.**[2] An FDA proceeding is pending for Class II status, focused on its use in people recovering from substance use conditions. At least six competing devices are on the market, of which five are pictured above.

5. In January of 2016, the FDA proposed reclassifying CES devices as Class II devices for **insomnia and/or anxiety**[3], but with restrictive special conditions:

Identified risk	Mitigation measures
Ineffective treatment	Clinical Performance Testing. Nonclinical (bench) performance testing. Characterization and verification of technical parameters. Labeling.
Skin irritation	Biocompatibility testing. Labeling.
Headaches	Clinical performance testing. Labeling.
Dizziness	Clinical performance testing. Labeling.
Electrical shocks and burns	Electrical safety and EMC testing. Software verification, validation, and hazard analysis.

6. Brown *et al.* mention that CES: "uses a weak electrical current, given to the ears or scalp. CES is reported to reduce anxiety during withdrawal from drugs, but most clinicians are likely to have difficulty referring to therapists experienced in this technique, and treatments are not reimbursable by [most] insurance."[4] Through electrodes placed on the earlobes, the maxilla-occipital junction, mastoid processes or temples, a current of up to four milliamps is passed through the cranium, treating anxiety, depression and insomnia with minimal risk.

7. The FDA proposes that CES remain a Class III device for depression and other uses.

8. The general and psychotropic mechanisms are unknown. According to Mischoulon, CES may affect endorphins, neurotransmitters and neuro-hormones; regulation of body energy flow; the limbic system, reticular activating system, and hypothalamus; the vascular system, brain neural firing patterns and default network connectivity; circadian regulation; and the adaptogenic function (assisting the body to battle effects of chronic stress): “All these

putative mechanisms may be relevant to CES's psychotropic effects, with the adaptogenic mechanism appearing to be the most favored, as it is the sum total of all the other mechanisms mentioned, and considering the role of stress in psychiatric illness (Feusner et al., 2012; Gunther and Phillips, 2010; Kavirajan et al., 2014; Smith, 2008)."[5]

9. The most common theory is that the pulses of electric current increase the ability of neural cells to produce serotonin, dopamine, DHEA, endorphins and other neurotransmitters stabilizing the neuro-hormonal system. Brown notes that increases in cerebrospinal fluid (CSF) levels of serotonin (e.g., CSF increase of 200%) and Beta-endorphins (CSF increase by 219%) after 20 minutes have been reported, as well as plasma level increases of gamma aminobutyric acid (GABA) (crucial for anxiety relief), DHEA (an important anti-stress hormone), dopamine, and others.4

10. The direct current [known as tDCS, for transcranial Direct Current Stimulation] versions such as the "BrainStimulator" pictured fourth in the photo gallery, are of comparable size but are less well-studied than CES. A recent review concluded that: "Active tDCS was statistically superior to sham tDCS in the treatment of MDD [depression], with a medium, significant effect size in both continuous (depression score change) and categorical (response and remission) outcomes. TDCS was also an acceptable intervention, with similar dropout rates in the active vs. sham groups. However, given the mixed results of previous trials and meta-analyses and the relatively small number of trials, there is not enough evidence to perform immediate treatment suggestion of tDCS in daily clinical practice."[6] Comparative trials with CES as well as further investigation of tDCS are both warranted.

11. Although a prescription is required, CES can be used safely and conveniently in the home, without professional supervision. It can be used adjunctively with any other treatment.

12. **EFFICACY: DEPRESSION, ANXIETY AND SLEEP DISORDERS**

- **The FDA has grandfathered CES for treatment of depression, anxiety and sleep disorders**
- **Brown and Gerbarg cited two early studies of CES that found increased attention and concentration in normal adults.[7] They add that in clinical practice, they have found that CES can improve attention, reduce anxiety, and relieve insomnia, all helpful in treating ADHD**.[8]
- **A 2010 survey of the research on brain-stimulation devices by Edelmuth, Nitsche, Battistella & Fregni found 16 well-controlled clinical studies of CES, with significant outcomes reported in 65% of the trials.** All of the 16were controlled trials, and the majority was double-blinded. Although the majority of trials were for depression, anxiety disorders, or insomnia (the FDA approved indications), some were for other conditions, such as recovery from substance use disorders, traumatic brain injury, pain, and enhancing attention and concentration.[9] See Suggested But Unproven Uses, below.
- **Three 2006 meta-analyses by Smith demonstrated significant improvement in anxiety, depression and insomnia from the use of CES.[10]** It should be noted, however, that the Smith monograph has not been peer-reviewed and that Dr. Smith is a consultant to the industry. Most studies cited as evidence for the effectiveness of CES failed to report all data necessary for meta-analysis. And while anxiety effects are well documented by the studies analyzed by Smith, **most depression studies have been small and not double-blind**.[11]
- The Smith meta-analyses were summarized as follows by Mischoulon:[12] Each meta-analysis focuses on a particular treatment indication, as follows:
  - **Insomnia: 18 studies, 648 subjects, mean improvement 62%**
  - **Depression: 18 studies, 853 subjects, mean improvement 47%**
  - **Anxiety: 38 studies, 1495 subjects, mean improvement 58%**

  Most of these studies are limited by small samples, heterogeneity of symptoms, and overlap of conditions, which limits their rigorousness and generalizability to specific conditions, though these results may be more reflective of “real world” populations in which co-morbidity tends to be the rule rather than the exception. CES appears to be a benign intervention with no serious adverse events.

- In 2012, the U.S. Federal Drug Administration concluded:[13]

    a. "**Depression**. In our literature search, we identified 12 papers that examined the effect of CES on measures of depression (6 RCTs and 6 observational studies). In most RCTs, depression levels did not differ significantly between patients who were treated with active CES compared to those treated with placebo. However, one randomized trial by Hearst et al. reported fewer depression symptoms in the active CES treatment versus placebo groups. Of the six observational studies that were reviewed, four studies reported improvement in depression symptoms after treatment with CES. Moore et al. also reported improvement in depression post- (versus pre-) CES treatment, but the findings were not statistically significant. The observational study by Marshall et al. reported no difference in depressive symptoms between the CES and placebo arms.

    b. "**Anxiety**. There were 24 studies that investigated the impact of CES on anxiety (11 RCTs, 11 observational studies, 1 meta-analysis, and 1 systematic review). Of the RCTs that were evaluated, some trials reported a statistically significant benefit of CES treatment versus placebo in reducing anxiety symptoms, while other studies demonstrated no difference in anxiety between the groups. Feighner et al. also conducted an RCT and reported a reduction in anxiety at 15 days post CES, but this effect was no longer significant at 26 days. The majority of observational studies reported a positive association between CES treatment and reduction in anxiety symptoms. In the single-arm observational study by Bystritsky et al., improvements were reported for some but not all measures of anxiety. Only 2 observational studies reported that CES did not have a significant impact on anxiety based on clinical assessment and standard inventories. A meta-analysis of 8 RCTs evaluating the efficacy of cranial stimulation on anxiety indicated that CES versus sham treatment was associated with significantly improved anxiety. Similar findings were reported in a systematic review that examined 34 controlled trials involving a total of 767 patients receiving CES and

an additional 867 patients serving as controls. 26 of 34 studies (77%) reported decreased anxiety after treatment with CES and the remaining 8 of 34 studies (24%) reported no such benefit.

c. "**Insomnia**. We identified 18 studies that evaluated the effectiveness of CES on insomnia. Of the 9 RCTs, some reported statistically significant reductions in insomnia symptoms in the CES group compared to placebo, while others reported no significant differences between the 2 groups. A study by Heffernan et al. also reported significant changes between the active CES treatment and placebo groups. Among the 8 observational studies, CES treatment was associated with less frequent and less intense sleep disturbances, less difficulty falling asleep and feeling more rested in the morning. Two observational studies reported no impact of CES on insomnia. In a study by Moore et al., subjective measures of insomnia were markedly improved during the first week of CES treatment but were no longer significant at 2 weeks. A study by Nagata et al reported a significant reduction in sleep latency in insomniacs but not in those without sleep disorders. Lastly, a meta-analysis with pooled results from 2 RCTs examining the efficacy of CES for insomnia indicated no difference between the active CES and sham groups.

d. "**Overall Literature Review Conclusions**: Of the 39 papers included in this literature review, some reported a beneficial effect of CES treatment on depression, anxiety and insomnia while others demonstrated no effect. Among studies that reported a clinical benefit of CES, few can be considered rigorous, high quality clinical studies. FDA believes that there are basic elements that should be present in any study seeking to evaluate the effectiveness of CES, including, but not limited to: randomized with a sham control group, eligibility criteria based on a specific diagnosis, a clinically relevant measure of effectiveness, [endnote: The FDA accepts only the Hamilton depression rating scale or the Montgomery-Asberg depression rating scale as measures of

depression] adequately powered sample size, predefined success criteria, and consideration for durability of effect. None of the studies identified in the literature review met all of these criteria. **Regardless of the main findings, many of these studies had key limitations in study design that likely obscure the true effectiveness of CES.**

e. "For example, only 12.8% (5 of 39) of the studies reported using the DSM criteria to diagnose depression, anxiety or insomnia. Without the use of established and clinically accepted diagnostic criteria, it is unclear what psychiatric condition, if any, CES was attempting to treat in the remaining 87.2% of studies… Other important study limitations that have been previously mentioned include: small sample size, placebo effect (due to either no masking or unsuccessful masking) and inadequate statistical methods. A reasonable assurance of effectiveness is defined in 21 CFR 860.7(e)(1) as clinically significant results in a significant portion of the target population, when used for these indications for use and conditions of use when accompanied by adequate directions for use and warnings against unsafe use. FDA believes the available valid scientific evidence does not demonstrate that CES will provide a reasonable assurance of effectiveness for the indication of "insomnia, depression, or anxiety."

f. **2012 FDA Panel Decision** Regarding whether the probable benefits to health from use of CES for the indications for treatment of insomnia, depression, or anxiety and the conditions of use outweigh the probable risks, the majority of FDA Neurological Devices Panel concluded on February 10, 2012 that "current evidence does not clearly establish probable benefits to health from use of CES for these indications (treatment of insomnia, depression, and anxiety) and conditions of use that would outweigh the probable risks. Some panel members expressed reservations about the panel's overall response to this question based on a lack of safety concerns."[14]

- **2014 Barclay and Barclay vs. 2015 Mischoulon Studies of Depression**. More recent double-blind research on the use of CES in depression has yielded inconsistent results. Barclay and Barclay[15] used the Alpha-stim CES device at unspecified dosages of less than 1 mA at 0.5 Hz and measured baseline and outcome measures at weeks one, three, and five. Response to treatment was defined as a reduction of ≥50% or more on the two Hamilton Depression Rating Scale measures. Analysis of covariance revealed a significant difference between the active CES group and the sham CES group on anxiety (p=0.001, d=0.94) and on depression (p=0.001, d=0.78) from baseline to endpoint of study in favor of the active CES group.

- Mischoulon et al.[16] conducted a shorter and smaller three-week study of subjects with treatment-resistant major depressive disorder, using the Fisher-Wallace CES device. Devices were calibrated such that the power knob was to be turned up all the way for the required dose, and subjects were explicitly told to set the wheel to the maximum level. The controller (or subject, in the case of a home session) slowly turned up the CES current until the knob was at the maximum setting. The device's electronic waveform contains a 15,000 Hz square wave carrier which is rectified, varying from 0 to 4 mA. The first 15 Hz modulating signal (to theoretically influence brain neurochemical activity) provides 50 ms of “on” time and 16.7 ms of “off” time (total pulse period 66.7 ms, 50% duty cycle). A second, 500 Hz modulating signal changes the “on” time series of 15,000 Hz carrier pulses (750 pulses in 50 ms) into 25 smaller bursts of 15 pulses each of the 15,000 Hz carrier signal, for 375 pulses in the same 50 ms. The consecutive positive burst and “off” time is followed by an equal and opposite negative burst and “off” time, balancing the direct current component to zero. Output voltage ranges from 0 to 40 V, first positive and then negative. CES was left at this level until it automatically shut off after 20 min. Based on the current strength, subjects receiving active or sham treatment were not expected to feel any current and were told that they should feel nothing.

- The primary outcome measure of the Mischoulon et al. study was improvement in the 17-item Hamilton Depression Rating Scale (HAM-D-17). Both treatment groups demonstrated improvement of about 3e5 points in HAM-D-17 scores ($p < 0.05$ for both), and no significant

differences were observed between groups. Remission rates were 12% for CES, and 15% for sham, a nonsignificant difference. Limitations include a small sample and lack of an active comparator therapy. Although both treatment groups improved significantly, this CES at the setting chosen did not separate from sham in this sample. Thus, the study could not rule out that the benefit from this setting used in this particular form of CES was due to placebo effects. Since this form of CES has other settings, Mischoulon et al. recommended that future studies test these other settings and compare the Fisher-Wallace against other CES devices.

- **2014 Cochrane Review of Depression**. An inconclusive 2014 Cochrane Collaboration review[17] concluded that: "There are insufficient methodologically rigorous studies of CES in treatment of acute depression. There is a need for double-blind randomized controlled trials of CES in the treatment of acute depression." The seven existing double-blind studies of the use of CES to treat depression were disregarded because the authors did not use standardized rating scales to measure depression and included some subjects with chronic rather than acute depression, and the sham treatment did not include low-current electrical stimulation adequate to simulate the "tingling" sometimes experienced with CES.

- In a personal communication, Mischoulon suggested that the authors might have "set the bar too high" with regard to conducting a full analysis of the 270 studies, and that the review might have been more informative had they attempted to analyze the seven studies to some degree, so as to give the readership and interested clinicians at least some sense of how to determine whether CES would be an appropriate choice for certain patients. Mischoulon also added that since CES uses a low current, it might be difficult to design and implement a sham intervention that would produce non-therapeutic tingling, that most patients experience no tingling during CES treatment and that patients that he has observed who experience tingling do not report different clinical effects, such as a greater improvement, compared to patients who don't experience tingling.

- The Cochrane review itself proposed to drop the tingling requirement in future reviews and meta-analyses: "Thus, in future updates, we will continue to specify that included trials use

sham CES as a comparator arm, but without the requirement that a local tingling sensation be produced by sham CES."[18]

- **2015 Bipolar Study**. A 2015 study at Beth Israel Hospital in New York showed the Fisher-Wallace CES device to be effective in bipolar depression with minimal side effects. This "pilot study" had only 16 participants, but showed a 32% reduction in the HAM-D score for the CES group vs. an 18% reduction in the control group: Active CES treatment but not sham treatment was associated with a significant decrease in the Beck Depression Inventory (BDI) scores from baseline to the second week ($p = 0.003$) maintaining significance until week 4 ($p = 0.002$).

- Results also showed "a significant decrease in clinician-rated illness severity scores of the active group relative to the sham group (Amr et al., 2013). In addition, quality-of-life scores also improved significantly in the active group but not in the sham group which may be associated with the decrease in depression symptoms and an improvement in functioning. Finally, on a trend level, CES treatment was associated with improvement in cognitive functioning and a decrease in the self-report of bodily pain in the active group only. …there were no significant changes in the hypomania/mania scores from baseline to the end of the treatment phase or the end of the follow-up in any group. Thus, there was no evidence of CES inducing a switch from depression to hypomania/mania."[19]

13. **SUGGESTED BUT UNPROVEN USES: SUBSTANCE ABUSE, ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD), OBSESSIVE-COMPULSIVE DISORDER, PTSD, COGNITIVE DYSFUNCTION, TRAUMATIC BRAIN INJURY, PAIN, ENHANCING ATTENTION AND CONCENTRATION, AND DECREASING ASSAULTIVE BEHAVIOR**

    - **A 2009 open-label study at Phoenix House,[20]** the nation's largest non-profit drug rehabilitation center, **found that CES was well accepted by both clients and treatment staff, and that it could be easily integrated into the treatment regimen.** Staff and clients viewed it as an alternative therapy that was similar to meditation but with the addition of small electrical stimulation, and the CES sessions were actually called the

"meditation group" by clients and staff alike. This meditation group was integrated into a daily schedule along with psychoeducation, cognitive-behavioral therapy (CBT), and other therapeutic groups.

- **Two additional 2006 meta-analyses by Smith demonstrated significant improvement in drug abstinence and cognitive dysfunction from the use of CES.[21] Fibromyalgia, stress and pain management have also been tested, with promising results.[22]** N.b. however that the Smith monograph has not been peer-reviewed and that Dr. Smith is a consultant to the industry.
- The Smith meta-analyses were summarized as follows by Mischoulon:[23] Each meta-analysis focuses on a particular treatment indication, as follows:
  - **Drug abstinence: 15 studies, 535 subjects, mean improvement 60%**
  - **Cognitive dysfunction: 13 studies, 648 subjects, mean improvement 44%**
- A 2002 bibliography by Kirsch listed 126 scientific studies of CES involving human subjects and 29 animal studies. An estimated 145 human studies have been completed, encompassing over 8800 people receiving active CES, but more rigorous controls are needed. Future studies should target an understanding of the mechanisms or neurophysiology of both DC and AC methods of neuromodulation, as well as results for a broad range of mental health conditions, particularly depression, past studies of which have not been well controlled. Bipolar disorder has not been studied at all, although the anecdotal evidence is positive.
- The Brown *et al*. II chapter co-authored by Kirsch contains an extensive discussion of the evidence, which is very promising. It states that there are three small, randomized, double-blind, sham-controlled studies showing the promise of CES.[24] To the studies described by Mischoulon, Brown *et al*. II add a small study of **48 subjects**, showing the **effectiveness of CES in reducing assaultive behavior by up to 41%**.[25] Only two of the 48 subjects failed to respond to CES.
- In a review of the efficacy of various forms of brain stimulation in the treatment of PTSD, Novakovic et al. found CES to be the most promising because of its demonstrated efficacy in treating anxiety: "There are no published studies of CES for PTSD. A meta-

analysis conducted at the Harvard School of Public Health concluded that CES was significantly more effective than sham treatment in improving anxiety but that inconsistent study methodology and lack of blinding complicated interpretation of these data (Klawansky et al., 1995). Recently, better controlled studies have been performed, which may be relevant in considering this treatment for PTSD…. In light of these studies, the relative safety and affordability of CES makes it an interesting target for further research in PTSD."[26]

- **MHA encourages additional research to determine whether the promise of CES can be fulfilled, without the serious side effects of large-current ECT, TES, or deep brain stimulation** (higher-intensity forms of brain stimulation).

14. **DRUG INTERACTIONS**: None noted.

15. **SIDE EFFECTS**: There are no known contraindications to the use of CES. **According to Brown, side effects are uncommon** (between 3 and 10% -- Brown *et al*. II estimates under 1%) and of **minimal severity** (e.g., rarely skin irritation at the site of electrode placement, headaches, light-headedness, or increased jitteriness as occurs with other antidepressants), generally resolved when electrodes are moved or current is reduced.[27] Brown et al II state that: "no serious adverse effect has ever been reported from using CES."[28] The sole negative finding in the literature was a 1996 animal study cited by Brown et al II that found lower fetal weights in the CES group.[29] Because the animals treated with CES were not as active and did not eat as much, their fetuses were smaller. There is no evidence that CES treatment causes humans to be less active or eat less, so this finding is of doubtful relevance to human health. Differential effects on children remain to be tested. The only side effects noted by Brown were feeling "spacey" or "woozy" after the treatment and perceiving a flashing light after the session due to stimulation of the optic nerve by the device. After a CES treatment, users generally are in an "alert, yet relaxed" state, characterized by increased alpha and decreased delta brain waves as seen on EEG.[30]

16. **DOSAGE**: Brown and Gerbarg state that CES treatments usually last 20 to 30 minutes, once or twice a day depending on the severity of the underlying condition. "The advantages of [CES] are that it is very safe, even for young children, when used in the correct doses. It can be used to improve response to medications [adjunctive use], to reduce the dose of medications, and sometimes to eliminate medications."[31] The manufacturer of the Fisher-Wallace device advises a dose of 2 mA for 20 minutes, and recent studies have used that dose, but Mischoulon calls for further study to establish the appropriate dose. In its 2012 review, the FDA took issue with the lack of additional precisions about the amount of CES to be administered in the absence of studies showing the differential effects: "…there has been no systematic attempt to determine the set of stimulation characteristics that are necessary for effectiveness. As the literature reviews have shown, there is little consensus about any of the characteristics. Electrode placement is also variable."[32]

17. **CONCLUSIONS: Unlike most of the other CAM treatments included in this outline, the use of CES in the treatment of psychological conditions is not yet supported by multiple double-blind, placebo-controlled sources, and there is controversy about how to mask sham treatment. However, the low incidence of side effects, the FDA's 2014 decision, the clinical experience of Brown and Gerbarg, and the promising findings in some available studies counsel responsible consumer use as more data are being developed.**

18. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing electrical field treatment and comparative assessment with other treatments -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects. Research on the use of CES in children and during pregnancy, studies of different devices and dosages, and larger, double-blind studies of treatment efficacy would be particularly helpful.

[1] Giovanni Aldini (1762–1834), Italian physicist, was a nephew of Luigi Galvani, whose treaties on muscular electricity he edited with notes in 1791. His scientific work was chiefly concerned with galvanism, anatomy and its medical applications.

[2] The NuTone 101 was on the market before the FDA acquired authority over devices in 1976.

[3] https://www.federalregister.gov/articles/2016/01/22/2016-01173/neurological-devices-reclassification-of-cranial-electrotherapy-stimulator-intended-to-treat#h-19

[4] Brown *et al.* at 329.

[5] Mischoulon, D., De Jong, M.F., Vitolo, O.V., Cusin,C., Dording, C.M., Yeung, A.S., Durham, K., Parkin, S.R., Fava, M. & Dougherty, D.D., "Efficacy and Safety of a Form of Cranial Electrical Stimulation (CES) as an Add-on Intervention for Treatment-resistant Major Depressive Disorder: A Three Week Double Blind Pilot Study," Journal of Psychiatric Research 2015 Nov;70:98-105. doi: 10.1016/j.jpsychires.2015.08.016. Epub 2015 Aug 29 (2015). For a thorough description of CES and a comparison with other forms of brain stimulation, see Kavirajan, H.C., Lueck, K. & Chuang, K., "Alternating Current Cranial Electrotherapy Stimulation (CES) for Depression (Review)," The Cochrane Library 2014, Issue 7.]

[6] Shiozawa, P., Fregni, F., Benseñor, I.M., Lotufo, P.A., Berlim, M.T., Jeff Z. Daskalakis, J.Z., Quirino Cordeiro, Q. & Brunoni, A.R., "Transcranial Direct Current Stimulation for Major Depression: An Updated Systematic Review and Meta-Analysis," International Journal of Neuropsychopharmacology 17:1443–1452 (2014). doi:10.1017/S1461145714000418

[7] *Id*. at 198, citing Hutchinson, D.O., Frith, R.W., Shaw, N.A., Judson, J.A.& Cant, B.R., "A Comparison Between Electroencephalography and Somatosensory Evoked Potentials for Outcome Predictions Following Severe Head Injury'" *Electroencephalography and Clinical Neurophysiology* 78(3):228-233(1991) and Southworth, S., "A Study of the Effects of Cranial Electrical Stimulation on Attention and Concentration," *Integrative Physiological and Behavioral Science* 34(1):43-53 (1999). In the Southworth study, 21 subjects received the placebo treatment. 31 subjects received 20 minutes/day of cranial electrical stimulation. 31% of the experimental group improved versus 4% of the control group.

[8] *Id.* at 199.

[9] Edelmuth, R.C., Nitsche, M.A., Battistella, L. & Fregni, F., "Why Do Some Promising Brain-Stimulation Devices Fail the Next Steps of Clinical Development?" *Expert Rev Med Devices* 7(1):67-97 (2010). doi: 10.1586/erd.09.64.

[10] Smith, R.B., "A Summary Look at Studies of Cranial Electrotherapy Stimulation: Its First Fifty Years, Plus Three" (monograph), published by Tate Publishing & Enterprises, Mustang, Oklahoma (2006). Available on line at http://www.fisherwallace.com/published-research-on-cranial-electrotherapy-stimulation

[11] Just seven of 18 studies were double-blind. *Id*. at 7.

[12] Mischoulon, D., Summary and Critique of CES Monograph "Cranial Electrical Stimulation: Its First Fifty Years, Plus Three" by Ray B Smith, PhD, monograph supplied by the author.

[13] http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/neurologicaldevicespanel/ucm290787.pdf

[14] The FDA's Neurological Devices Panel transcript and other meeting materials are available on FDA's Web site at http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/neurologicaldevicespanel/ucm291805.pdf and

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm289361.htm.

[15] Barclay, T.H. & Barclay, R.D., "A Clinical Trial of Cranial Electrotherapy Stimulation for Anxiety and Comorbid Depression," Journal of Affective Disorders 164:171–177 (2014), https://www.alleviahealth.com/wp-content/uploads/2014/06/Barclay-Barclay-2014.pdf

[16] Mischoulon, *et al*, "Efficacy and Safety of a Form of Cranial Electrical Stimulation (CES) as an Add-on Intervention for Treatment-resistant Major Depressive Disorder: A Three Week Double Blind Pilot Study," , *op. cit.* (2015)

[17] Kavirajan, H.C., Lueck, K. & Chuang, K., "Alternating Current Cranial Electrotherapy Stimulation (CES) for Depression (Review)," The Cochrane Library 2014, Issue 7

[18] *Id.*

[19] McClure, D., Greenman, S.C., Koppolu, S.S., Varvara, M., Yaseen, Z.S. & Galynker, I.I., "A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression, *J Nerv Ment Dis*. 2015 Sep 25. [Epub ahead of print] (2015).]

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[22] http://en.wikipedia.org/wiki/Cranial_electrotherapy_stimulation

[23] Mischoulon, D., Summary and Critique of CES Monograph "Cranial Electrical Stimulation: Its First Fifty Years, Plus Three" by Ray B Smith, PhD, monograph supplied by the author.

[24] Muskin, P.R., Gerbarg, P. L. & Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders*, Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) (Brown *et al.* II) at 171.

[25] Childs, A. & Price, L., " Cranial Electrotherapy Stimulation Reduces Aggression in Violent Neuropsychiatric Patients," Prim Psychiatr 14:50-56 (2007).

[26] Novakovic, V., Sher, L., Lapidus, K.A.B., Mindes, J., Golier, J.A.. & Yehuda, R., "Brain Stimulation in Posttraumatic Stress Disorder, " *European Journal of Psychotraumatology* 2: 5609 - DOI: 10.3402/ejpt.v2i0.5609 (2011).

[27] Brown, R.P., letter of September 18, 2010, available from Fisher Wallace.

[28] Brown et al II, at 174.

[29] Little, B. & Patterson, M.A., "Embryofetal Effects of Neuroelectric Therapy," Electromagnetic Biology and Medicine 15(1):1-8 (1996)

[30] Kennerly, R., "QEEG Analysis of Cranial Electrotherapy: a Pilot Study," *Journal of Neurotherapy* (8)2 (2004).

[31] Brown, R.P. and Gerbarg, P.L., *Non-drug Treatments for ADHD* (W.W. Norton and Company, New York 2012) at 202

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http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/neurologicaldevicespanel/ucm290787.pdf

TRANSCRANIAL MAGNETIC STIMULATION ("TMS") FOR DEPRESSION

SUMMARY

WHAT WE KNOW

Transcranial Magnetic Stimulation ("TMS") has been FDA-approved for treatment of depression since 2008 and has been approved for this use in Europe, Canada, Australia, and the United States. Other promising areas of research include treating the negative symptoms of schizophrenia. However, TMS is expensive compared to CES, and the Cochrane Collaboration seriously questions its efficacy. TMS is experimental, not supported by persuasive clinical evidence or endorsed by any source, and usually not reimbursed by insurance. Moreover, unlike CES, TMS treatments require a therapist in attendance and are expensive.

SIDE EFFECTS

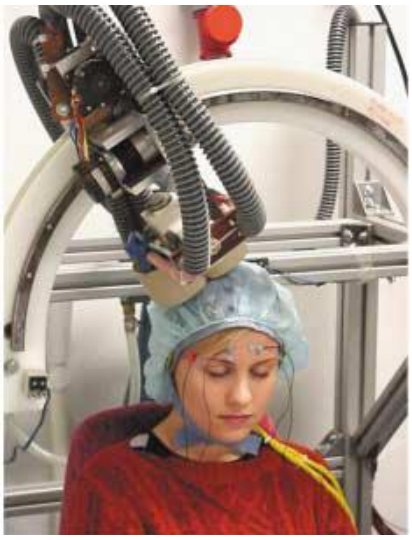
No drug interactions have been noted. Single pulse TMS stimulation is considered safer than repetitive TMS ("rTMS"). However, in rare cases, seizures may follow single pulse TMS stimulation in people with stroke or other disorders involving the central nervous system. RTMS has been reported to cause seizures in individuals without pre-existing conditions when certain combinations of stimulation frequency and intensity are used, and guidelines have been developed to avoid this. Common adverse effects of rTMS are discomfort or pain from the stimulation of the scalp and associated nerves and muscles on the overlying skin. This is more common with rTMS than single pulse TMS.

CONCLUSION

Promising, but not yet proven. But given minimal side effects, experimentation with TMS is a reasonable choice if other treatments prove ineffective or poorly tolerated.

Photo Gallery

NeuroStar



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OUTLINE

EFFICACY

DRUG INTERACTIONS

SIDE EFFECTS

CONCLUSIONS

RESEARCH

1. The first successful transcranial magnetic stimulation (TMS) study was performed in 1985 by Anthony Barker in Sheffield, England.[1] A January, 2007 review panel of the United States Food and Drug Administration failed to approve a TMS device, stating it had a good safety record but failed to demonstrate it was effective for the treatment of depression. Nearly two years later **in December of 2008, the FDA approved the use of a TMS device "for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication** at or above the minimal effective dose and duration in the current episode."[2]

2. None of the cited sources discusses TMS. This discussion is included in the outline in order to contrast TMS with CES, a comparison that points to the superior (though still unproven) efficacy, less side effects, and lower cost of CES. Also, unlike CES, it is difficult to establish a convincing form of "sham" TMS to test for placebo effects in conscious individuals, due to the neck pain, headache and twitching in the scalp or upper face associated with the TMS intervention. "Sham" TMS manipulations can affect cerebral glucose metabolism and MEPs, which may confound results. This problem is exacerbated when using subjective measures of improvement. Depending on the research question asked and the experimental design, matching this discomfort to distinguish true effects of TMS can be an important and challenging issue.

3. TMS is classified as a Class II device, placing it, probably only temporarily, at a level of assigned risk below that of CES. In July 2011 the FDA published a final rule in the *Federal Register* that classified the rTMS system into Class II (special controls), "in order to provide a reasonable assurance of safety and effectiveness of these devices." The rule identified the rTMS system as, "an external device that delivers transcranial pulsed magnetic fields of

sufficient magnitude to induce neural action potentials in the prefrontal cortex to treat the symptoms of major depressive disorder without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy." The exact details of how TMS functions are still being explored. TMS can be divided into two types depending on the mode of stimulation:

- Single or paired pulse TMS causes neurons in the neocortex under the site of stimulation to depolarize and discharge an action potential.
- Repetitive TMS ("rTMS") produces longer-lasting effects which persist past the initial period of stimulation. rTMS can increase or decrease the excitability of the corticospinal tract. The mechanism of these effects is not clear although it is widely believed to reflect changes in synaptic efficacy akin to long-term potentiation (LTP) and long-term depression (LTD).[3]

4. **EFFICACY**

- A 2003 **depression** meta-analysis by Gershon *et al*.[4] found that most data support an antidepressant effect of high-frequency repetitive TMS administered to the left prefrontal cortex. The absence of psychosis, younger age, and certain brain physiological markers might predict treatment success. Technical parameters possibly affecting treatment success include intensity and duration of treatment, but these suggestions require systematic testing.[5]
- Gershon *et al*. concluded that: "41% of 139 patients treated with high-frequency rTMS to the left prefrontal cortex achieved either a 50% decrease in their Hamilton depression scale scores or a final score of ≤8. Recent studies have pointed to, but not yet proven, longer treatment courses, more magnetic pulses, and increased field intensity as likely contributors to treatment success, even when rTMS is the only antidepressant therapy, and have produced **results with rTMS that are comparable to those of ECT**."[6]

- But Gershon *et al.* added that TMS is comparable to ECT in efficacy only when there is no indication of psychosis: "Four studies have compared high-frequency rTMS with ECT. These studies are particularly important because if rTMS, with its more benign side effect profile, is as effective as ECT even for only a subset of people, then it might provide a safer and more tolerable alternative. **For people experiencing psychosis, ECT was clearly superior to rTMS, with 10 of 10 patients responding to ECT but only two of nine responding to rTMS. But among people not experiencing psychosis, both treatments met with similar success rates, with six (60%) of 10 patients responding to ECT and seven (64%) of 11 responding to rTMS**."[7]
- The Mayo Clinic says that electromagnets "may hold some potential for treating conditions such as depression." [8]
- On the other hand, **2003 and 2009 Cochrane reviews**, prepared and maintained by The Cochrane Collaboration, **found inadequate evidence to recommend the use of transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder or depression**.[9]
- Sixteen trials were included in the reviews and fourteen contained data in a suitable form for quantitative analysis. Most comparisons did not show differences between rTMS and other interventions. **No difference was seen between rTMS and sham TMS using the Beck Depression Inventory or the Hamilton Depression Rating Scale**, except for one time period (after two weeks of treatment) for left dorsolateral prefrontal cortex and high frequency; and also for right dorsolateral prefrontal cortex and low frequency, both in favor of rTMS and both using the Hamilton scale. Comparison of rTMS (left dorsolateral prefrontal cortex and high frequency) with electroconvulsive therapy showed no difference except for psychotic patients after two weeks treatment, using the Hamilton scale, which indicated that **electroconvulsive therapy was more effective than rTMS**.[10]
- The information in the Cochrane reviews suggests that, "there is no strong evidence for benefit from using transcranial magnetic stimulation to treat depression or obsessive-

compulsive disorder, although the small sample sizes do not exclude the possibility of benefit."[11]

5. **DRUG INTERACTIONS**: None noted.

6. **SIDE EFFECTS**:
   - Although TMS is often regarded as safe, the greatest acute risk of TMS is the rare occurrence of induced seizures. Single pulse TMS is regarded as safer, but seizures may still occur. Seizures are most likely in people with stroke or other disorders involving the central nervous system. RTMS has been reported to cause seizures in individuals without pre-existing conditions when certain combinations of stimulation frequency and intensity are used, and guidelines have been developed to minimize this risk.
   - More than 16 cases of TMS-related seizure have been reported in the literature, with at least seven reported before the publication of safety guidelines in 1998, and more than nine reported afterwards. The seizures have been associated with single-pulse and rTMS. Reports have stated that in at least some cases, predisposing factors (medication, brain lesions or genetic susceptibility) may have contributed to the seizure. A review of nine seizures associated with rTMS that had been reported after 1998 stated that four seizures were within the safety parameters, four were outside of those parameters, and one had occurred in a healthy volunteer with no predisposing factors. A 2009 international consensus statement on TMS concluded that based on the number of studies, subjects and patients involved with TMS research, the risk of seizure with rTMS is considered very low.[12]
   - Besides seizures, other risks include fainting, minor pains such as headache or local discomfort, minor cognitive changes and psychiatric symptoms (particularly a low risk of mania in depressed patients). Though other side effects are thought to be possibly associated with TMS (alterations to the endocrine system, altered neurotransmitter and immune system activity), they are considered "investigational" and lacking substantive proof.[13]

- According to Wikipedia, the **most common adverse effects** of rTMS are:
  - Discomfort or pain from the stimulation of the scalp and associated nerves and muscles on the overlying skin. This is more common with rTMS than single pulse TMS.
  - Rapid deformation of the TMS coil produces a loud clicking sound which increases with the stimulator intensity that can affect hearing with sufficient exposure, particularly relevant for rTMS (hearing protection may be used to prevent this).
  - rTMS in the presence of EEG electrodes can result in electrode heating and, in severe cases, skin burns.[14]

7. **CONCLUSIONS**:

- **TMS has been found effective for treatment-resistant major depression and has been approved for this use in Europe, Canada, Australia, and the United States. Other promising areas of research include treating the negative symptoms of schizophrenia. However, the Cochrane Collaboration seriously questions the efficacy of TMS.** Nonetheless, TMS needs more investigation, directed to an understanding of the neurophysiology of magnetic stimulation of the brain, and how it compares with DC or AC stimulation of the brain. These are fascinating findings in search of good clinical studies and needed developments in our understanding of the effects of various kinds of brain stimulation.
- **TMS is experimental, not supported by persuasive clinical evidence, and usually not reimbursed by insurance. Moreover, treatments require a therapist and are very expensive compared to CES. However, though apparently greater than CES, the low incidence of side effects with TMS and the suggestive – though controverted -- findings in small studies require additional research attention and counsel responsible consumer use as the data are being developed.**

8. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing magnetic field treatment and comparative assessment with other treatments -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects**.**

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[1] Barker, A.T., Jalinous, R., Freeston, I.L.. "Non-invasive Magnetic Stimulation of Human Motor Cortex," *The Lancet* 1 (8437):1106–1107 (1985).

[2] Melkerson, M.N., "Special Premarket 510(k) Notification for NeuroStar TMS Therapy System for Major Depressive Disorder," FDA (2008)

[3] http://en.wikipedia.org/wiki/Transcranial_magnetic_stimulation

[4] Gershon, A.A., Dannon, P.M., & Grunhaus, L., "Transcranial Magnetic Stimulation in the Treatment of Depression," *Am. J. Psychiatry* 160:835–845 (2003). http://www.ncbi.nlm.nih.gov/pubmed?term=Gershon%2C%20A.A.%2C%20Dannon%2C%20P.M.%2C%20%26%20Grunhaus%2C%20L.%2C%20%E2%80%9CTranscranial%20Magnetic%20Stimulation%20in%20the%20Treatment%20of%20Depression%2C%E2%80%9D%20Am.%20J.%20Psychiatry%20160%3A835%E2%80%93845%20(2003).

[5] *Id*. at 835.

[6] *Id*. at 842.

[7] *Id.* at 839.

[8] See http://www.mayoclinic.com/health/transcranial-magnetic-stimulation/MY00185

[9] Rodriguez-Martin, J.L., Barbanoj, J.M., Pérez, V. & Sacristan, M., "Transcranial Magnetic Stimulation for the Treatment of Obsessive-compulsive Disorder" Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD003387. DOI: 10.1002/14651858.CD003387 (2003), http://summaries.cochrane.org/CD003387/transcranial-magnetic-stimulation-tms-for-the-treatment-of-obsessive-compulsive-disorder-ocd. The full text of the review is available in *The Cochrane Library* (ISSN 1464-780X). Rodriguez-Martin, J.L., Barbanoj, J.M., Schlaepfer, T., Clos, S.S.C., Pérez, V., Kulisevsky, J. & Gironelli, A., "Transcranial Magnetic Stimulation (TMS) for Depression," Published Online: January 21, 2009. http://summaries.cochrane.org/CD003493/transcranial-magnetic-stimulation-tms-for-depression. Full text: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003493/abstract;jsessionid=08FE22AEC7C9631B21C0E02E105916C9.d03t03 .

[10] http://summaries.cochrane.org/CD003493/transcranial-magnetic-stimulation-tms-for-depression., Plain Language Summary

[11] http://www.ncbi.nlm.nih.gov/pubmed/12076483 Accord: Slotema, C.W., Blom, J.D., Hoek, H.W. & Sommer, I.E.C. (2010). "Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)?". *The Journal of Clinical Psychiatry* 71(7):873-884. DOI:10.4088/JCP.08m04872gre.PMID 20361902. 34 studies comparing rTMS to sham treatment for the acute treatment of depression showed an effect size of 0.55 (p<.001). This is comparable to commonly reported effect sizes of pharmacotherapeutic strategies for treatment of depression in the range of 0.17-0.46. However, that same meta-analysis found that rTMS was significantly worse than electroconvulsive therapy (effect size -0.47), although side effects were significantly better with rTMS. An analysis of one of the studies included in the meta-analysis

showed that one extra remission from depression occurs for every 3 patients given electroconvulsive therapy rather than rTMS (number needed to treat 2.36).

[12] http://en.wikipedia.org/wiki/Transcranial_magnetic_stimulation

[13] *Id.*

[14] *Id.*

FOLATE FOR DEPRESSION AND TO ENHANCE THE EFFECTIVENESS OF ANTIDEPRESSANTS AND AS A POSSIBLE NEUROPROTECTANT

SUMMARY

WHAT WE KNOW

Folate, also known as folic acid or Vitamin $B_{9,}$ is an important nutrient, present in leafy green vegetables and in fortified grain products. Low folate levels have been associated with depression and dementia in some studies-- those studies need to be updated to take account of the widespread use of fortified grain products (required in the U.S. since 1998) and B vitamin supplements (B6 and B12 in addition to B9).

Folate issues

Folate is easily inactivated by cooking and processing food, and folate levels may be affected by many other factors, including chronic disease, diabetes and other metabolic problems, cancer, smoking, alcohol use, poor diet, and medications such as mood stabilizers, L-dopa, statins, oral anti-diabetic drugs, and cancer chemotherapy. In addition, genetic variations in the MTHFR gene may reduce the ability to benefit fully from oral folate supplements, and may be related to folate deficiency. Thus, folate levels should be tested before more intrusive treatment is used for depression or mild cognitive impairment.

Efficacy

A 2009 review coauthored by Mischoulon showed methylfolate supplementation to be effective as an adjunctive therapy with psychotropic drugs or as a stand-alone treatment for both men and women in:

- reducing depressive symptoms in people with normal and low folate levels,
- improving cognitive function and reducing depressive symptoms in elderly people with folate deficiency, and

- reducing depressive and other symptoms in people with depression and alcoholism.

The risk is minimal.

MENTAL HEALTH IMPLICATIONS

Depression

Folate is a promising stand-alone and adjunctive treatment for depression. Supplementation of folate deficiencies is recommended by five sources and only disavowed by one, the *Natural Standard*, and adjunctive treatment of depression with folate is a promising practice, especially for women, even if folate levels are not low. Although the *Natural Standard* concedes that folate has been used adjunctively, for enhancing treatment response to antidepressants, it does not credit the evidence in its rating. Two of the sources counsel supplementation even in the absence of folate deficiency, and while one leading researcher (Bottiglieri) does not explicitly concur with that recommendation, his description of the research would place him in the same camp. Another leading researcher (Mischoulon) does not view folate supplementation as effective in people with normal folate levels.

Neuroprotection

Researchers have observed some potential positive effects of folate and other B vitamins (B6 and B12 in addition to B9) on the aging brain, , but folate supplementation appears to be a promising practice only for mild cognitive impairment. Like ginkgo biloba (see that topic), it may not help prevent or treat dementia. Still, almost everyone should be sure to eat lots of leafy green vegetables (and fortified grains, if they are well tolerated)--especially as they get older and their appetites decrease and maladies multiply. And B vitamin supplements are a prudent neuroprotectant.

SIDE EFFECTS & DRUG INTERACTIONS

Aside from allergic reactions, folate and B vitamins are generally quite safe. However, the *Natural Standard* lists many medical conditions that may require folate supplementation and possible prescription drug interactions which should be considered by prescribing physicians.

No interactions with psychotropic drugs have been noted. Folate is not toxic. There appears to be no reason for children or pregnant or lactating women to avoid folate.

CONCLUSION

Promising, but not yet proven.

- Folate is especially promising for depression if lithium or SSRIs are ineffective or poorly tolerated, and it is particularly promising for women.
- Folate is also promising for mild cognitive impairment.
- A diet rich in leafy green vegetables is good for almost everyone.
- B vitamin supplements are a prudent neuroprotectant.

OUTLINE

1. Folic acid (also known as vitamin B_9 or folacin) and folate (the naturally occurring form), as well as folinic acid (leucovorin), pteroyl-L-glutamic acid and pteroyl-L-glutamate, are forms of the water-soluble vitamin B_9. Folate is not biologically active. Its biological importance is due to its production of L-methyltetrahydrofolate (known as methylfolate) and other derivatives after its conversion to dihydrofolic acid in the liver.

2. Folate is essential to numerous bodily functions ranging from nucleotide biosynthesis to the remethylation of homocysteine. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in other biological reactions.

3. Folate and vitamin B12 are required for the synthesis of S-adenosyl-L-methionine (SAM-e). SAM-e is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism, and is discussed in a separate chapter of this outline. These are critical protective processes for the brain to ward off depression.

4. Children and adults both require folic acid in order to produce healthy red blood cells and prevent anemia.

5. Folate and folic acid derive their names from the Latin word *folium* (which means "leaf"). Leafy vegetables are a principal source, although, in Western diets, fortified cereals and bread may be a larger dietary source. Fortification of grains with folate has been required in the U.S. since 1998. Lake and Spiegel caution that folate is easily inactivated by cooking and processing.

6. According to Brown *et al*., "the most important vitamins and nutrients for mental health are those that are essential for the functioning of nerve cells and those that are likely to be depleted due to poor nutrition, malabsorption, rapid utilization, or deterioration due to illness or environmental stress."[1] Folate is a prime example.

7. Brown *et al*. caution that folate levels may be affected by chronic disease, diabetes, cancer, smoking, alcohol use, poor diet, and medications such as mood stabilizers, L-dopa, statins, oral anti-diabetic drugs, and cancer chemotherapy.

8. **Several older studies found that up to 35% of depressed patients are folate deficient. In older people, the incidence of deficiency was even more marked and might still be as high**

as 90%. However, at least in the U.S., FDA-required folate supplementation of grain products since 1998 and higher public awareness of the need for B-vitamin consumption and supplementation have reduced the relevance of these studies.

9. **EFFICACY: DEPRESSION: Folate is a promising monotherapy and adjunctive treatment for depression. Supplementation of folate deficiencies is recommended by five sources and only disavowed by one, and adjunctive treatment of depression with folate is a promising practice, especially for women, even if blood serum folate levels are not low. Two (implicitly, three) of the sources counsel supplementation even in the absence of folate deficiency.**
    - According to Fugh-Berman and Cott, **folate deficiency is one of the most common nutritional deficiencies in the world and has often been associated with neuropsychiatric disorders.** This deficiency may be an understudied risk factor for depression, especially since studies have shown that folate deficiency can significantly reduce the efficacy of prescribed antidepressants.
    - **Fugh-Berman and Cott recommend folate supplementation as an adjunctive treatment for depression** based principally on a study by Fava *et al.*(1997),[2] which examined the relationships between levels of folate, vitamin B12, and homocysteine and response to fluoxetine (Prozac) (20 mg per day for 8 weeks) treatment in 213 outpatients with major depressive disorder. Response to treatment was determined by the percentage change in score on the HAM-D depression scare. **Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine.** The researchers concluded that there was a link between low folate levels and poorer response to antidepressant treatment. They suggested that folate levels be considered in the evaluation of depressed people who do not respond to antidepressant treatment.
    - Relying on the scholarly work of Bottiglieri,[3] **Brown *et al.* note that low levels of folate (B9) and other B vitamins (B6 and B12) are associated with depression and with genetic precursors of depression. They posit that folate deficiency is likely to suppress**

remethylation of homocysteine, thus reducing the body's production of SAM-e, which may have serious effects on mood.

- Recent genetic studies may explain why some individuals respond better to folate supplementation than others. The methylene tetrahydrofolate reductase (MTHFR) gene limits the conversions of folic acid to L-methyltetrahydrofolate (known as methylfolate), the biologically active form. **Genetic variations in the MTHFR gene may reduce the ability to benefit fully from oral folate supplements, and may be related to folate deficiency. Both Lake and Spiegel and Brown and Gerbarg emphasize this critical genetic factor.** Individuals who do not respond adequately to folate supplements can be tested for MTHFR variants. Those found to be positive for the variants can be treated with methylfolate which avoids the need for conversion.
- The 2000 Coppen and Bailey study[4] showed that **93% of women had a good response to a mixture of folate and the antidepressant fluoxetine (Prozac), while only 61% of the group of women who received only placebo in addition to fluoxetine had a good response**. The dose was 500 mcg per day.
- **Women** in the Coppen and Bailey study **achieved a 20.6% reduction of homocysteine on fluoxitine and folate, while the men got no apparent benefit.**
- Like Brown *et al*., Mischoulon and Rosenbaum cite Bottiglieri's research on the effect of folate deficiency on the cycle that furnishes the body with SAM-e, and the resultant deficiency of SAM-e and elevation of homocysteine levels that are associated with depression.[5] But they concede that supplementation with folate may not release or furnish SAM-e or lower homocysteine.
- Although the link with vitamin B12 deficiency is not so strong or clear, at least in younger people, a 2007 meta-analysis by Gilbody *et al*.[6] is cited by Mischoulon and Rosenbaum for the proposition that **there is a "robust" relationship between low folate and depression**, **but much more so in women than in men**.[7]
- The 1997 Fava *et al.* study cited by both Fugh-Berman and Cott and Brown *et al*., is cited by Mischoulon and Rosenbaum for the proposition that **pretreatment folate status was**

significantly related to treatment response. Thus, **without supplementation, low folate appeared to inhibit people's response to SSRIs.**

- **This result was replicated in the 2005 Papacostas *et al.* study which linked the timing of lithium and SSRI treatment effectiveness and the risk of relapse to low pretreatment folate levels, using fluoxetine, lithium, and desipramine (Norpramin)**.[8] The seven subjects with low folate levels had a 43% relapse rate, compared to 3% for the 64 with normal folate levels. Conversely, when people with folate deficiencies received supplementation with methylfolate to counteract low folate levels, a small 1990 study showed an improved treatment response. This study was criticized because the non-CAM treatments were diverse and not comparable.[9]
- **In the 2002 Alpert *et al*. open label study in which Mischoulon participated, adjunctive use of folinic acid with an SSRI produced more than 50% improvement in more than 25% of the subjects.[10] No individuals in this group were folate-deficient.** The dose was 15-30 mg per day of folinic acid, which is metabolized to methylfolate. **Of 22 subjects who had minimally responded to 4 weeks of SSRI treatment prior to folate supplementation, 33% improved, and 19% achieved full remission. The effect was not limited to women.**
- **A 2009 Fava and Mischoulon review[11] yielded firmer conclusions**: "**The methylfolate formulation indicated efficacy as adjunctive therapy or monotherapy in reducing depressive symptoms in patients with normal and low folate levels**, **improving cognitive function and reducing depressive symptoms in elderly patients with dementia and folate deficiency, and reducing depressive and somatic symptoms in patients with depression and alcoholism.**" **The noted effects were not limited to women.**
- **In Brown *et al*. II, Bottiglieri** analyses the six randomized studies that have focused on folate supplementation for depression, all but one of which has been adjunctive with use of lithium or SSRIs. He concludes that they show promise, even in the absence of folate deficiency. He also **cites the 2012 series of trials conducted by Papacostos *et al*. (and still not posted on PubMed) that "support the use of methylfolate as an**

adjunctive treatment for SSRI-resistent depression" even in the absence of baseline folate deficiency.[12]

- **The *Natural Standard* rates folate for depression as "C," "unclear scientific evidence for this use."** The *Natural Standard* rates folate as "A," "strong scientific evidence for this use," only for folate deficiency and related anemia. As to depression, the *Natural Standard* states only that folic acid deficiency has been found among people with depression and has been linked to poor response to antidepressants. Although the *Natural Standard* concedes that folate has been used adjunctively, for enhancing treatment response to antidepressants, it does not credit the evidence in its rating. **The *Natural Standard* states that folate is "not effective" as a replacement for antidepressants, but it does not comment on adjunctive use**.
- *Berkeley Wellness* does not discuss any effect of folate on depression, focusing instead on dementia, for which it reports contradictory findings.
- **Notwithstanding the promising studies and the 2007 meta-analysis and 2009 review, Mischoulon and Rosenbaum conclude that the data are still too preliminary to recommend consumer action beyond supplementation of folate deficiencies at this point.** They suggest that assessment of folate status ought to be included in any comprehensive medical workup for depression and that folate replacement is essential for individuals with conditions leading to folate deficiency, such as alcoholism, metabolic problems, and malabsorption. They add that blood tests for folate may not be enough, that SAM-e and homocysteine levels may be as important, and that genetics (the common mutations of the MTHFR enzyme gene discussed above) also must be evaluated.
- **Lake and Spiegel observe that the proportion of folate deficiency "appears to correlate with the severity of psychiatric symptoms. Even among individuals with normal folate levels, higher folate levels are correlated with less severe depression, higher age at onset,"[13] and improved response to antidepressants.**
- **The Mayo Clinic** is also positive, giving folate a **green light** as a supplement, but **without any discussion of potential use for depression or cognition**.

- **Weil recommends supplementation with 400 mcg per day of folic acid to prevent and treat mental health conditions.** He recommends a comprehensive vitamin and mineral supplementation program, including B6 and B12 as well as folate.[14]
- On balance, the data concerning adjunctive use of folate show such a dramatic effect that people, and especially women, considering or using psychotropic medications may reasonably wish to discuss the possibility of folate supplementation with the prescribing physician. No drug interaction has yet been noted by any source between folate and psychotropic medications, and the remaining risk is low. In the case of SSRI-resistent depression, folate seems particularly valuable to try, and the risk is low.

10. **METHYLFOLATE: Mischoulon *et al*. strongly advocate methylfolate for folate supplementation, to bypass the conversion process. Brown *et al.* note that MTHFR genetic testing can identify individuals most likely to have a better response to supplementation with methylfolate rather than folic acid.**

11. **SUGGESTED BUT UNPROVEN USE: NEUROPROTECTION**: Brown *et al*. discuss the use of folate supplementation for **cognition and memory disorders**, citing the promising (albeit very preliminary) research linking B vitamins to cognitive performance.[15] In a chapter authored by Bottiglieri, Brown *et al*. II discuss the conflicting results of seven trials, concluding that folate and other B vitamins "may slow the rate of cognitive decline in subjects less severely affected at baseline**."[16] Thus, folate is a promising treatment for mild cognitive impairment, but, like ginkgo, may not be effective to prevent or treat Alzheimer's dementia. Mischoulon and Rosenbaum recommend methylfolate over folate as less toxic for older people with mild cognitive impairment because it crosses the blood-brain barrier**.[17] Lake and Spiegel note that higher folate levels correlate with higher scores on the Mini-Mental State Exam. *Berkeley Wellness* discusses potential use of folate for prevention and treatment of cognitive impairment and dementia but asserts, as conceded by all of the sources, that studies on the effects of taking folic acid have yielded contradictory findings. B vitamins (B6 and B12 in addition to folate) appear to help with

cognition, but the role of folate is unclear, and effects on dementia have not been demonstrated. Still, folate is a promising neuroprotectant. **B vitamins should be part of any strategy to maintain healthy thinking and feeling as our brains age.**

12. **DRUG INTERACTIONS**: The *Natural Standard* cites reduced serum folate levels in women taking conjugated estrogens (Premarin) or birth control pills and (theoretically) with estrogenic herbs and supplements. Alcohol, smoking, aspirin, antacids, antibiotics, carbamazepine (Tegretol), especially in pregnant women, cholestyramine (Questran), Colestipol (Colestid), cycloserine, diuretics, h2 blockers such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid) and ranitidine (Zantac), proton pump inhibitors such as esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprozole (Acip-Hex), methotrexate, pancreatic enzymes, Phenobarbital (Luminal), primidone (Mysoline), pyrimethamine (Daraprim), sulfasalazine, triamterine (Dyrenium) and trymethoprim all may reduce serum folate levels, though in different ways. Taking folic acid with vitamin B-12 may increase the risk of B-12 deficiency (because it may be screened by folic acid).

13. **SIDE EFFECTS:**
    - Aside from allergic reactions, folate and B vitamins are described by Brown *et al*. as "**generally quite safe**."
    - The *Natural Standard* states that folate is "**generally well tolerated in standard doses**." However, stomach upset, hair loss, myelosupression (bone marrow suppression), zinc depletion, erythema (skin inflammation), pruritus (skin itch), urticaria (hives), nausea, bloating, flatulence, cramps, bitter taste, diarrhea, anemias caused by vitamin B12 deficiency, irritability, excitability, malaise, altered sleep patterns, vivid dreaming, overactivity, confusion, impaired judgment, increased seizure frequency and psychotic behavior have been reported. Significant central nervous system side effects have been observed with high doses.

- In addition to the side effects reported by the *Natural Standard*, below, Mischoulon, Fava and Stahl replied to a letter in the *Journal of Clinical Psychiatry* in June, 2009,[18] to concerns about folate masking Vitamin B-12 deficiencies or affecting colorectal cancer. Mischoulon *et al.* conceded that folate supplementation could mask a **vitamin B-12 deficiency**, requiring extra care for vulnerable people. Brown *et al*. point out that this problem of masking can be reduced by testing serum methylmalonic acid and homocysteine levels.
- As to **cancer** risk, Mischoulon and Rosenbaum give evidence for and against but in the end recommend only counseling caution for people with a history of polyps or a family history of colorectal cancer.
- The *Natural Standard* gives age-calibrated dosages for children; *Berkeley Wellness* gives a dose for pregnant women. Fugh-Berman adds that "we give folate specifically to pregnant women, and it's water-soluble so you can't overdose." Thus, **there appears to be no reason for children or pregnant or lactating women to avoid folate.**

14. **DOSAGE:**

- The *Natural Standard* recommends: For infants up to 6 months old, 65 mcg. per day, 7-12 months, 80 mcg. per day, 1-3 years, 150 mcg. per day, 4-8 years, 200 mcg. per day, 9-13 years, 300 mcg. per day, 14-18 years, a maximum of 800 mcg per day, and **adults, a maximum of 1,000 mcg per day**. **Recommended dosages are 400 mcg per day for adults, increasing to 500 mcg per day for breastfeeding women and 600 mcg per day for pregnant women.** For adjunct treatment with antidepressants, the *Natural Standard* states that dosages of from **200 to 500 mcg per day** have been used**.**
- ***Berkeley Wellness* is concerned about over-supplementation:** The recommended dietary allowance for folate is **400-1000 mcg per day for adults** and 600 mcg per day for pregnant women. But many Americans get much more than that, since about 40% of those over age 60 take a multivitamin, which typically supplies the recommended dietary allowance of folate. In addition, many people take a supplement of B vitamins

and eat highly fortified foods, which risks excessive consumption of folate. **But folate is non-toxic**, so the effect should be the same as eating too many leafy green vegetables.

- **Weil recommends 400 mcg per day.**
- In contrast, one of the cited studies used 15-30 mg per day – 15,000 to 30,000 mcg. This discrepancy is disturbing, and *Berkeley Wellness's* concerns caution that the lower dosages are more appropriate. Commenting on the discrepancy, **Lake and Spiegel** state that there is evidence that people with affective disorders or schizophrenia may have higher requirements. They **recommend 1 mg (1000 mcg) per day and recommend that folate be coupled with 2.4 mcg of B12 per day to avoid masking a B12 deficiency.**

15. **RESEARCH:** More rigorous, randomized studies are needed to address important clinical questions regarding the magnitude of the effect of folate compared with standard therapies as compared across different oral folate doses and folate forms, including folic acid, methylfolate, and folinic acid. Further investigation of possible predictors of response would help identify the people most likely to benefit from folate supplementation. Genetic variations require additional study, following up on the MTHFR gene studies. Gender differences and the effect of folate supplementation in the absence of baseline folate deficiency require concerted research. Long-term outcomes -- benefits and liabilities from continuing treatment with folate, measuring precise folate levels through the treatment cycle and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects.

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[1] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009), at 38.

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[9] Godfrey, P.S., Toone, B.K., Carney, M.W., *et al*., "Enhancement of Recovery from Psychiatric Illness by Methylfolate," *Lancet* 336:392-395 (1990).

[10] Alpert, J.E., Mischoulon, D., Rubenstein, G.E.F*., et al*., "Folinic Acid as an Adjunctive Treatment for SSRI-refractory Depression," *Ann. Clinical Psychiatry* 14:33-38 (2002).

[11] Fava, M. & Mischoulon, D., "Folate in Depression: Efficacy, Safety, Differences in Formulations, and Clinical Issues," *J. Clin. Psychiatry*, 70 Suppl. 5:12-7.

[12] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 4.

[13] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 123.

[14] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011) at 204.

[15] Brown *et al., op. cit*., at 147.

[16] Brown *et al.* II, *op. cit*., at 6.

[17] Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. In its neuroprotective role, the blood–brain barrier functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. Therapeutic molecules and genes that might otherwise be effective in diagnosis and therapy do not cross the BBB in adequate amounts. Mechanisms for drug targeting in the brain involve going either "through" or "behind" the BBB.

[18] *J. Clinical Psychiatry* 70:5 (May, 2009).

GINKGO BILOBA AS A POTENTIAL NEUROPROTECTANT

SUMMARY

WHAT WE KNOW

Ginkgo biloba is an ancient Chinese herbal remedy that has been shown to have significant neuroprotective effects, confirmed by all sources. However, two recent major studies and a Cochrane review cast doubt on the validity of the prior, smaller and shorter studies, and determined that in the aggregate the data do not support the use of ginkgo in the prevention of Alzheimer's disease. The recent evidence is mostly negative, though the studies are still inconsistent. Although ginkgo has a mild effect in protecting against mild cognitive impairment/dementia, it probably does not prevent it. But all sources except one remain optimistic for some ongoing neuroprotective role for Ginkgo.

The risk is minimal.

MENTAL HEALTH IMPLICATIONS

Neuroprotection: Despite the evidence from these studies and review, all sources except *Berkeley Wellness* remain optimistic for some ongoing neuroprotective role for ginkgo. Pending subsequent studies, the jury is still out on ginkgo and memory/dementia.

Until a scientific and popular consensus emerges, ginkgo will continue to be used as one of the few known neuroprotective CAM treatments for dementia, preventing and treating memory impairment, lack of concentration, and cerebral-vascular insufficiency, as well as age-related and dementia-related cognitive weaknesses.

Alternatives: Rhodiola, SAM-e, folate, omega-3s, and CDP-choline (see those chapters of this outline) may provide alternatives now that ginkgo has been shown to be less effective a remedy than it had long been supposed to be.

No Reason to Stop: The recent negative evidence should lead consumers to question the efficacy of ginkgo to prevent or delay cognitive impairment. However, a single study cannot be viewed as definitive, and ginkgo may be considered as an evidence-based CAM treatment for mild and possibly incipient dementia, albeit apparently with limited preventive benefit in delaying or avoiding some of the symptoms of Alzheimer's disease. If you are using ginkgo and tolerating it well, there is no reason to stop.

Other Uses: Ginkgo is being investigated as adjunctive therapy for schizophrenia and attention deficit hyperactivity disorder (ADHD), for protection against the neural damage caused by antipsychotics, and for the treatment of depression. The *Natural Standard* also states that "good" evidence demonstrates ginkgo's efficacy in the treatment of "cerebral insufficiency." But these are at best promising practices.

These are all unproven uses, but given ginkgo's relatively low cost and benign risk profile, consumers may well wish to try ginkgo for these conditions. Caution is advisable if ginkgo is used with psychotropic drugs, in the absence of studies validating lack of adverse drug interactions. Adjunctive treatment with antipsychotics requires careful coordination with the prescribing physician.

DRUG INTERACTIONS

Ginkgo has anticoagulant effects (though bleeding problems have not been noted in the studies), may increase blood concentrations of some drugs used for treating hypertension, may affect insulin and blood sugar levels, and may affect blood pressure. Potential interactions with MAOI, SSRI and antipsychotic drugs have been noted, but have not yet been confirmed in humans. The prescribing physician should be consulted before using ginkgo in connection with these drugs.

SIDE EFFECTS

According to Mischoulon and Rosenbaum, ginkgo "has an excellent safety record; and except for the assumed possible risk of hemorrhage in patients taking anticoagulants, having bleeding disorders, or [about to] undergo surgery, [ginkgo] appears to be very safe." All sources agree

that ginkgo appears safe overall and that side effects are rare. It follows that concerns about pregnancyy, breast-feeding and child use are minimal

CONTAMINATION

Berkeley Wellness cautions that commonly available products may be different than the preparations used in clinical studies. EGb 761 is the only preparation of ginkgo that should be used. And tests by ConsumerLab have found problems in some ginkgo products. For instance, in 2008, tests on seven of the most popular ginkgo products sold in the United States found that five were contaminated or low in key compounds.

CONCLUSION

Traditional uses of ginkgo as a neuroprotectant are now in question. The split of the sources confirms that this is a controversial supplement, and the recent evidence, from large-scale, long-term studies, is all negative. But the risk is minimal, and the sources continue to argue that ginkgo has neuroprotective efficacy, even if it doesn't prevent Alzheimer's dementia.

OUTLINE

1. Common Names include ginkgo**,** *Ginkgo biloba***,** fossil tree, maidenhair tree, Japanese silver apricot, baiguo, bai guo ye, kew tree, yinhsing (yin-hsing). Extracts are taken from the ginkgo leaf and are used to make tablets, capsules, or teas. In the past 30 years, methodical procedures of extraction and standardization among manufacturers and researchers has allowed the production of a highly concentrated and stable extract, EGb 761, which has been systematically studied in scientific programs.

2. **EFFICACY: NEUROPROTECTION, BUT NOT PREVENTION: There is a large body of data to support the efficacy of *Ginkgo biloba* (EGb 761) ("ginkgo") as a neuro-protector and an enhancer of neural functioning, well summarized by Fugh-Berman and Cott, Lake and Spiegel** (through Lee, R., Yee, P.S. & Naing, G.)**, Mischoulon and Rosenbaum and the *Natural Standard*. However, Fugh-Berman, Brown *et al.*, *Berkeley Wellness* and the Mayo Clinic question ginkgo's effect on memory and specifically its apparent inability to prevent Alzheimer's dementia, based on the negative NCCAM-sponsored GEM study and Cochrane Collaboration meta-analysis. The recent evidence is mostly negative, including the 2012 publication of the GuidAge Study. But all sources except Berkeley Wellness remain optimistic for some ongoing neuroprotective role for Ginkgo:**

3. **SOURCES**
    - Writing in 1999, **Fugh-Berman and Cott found support for the use of ginkgo for mild dementia from four credible double-blind studies and a meta-analysis of forty controlled trials of treatment for "cerebral insufficiency."**[1] Fugh-Berman and Cott concluded that **there is a small but significant effect of 3 to 6 months of treatment with 120 to 240 mg per day of ginkgo extract on objective measures of cognitive function.** However, **Fugh-Berman now states that ginkgo appears to be ineffective in preventing or delaying cognitive impairment.** Fugh-Berman is persuaded that though ginkgo has a mild effect in treating dementia (it's about as effective as conventional drugs used to treat dementia), it does not prevent it.
    - Writing in 2006, **Lake and Spiegel concluded that ginkgo, "can be used for a number of conditions, including dementia and cerebral insufficiency**," citing the same studies used by Fugh-Berman and Cott.[2] They noted that most reports of improvement had involved elderly subjects with some cognitive impairment and called for more extensive trials with healthy subjects.
    - **Mischoulon and Rosenbaum** (through Amri, H., Mones, A-A, Le Bars, P. & Kastelan, J.) **consider the standardized EGb 761 ginkgo extract formula to be "one of the most**

highly recognized herbal supplements with well-proven efficacy. It is recommended for managing symptoms associated with a range of neurologic and vascular disorders including dementia …. It is approved for treatment of Alzheimer's disease in Belgium, the Czech Republic and Germany, and suggested for memory complaints in France and Spain. It is classified by the World Health Organization ("WHO") as among the available anti-dementia drugs."[3]

- **In addition, Germany's Commission E specifies use for primary degenerative dementia (mental degeneration due to aging), vascular dementia, and a combination of both**.[4]
- **Mischoulon and Rosenbaum conclude that: "there is a large body of data to support the efficacy of EGb761 as a neuroprotector and an enhancer of neural functioning. Evidence from biomedical research supports its effects on memory impairment, lack of concentration, cerebral-vascular insufficiency, as well as age-related and dementia-related cognitive weaknesses."**[5]
- Inconsistent results are explained as derived from the characteristics of the population studied, the type of outcome measurements selected, and the EGb 761 regimen tested in the trial. Mischoulon and Rosenbaum further conclude that: "assessments measuring accuracy and speed, which are most closely related to working memory, better demonstrate the effect of EGP 761 rather than assessments that measure long-term storage and retrieval abilities, regardless of the study population."[6] They conclude that EGb 761: "**seems to enhance complex attention, speed of information processing, and the rate of working memory**."[7]
- With regard to the studies measuring EGb 761's effect on Alzheimer's disease, Mischoulon and Rosenbaum conclude that "There are several large scale studies and literature analyses that support the prophylactic and treatment use of EGb 761 for Alzheimer dementia."[8] In particular, they cite with approval the Oken *et al*.'s meta-analysis of EGb 761's effect on Alzheimer's disease and associated dementia, which reviewed over 50 clinical studies and was relied on by Fugh-Berman and Cott. "After applying several exclusion criteria, the authors concluded that their quantitative analysis of the literature showed a **small significant effect on objective measures of cognitive**

function in Alzheimer's disease after 3 to 6 months of treatment with 120 to 240 mg per day of EGb 761."[9]

- The 2010 edition of **the *Natural Standard* continues to list use of ginkgo for "dementia (multi-infact and Alzheimer's type)" in the "A" category, "strong scientific evidence for this use," stating: "The scientific literature overall does suggest that ginkgo benefits people with early stage Alzheimer's disease and multi-infarct dementia and may be as helpful as acetylcholinesterase inhibitor drugs such as donepezil (Aricept)**."[10] The *Natural Standard* also states that "good" evidence demonstrates ginkgo's efficacy in the treatment of "cerebral insufficiency" (a syndrome secondary to atherosclerotic disease, characterized by impaired concentration, confusion, decreased physical performance, fatigue, headache, dizziness, depression, and anxiety, and commonly diagnosed in Europe). This is the "B" category: "good scientific evidence for this use." Significantly, the 2010 edition of the *Natural Standard* does not cite the 2008 GEM study.
- **Brown *et al*., while agreeing that there is a small but significant effect of 3 to 6 months of treatment with 120 to 240 mg per day of ginkgo extract on memory, describe these effects as "slight at best."[11]**
- However, Brown, *et al.* consider ginkgo to have neuro-protective effects and benefits for **vascular dementia.**[12]
- Writing in **Brown et al. II,** Diamond, B.J. and Bailey, M.R., **while citing all of the recent negative data, still summarize that ginkgo, "has shown potential in ameliorating the effects of a variety of symptoms and disorders."[13]**
- The **Mayo Clinic** is counted as a negative because it relies on the 2008 NCCAM-funded study and the 2009 Cochran Collaboration meta-analysis to conclude that: "**Ginkgo doesn't reduce the risk of Alzheimer's or other dementias**." But Mayo, like Brown *et al*., remains optimistic for an ongoing neuro-protective role, acknowledging that "**some evidence" shows ginkgo to "benefit" early-stage Alzheimer's disease and "some dementia," and to be as helpful as "some [prescription] drugs."** Mayo gives ginkgo a yellow "caution" light, stating that while studies have produced "some **encouraging results** for the use of ginkgo as the treatment of certain circulation disorders and what

are sometimes called **cerebral insufficiencies -- symptoms such as absent-mindedness and confusion** -- which may be associated with Alzheimer's disease."[14]

- Still, Mayo concludes: "Studies have found ginkgo isn't an overall 'brain booster,' and the safety and effectiveness of ginkgo haven't always been proved."[15]
- ***Berkeley Wellness*** **is the most critical of ginkgo, stating flatly that: "Although ginkgo is one of the best studied herbs, there is no convincing evidence that it has any effect on memory or other mental functions in healthy older people -- that is, it doesn't sharpen an already clear mind, help prevent what is considered normal age-related memory loss, or delay or prevent dementia."[16]**
- *Berkeley Wellness* concludes: **"**If you or a family member has Alzheimer's or another dementia, talk to your doctor about trying ginkgo, but keep in mind that drug treatments may be better."[17] **Thus, *Berkeley* does not recommend ginkgo as a CAM treatment to slow or prevent memory of other cognitive problems in healthy people. Based on the 2008 GEM study, *Berkeley* does not support prophylactic use of ginkgo to slow or avoid dementia, cognitive impairment, or Alzheimer's disease.** It has gone so far as to drop ginkgo from its list of dietary supplements (in the 2011 edition ff.).

4. **CHALLENGING GINKGO**

- **THE 2008 NCCAM-FUNDED GINKGO EVALUATION OF MEMORY (GEM) STUDY of the standardized ginkgo product, EGb 761, found it INEFFECTIVE in lowering the overall incidence of dementia and Alzheimer's disease in older people with normal cognition. Further analysis of the data also found ginkgo to be ineffective in slowing cognitive decline.[18]** In this landmark clinical trial, researchers recruited more than 3,000 volunteers age 75 and over who took 240 mg of ginkgo or placebo daily, in two doses. Participants were followed for an average of approximately 6 years.
- Five hundred twenty-three individuals developed dementia (246 receiving placebo and 277 receiving ginkgo) with 92% of the dementia cases classified as possible or probable Alzheimer's Disease (AD), or AD with evidence of vascular disease of the brain. Rates of dropout and loss to follow-up were low (6.3%), and the adverse effect profiles were

similar for both groups. **The overall dementia rate was 3.3 per 100 person years in participants assigned to ginkgo and 2.9 per 100 person-years in the placebo group.** The hazard ratio (HR) for ginkgo compared with placebo for all cause dementia was 1.12 (95% confidence interval [CI], 0.94-1.33; *P*=.21) and for AD, 1.16 (95% CI, 0.97-1.39; *P*=.11). Ginkgo also had no effect on the rate of progression to dementia in participants with MCI ("mild cognitive impairment") (HR, 1.13; 95% CI, 0.85-1.50; *P*=.39).[19]

- **GEM STUDY CONCLUSION: "In this study, ginkgo at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or Alzheimer's disease incidence in elderly individuals with normal cognition**…."[20] This conclusion cast doubt on the conclusions quoted above.

- **THE 2009 COCHRANE COLLABORATION META-ANALYSIS OF GINKGO STUDIES cast further doubt on the validity of prior, more limited, biomedical research supporting ginkgo's effects, concluding that "the evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable."[21]**
- The 2009 Snitz, B.E. *et al*. study published in the *Journal of the American Medical Association*[22] for the "Ginkgo Evaluation of Memory (GEM) Study Investigators" determined there to be **"no evidence that ginkgo slows the rate of cognitive decline in older adults."**
- **New York Times**, August 28, 2010 review of an NIH panel on Alzheimer's prevention: "**In the end, [the panel] said it was highly confident in the findings for just one thing, the herb ginkgo. But in that case the evidence pointed in only one direction: it did not prevent Alzheimer's."**
- Contra, as part of the large longitudinal EPIDOS study in France, 69 Alzheimer's patients were matched with 345 women with normal cognitive functioning. A multivariate analysis showed that treatment with vasodilators including EGb 761 for at least two years reduced the risk of developing Alzheimer dementia.[23]
- Of four recent trials, three found no difference between ginkgo and placebo, but one reported very large treatment effects in favor of ginkgo. There were no significant

differences between ginkgo and placebo in the proportion of participants experiencing adverse events. A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from nine trials) also showed no consistent pattern of any benefit associated with ginkgo.

- **GUIDAGE STUDY: THE 2012 GuidAge Study, complementing the NCCAM-FUNDED GINKGO EVALUATION OF MEMORY (GEM) STUDY of the standardized ginkgo product, EGb 761, found it INEFFECTIVE in lowering the overall incidence of dementia and Alzheimer's disease in older people with normal cognition.** 2854 participants were randomly assigned, "of whom 1406 received at least one dose of ginkgo biloba extract and 1414 received at least one dose of placebo. By 5 years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (**1.2 cases per 100 person-years**) compared with 73 participants in the placebo group (**1.4 cases per 100 person-years**; hazard ratio [HR] 0·84, 95% CI 0·60—1·18; p=0·306), but the risk was not proportional over time. Incidence of adverse events was much the same between groups. 76 participants in the ginkgo group died compared with 82 participants in the placebo group (0·94, 0·69—1·28; p=0·68). 65 participants in the ginkgo group had a stroke compared with 60 participants in the placebo group (risk ratio 1·12, 95% CI 0·77—1·63; p=0·57). Incidence of other haemorrhagic or cardiovascular events also did not differ between groups."[24]
- **GUIDAGE STUDY CONCLUSION: Long-term use of standardized ginkgo biloba extract in this trial did not reduce the risk of progression to Alzheimer's disease compared with placebo.[25]**
- Given the inconsistent use pattern, some further analysis seems warranted. Analysis sponsored by a supplement manufacturer showed that ginkgo might yet be shown to protect the subgroup of long-term users: 15 out of 947 patients (1.6%) in the EGb 761 group who took ginkgo for at least four years converted to AD versus 29 out of 966 (3.0%) in the placebo group (statistically significant at p=0.03). However, the Guidage Study Group confirmed the Evaluation of Memory (GEM) Study conclusion that ginkgo did not prevent AD: **Significantly, the manufacturer-sponsored early analysis of the**

GuidAge results admitted that the results were not statistically significant for the study group as a whole.[26] But for those unwilling to concede that Ginkgo is ineffective in preventing AD, the remaining contention is: "The brain pathology that leads to overt Alzheimer's disease develops over the course of many years. It is therefore not surprising that those study participants who developed dementia early in the study gained less protective benefit from EGb 761 treatment, because they already had the disease. When these subjects as well as those who left the study prematurely (i.e., all study participants) were included in the analysis, the overall treatment effect was still detectable, although not statistically significant."[27]

- Kaschel, professor of clinical neuropsychology at the University of Osnabruck, concluded: 'Meta-analyses of the data by independent scientists consistently substantiate the efficacy of EGb 761 at the onset of cognitive decline.'"[28] Pending further analysis of the GuidAge and subsequent studies, though its efficacy is in serious doubt, the jury is still out on ginkgo.

5. **CONCLUSIONS**

- **Until a scientific and popular consensus emerges, ginkgo will continue to be used as a neuro-protective CAM treatment for incipient dementia, in preventing and treating memory impairment, lack of concentration, and cerebral-vascular insufficiency, as well as age-related and dementia-related cognitive weaknesses.** Absent any other obvious CAM alternative for preservation of cognitive faculties through the aging process, many researchers and health care practitioners are awaiting further developments before discarding ginkgo as a CAM treatment for mild cognitive impairment/dementia. **If you are using ginkgo and tolerating it well, there is no reason to stop.**
- **However, the evidence counsels looking at additional CAM treatments for cognitive challenges, including rhodiola, SAM-e, folate, omega-3s, and CDP-choline, discussed in separate chapters of this outline.**

- **Despite the weight of the GEM, Cochrane and GuidAge results, recent NCCAM and National Institute on Aging results point to neuro-protective effects with long-term with regular use of ginkgo.** Mischoulon and Rosenbaum conclude that EGb 761: "seems to enhance complex attention, speed of information processing, and the rate of **working memory**."[29]
- This is an encouraging suggestion for those using or considering ginkgo supplementation, and consistent with the suggestion that supplementation at the onset of cognitive impairment may be significant in ginkgo's efficacy. But the efficacy of ginkgo in combating cognitive impairment is definitely controverted**.**

6. **SUGGESTED BUT UNPROVEN USES**: **PROTECTION AGAINST THE NEURAL DAMAGE CAUSED BY ANTIPSYCHOTICS, DEPRESSION, ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD), SCHIZOPHRENIA, AND SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS: Brown, *et al.* recommend the use of ginkgo for protection against the neural damage caused by antipsychotics**. **In addition, the WHO and Germany list EGb 761 for the treatment of depression. This use is not supported by Lake and Spiegel.** Weil, whose focus is mood disorders, does not mention ginkgo at all. The *Natural Standard* states that "good" evidence demonstrates ginkgo's efficacy in the treatment of "**cerebral insufficiency**" (a syndrome secondary to atherosclerotic disease, characterized by impaired concentration, confusion, decreased physical performance, fatigue, headache, dizziness, depression, and anxiety, and commonly diagnosed in Europe). This is the "B" category.

7. **ADJUNCTIVE USE**
   - Brown, *et al.* recommend the use of ginkgo as an adjuctive treatment for **attention deficit and hyperactivity disorder (ADHD).** Brown *et al*. and Mischoulon and Rosenbaum recommend use of ginkgo as **adjunctive therapy (with antipsychotics) for schizophrenia**, citing the 2006 Zhang study.[30] Lake and Spiegel discuss use of ginkgo with antidepressants to counteract **sexual side effects**. The studies are split on this use.

- **Caution is advisable if ginkgo is used with psychotropic drugs, especially antidepressants**, in the absence of studies validating lack of adverse drug interactions. Although it is a suggested use, there is scant evidence in the sources consulted for the use of ginkgo for depression and no evidence about adjunctive use for depression. **Adjunctive treatment with antipsychotics** requires careful coordination with the prescribing physician, and adjunctive use with antidepressants requires extra precautions if it is to be attempted at all.

8. **DRUG INTERACTIONS**

- According to the *Natural Standard*, ginkgo has **anticoagulant effects**, may suppress platelet aggregation, and in rare cases has been associated with serious bleeding problems, and thus suggests that people with clotting disorders who are receiving any anticoagulant therapy, such as warfarin (Coumadin), heparin, aspirin, or ibuprofen, ticlodipine (Ticlin), antiplatelet drugs such as clopidogrel (Plavix), and nonsteroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve), or have scheduled surgery or dental procedures, should use caution and talk to a health care provider if using ginkgo.
- Fugh-Berman is skeptical about these concerns. She relies on studies that have shown no interaction with ticlopidine. None of the studies has noted significant bleeding problems.
- The *Natural Standard* adds that ginkgo may increase blood concentrations of some drugs used for treating hypertension.
- Citing "preliminary research," the *Natural Standard* also advises that ginkgo may affect insulin and blood sugar levels. Thus, caution is advised when medications that lower blood sugar are used.
- Ginkgo has also been found to affect blood pressure in healthy volunteers, although the studies disagree. The *Natural Standard* suggests that nifedipine should not be used in conjunction with ginkgo for this reason.

- **According to the *Natural Standard*, potential interactions with MAOI, SSRI and antipsychotic drugs have been noted**, **but have not yet been confirmed in humans**. Thus**, caution is appropriate to avoid the potential of serotonin syndrome**, and the prescribing physician should be consulted before using ginkgo in connection with these drugs. Serotonin syndrome is a condition defined by muscle rigidity, fever, confusion, increased blood pressure and heart rate, and coma. Fugh-Berman is skeptical about these concerns. She relies on studies that have shown no interaction with diazepam (Valium) and others.
- In theory, ginkgo may increase the actions of drugs used for erectile dysfunction such as sildenafil (Viagra).
- In theory, drugs such as donepezil (Aricept) and tacrine (Cognex) may have an additive effect when used at the same time as ginkgo, particularly increasing salivation and urination.

9. **SIDE EFFECTS**

- Brown *et al*. describe gingko's **side effects** as "**minimal**," citing only headache, reduced platelet aggregation and interaction with anticoagulant drugs, and "**rare**: agitation."[31] Brown *et al*. counsel not to use ginkgo prior to surgery or dental procedures. Fugh-Berman and Cott concluded that "**side effects from the use of ginkgo are rare**. Side effects include nausea, headache, stomach problems, diarrhea, allergy, anxiety, and restlessness.[32] According to Mischoulon and Rosenbaum, ginkgo, "**has an excellent safety record**; and except for the assumed possible risk of hemorrhage in patients taking anticoagulants, having bleeding disorders, or [about to] undergo surgery, EGb 761 **appears to be very safe**."[33] *Berkeley Wellness* concurs that ginkgo **appears safe overall.**
- According to the *Natural Standard*, side effects of ginkgo may include headache, nausea, gastrointestinal upset, diarrhea, dizziness, palpitations, anxiety, allergy or allergic skin reactions (rashes), bleeding, blood sugar levels, muscle weakness, loss of muscle tone, restlessness, racing heart, rash, and irritation around the mouth, reduction of male and female fertility, and efficacy of electro-convulsive therapy. There may be a risk of seizure

when ginkgo is taken, particularly in people with a history of seizure disorder. However, most reports of seizures have been due to eating ginkgo seeds, rather than the leaf extract, which is the standardized study product. Still, according to the *Natural Standard*, overall, ginkgo leaf extract appears to be **well tolerated at recommended doses for up to six months**.

- Gingko's safety for children and during pregnancy and breastfeeding is unknown, but the concern is minimal.

10. **DOSAGE:** Study dosage is standardized at **between 40 and 240 mg. per day** of EGb 761.

11. **CONTAMINATION:** *Berkeley Wellness* cautions that commonly available products may be different than the preparations used in clinical studies. EGb 761 is the only preparation of ginkgo that should be used. And tests by ConsumerLab have found problems in some ginkgo products. For instance, in 2008, tests on seven of the most popular ginkgo products sold in the United States found that five were contaminated or low in key compounds.

12. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with ginkgo and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects.

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[1] "Dietary Supplements and Natural Products as Psychotherapeutic Agents," by Adriane Fugh-Berman, M.D. (of Georgetown Medical School) and Jerry M. Cott, Ph.D. (of the National Institutes of Health), *Psychosomatic Medicine* 61:712-728 (1999), at 716; Oken, B.S., Storzbach, D.M., Kaye, J.A. "The Efficacy of *Ginkgo Biloba* on Cognitive Function in Alzheimer Disease." *Arch. Neurol.* 55:1409–15 (1998).

[2] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 104-107.

[3] Amri, H., Mones, A.A., Le Bars, P. & Kastelan, J., "Ginkgo biloba Extract in Cognitive Disorders, in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008), at163.

[4] *Id.*

[5] *Id*. at 170.

[6] *Id.*

[7] *Id*.

[8] *Id*. at 181.

[9] *Id.*

[10] *Natural Standard Herb and Supplement Guide: An Evidence-based Reference*, Ulbricht, Catherine, Ed. and founder (copyright 2010 by Mosby, Inc., an affiliate of Elsevier, Inc., Maryland Heights, MO)., "Gingko," at 358-361.

[11] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009), at 174.

[12] Brown *et al., op. cit*. at 270-271, citing Zhang, X.Y., Zhou, D.F., Zhang, P.Y., Wu, G.Y., Su, J.M. & Cao, L.Y., "A Double-blind, Placebo-controlled Trial of Extract of Ginkgo biloba Added to Halperidol in Treatment-resistant Patients with Schizophrenia," *Journal of Clinical Psychiatry* 62(11): 878-883 (2001).

[13] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 82.

[14] *The Mayo Clinic Guide to Alternative Medicine 2011* (Time Home Entertainment, Inc., New York 2010), at 48.

[15] *Id.*

[16] Berkeley (University of California) Wellness Reports – *Dietary Supplements* (2010 edition), "Ginkgo," at 45. Omitted from the 2011 edition.

[17] *Id.*

[18] Dekosky, S.T., Williamson, J.D., Fitzpatrick, A.L., Kronmal, R.A., Ives, D.G., Saxton, J.A., Lopez, O.L., Burke, G., *et al*., "Ginkgo Biloba for Prevention of Dementia: a Randomized Controlled Trial," *JAMA* 300(19):2253–62 (2008). http://jama.ama-assn.org/cgi/reprint/300/19/2253

[19] *Id*.

[20] *Id.*

[21] Birks J, Grimley Evans J., "Ginkgo biloba for Cognitive Impairment and Dementia," Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD003120. DOI: 10.1002/14651858.CD003120.pub3 (2009). http://www2.cochrane.org/reviews/en/ab003120.html

[22] Snitz, B.E., O'Meara, E.S., Michelle C. Carlson, M.C., Arnold, A.M., Ives, D.G., Rapp, E.R., Saxton, J., Lopez, O.L., Dunn, L.O., Sink, K.M., DeKosky, S.T., for the Ginkgo Evaluation of Memory (GEM) Study Investigators "Ginkgo biloba for Preventing Cognitive Decline in Older Adults: A Randomized Trial," *JAMA* 302(24):2663-2670 (2009). http://jama.ama-assn.org/cgi/reprint/302/24/2663

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[25] *Id.*

[26] http://www.schwabepharma.com/international/media-relations/press-releases/items/2010_06_22_GuidAge.php

[27] *Id.*

[28] See Williamson, J. D., Vellas, B., Furberg, C., Nahin, R., Dekosky, S. T., "Comparison of the Design Differences Between the Ginkgo Evaluation Of Memory Study and the GuidAge Study" *Journal of Nutrition, Health & Aging* 12(1):73S-9S (2008). http://www.ncbi.nlm.nih.gov/pubmed/18165850

[29] Mischoulon and Rosenbaum, *op. cit.* at 170.

[30] *Id.* at 183, citing Zhang, X.Y., Zhou, D.F., Cao, L.Y. & Wu, G.Y., *op. cit.*

[31] Brown *et al., op. cit.* at side effect tables, 137t,191t, etc.

[32] Fugh-Berman and Cott, *op. cit*. at 715-717.

[33] Mischoulon and Rosenbaum, *op. cit.* at 186.

INOSITOL FOR DEPRESSION AND PANIC DISORDER

SUMMARY

WHAT WE KNOW

Inositol--Vitamin B8--has been found to reduce depression, hostility, tension and fatigue. It is a folk remedy for anxiety and sadness. Inositol has been shown in very small studies to be helpful for depression and panic disorder, and promising for treatment of obsessive-compulsive disorder, eating disorders and bipolar disorder. Research has not yet shown any adjunctive benefit when inositol is used with psychotropic drugs. Inositol is a part of our diet, and supplementation seems benign. The risk is minimal.

MENTAL HEALTH IMPLICATIONS

Depression and Panic Disorder

All four sources that discuss it support use of inositol for depression and panic disorder. Writing in Mischoulon and Rosenbaum's compendium, Belmaker and Levine propose inositol as a stand-alone supplement for depression and panic disorder rather than as a complement for other psychotropic drugs, noting responses in the same people and no proven additional benefit from using both drugs in combination. But in a 2011 analysis that included Mischoulon as a participant, Iovieno *et al*. summarize the evidence as "conflicting." Adjunctive use of inositol remains to be investigated.

Other Mental Health Conditions

Though promising, due to study design issues inositol has not yet been established as a treatment for

- obsessive-compulsive disorder,
- bipolar disorder, and
- eating disorders.

Belmaker and Levine found inositol ineffective in treating:

- schizophrenia,
- dementia,
- electroconvulsive treatment (ECT)-induced memory impairment,
- attention deficit hyperactivity disorder (ADHD), and
- autism.

DRUG INTERACTIONS AND SIDE EFFECTS

There have been no documented cases of drug interactions in studies where inositol was co-administered with FDA-approved medications. Gastrointestinal side effects may be a problem for some people, but inositol is generally well tolerated and appears to have a favorable safety profile. There is no special concern in pregnancy, lactation or child use. However, there have been case reports of inositol-induced mania in people with bipolar disorder. It is uncertain how significant this effect would be if inositol were in wider use as a supplement. People with bipolar disorder should exercise appropriate caution, including consideration of using a mood stabilizer while using inositol.

CONCLUSION

Inositol is a very promising treatment for depression and panic disorder. It is promising for bipolar disorder, anxiety, obsession, compulsion, eating disorders, hostility, sadness, tension and fatigue. It is quite safe. Adjunctive use may not benefit but will not hurt. People with bipolar disorder should exercise greater caution.

OUTLINE

1. Inositol is a sugar alcohol and a structural isomer of glucose. It is often sold as a dietary supplement in combination with other nutraceuticals. Inositol is present in a variety of foods, particularly beans, grains, nuts, and many fruits. The average adult human consumes about 1 g per day of inositol. Inositol is classified as a member of the vitamin B family, specifically vitamin B8.

2. **EFFICACY**: **DEPRESSION AND PANIC DISORDER: Inositol monotherapy has been shown in very small studies to be helpful for depression and panic disorder:**
   - Brown *et al.* report 1995 and 1996 studies in which inositol was found to function better than placebo in alleviating symptoms of **depression**, **panic disorder**.[1]
   - Brown *et al.* consider inositol to be a **"third-line augmentation" because of the gastrointestinal side effects.**
   - **Brown et al. II** (through Akhondzadeh, Gerbard, P.L. and Brown, R.P.) **confirm evidence for the use of inositol as an adjunctive treatment for depression and panic disorder.[2]**

- **Lake and Spiegel** note that people with unipolar and bipolar depression have "markedly low levels" of inositol. They assert that, "many small well-designed studies have provided promising evidence to support inositol's therapeutic efficacy in the same spectrum of psychiatric disorders that respond to SSRIs, including **depression, panic disorder,** and obsessive-compulsive disorder."[3] As their principal source, they cite Levine's 1997 review of 8 controlled studies, which is augmented by his discussion in Mischoulon and Rosenbaum.
- Although none of the other originally consulted sources even mentions inositol, Mischoulon and Rosenbaum dedicate an entire chapter to it, authored by **Robert H. Belmaker and Joseph Levine**,[4] who describe their investigation of the use of inositol to treat a range of psychiatric disorders, including small studies of **depression (alone and in combination with other antidepressant drugs), panic disorder,** obsessive-compulsive disorder, bulimia and binge eating**.**[5] The depression study is the most robust, but the panic disorder results are also significant. The remaining observations are promising.
- **In the 1995 Levine *et al.* depression study,[6] treatment with inositol resulted in significantly greater improvement in HAM-D scores at four weeks compared to placebo, 33% improvement with inositol vs. 12% with placebo. (p=.04).** The significance of this result is limited by the size of the study (27 subjects) and the four-week duration.[7] There were no significant results at two weeks.
- The **2006 Nierenberg, *et al.*** depression study was more convincing, comparing HAM-D scores with randomized administration of lamotrigine (Lamictal, an anti-seizure medication), resperidone (Risperdal), as active placebo, and inositol. The **rate of recovery** was 23.8% with lamotrigine, **17.4% with inositol, and 4.6% with resperidone**.[8]
- **In comparison with fluoxetine (Prozac), an SSRI**, a double-blind, random-order, crossover study of **panic disorder showed a greater reduction in the number of panic attacks with inositol** in the first week, and similar results over the nine-week course. Attacks fell from ten to six on placebo and from ten to three and a half on inositol. Ten of 21 subjects responded to inositol, 3 to placebo.[9] [10]

- **ADJUNCTIVE USE WITH SSRIS MAY BE INEFFECTIVE. Studies using inositol as an adjunctive treatment with SSRIs have not shown any therapeutic benefit.[11] Belmaker and Levine thus propose inositol as a stand-alone supplement** rather than as a complement for SSRIs, noting responses in the same people, equal efficacy, and no additional benefit from using both drugs in combination**.**
- But in a 2011 analysis that included Mischoulon as a participant, **Iovieno *et al*.[12] summarize the evidence as "conflicting:"** There are six published clinical trials of inositol **for outpatient treatment of depression**, of which five were placebo-controlled. Only the 1995 Levine *et al*. study used inositol as monotherapy; the others augmented conventional antidepressants and mood stabilizers with inositol. **Inositol outperformed placebo in three of the five controlled studies**, but all sample sizes were small, and statistical significance was reached in only one study.

3. **SUGGESTED BUT UNPROVEN USES: OBSESSIVE-COMPULSIVE DISORDER:** Brown et al, Brown et al II and Lake and Spiegel all find evidence of the efficacy of inositol in treating obsessive-compulsive disorder. The obsessive-compulsive study used a crossover design that makes it hard to evaluate, since there is a delay in the effects of inositol supplementation. Thus, Belmaker and Levine did not accept it. But the use of inositol in OCD is certainly promising.

4. **SUGGESTED BUT UNPROVEN USES: BIPOLAR DISORDER:** Brown et al. II find evidence that inositol can be effective in treating bipolar disorder. Belmaker and Levine agree that the studies cited by Brown *et al.* suggest that a large, well-controlled study might show that inositol could be effective in treating bipolar disorder, but they caution that the results so far are not significant. A 1996 study by Levine *et al.* reported three cases of possible inositol-induced hypomania.

5. **SUGGESTED BUT UNPROVEN USES: EATING DISORDERS:** Brown *et al.* II and Lake and Spiegel accepted the inositol monotherapy used by Gelber et al. (2001) for previously

unresponsive bulimia subjects, producing complete remission of symptoms for six months. The obsessive-compulsive disorder and eating disorder studies all used a crossover design that makes them hard to evaluate, since there is a delay in the effects of inositol supplementation. Thus, Belmaker and Levine did not accept them. But they are certainly promising.

6. **DISPROVEN USES: Belmaker and Levine also investigated use of inositol for schizophrenia, dementia, electroconvulsive treatment (ECT)-induced memory impairment, attention deficit hyperactivity disorder (ADHD), and autism. Inositol proved ineffective in these studies.**

7. Finally, Belmaker and Levine tested the effects of inositol in **"normal" people**. Eleven volunteers were given inositol or placebo in a double-blind, randomized, crossover design. Inositol was found to reduce depression, hostility, tension and fatigue compared with placebo over six hours. "These **results are consistent with use of inositol as a folk remedy for anxiety and sadness**."[13]

8. **DRUG INTERACTIONS**: According to Iovieno *et al.,* there have been no documented cases of drug–drug interactions in studies where inositol was co-administered with FDA-approved medications.

9. **SIDE EFFECTS:** Brown *et al.* describe gastrointestinal side effects that can be severe, including diarrhea and flatulence. Belmaker and Levine and Lake and Spiegel both characterize the symptoms as "mild." Iovieno *et al*. round out the picture: Inositol is **generally well tolerated** and appears to have a favorable safety profile. Side effects reported in the reviewed clinical trials, at doses of inositol ranging from 6 to 25 g per day, include mild incr**e**ases in plasma glucose, flatus, nausea, sleepiness, insomnia, dizziness and headache. **However, there have been case reports of inositol-induced mania in bipolar depressed patients.** It is uncertain how significant this effect would be if inositol were in

wider use as a supplement. People with bipolar disorder should exercise appropriate caution, including consideration of a mood stabilizer while using inositol. There are no studies or cautions concerning use of inositol in breast-feeding women or in children, but Lake and Spiegel caution that inositol **may cause uterine contractions**, ruling out its use in pregnant women.

10. **DOSAGE:** Brown *et al.* report dosages of **12-20 g per day.** Belmaker and Levine and Lake and Spiegel both used a dose of **12-18 g per day.** This is 10 – 18 times the average daily intake of 1 g per day.

11. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with inositol and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects.

[1] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009) at 47.

[2] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 34.

[3] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 138.

[4] Belmaker, R.H. & Levine, J., "Inositol in the Treatment of Psychiatric Disorders," in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008), at 105-115.

[5] Mischoulon and Rosenbaum, *op. cit*. at 105-109.

[6] Mischoulon and Rosenbaum, *op. cit.* at 105.

[7] Levine, J., Barak, Y., Gonzalves, M., et al., "Double-blind Controlled Trial of Inositol Treatment of Depression," *American Journal of Psychiatry* 152:792-794 (1995).

[8] Nierenberg, A.A., Ostracher, M.J., Calabrese, J.R., et al., « Treatment-resistant Bipolar Depression : A STEP-BD Equipoise Randomized Effectiveness Trial of Antidepressant Augmentation with Lamotrigine, Inositol or Respiridone," *American Journal of Psychiatry* 163(2):210-216 (2006).

[9] Benjamin, J., Levine, J., Fux, M., *et al.,* "Double-blind, Placebo-controlled, Crossover Study of Inositol Treatment for Panic Disorder," *American Journal of Psychiatry* 152:792-794(1995).

[10] Mischoulon and Rosenbaum, *op. cit*. at 106.

[11] Levine, J., Mishory, A., Susnosky, S., *et al*., "Combination of Inositol and Serotonin Reuptake Inhibitors in the Treatment of Depression," *Biological Psychiatry* 45:270-273 (1999).

[12] Iovieno, N., Dalton E. D., Fava, M. & Mischoulon, D., "Second-tier Natural Antidepressants: Review and Critique," *Journal of Affective Disorders* 130(3):343-57 (2011).

[13] Mischoulon and Rosenbaum, *op. cit*. at 112.

KAVA FOR MILD ANXIETY AND STRESS

SUMMARY

WHAT WE KNOW

Kava has been shown in more than a dozen placebo-controlled studies to be effective with good tolerability for treatment of generalized anxiety, with some evidence for stress, depression and insomnia. Kava is generally safe for short-term use but can in rare cases cause catastrophic damage to the liver. Thus, its use is very controversial, and the sources are split four to three on whether it should ever be recommended.

MENTAL HEALTH IMPLICATIONS

Seven sources confirm the beneficial uses of kava as a mild intoxicant and analgesic, and for treatment of generalized anxiety, depression, stress, tension, agitation, agoraphobia, specific other phobias, generalized anxiety disorder, adjustment disorder, menopausal symptoms and insomnia. But Brown *et al*. caution that the benefits are "modest," and all sources caution about the danger of liver damage. There is no proof that kava is effective for treatment of severe anxiety. No published studies have yet tested kava's efficacy for panic disorders. Kava has not been found effective for adjunctive use, should not be used with MAOIs, and should only be used with tricyclics or SSRIs after careful coordination with the prescribing physician.

DRUG INTERACTIONS

Kava has the potential to interact with several drugs and medications. It is vitally important to discuss kava use with any prescribing physician.

Alcohol, other sedatives, muscle relaxants, dopamine, haloperidol, acetaminophen, and benzodiazepines. Taking kava with alcohol, other sedatives, or muscle relaxants can result in additive effects up to and including coma. Kava may interact with several drugs, including drugs

used for Parkinson's disease and benzodiazepines used for anxiety. Alcohol or acetaminophen (Tylenol), which may injure the liver, should never be used with kava. Kava may interfere with the effects of dopamine and drugs that are similar to dopamine and may worsen the neurological side effects of drugs that block dopamine, such as haloperidol (Haldol).

Psychotropics and anesthesia. Kava may have chemical properties similar to monoamine oxidase inhibitors (MAOIs), and may be additive to the effects of MAOI antidepressants, such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate). Thus, kava should never be used with MAOIs. Adjunctive use with other psychotropic drugs, including tricyclic antidepressants and SSRIs, has not been tested, but should not be attempted without careful coordination with the prescribing physician. Kava may cause excessive drowsiness when taken with SSRI antidepressant drugs such as fluoxitine or sertraline. Kava may also cause anesthesia to last longer and use should be carefully coordinated with the prescribing physician or anesthesiologist.

Anti-cancer and birth control drugs. Kava may also interact with anti-cancer and birth control drugs.

SIDE EFFECTS

CAUTION: **LIVER TOXICITY:** Reports from health authorities in Germany, Switzerland, France, Canada, and the United Kingdom have linked kava use to at least 30 cases of liver toxicity, including hepatitis, cirrhosis, and liver failure. Kava is banned in Germany, Canada and Switzerland**.** The U.S. FDA issued a consumer advisory in 2002, which is still in effect. The FDA cautions: Persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements.

Of the consulted sources, *Consumer Reports* is the most directive: Based on the 2002 FDA warning, kava is one of 12 supplements that *Consumer Reports* advises that you should avoid. Brown *et al.* also do not recommend kava, and Fugh-Berman no longer recommends it, because

of the catastrophic liver damage associated with its use in the cases noted by the FDA. Four sources still recommend careful use of kava. Lake and Spiegel, Mischoulon and Rosenbaum, the *Natural Standard*, and Weil counsel that kava should be avoided in individuals with a history of liver disease or alcohol use, and in those who are taking concurrent medications with potential liver toxicity. Mischoulon and Rosenbaum conclude: “Kava should be prescribed and used with great caution.” Use of kava is not recommended to exceed three months.

More research pinpointing risk factors could modify these recommendations, since liver toxicity appears to be extremely rare, and bad experience with other anxiolytics could prompt a trial of kava if the risk factors appear to be low, with proper medical supervision. Pregnancy, lactation or child use would appear not to impose a separate challenge.

CONCLUSION

Caution. The risk of liver damage is substantial and may be irreversible, even though it appears to be rare.

OUTLINE

1. Kava**,** *Piper methysticum,* is native to the islands of the South Pacific and is a member of the pepper family. Kava has been used as a ceremonial beverage in the South Pacific for centuries. Common names include kava, kava kava, awa, and kava pepper. The root and rhizome (underground stem) of kava are used to prepare beverages, extracts, capsules, tablets, and topical solutions.

2. Kava has been used to help people fall asleep and fight fatigue, as well as to treat asthma and urinary tract infections. Topically, kava has been used as a numbing agent. Today, kava is used primarily for anxiety, insomnia, and menopausal symptoms.

3. **EFFICACY: MILD ANXIETY AND STRESS: Kava has been shown in more than a dozen placebo-controlled studies to be effective with good tolerability for treatment of mild anxiety and stress. Six sources confirm the beneficial uses of kava as a mild intoxicant and analgesic, but Brown *et al*. caution that the benefits are "modest," and all sources caution about the danger of liver damage/ failure, which can cause death. Fugh-Berman, Brown *et al*. and Consumer Reports advocate against the use of kava.**

- **Writing prior to the FDA warning**, Fugh-Berman and Cott cited seven studies of kava, demonstrating its beneficial effects on anxiety and stress, and emphasizing the German health system's approval of its use for that purpose, since withdrawn because of the concern about liver toxicity. Fugh-Berman has withdrawn her recommendation as well.
- After citing conflicting meta-analyses by Pittler & Ernst (2000) and Connor, Payne & Davidson (2006), Brown *et al.* conclude that: "**Kava has modest benefits in short-term studies of mild anxiety. [But]Considering the risks of intoxication, the risk of abuse, and rarely severe adverse effects, the authors do not recommend kava, until more compelling data on safety and efficacy become available**."[1] Brown *et al*. II concur. Thus, as of 2013, adequate data are not available to show safety and efficacy.
- **Lake and Spiegel** (through Lee, Yee & Naing) **confirmed moderate efficacy in the treatment of [mild] anxiety**, primarily based on Pittler and Ernst's two meta-analyses, and added that the reports of liver toxicity, though severe, remain very rare (2 in 250 million doses, and both using large dosages), and **benzodiazepines have a far higher rate of adverse event reports.**
- Mischoulon and Rosenbaum[2] give a more comprehensive critique of the kava studies, all but two of which involved double-blind, placebo-controlled, randomized clinical trials using a passive placebo. Only two reported studies compared kava to an active therapy. **Kava was shown in "more than a dozen" passive placebo studies to be effective with good tolerability for treatment of "generalized anxiety, tension, agitation, agoraphobia, specific [other] phobias, generalized anxiety disorder, adjustment disorder, and insomnia**."[3] These studies used sample sizes of between 20 and 141 people, for a duration of four to eight weeks (although some studies went on for three to six months), at a **dosage of 150 to 400 mg. per day.**
- The studies that have compared kava with standard anxiolytics and antidepressants in the treatment of anxiety showed that kava had equivalent effects to buspirone (Buspar), opipramol (Insidon, Pramolan, Ensidon, Oprimol), and venlafaxine (Effexor, Efexor), at manufacturers' recommended dosages.[4]

- Weil lauds kava as: "**an excellent anti-anxiety remedy, shown in controlled human trials to be as effective as benzodiazepine drugs**."[5]
- Consumer Reports listed kava as **one of "12 supplements you should avoid**," in its September, 2010 issue. The reasons given were: "Possibly unsafe. The FDA issued a warning to consumers in March 2002. Banned in Germany, Canada and Switzerland."
- There are no studies addressing the question of safety in pregnancy or breast feeding, and no studies of children, and for this reason, kava is not recommended for use in pregnant or lactating women or in children. Because of the danger of bleeding, use during pregnancy is strongly discouraged.

4. **SUGGESTED BUT UNPROVEN USES: ANXIETY, AND TO IMPROVE COGNITIVE FUNCTION AND POSITIVE AFFECT IN ANXIOUS SUBJECTS, INSOMNIA, PANIC DISORDERS:**
   - The sources recommend kava as a promising but unproven CAM treatment for generalized anxiety, stress, tension, agitation, agoraphobia, specific other phobias, generalized anxiety disorder, adjustment disorder, menopausal symptoms and insomnia, and to improve cognitive function and positive affect in anxious subjects. Anxiety, insomnia and panic disorders would all be studied as promising practices if kava were not implicated in a few catastrophic cases of liver toxicity. But these studies are unlikely to proceed.
   - The sources all agree that **there is no proof that kava is effective in treatment of severe anxiety**. Most of the studies are limited by small samples, short duration of treatment, and a lack of rigorous diagnostic criteria. Moreover, no published studies have yet tested kava's efficacy for panic disorders.
   - **Nonetheless, the *Natural Standard* gives an "A" rating for the use of kava for anxiety,** affirming that there is "strong scientific evidence for this use." The write-up is more cautious, stating only that the clinical studies have found "at least moderate benefit" for the treatment of anxiety. The *Natural Standard* affirms the studies finding the efficacy of kava to be similar to benzodiazepine drugs such as diazepam (Valium) or the

anxiolytic drug buspirone (Buspar). However, concerns about potential liver toxicity are emphasized.

- The *Natural Standard* rates use of kava for insomnia and stress "C," "unclear scientific evidence for this use."

5. **DRUG INTERACTIONS**:
    1. **Taking kava with alcohol, other sedatives, or muscle relaxants can result in additive effects up to and including coma.** Kava may interact with several drugs, including drugs used for Parkinson's disease and benzodiazepines used for anxiety. Alcohol or acetaminophen (Tylenol), which may injure the liver, are strongly contraindicated for use with kava. **Kava may interfere with the effects of dopamine and drugs that are similar to dopamine and may worsen the neurological side effects of drugs that block dopamine such as haloperidol (Haldol).**
    2. **Kava may have chemical properties similar to monoamine oxidase inhibitors ("MAOIs"), and may be additive to the effects of MAOI antidepressants, such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate). Thus, kava should never be used with MAOIs. Adjunctive use with other psychotropic drugs, including tricyclic antidepressants and SSRIs, has not been tested, but should not be attempted without careful coordination with the prescribing physician. Kava may cause excessive drowsiness when taken with SSRI antidepressant drugs such as fluoxitine or sertraline.** Kava may also cause anesthesia to last longer and use should be carefully coordinated with the prescribing physician or anesthesiologist.
    3. Laboratory tests suggest a danger of bleeding, but this has not yet been found in human subjects. Still, *Natural Standard* cautions against using anticoagulants or antiplatelets with kava. This includes warfarin (Coumadin), heparin, aspirin, and clopidogrel (Plavix).
    4. Since kava has diuretic properties, it may have an additive effect when taken with diuretic drugs such as furosemide or with ACE inhibitors such as benazopril or captopril. The *Natural Standard* specifically cautions avoidance of kava, in patients with Parkinson's disease or those with a "history of medication-induced extrapyramidal

effects." Busperone and opipramol may also have additive effects when taken with kava, or with opioid analgesics like oxycodone and propoxyphene or herbs like valerian. **Kava may also interact with anti-cancer and birth control drugs**.

6. **SIDE EFFECTS:**

- Fugh-Berman and Cott cited mild gastrointestinal complaints or allergic skin reactions (incidence, 1.5%) as the most common effects. Chronic use of kava up to 100 times the therapeutic dose results in an ichthyosiform eruption (yellowed skin) known as kava dermopathy, which is often accompanied by eye irritation. Abstaining from kava results in complete resolution of symptoms.
- According to Brown *et al*., post marketing studies have revealed a **1.5% to 2.3% incidence of side effects** from kava, primarily gastrointestinal upset, allergic reactions, headache, and light sensitivity. Less common side effects include restlessness, drowsiness, lack of energy, and tremor. In four cases, kava was associated with dyskinesias or worsening Parkinsonian symptoms.
- According to Mischoulon and Rosenbaum, the most common side effects of kava use are gastrointestinal upset, allergic skin reactions, headaches and dizziness. Liver toxicity has been noted with prolonged aboriginal use as well as in the cases cited by the FDA. There are reports of adverse interactions with benzodiazepines[6] and alcohol. According to Mischoulon and Rosenbaum, the more serious toxic reactions have been associated with high doses (over 300 g. per week, 43 g. per day – 43,000 mg per day) or prolonged use of kava, and use of kava without physician supervision.

- Lake and Spiegel (Lee, Yee and Naing) add antiplatelet activity and apathy with long-term use.
- The *Natural Standard* relates the history, that kava had generally been thought to be "safe in otherwise healthy people not taking any other drugs, herbs or supplements, over short periods of time (1 to 2 months), and at recommended doses." However, the facts recited in the FDA release have required a change in the *Natural Standard*'s stance, concluding that, " **kava should be used only under the supervision of a qualified**

healthcare professional, should never be used above recommended doses, and should be avoided by people with liver problems and by those taking drugs that affect the liver."

- Reports from health authorities in Germany, Switzerland, France, Canada, and the United Kingdom have linked kava use to at least 30 cases of liver toxicity, including hepatitis, cirrhosis, and liver failure. **Kava is banned in Germany, Canada and Switzerland. The US FDA issued a consumer advisory in 2002, which is still in effect. The FDA cautions: Persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver, should consult a physician before using kava-containing supplements.**
- **In view of the evidence of liver toxicity, four of the seven sources consulted for this section of this outline, Lake and Spiegel, Mischoulon and Rosenbaum, the *Natural Standard*, and Weil, counsel that kava should be avoided in individuals with a history of liver disease or alcohol use, and in those who are taking concurrent medications with potential liver toxicity. Anyone who uses kava should do so under physician supervision, which should include regular monitoring of liver function tests, particularly ALT, GGT and ALP. If any abnormalities are found, then kava should be discontinued immediately** and liver enzymes should be retested in about two weeks, by which time they should return to normal.
- **The other three sources, Fugh-Berman, Brown *et al*. and Consumer Reports, dissent and counsel complete avoidance of kava.**
- If you use kava without medical consultation, **get help right away if you start feeling bad.** FDA urges consumers and their health care professionals to report any cases of liver and other injuries that may be related to the use of kava-containing dietary supplements. Adverse events associated with the use of dietary supplements should be reported as soon as possible to FDA's MedWatch program by calling their toll-free number (1-800-332-1088) or through the Internet.
- Other side effects include dystonia (abnormal muscle spasm or involuntary muscle movements), gastrointestinal upset, allergic reactions, headache, light sensitivity and

scaly, yellowed skin, blood abnormalities, apathy, kidney damage, seizures, psychotic syndromes, and increased blood pressure in the lungs (pulmonary hypertension). Blood in the urine has also been reported. Less common side effects include restlessness, drowsiness, lack of energy, and tremor. In four cases, kava was associated with dyskinesias or worsening Parkinsonian symptoms.

- Feelings of sedation (drowsiness) are inherent in the use of kava. The *Natural Standard* adds: eye irritation, ECG abnormalities, shortness of breath, bleeding, irritation in the layers around the brain and spinal cord, urinary retention, skin lesions, enhanced or decreased cognitive performance, anorexia, sleeplessness, abnormal sensations called paresthesias, vomiting, and dangerously high blood pressure.
- People should use great care in operating heavy machinery while taking kava because the herb has been reported to cause drowsiness.

7. **DOSAGE:** A dose-finding study using 150 to 300 mg. per day found that improvement was more "robust" with higher doses. Mischoulon and Rosenbaum report that there is no consensus on the optimal daily dose, and lack of a standardized extract makes comparison impossible. But Mischoulon and Rosenbaum cite dosages of **150 to 300 or 400 mg. per day**. Weil recommends 100 to 200 mg two or three times a day, as needed (**300-600 mg per day**). Lake and Spiegel agree on three doses of 100 mg per day. The more serious toxic reactions have been associated with high doses or prolonged use of kava, and use of kava without physician supervision.

8. **CAUTION: Duration of use of kava is not recommended to exceed three months**. Mischoulon and Rosenbaum conclude that: "**Kava should be prescribed and used with great caution**."[7]

9. **RESEARCH:** More research pinpointing risk factors could modify these recommendations, since liver toxicity appears to be extremely rare, and bad experience with other anxiolytics

could prompt a trial of kava if the risk factors appear to be low, with proper medical supervision.

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[1] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009), at 125.

[2] Mischoulon, D., "Herbal Remedies for Anxiety and Insomnia," in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008), at 119.

[3] *Id.*

[4] *Id*. at 122.

[5] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 117.

[6] Miller, L.G., "Herbal Medicinals: Selected Clinical Considerations Focusing on Known or Potential Drug-herb Interactions" (1998), Archives of Internal Medicine, 158:2200-2211; Almeida, J.C.& Grimsley, F.W., " Coma from the Health Food Store: Interaction Between Kava and Alprazolam" [letter] 1996 *Annals of Internal Medicine* 125:940-941.

[7] Mischoulon and Rosenbaum, *op. cit*., at 123-124.

MELATONIN FOR JET LAG AND SLEEP DISORDERS

SUMMARY

WHAT WE KNOW

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone associated with sleep. Although the U. S. Agency for Healthcare Research and Quality (AHRQ) questions the evidence, the five sources that deal with melatonin all recommend it for:

- jet lag and
- shift work adjustment,

Melatonin is a promising treatment for other sleep disorders, especially:

- sleep latency (delay in falling asleep) in older people.
- insomnia in the elderly,
- sleep disturbances in children with neuro-psychiatric disorders, and
- sleep enhancement in healthy people

However, some of the evidence is tentative, and much more study is needed. Uses of melatonin to

- treat insomnia and
- maintain cognitive capacity (neuroprotection)

are particularly interesting but remain unresolved. Other suggested but unproven uses include:

- circadian sleep disorders [cyclical melatonin deficiency]
- dealing with the side effects of treatment for schizophrenia, particularly tardive dyskinesia and weight gain,
- benzodiazepine withdrawal,
- high-altitude adjustment,

- insomnia in dementia,
- insomnia in people with autism,
- “sundowning”/sleep pattern adjustment,
- rapid eye movement behavior disorder,
- seasonal affective disorder,
- drug withdrawal syndrome,
- major depression, and
- adjunctive use.

MENTAL HEALTH IMPLICATIONS

Melatonin is a promising treatment for jet lag and many mild to moderate sleep disorders. All other potential uses remain to be studied. Risks appear manageable, but caution is appropriate since melatonin is commonly over consumed, and, absent testing, people should “work up” to a therapeutic dose.

DRUG INTERACTIONS

Drug interactions with melatonin have not been sufficiently studied, but appear manageable. Alcohol, caffeine and aspirin may affect melatonin levels. Psychotropic drugs that affect norepinephrine or serotonin levels might alter the pattern of melatonin production and that any drugs that might affect the metabolism of melatonin in the liver, such as valproic acid or methoxypsoralen, could affect blood serum levels of melatonin. Consultation with the prescribing physician is essential if any prescription drug is being taken with melatonin. Special care is appropriate for people taking:

- zolpidem (Ambien),
- benzodiazepines such as lorazepam (Ativan), triazolam (Halcion), or diazepam (Valium),
- barbiturates such as phenobarbital,
- narcotics such as codeine,
- antidepressants,
- blood thinning medication such as warfarin (Coumadin),

- methamphetamine,
- medication for glaucoma.
- beta blockers, and
- tranquilizers.

SIDE EFFECTS

- Melatonin is classified by the FDA as “generally regarded as safe” in recommended doses for short-term use.
- The most common side effect is gastric distress.
- There is controversy about the effect of melatonin on seizure disorders. In the absence of better science, consultation with the health care professional providing care for an existing seizure disorder is essential if considering using melatonin.
- Mood changes have been reported, both highs and lows, and even psychotic symptoms such as hallucinations and paranoia. Persons with major depression or psychotic disorders should consult with the health care professional providing care for the underlying disorder before using melatonin.
- Given the lack of experimental data concerning melatonin supplementation in children, Mischoulon and Rosenbaum caution that melatonin treatment in children should be used only “very conservatively," when the benefits of melatonin treatment clearly outweigh any possible risks. There are no data concerning use during pregnancy or breastfeeding.
- **Overconsumption** of melatonin can have significant risks. It has been suggested that millions of Americans currently consume melatonin in excessive quantities, elevating their melatonin levels many times over those that occur normally. The notion that uncontrolled use of melatonin is completely safe rests on little research and on the common public experience of lack of significant short-term toxic effects. However, disruption of the delicate mechanism of the circadian system is, in and of itself, a significant potential side effect.

- Because individual rates of melatonin metabolism vary substantially, with older and smaller people disproportionately affected, adjustment of the dosage is essential to avoid decreased effects in the latter part of the night due to excessive use of "slow release" melatonin on the one hand or disturbance of circadian patterns by use of excessive amounts of "fast release" melatonin on the other.
- Over-the-counter melatonin supplements typically contain 3-5 mg, but studies show that even a relatively low dose of 0.3 mg per day may induce circadian levels of the hormone well in excess of the normal level in people over 50 years old. Thus, before deciding on a therapeutic dose to deal with insomnia, people should consult with a physician to determine the precise amount of supplementation needed. Absent testing, leading researchers (Mischoulon and Rosenbaum) recommend that people “work up” to a therapeutic level, beginning with 0.1 to 0.2 mg per day.

JET LAG

The sources differ in their prescription for jet lag, with Mischoulon and Rosenbaum’s prescription the best reasoned: If melatonin is administered to contract the effect of eastward-travel jet lag, a dose of 0.1 to 0.3 mg at the local bedtime following the flight is recommended. Such treatment will restore the deficit in melatonin that the traveler will experience due to the advance of bedtime at the destination. Following a westward flight, when the day is extended rather than shortened, it would be advisable not to take melatonin at the local bedtime, when the endogenous level of the hormone is already increased. However, it might be helpful to take a half dose (e.g., 0.1 mg) immediately following a night or early morning awakening, as is typically experienced in westward flights. In principle, this would facilitate resumption of sleep and its maintenance, plus delaying the circadian phase and adjusting to the new location.

CONCLUSION

- Jet lag and sleep problems associated with shift work are the most promising uses, but many other suggested uses remain to be studied.

- Melatonin does not have significant toxic effects, but it may interfere with sleep rhythms.
- Risks appear manageable so long as drug interactions are avoided, but caution is appropriate since melatonin is commonly over consumed, and, absent testing, people should “work up” to a therapeutic dose.

OUTLINE

1. Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone that is primarily produced by the pineal gland, located behind the third ventricle in the brain. In the synthesis of

melatonin, tryptophan is hydroxylated to 5-hydroxytryptophan (5-HTP), which in turn is decarboxylated to 5-hydroxytryptamine (serotonin). Serotonin is converted to the melatonin precursor and metabolite Nacetylserotonin by the enzyme N-acetyl transferase. N-acetylserotonin is methylated via the enzyme hydroxyindole-o-methyltransferase to produce melatonin. Approximately 90 percent of melatonin is cleared in a single passage through the liver. A small proportion of non-metabolized melatonin is also excreted in the urine. Commercially available melatonin may be isolated from the pineal glands of beef cattle or chemically synthesized. However, there is no standard preparation, making studies very difficult to compare.

2. **THE AGENCY FOR HEALTHCARE RESEARCH AND QUALITY (AHRQ, part of the U.S. Department of Health and Human Services) determined in 2004 that: "Evidence suggests that melatonin is not effective in treating most primary sleep disorders with short-term use, although there is some evidence to suggest that melatonin is effective in treating delayed sleep phase syndrome with short-term use. Evidence suggests that melatonin is not effective in treating most secondary sleep disorders with short-term use. No evidence suggests that melatonin is effective in alleviating the sleep disturbance aspect of jet lag and shift-work disorder. Evidence suggests that melatonin is safe with short-term use."** The AHRQ suggested that the apparent effectiveness of melatonin in alleviating jet lag may not involve alleviation of the sleep disturbance, but rather, alleviation of the daytime fatigue associated with jet lag.

3. **EFFICACY: JET LAG AND SLEEP DISORDERS: Dissenting from the AHRQ, all five sources that mention melatonin except the federal government (Brown *et al*., Mischoulon and Rosenbaum** (through Zhdanova, I.V. and Friedman, L.)**, the *Natural Standard*, *Berkeley Wellness*, the Mayo Clinic and Weil) find melatonin to be effective for jet lag and shift work adjustment, and all except the federal government and *Berkeley Wellness* recommend it for sleep latency (delay in falling asleep), at least in older people. Other uses of melatonin remain controversial, particularly in cognition maintenance and**

treatment of other forms of insomnia, but melatonin is a promising treatment for many mild to moderate sleep disorders:

- **Brown *et al*. state that: "Melatonin is … beneficial in mild to moderate sleep disorders. Unlike most hypnotics, it does not disturb sleep architecture and does not lead to habituation. Double-blind randomized placebo-controlled trials show that melatonin improves sleep, reduces sleep onset latency[1] and restores sleep efficiency[2] in patients with insomnia."[3]**
- **The evidence is "robust" concerning the use of melatonin to counteract jet lag or advance or to deal with shift pattern changes, which Mischoulon and Rosenbaum support.**
- Mischoulon and Rosenbaum counsel that supplementation be administered at the right circadian time, in low light situations, and in therapeutic dosages.
- **The *Natural Standard* rates only use of melatonin for jet lag as "A," "supported by strong scientific evidence," stating that despite inconsistent studies, "overall, the scientific evidence does suggest benefits of melatonin in up to 50% of people who take it for jet lag." Although the premise is unstated, this endorsement should be read to include shift work adjustment as well.**
- ***Berkeley Wellness* states that melatonin may be effective to help people whose sleep patterns are disrupted by shift work or jet lag.** Like Mischoulon and Rosenbaum, *Berkeley Wellness* advises talking to a physician first and assuring that the dosage and timing of melatonin use are appropriate.

4. **DELAYED PHASE SLEEP SYNDROME, INSOMNIA IN THE ELDERLY, SLEEP DISTURBANCES IN CHILDREN WITH NEURO-PSYCHIATRIC DISORDERS, AND SLEEP ENHANCEMENT IN HEALTHY PEOPLE**

    - **Delayed phase sleep syndrome, insomnia in the elderly, sleep disturbances in children with neuro-psychiatric disorders, and sleep enhancement in healthy people are all rated as "B," "good scientific evidence for this use," meaning that there are enough studies of sufficient reliability to make these "promising practices."**

- **Based on the *Natural Standard*, the 2011 edition of *Berkeley Wellness* also endorses use of melatonin for insomnia or to promote better sleep, but only for occasional short-term use.**
- **The Mayo Clinic goes further than most sources in stating flatly that "melatonin can promote sleep." But Mayo recommends using melatonin for occasional jet lag or difficulty in making any other sleep adjustment, not for insomnia, which is the critical area of controversy.**
- Weil is even more positive, speaking for himself, stating that: "I take [melatonin] most nights both for its effect on sleep and dreaming, and its useful influence on immunity."[4]

5. **SUGGESTED BUT UNPROVEN USES**--**NEUROPROTECTION**:
   - In addition to sleep disorders, Brown *et al.* assert that melatonin: "has numerous neuro-protective properties," has "anti-excitotoxic effects," "suppresses lipid peroxidation" and increases the effect of anti-oxidants.[5] Thus, they suggest that **"melatonin may possibly improve cognitive function to some extent in long-term use, with its strongest effects being preventative."[6]** They add that the relative melatonin deficit associated with Alzheimer's and Parkinson's diseases might indicate a preventative effect with supplementation. But the single study cited by Brown,[7] while showing Alzheimer's symptom improvement with melatonin supplementation, showed no mental status improvement compared to the placebo group.
   - Brown *et al*. comment that, "In elderly patients, including those with Alzheimer's and Parkinson's disease, melatonin in doses of 3 to 9 mg at bedtime can help to improve sleep, mood, memory, and sundowning**. It may slow progression of cognitive decline** in patients with early Alzheimer's disease. Melatonin may have a role in long term prevention of neuro-degeneration, particularly if it is started at the age of 40 or 45."[8]
   - *Berkeley Wellness* makes no mention of use of melatonin for any kind of cognitive function, stating that the evidence is conflicting or inconclusive.

6. **SUGGESTED BUT UNPROVEN USES**: **INSOMNIA:**

- Brown *et al*. reviewed 14 controlled trials and determined that melatonin is **effective in treating delayed sleep-phase disorder** (DSPD), also known as delayed sleep-phase syndrome (DSPS) or delayed sleep-phase type (DSPT), a circadian rhythm sleep disorder affecting the timing of sleep, the peak period of alertness, the core body temperature rhythm, hormonal and other daily rhythms.[9] According to Brown *et al*., melatonin is also useful in treating **insomnia in people with autism, epilepsy and developmental disabilities**.[10]
- **With regard to insomnia, Mayo states that research with older adults has shown a decline in sleep latency (time needed to get to sleep) if melatonin is taken at least a half hour before bedtime.** Mayo emphasizes that it is unknown whether melatonin can help them stay asleep, or whether its effects would carry over in younger people. In addition, Mayo cautions that the studies have been flawed and that little is known of long-term effects of melatonin. Comparison with other insomnia medications is also necessary.

7. **SUGGESTED BUT UNPROVEN USES**: **SCHIZOPHRENIA:** Brown *et al.* suggest that melatonin is helpful in dealing with the **side effects of treatment for schizophrenia, particularly tardive dyskinesia and weight gain**.[11] These studies are small in scale but suggestive, and worth considering until further research is done. Of course, complementary use of melatonin with psychotropic drugs should always be discussed with the prescribing physician due to the usual polypharmacy concerns. However, given the mildness of the side effects of melatonin, such complementary use should be considered if the side effects of psychotropic medication develop or are feared. **The *Natural Standard* concurs: "Preliminary reports suggest that melatonin may aid in reversing … tardive dyskinesia associated with [use of] haloperidol (Haldol).**"

8. **SUGGESTED BUT UNPROVEN USES**: **BENZODIAZEPINE WITHDRAWAL AND HIGH-ALTITUDE ADJUSTMENT: Brown *et al*. also recommend melatonin for benzodiazepine withdrawal and high-altitude adaptation.**[12] Brown *et al.* state that consumers who experience cognitive

or memory impairment or daytime drowsiness from benzodiazepine use may respond to melatonin with fewer adverse effects.

9. **SUGGESTED BUT UNPROVEN USES**: **SLEEP PATTERNS:** Mischoulon and Rosenbaum (through Zhdanova, I.V. and Friedman, L.) conclude, significantly, that changes in melatonin levels are not part of the genesis of age-related insomnia or psychiatric diseases. However, a number of clinical symptoms characteristic of these disorders, such as sleep alterations and anxiety, might benefit from timely melatonin treatment, given the strong "indirect signs of a close relationship between melatonin and sleep…**Collectively, the available data on the effects of melatonin on sleep suggest that a nocturnal surge in melatonin production may be an important factor in normal human sleep regulation, and that melatonin deficiency might contribute to an altered sleep pattern**."[13]

10. **SUGGESTED BUT UNPROVEN USES**: **CIRCADIAN SLEEP DISORDERS [CYCLICAL MELATONIN DEFICIENCY]** As in her 2001 study (cited by Brown *et al*.), Zhdanova (writing in Mischoulon and Rosenbaum) asserts fairly weakly that, "…**melatonin MIGHT provide a useful tool for improving sleep and mood in those people who suffer from psychiatric disease, circadian sleep disorders [cyclical melatonin deficiency], or insomnia of other origin**."[14]

11. **SUGGESTED BUT UNPROVEN USES**: **MAJOR DEPRESSION, SEASONAL AFFECTIVE DISORDER, AND DRUG WITHDRAWAL: Mischoulon and Rosenbaum suggest broadly that, "the observed effects of melatonin treatment on sleep and mood might be of substantial benefit to patients suffering from a variety of psychiatric disorders that are typically associated with insomnia and anxiety, including major depression, seasonal affective disorder, schizophrenia, or drug withdrawal syndrome."**

12. **INSOMNIA IN DEMENTIA, RAPID EYE MOVEMENT BEHAVIOR DISORDER, INSOMNIA IN PEOPLE WITH AUTISM AND "SUNDOWNING" /SLEEP PATTERN ADJUSTMENT** According to Brown *et al*., melatonin is particularly useful in treating, "delayed sleep phase syndrome,

insomnia in dementia, rapid eye movement behavior disorder, insomnia in [people with] autism, and jet lag."[15] Three studies have documented decreased "sundowning" (agitation at night) and improvements in mood, memory and sleep in persons with dementia taking melatonin, although the sample sizes have been very small and the studies have been short (under three months).[16]

13. **SUGGESTED BUT UNPROVEN USES**: **ADJUNCTIVE USE:** Many of these suggested uses would be adjunctive to the use of other psychotropic drugs, especially antidepressants. This would require careful monitoring of melatonin levels, since psychotropic drugs that affect norepinephrine or serotonin levels might alter the pattern of melatonin production. Although no dangerous interaction is known, adjunctive use of melatonin with psychotropics should be coordinated with the prescribing physician.

14. **THE *NATURAL STANDARD* DISSENTS: Other than jet lag, the uses of melatonin approved by Brown *et al.* and Mischoulon and Rosenbaum are categorized by the *Natural Standard* as "C," "unclear scientific evidence for this use," even though in most cases there are studies suggestive of effective use of melatonin for these conditions.** These include Alzheimer's disease (sleep disorders), attention deficit hyperactivity disorder, benzodiazepine tapering, bipolar disorder (sleep disturbances), circadian rhythm entraining (in blind persons), depression (sleep disorders), insomnia (of unknown origin in non-elderly persons), sedation, REM sleep behavior disorder, schizophrenia (sleep disorders),shift work adjustment, tardive dyskinesia(despite the comment quoted above), and seasonal affective disorder.

15. **DRUG INTERACTIONS**:

- Drug interactions with melatonin have not been sufficiently studied, and Mischoulon and Rosenbaum's discussion is essentially theoretical. However, they caution against the potential that psychotropic drugs that affect norepinephrine or serotonin levels might alter the pattern of melatonin production and that any drugs that might affect the

metabolism of melatonin in the liver, such as valproic acid or methoxypsoralen, could affect serum levels of melatonin.

- They further caution that melatonin is likely to modulate the effects of other substances, which requires careful consideration of appropriate dosages if any other drugs or herbs are being used, and may require that Mischoulon and Rosenbaum's lower melatonin dosages be increased.
- Likewise, generally, the *Natural Standard* cautions that melatonin may increase drowsiness caused by other drugs, such as zolpidem (Ambien), benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants (unspecified) and alcohol.
- The *Natural Standard* cautions generally that since melatonin is broken down (metabolized) by the liver enzymes, drugs that alter the activity of these enzymes may increase or decrease effects of melatonin supplements.
- "Based on preliminary evidence," the *Natural Standard* cautions that melatonin should be avoided in people taking the blood thinning medication warfarin (Coumadin) and possibly by people using other blood thinners (anticoagulants) such as aspirin or heparin if problems become apparent.
- Since melatonin may cause adverse changes in blood pressure and cholesterol levels, caution is advised to persons on blood pressure or cholesterol medication and persons with or at risk of cardiovascular disease. Abnormal heart rhythms have been reported.
- It is not clear if or how caffeine affects melatonin supplementation. Caffeine may raise melatonin levels, but its stimulative effects may also alter wake-sleep rhythms.
- Alcohol consumption seems to alter melatonin secretion at night.
- According to the *Natural Standard*: "Preliminary reports suggest that melatonin may aid in reversing … tardive dyskinesia associated with [use of] haloperidol… [and] may increase the effects of isoniazid against [tuberculosis]."
- On the other hand, melatonin may increase the adverse effects of methamphetamine on the nervous system.

- There is controversy concerning the effects of melatonin on inter-ocular pressure, and thus on persons taking medication for glaucoma. The *Natural Standard* urges monitoring by the physician prescribing the medication.
- *Berkeley Wellness* warns that aspirin, beta blockers, and tranquilizers can affect melatonin levels. Like benzodiazepines (such as diazepam (Valium) or triazolam (Halcion)), often described as sleeping pills, melatonin can produce a "hangover" and drowsiness the next day. Persons taking benzodiazepines should beware of the potential for an additive effect.

16. **SIDE EFFECTS**:

- **Melatonin is classified by the FDA as "generally regarded as safe" in recommended doses for short-term use. The AHRQ confirms that evidence suggests that melatonin is safe with short-term use.**
- **Mild gastrointestinal distress commonly occurs**, including nausea, vomiting or cramping. Melatonin has been linked to a case of autoimmune hepatitis and with triggering Crohn's disease symptoms.
- **Brown *et al*. list fatigue, dizziness, headache, and irritability as "infrequent and usually mild" side effects** of melatonin supplementation**.**
- *Berkeley Wellness* warns that "chronic" (long-term) use of melatonin supplements may suppress the body's own melatonin production and can interact with other hormones. Therefore, Berkeley says, pregnant women and children should never take melatonin.
- Brown *et al.* state that consumers who experience cognitive or memory impairment or daytime drowsiness from benzodiazepines may respond to melatonin with fewer adverse effects.
- "Fortunately," Weil adds, "**one does not develop tolerance to melatonin as with other sleep aids, and it rarely has negative side effects**."[17]
- Commonly reported side effects include mild fatigue, dizziness, headache, irritability, and sleepiness, although the *Natural Standard* acknowledges that these may be caused more by the jet lag than by the melatonin. Fatigue can be more pronounced with

morning use or high doses, and irregular wake-sleep cycles, disorientation, vision, sleepwalking, vivid dreams, and nightmares are all possible side effects. Difficulties with walking and balance may occur following overdose.

- Case reports raise concerns about risks of blood clotting abnormalities, increased risk of seizure, and disorientation with overdose.
- *Berkeley Wellness* warns that "chronic" (long-term) use of melatonin supplements may suppress the body's own melatonin production and can interact with other hormones. Therefore, pregnant women and children should never take melatonin. *Berkeley* also lists high blood sugar, breast swelling in men, decreased sperm count, gastrointestinal irritation, sleepwalking, the morning hangover effect (drowsiness in the morning) and dizziness as potential side effects. For some people, melatonin may cause dozing off but not staying asleep.
- There is **controversy about the effect of melatonin on seizure disorders**. In the absence of better science, consultation with the health care professional providing care for the seizure disorder is essential while using melatonin.
- **Mood changes have been reported, both highs and lows (depression), and even psychotic symptoms such as hallucinations and paranoia. Persons with severe depression or psychotic disorders should consult with the health care professional providing care for the underlying disorder before using melatonin.**
- Since melatonin may cause adverse changes in blood pressure and cholesterol levels, caution is advised to persons with or at risk of cardiovascular disease. Abnormal heart rhythms have been reported.
- Melatonin may increase blood sugar levels for people with type 1 diabetes and may lower them in type 2 diabetes. Anyone with diabetes should monitor blood sugar levels while using melatonin.
- **Hormonal effects are to be expected with the use of an estrogen-like hormone.** These effects include decreases or increases in levels of luteinizing hormone, progesterone, estradiol, thyroid hormone, growth hormone, prolactin, cortisol, oxytocin, and

vasopressin. Increased breast size and decreased sperm count and motility have been reported in men.

- Given the lack of experimental data concerning melatonin supplementation in children, Mischoulon and Rosenbaum caution that melatonin treatment in children should be used only “very conservatively," when the benefits of melatonin treatment clearly outweigh any possible risks. There are no data concerning use during pregnancy or breastfeeding.
- **The safety of high-dose or long-term melatonin use have not been evaluated.** Doses above 50 mg per day may have long-term effects on testosterone or prolactin levels. Thus, patients on long-term daily melatonin should be monitored for possible adverse effects.
- Mischoulon and Rosenbaum caution that **millions of Americans currently consume melatonin in quantities that elevate their hormone levels “manyfold” over those that occur normally. The notion that uncontrolled use of melatonin is completely safe rests on little research and on the common public experience of lack of significant short-term toxic effects. Long-term clinical and experimental studies are needed to address this important question, since disruption of the "delicate mechanism" of the circadian system is, in and of itself, a significant potential side effect.**

17. **CIRCADIAN PATTERNS AND DOSAGE:** Over-the-counter melatonin supplements typically contain 3-5 mg, but Mischoulon and Rosenbaum caution that even a relatively low dose of 0.3 mg per day may induce circadian levels of the hormone in people over 50 years old well in excess of the normal level. Other potential effects of large doses of melatonin include lowering of body temperature, reflecting changes in either energy metabolism or temperature regulation, and unwanted modifications in human reproductive function. Finally, Mischoulon and Rosenbaum caution that it is important to avoid bright light exposure during melatonin treatment, since even regular room light can rapidly suppress melatonin production. In addition, exposure to bright light could produce an adverse effect, since melatonin has been reported to increase photoreceptor susceptibility.

18. **DOSAGE:**

- Melatonin is available in both fast-release and sustained-release forms. Brown *et al.* recommend **dosages between** 2-6 total mg per day (50% fast-acting and 50% slow acting) at bedtime, **up to 9 mg per day maximum**, which they state usually induces drowsiness. They caution against doses of over 50 mg per day. For jet lag, they recommend 5-10 mg of fast-release melatonin just prior to departure.
- The *Natural Standard* notes dosages of **0.5 to 50 mg per day – a wide range --** in the studies, without any recommendation, or up to 20 mg per day by intramuscular injection.
- Weil recommends **2.5 mg per day**, using sublingual tablets.
- **Fugh-Berman warns that these are high doses, stating that as little as 0.1-0.3 mg may work for sleep**. Mischoulon and Rosenbaum agree. See below.
- Mischoulon and Rosenbaum recommend using preparations that use solid dilutants such as lactose or micro cellulose in addition to preparations that use only oil, which is absorbed faster but does not stay on the blood as long, since such **"fast-release" melatonin preparations may not sustain adequate serum levels throughout the night. Thus, as recommended by Brown *et al*., a combined dosage may be best**, but Mischoulon and Rosenbaum caution that individual rates of melatonin metabolism very substantially, that older and smaller people are disproportionately affected, and that **adjustment of the dosage is essential** to avoid decreased effects in the latter part of the night due to excessive use of "slow release" melatonin on the one hand or disturbance of circadian patterns by use of excessive amounts of "fast release" melatonin on the other.
- Since human bodies cannot get meaningful amounts of melatonin from food, but manufacture it within the body, Mischoulon and Rosenbaum postulate that the aim should be to mimic normal melatonin levels**. This is best done by measuring melatonin levels in the blood, saliva, or urine in order and supplementing according to the precise amount of the deficiency found**. **Mischoulon and Rosenbaum caution that**

even a relatively low dose of 0.3 mg per day may induce circadian levels of the hormone in people over 50 years old well in excess of the normal level. Thus, before deciding on a therapeutic dose to deal with insomnia, people should consult with a physician to determine the precise amount of supplementation needed. Absent testing, people should "work up" to a therapeutic level, beginning with 0.1 to 0.2 mg. Note that these recommended dosages follow Fugh-Berman's recommendation and are less than those recommended by Brown *et al* and Weil.

- Mischoulon and Rosenbaum advise that **if melatonin is taken to improve nighttime sleep, it should be taken about 30 minutes before bedtime** to minimize the possibility of an undesired circadian phase shift.
- **If melatonin is administered to contract the effect of eastward-travel jet lag,** Mischoulon and Rosenbaum recommend **a dose of 0.1 to 0.3 mg at the local bedtime following the flight.** Such treatment will restore the deficit in melatonin that the traveler will experience due to the advance of bedtime at the destination. Following a westward flight, when the day is extended rather than shortened, it would be advisable not to take melatonin at the local bedtime, when the endogenous level of the hormone is already increased. However, it might be helpful to take a half dose (e.g., 0.1 mg) immediately following a night or early morning awakening, as is typically experienced in westward flights. In principle, this would facilitate resumption of sleep and its maintenance, plus delaying the circadian phase and adjusting to the new location.
- **The *Natural Standard* differs from Mischoulon and Rosenbaum in recommending that the melatonin be initiated before travel (at the destination bedtime) rather than on arrival and recommending that supplementation continue for "several days."** Quick-release is recommended as "more effective" than slow-release melatonin, but without the elaboration given by Brown *et al.* and Mischoulon and Rosenbaum.
- **For jet lag, the Mayo Clinic recommends use of melatonin on the day of travel, and continuing for several days.** No timing or dosage is specified.

19. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with melatonin and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects. Sleep laboratory studies are essential to understanding melatonin's effect on quality of sleep.

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[3] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009), at 117.

[4] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 97

[5] Mischoulon & Rosenbaum*, op. cit.* at 186.

[6] *Id.*

[7] Asayama, K., Yamadera, H., Ito, T., Suzuki, H., Kudo, Y., & Endo, S., "Double Blind Study of Melatonin Effects on Sleep-wake Rhythm , Cognitive and Non-cognitive Functions in Alzheimer Type Dementia" *Journal of the Nippon Medical School* 70(4):334-341 (2003).

[8] Mischoulon & Rosenbaum, *op. cit*. at 186.

[9] Brown *et al*., *op cit*. at 118.

[10] *Id*. at 119.

[11] *Id*. at 272-273

[12] *Id.* at 121.

[13] Mischoulon & Rosenbaum, *op. cit.* at 145.

[14] Zhdanova, I. V. & Friedman, L., "Therapeutic Potential of Melatonin in Sleep and Circadian Disorders," in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008), at 150.

[15] Brown *et al*., *op cit*. at 117.

[16] *Id.*

[17] Weil, *op. cit*. at 97.

OMEGA-3 ESSENTIAL FATTY ACIDS FOR MOOD STABILIZATION AND DEPRESSION AND TO ENHANCE THE EFFECTIVENESS OF CONVENTIONAL ANTI-DEPRESSANTS AND AS A POSSIBLE NEUROPROTECTANT

SUMMARY

Omega-3 essential fatty acids ("omega-3s")—most commonly associated with fish and fish oil—have been widely studied for their benefits for heart health.

WHAT WE KNOW

- Experts agree: Include omega-3s in your heart-healthy diet. http://examine.com/supplements/Fish+Oil/#summary1-0
- And it may help your mind as well.
- The risk is minimal.

MENTAL HEALTH IMPLICATIONS

Depression

The prevalence of depression in a society is inversely related to that society's consumption of fish: the more that people eat fish, the healthier the population, both physically and mentally. But studies are split when it comes to proving a link between an individual's consumption of omega-3s and lowered depression. All of the eight sources that discuss omega-3s acknowledge that there is promising evidence for omega-3s in the treatment of depression. Five of those studies recommend omega-3 supplementation for depression. Three studies do not recommend it, saying that the evidence is not conclusive enough.

Bipolar Disorder and Adjunctive Use

The same five sources state that omega-3s may have a mood stabilizing effect and help with short-term symptoms of bipolar disorder, and may be used as an adjunct to psychotropic medications, particularly antidepressants.

Other Mental Health Conditions

Experts are researching potential effects of omega-3s on:

- cognitive impairment/dementia,
- perinatal and postpartum depression,
- schizophrenia,
- borderline personality disorder,
- attention deficit hyperactivity disorder (ADHD),
- seasonal affective disorder,
- violent and impulsive behavior,
- dyslexia,
- self-harm, and
- childhood mood disorders.

The evidence is slim, but these are additional reasons to consider a heart-healthy diet rich in omega-3s.

SIDE EFFECTS & DRUG INTERACTIONS

Side Effects

- May affect blood sugar levels (if concerned, check with your doctor)
- May worsen low-density lipoprotein (LDL) aka “bad” cholesterol
- May trigger fish allergy
- May elevate levels of Vitamins A and D (in commercial supplements only)
- May cause hypervitamonosis A in rare cases when fish liver oil is used in high doses.

Side effects and drug interactions are the same as eating fish, and appear minimal. The most

likely effect is indigestion, best addressed by taking omega-3s (or fish) with other food and, when taking supplements, taking smaller doses at different times of day rather than taking it all at once. Given the side effects and the likely benefits, the use of omega-3s in pregnancy and breastfeeding and in young children seems reasonable.

Drug Interactions/Contaminants

- Anticoagulants, like aspirin, warfarin, or heparin may interact to increase the risk of bleeding, though clinical evidence does not confirm this.
- Blood pressure medication may need to be adjusted.
- Contaminants may include mercury, PCBs, and dioxins in predatory fish (predatory fish include tuna, salmon, perch, pike, and swordfish).

Vegetarians, Vegans, and Plant Sources

Vegetarian and vegan diets are almost always very low in omega-3s, since fish oil is the most efficient way to obtain omega-3s. Some plant-based supplements are available, but they generally are low in the essential omega-3 elements, EPA and DHA. This requires taking a lot of capsules to get a therapeutic dose.

CONCLUSION

Promising, but not yet proven. A diet rich in small, non-predatory fish — typically about 2 meals a week — is good for almost everyone. Use of a diet rich in non-predatory fish or fish oil may prevent or moderate both depression or bipolar disorder and may be effective in stabilizing mood and enhancing the effectiveness of conventional anti-depressants. Although the evidence is preliminary, omega-3s may also serve as a neuroprotectant. Other uses being studied may encourage use of omega-3s pending development of evidence to the contrary.

FISH IS BEST

Fish oil and other supplements supply omega-3s. But fish also contains vitamins, minerals, other fats, and other substances that may work with the omega-3s to protect the heart and

overall health. Moreover, fish (but not fried fish), which is rich in protein and low in saturated fat, can replace less-healthful foods such as red meat. The benefits of fish far outweigh the potential risks from contaminants, especially if you eat it in moderation (two servings a week, about 8 to 12 ounces total, is the base recommendation) and vary the types of fish. Small, shorter-lived fish lower in the food chain, such as sardines and mackerel, accumulate less toxins.

- The EPA and DHA content of fish depends on the species. A good listing is found at http://fn.cfs.purdue.edu/fish4health/HealthBenefits/omega3.pdf
- Lake Trout is the highest concentration, at 3% EPA and DHA. Atlantic salmon is almost 2%, but most fish are under 1%, meaning 100 grams of fish for each gram of omega-3s. At that rate, a therapeutic dose of 9.6 grams would take a lot of fish: up to two pounds a day. So if you are taking omega-3s as medicine, supplementation is essential.

OUTLINE

1. From the beginning of human evolution up until about 1920, the human diet consisted of between a 1:1 and a 2:1 ratio of omega-6 to omega-3 essential fatty acids.[1] The modern (American) diet has shifted this balance to between 10:1 and 30:1, as omega-3 essential fatty acids have declined due to (1) the prevalent use of omega-6 seed oils (especially corn) instead of omega-3-rich plants to feed the animals and farmed fish that make up our animal protein, (2) decline of fish consumption and general lack of flax seed oil, canola oil, walnuts, and leafy green vegetables in our diet, (3) hydrogenization of oils for use in processed foods, thus increasing *trans*-fatty acid intake which interferes with fatty acid synthesis (4) loss of cereal germ by modern milling processes, and (5) increase in sugar intake which interferes with the enzymes of fatty acid synthesis.[2]

2. Hibbeln has shown that depression is inversely correlated with fish consumption. Japan has the lowest levels of depression (0.12% of population), Iceland the lowest levels of bipolar depression, and Hong Kong the lowest homicide levels. These countries also have the fish oil consumption with about 730 to 1000 mg per day of EPA and DHA, compared to the US, where consumption of EPA and DHE on average is about 180 mg per day.[3]

3. Stoll presents studies of the blood and tissue characteristics of people with major depression.[4] These studies are striking, showing the correlation of EPA depletion with clinical symptoms of depression, using the usual clinical scales.

4. **EFFICACY**: Although larger and longer-term studies of depression are needed, as are studies targeting the effect of omega-3 essential fatty acid supplementation on other mental health conditions, and the sources consulted for this outline are split, it appears likely that **omega-3s will eventually be found effective as CAM treatments for bipolar disorder and depression and to enhance the effectiveness of conventional anti-depressants.** Of eight sources that discuss omega-3s, three sources do not recommend omega-3 supplementation

for depression or bipolar disorder, but five do, and all eight acknowledge that there is promising evidence for its use in the treatment of depression and bipolar disorder.

5. **MOOD STABILIZATION IN BIPOLAR DISORDER:**

- Bipolar disorder (manic-depressive illness) is a common neuropsychiatric illness with a high morbidity and mortality. Despite the use of mood-stabilizing drugs, including lithium and valproate, there are high rates of recurrence. All of the currently available mood-stabilizing drugs appear to affect neuronal signal transduction (or second messenger) mechanisms. Biochemical studies have shown that dietary treatment with omega-3 essential fatty acids leads to the incorporation of these compounds into the membranes crucial for cell signaling. This mechanism may be similar to some of the actions of lithium and valproate.

- **Fugh-Berman and Cott relied on Stoll's pioneering bipolar study to indicate the potential of omega-3s as psychotropic agents for mood stabilization**: A double-blind study by Stoll, A. *et al*. (1999)[5] demonstrated that dietary supplementation with omega-3 essential fatty acids resulted in marked mood-stabilizing activity for persons with bipolar disorder. Significant group differences in favor of fish oil were seen on the Hamilton Depression Scale, the Global Assessment Scale and the Clinical Global Impression Scale. The authors concluded that omega-3 essential fatty acids were well tolerated and improved the short-term course of the illness.
- **In Brown et al**. II, Mischoulon and Freeman surveyed the conflicting studies, plus the meta-analysis by Sarris *et al*. (2012), concluding that people with rapid cycles may benefit less from omega-3 supplementation and that most of the benefit is probably in the depressive rather than in the manic phase of the illness.[6]

6. **DEPRESSION**

- It has been theorized that omega-3 essential fatty acids may reduce the development of depression, since depressive patients show significant depletion of omega-3s. There appears to be an inverse relationship between the prevalence of major depression and

the amount of fish consumed per capita worldwide.[7] There are at least four studies showing reduced levels of omega-3 essential fatty acids in the blood of depressed people[8]. Uncontrolled clinical trials of omega-3 essential fatty acid supplements have shown promise in the treatment of major depression, and several controlled trials are underway.

- **Brown *et al.* recommend omega-3 essential fatty acids for depression** based on the preliminary studies summarized by Parker *et al* in a 2006 review.[9] According to Brown *et al*., "the mixed results [of the studies cited by Parker *et al*.] reflect differences in the dose and proportions of EPA and DHA, patient selection, and other [unspecified] factors."[10] The 2006 review included Mischoulon as a coauthor. Brown *et al*. II included Mischoulon as the lead author on omega 3s. See below.
- Mischoulon and Rosenbaum's perspective on omega-3 fatty acids is provided by Andrew L. Stoll, M.D., Director, Psychopharmacology Research Laboratory, McLean Hospital Faculty, Harvard Medical School. Writing one year before his book was published, Stoll updates his single 1999 bipolar study with three more double-blind, placebo controlled studies of bipolar disorder and seven of unipolar depression. As of 2007, the score stood at two positive studies and two no benefit studies of the use of omega-3s in bipolar disorder and four positive studies and three no benefit studies of the use of omega-3s in unipolar depression.[11] Stoll concludes that the problem with the studies is that the optimal omega-3 fatty acid formulation for mood disorders needs to be determined.[12]
- Stoll critiques the studies, including his own 2007 study which showed no benefit in depression. In that case, the formula of omega-3s that was used was DHA 2.2 g. per day and EPA 0.6 g. per day, the reverse of the ratios recommended by Stoll and Brown *et al*., and less than 1/3 of the dose used by Stoll himself in his 1999 bipolar study. But many other methodological issues are debatable, including, in particular, the lack of an active placebo, since most of the consumers were taking antidepressants (both tricyclics and SSRIs) throughout the studies. Interestingly, one of the no benefit studies involved consumers who had gone off their anti-depressants at least two weeks before the study began. In addition, the same study used a dose of 2 g. per day of DHA, with no EPA at

all. Both of these factors may have contributed to the no benefit result.[13] **As analyzed by Stoll, the studies as a whole suggest that a high EPA to DHA formula of omega-3 essential fatty acids is potentially beneficial as an adjunctive therapy, when used with other medications.** No studies have yet tested the effect of an appropriate dose of omega-3s without other medication in bipolar illness.

- In his comprehensive book, ***The Omega-3 Connection,***[14] Stoll asserted: "We are learning that restoring the body's natural balance of omega-3 oils **may improve a multitude of medical disorders, including** coronary artery disease, **major depression, and bipolar disorder.**" Stoll added that: Furthermore, it is possible that omega-3 fatty acids **may actually prevent these disorders from developing as well.**[15]
- Weil puts omega-3s at the top of his recommended supplement list, finding the literature on omega-3s "**the strongest evidence we have for non-drug treatment of depression."**[16] Weil recommends two – four g per day of omega-3s as the basic building block of his "Program for Optimal Emotional Well-being."[17]
- **Lake and Spiegel confirm the efficacy of omega-3s in the treatment of depressed mood and bipolar disorder.**[18] However, they caution against use of omega-3s as monotherapy for depression unless antidepressants have proven ineffective or are poorly tolerated.
- The National Center for Complementary and Alternative Medicine has sponsored studies investigating the effects of omega-3 fatty acids/fish oil on major depression in adults, adolescent depression, and depression in people with multiple sclerosis. It concludes that more research is needed to determine whether omega-3 fatty acids help symptoms of depression.[19]
- However, NCCAM cites with approval the 2010 meta-analysis of Appleton et al. that concluded that: "the evidence provides some support of a benefit of n-3 PUFAs in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness."[20]

7. ADJUNCTIVE USE FOR DEPRESSION

- The interaction of omega-3 essential fatty acids and many other medicines, particularly psychotropic medicines, remains to be studied.
- As analyzed by Stoll, the studies as a whole suggest that a **high EPA to DHA formula** (Brown *et al* suggest 2:1, but the usual fish oil concentration is 3:2, and more study is needed to make a recommendation) of omega-3 essential fatty acids is **potentially beneficial as an adjunctive therapy, with very few side effects, when used with psychotropic medications.** However, a recent trial found no benefit, and the studies are split. Also, many potential adjunctive medicines remain to be tested. Thus, caution is advised in considering adjunctive use of omega 3s, even though no interaction has yet been shown. This requires consultation with the prescribing physician.
- Writing in Brown *et al.* II, Mischoulon, D. and Freeman, M.P. recommend a ratio of 3:2 or greater.[21]
- In one well-designed 2009 study, published in JAMA, treatment of patients with coronary heart disease and major depression with sertraline (Zoloft) and omega-3 fatty acids did not result in superior depression outcomes at 10 weeks, compared with sertraline and placebo.[22] As stated by the researchers, this study has no bearing on persons without coronary heart disease, and whether higher doses of omega-3 or sertraline, a different ratio of EPA to DHA, longer treatment, or omega-3 monotherapy can improve depression in patients with coronary heart disease remains to be determined. It may be that omega-3s are less additive to SSRIs than to tricyclic antidepressants, or the EPA/DHA formula may require adjustment, although it seems to have followed the Stoll/Brown *et al*. ratio.
- A 2010 study by Canadian researchers came to the opposite conclusion.[23] In the Canadian study, the results were inconclusive until persons with anxiety were screened out. The new figures showed that supplementation with EPA and DHA significantly reduced the number of major depressive episodes reported by patients with major depression without a comorbid anxiety disorder. One is left to wonder whether such screening would affect other studies as well.

- Given the reasonable known drug interactions and side effects, there is no question that **use of omega-3s as adjunctive treatment under physician supervision is justified by the available evidence**, except for persons using sertraline, who should consult their prescribing physician about the impact of the 2009 study on that decision. Although no adverse drug interactions were noted in the 2009 study, the benefit of such adjunctive treatment may also be small.

8. **DISSENT**

- **The *Natural Standard*, *Berkeley Wellness Reports* and *Consumer Reports* all dissent**. Thus, **three of the ten sources consulted,** while acknowledging "promising" evidence for the efficacy of omega-3 essential fatty acids in depression and bipolar disorder**, did not recommend use of omega-3s for any mental health condition.**
- The ***Natural Standard*** acknowledges "promising" evidence for the efficacy of omega-3 essential fatty acids in depression, bipolar disorder and schizophrenia, but rates all three as "C," "**unclear scientific evidence for this use**." The *Natural Standard* particularly acknowledges the "positive" results of recent studies in postpartum depression and childhood depression, but continues to call for more studies before endorsing its use to address mood disorders. The *Natural Standard* rates omega-3s as "A" ("strong scientific evidence") for secondary cardiovascular disease prevention and "B" ("good scientific evidence") for primary cardiovascular disease prevention and for use in rheumatoid arthritis.[24]
- While touting the effectiveness of omega-3 essential fatty acids in the prevention and treatment of heart disease, the treatment of high triglycerides, and the treatment of inflammatory effects of autoimmune disorders such as psoriasis and psoriatic and rheumatoid arthritis, Berkeley Wellness avoids taking a position on the effectiveness of omega-3s in depression and other mood disorders, stating only: "A 2007 review by the American Psychiatric Association suggested that people who have mood or depressive disorders consume at least 1 g of EPA/DHA per day from fatty fish or supplements. However, a study in the *Journal of the American Medical Association* in October 2009

[cited above under Adjuctive Use] found that omega-3 supplements (2 g a day) worked no better than a placebo in treating depression in people with heart disease. In early 2010 a research review in the *American Journal of Clinical Nutrition* concluded that there is some evidence of a beneficial effect, but only in people with clinically diagnosed depression."[25]

- Consumer Reports lists fish oil as one of eleven "supplements to consider," but only describes it as "effective" for triglyceride reduction and as "likely effective" for prevention of heart disease and stroke. None of the potential effects of omega-3s on mood disorders is mentioned.

9. **CONCLUSIONS**: Given the undoubted need for a diet rich in fish or supplemented by other sources of omega-3s in order to maintain a healthy heart and circulatory system, the promising studies of depression and bipolar disorder cited in this outline, the strong endorsements by four sources, and the minimal drug interactions and side effects, consumers may reasonably conclude from the current evidence that **omega-3s are worth a try to help in coping with mental health conditions despite lack of compelling evidence of effectiveness. Omega-3s are promising prevention and treatment strategies for depression and bipolar disorder. See below for the areas of possible efficacy in addition to depression and bipolar disorder.**

10. **SUGGESTED BUT UNPROVEN USES: PERINATAL AND POSTPARTUM DEPRESSION:**
    - Depletion of maternal omega-3 essential fatty acids has been noted during pregnancy. The physiology of pregnancy involves the mobilization of essential fatty acids from maternal stores to the fetus and especially the developing brain and nervous system. Supplementation with omega-3 essential fatty acids may ensure adequate supplies for the needs of the mother and the developing fetus and should be as common as folic acid supplementation--now an almost universal health precaution to prevent birth defects (e.g. Spina bifida). Stoll is an outspoken champion of such supplementation. Without dietary supplementation, levels of omega-3 essential fatty acids may remain low for some time postpartum, particularly in lactating women since considerable

amounts of omega-3s are found in breast milk. Thus, it is possible that maternal omega-3 essential fatty acids depletion may contribute to postpartum depression. Joseph Hibbeln followed this same logic from depletion to supplementation with major depression.[26]

- In Brown *et al.* II, Mischoulon and Freeman describe Freeman et al.'s own study that showed 50% improvement in postpartum depression from omega-3 supplementation, regardless of the dose. However, two open label studies have shown no preventative effect.[27] Mischoulon and Freeman counsel use of omega-3s in pregnancy and during lactation to minimize the risk of other medications.

11. **SUGGESTED BUT UNPROVEN USES: BREAST MILK AND INFANT FORMULA:**
    - Breast milk, unlike infant formula, has relatively high concentrations of omega-3 and omega-6 essential fatty acids. The World Health Organization recommends that essential fatty acids be added to infant formulas. European infant formulas are routinely fortified, and the FDA has only recently allowed the addition of fatty acids to infant formulas sold in the United States. It goes without saying that lactating mothers should also consider taking omega-3 essential fatty acid supplements as long as they are breast-feeding. Omega-3 essential fatty acids are crucial in the development of the fetal and neonatal brain and nervous system. One study showed that intellectual development may also suffer in infants deprived of these fatty acids.[28]
    - The *Natural Standard* dissents, stating that it is unknown whether use of omega 3s by pregnant and breastfeeding mothers is beneficial to infants, nor are there any safety data, particularly on large doses. Although it is used in infant formulas, there are no data supporting that use either.

12. **SUGGESTED BUT UNPROVEN USES: SCHIZOPHRENIA:** There is increasing evidence that neuronal injury due to oxidative stress (excess oxygen radicals) contributes to the pathophysiology of schizophrenia. Considerable effort has been directed towards determining the respective roles of increased oxidative stress (resulting in increased fatty

acid breakdown) versus dietary deficiencies or defective metabolic pathways on membrane fatty acid concentration.[29] It is likely that both processes are important for the development of a pathological state. In an uncontrolled study, dietary supplementation with concentrated fish oil led to significant improvement in negative (alogia, flat affect, anhedonia, apathy, motor retardation) but not positive symptoms (hallucinations, disorganized thought) as rated by the Positive and Negative Syndrome Scale. Improvement in clinical symptoms was related to increased levels of omega-3 essential fatty acids in the blood.[30] Thus, it is conceivable that dietary supplementation with antioxidants and omega-3 essential fatty acids at the initial stages of illness may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia. Dr. Stoll is strongly supportive of this hypothesis. Lake cites the studies, which are split, partially because the improvement in positive and negative symptoms has been shown mostly in people NOT taking antipsychotics.[31] Adjunctive use studies have been inconsistent. Hibbeln and Mischoulon have suggested that omega-3 fatty acids are less effective in schizophrenia and dementia than in depression and bipolar disorder.32 In Brown *et al* II, Mischoulon and Freemen cite the newer studies, which concur.[33]

13. **SUGGESTED BUT UNPROVEN USES: BORDERLINE PERSONALITY DISORDER**: As to borderline personality disorder, a use supported by Brown *et al*., the evidence is week, but a 12-week randomized, placebo-controlled clinical trial (albeit using only a passive placebo) of persons with a history of self-injury found that those given omega-3 essential fatty acids had significantly greater improvements on both the Beck Depression Inventory and the Hamilton Rating Scale, as well as on scales measuring suicidality and stress.[34]

14. **SUGGESTED BUT UNPROVEN USES: COGNITIVE IMPAIRMENT/DEMENTIA**: No adequate study has been done of long-term use of omega-3s for prevention/treatment of cognitive impairment or dementia. But the evidence cited by Brown *et al*. [35] is suggestive: Low levels of omega-3 essential fatty acids have been found in persons with dementia and Alzheimer's

disease. In an eight year prospective study of 1200 elderly subjects, those with low serum DHA had a 67% greater chance of developing Alzheimer's disease than those with high DHA. In a double-blind randomized placebo-controlled study of 174 very mildly impaired Alzheimer's disease patients, 600 mg of EPA per day slowed cognitive decline over a six-month period. The 2012 Oregon Brain Study results confirmed the coincidence of higher omega-3 levels and higher cognitive function.[36] Brown *et al*. concede that more studies are needed to confirm or refute the potential neural protective effects of omega-3s suggested by these studies. Berkeley Wellness adds that research suggests that omega-3's may "help preserve cognitive function in older people." [37]

15. **SUGGESTED BUT UNPROVEN USES: ADHD**

- Brown, Gerbarg, Mischoulon, Freeman, Weil and Stoll all consider omega-3s to be potentially beneficial for **attention deficit hyperactivity disorder (ADHD).** A 2011 review and meta-analysis of ten studies by Bloch *et al*, cited in Brown *et al*. II, showed a "modest but significant benefit in reducing ADHD symptoms from formulas rich in EPA.[38]
- In his book, *ADHD Without Drugs,*[39] Sanford Newmark, M.D., an integrative pediatrician and colleague of Weil's, summarizes the evidence. Newmark concludes that: "In my opinion, every single child who has ADHD would benefit from taking, or needs to have at least tried, a daily omega-3 fatty acid supplement."[40] He starts with the proposition that children with ADHD have lower omega-3 levels in their bodies as a result of an unknown metabolic process related to their condition. [41] Then, disregarding the studies in which the children took stimulants in addition to omega-3s, he demonstrates the improvement in symptoms when children with ADHD are given omega-3 supplements as monotherapy. In one study, in which 40 children were given either a fish oil supplement or olive oil placebo every day for three months, the children taking the fish oil improved significantly in their ADHD symptoms as well as in measures of learning ability. In fact, on almost every measure, including attention, hyperactivity, and cognition, the children taking fish oil showed substantial improvement, whereas those taking placebo had minimal or no improvement.[42] In another study, this same group of

researchers looked at improvements in reading, with subjects taking omega-3's showing a 9.5 month increase in reading skills over the three months of the study, compared to 3.3 month increase in reading skills for the placebo group.[43]

- In *Non-Drug Treatments for ADHD*, Brown, R.P. and Gerbarg, P.L.[44] encourage trials of EPA/DHA particularly in subtypes of ADHD that have shown better responses: hyperactive, inattentive, or mixed.[45]
- A recent meta-analysis of 10 reliable studies by Bloch and Qawasmi[46] found no significant difference in the efficacy of omega-3 treatment for ADHD based on whether the supplementation was given as monotherapy or as adjunctive treatment with traditional ADHD drugs. Finding that the studies are split, and that the ratio of EPA to DHA in the zone is a critical uncontrolled variable (generally, Bloch and Qawasmi found, the higher the EPA dose, the greater the effect), the meta-analysis recommended against monotherapy if the ADHD symptoms are severe, opting for adjunctive treatment as "**a reasonable treatment strategy as augmentation to traditional pharmacotherapy or for those families reticent to use [stimulants].**"[47] They emphasized that the efficacy of omega 3s appears to be "modest" compared to other available drug treatments for ADHD.

16. **SUGGESTED BUT UNPROVEN USES: OTHER CONDITIONS: Weil adds seasonal affective disorder.[48] Lake and Spiegel add violent and impulsive behavior and dyslexia**.[49] **Writing in Brown et al. II, Mischoulon and Freeman add self-harm and childhood mood disorders.** Of great interest in light of the ongoing controversy over EPA to DHA ratios, a military suicide study reported by Mischoulon and Freeman showed that higher serum DHA appeared to have a greater protective effect.[50] These indications are all encouraging but preliminary.

17. **DRUG INTERACTIONS**

- The *Natural Standard* points out the theoretical potential of interaction with aspirin, anticoagulants such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and nonsteroidal anti-inflammatory drugs such as ibuprofen

(Motrin, Advil) or naproxen (Naprosyn, Aleve), all of which could exacerbate bleeding. In addition, omega-3 essential fatty acids may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding such as ginkgo, garlic and salt palmetto. Writing in Brown *et al*. II, Mischoulon and Freeman counsel that special care should be taken by people taking medications that affect platelet function. However, Fugh-Berman and Gerbarg state categorically that fish and fish oil do not increase bleeding risk.

- Berkeley Wellness minimizes concerns about bleeding: "Contrary to previous thinking, fish oil does not cause excessive bleeding, even when combined with blood-thinning drugs. An interaction with anti-clotting medication (such as warfarin) is theoretically possible, but recent research has found no evidence of significant risk, even at high doses.... Similarly, [one] need not worry about interactions with aspirin, which also has an anti-clotting effect. Indeed the American Heart Association advises low-dose aspirin and omega-3s for people with heart disease." Low-dose aspirin used for the prevention of myocardial infarction appears safe in combination with omega-3s.
- Stoll comments that "only rare and sporadic cases of abnormal bleeding have been reported" in the use of omega-3s. Specifically, he states that: "No cases of bleeding have been reported in the greater than 17,000 subjects that have participated in omega-3 clinical trials."[51]
- The *Natural Standard* cautions that omega-3's may lower blood pressure and add to the effect of blood pressure medications, commenting that multiple clinical trials have reported "small" reductions in blood pressure (two to five mm. of mercury), with the effect proportional to the dosage. Thus, caution is warranted if the consumer has low blood pressure or is taking blood-pressure-lowering medications. The *Natural Standard* concludes that the risk of blood pressure changes at lower dosages is low. Still, people contemplating surgery or dental procedures should discuss significant omega-3 supplementation with their surgeon or dentist and consider tapering off for the procedure.

- Omega 3s may lower blood sugar levels “a small amount,” and may lower triglyceride levels but actually worsen low-density lipoprotein (LDL) (“bad”) cholesterol levels. LDL increases in the range of five to ten percent have been observed with the intake of omega-3 essential fatty acids. However, the *Natural Standard* states that significant blood sugar effects are “unlikely.”
- Although the *Natural Standard* documents “slight” increases in fasting blood glucose levels in persons with type II diabetes, it adds that "available scientific evidence suggests that there are no significant long-term effects of fish oil in patients with diabetes, including no changes in hemoglobin A1c levels." The *Natural Standard* discounts reports of increased insulin needs in persons taking omega-3 supplements. Berkeley Wellness cites a 2006 review by researchers at Tufts, which, "found that the doses used in most studies have little or no effect on blood sugar control." On the other hand, Berkeley cautions that, "in a Norwegian study the next year, very high dosages [six g per day] did raise blood sugar in people with type II diabetes. The Norwegian researchers suggested that taking one g of omega-3s a day would have a negligible effect on blood sugar." The American Heart Association advises that taking more than three g of omega-3s per day can worsen glucose control in people with diabetes.
- With regard to cholesterol and triglycerides, the *Natural Standard* cautions that omega-3's may add to the potential triglyceride lowering effect of agents such as niacin but may work against the potential LDL-lowering properties of agents such as barley, garlic, guggul, psyllium, soy, or sweet almond.

18. **SIDE EFFECTS**

- The FDA classifies low intake of omega-3 essential fatty acids from fish as “generally regarded as safe." Essentially, the side effects are those of eating fish, which is generally viewed as presenting a favorable proportion of benefit to justify the risk, except in people allergic to fish. And the effect of fish and fish oil on the heart and circulatory system is sufficiently demonstrated that we all need to eat more.

- The *Natural Standard* adds that: “Caution may be warranted, however, [in people with low blood pressure], in [people with diabetes or] at risk of bleeding, or in those with high levels of …LDL." NCCAM concurs. However, Berkeley Wellness, Fugh-Berman and Gerbarg dissent, as set forth above.
- The *Natural Standard* cautions that vitamins A and D are added to many commercial fish oil products. As a result, regular use may lead to elevated levels of these fat soluble vitamins. Since fat soluble vitamins can build up in the body and cause toxicity, consumers should be aware of any vitamins added to fish oil products in order to assure appropriate total vitamin dosages.
- Hypervitaminosis A is generally only seen when cod or other fish liver oil is used in very high dosages. Hypervitaminosis A occurs when the maximum limit for liver stores of retinoids is exceeded. The excess vitamin A enters the circulation causing systemic toxicity.
- According to Brown *et al*., the most common side effects of omega-3s are gastrointestinal nausea, heartburn, stomach pain, belching, bloating, or diarrhea. These side effects are most apparent in large doses. Brown *et al*. indicate that **the possibility of triggering manic episodes is "probably low," but should be kept in mind.**
- Finally, the *Natural Standard* documents “mild” elevations in liver function tests, "rare" skin rashes, and “rare" reports of mania or restlessness.
- According to the *Natural Standard*, it is unknown whether use of omega 3s by pregnant and breastfeeding mothers is beneficial to infants; nor are there any safety data, particularly in large doses. Although it is used in infant formulas, there are no data supporting that use either. Given the side effects and the likely benefits, the use of omega-3s by pregnant and breastfeeding mothers as well as young children seem reasonable. But large doses should be monitored by a physician.

19. **FISH CONTAMINATION/NO TESTING**:

- Fish may contain mercury and PCBs and dioxins which could be especially dangerous to young children and pregnant or breastfeeding women. Contaminants are much more

likely in fish meat than in fish oil, but absent uniform testing, this is difficult to verify, and the brutal truth is that unless government does it or requires it, sellers of fish are unlikely to test for contaminants because of the cost of testing and the potential that testing could make the fish unmarketable.

- Berkeley Wellness minimizes concerns about contamination of fish oil: "Recent analyses of fish oil supplements, including testing by ConsumerLab.com, did not find detectable or significant levels of mercury or unsafe levels of PCBs, dioxins, or other contaminants, in inexpensive as well as pricey brands. This is not surprising, since mercury tends to accumulate in larger fish, and supplements are generally made from smaller species (such as anchovies or sardines) or algae (which supply only DHA). Moreover, the mercury in fish is water soluble and thus tends to accumulate in fish meat, not in the fat or oil. Finally, most supplements are processed to reduce levels of PCBs and other contaminants.... The slightly higher levels in a few products may unnecessarily contribute to PCB exposure, but are unlikely to endanger human health."

20. **CHOICE OF FISH**: Contaminants can best be avoided by avoidance of fish liver oils (such as cod liver oil) and very limited consumption of predator fish. Small, short-lived fish such as anchovies, sardines, menhaden, carp, catfish, herring, lake trout, and mackerel, and small predators like bluefish, pompano, salmon, striped sea bass, tuna (albacore), and the like are preferred, since large, predatory, long-lived fish tend to concentrate pollutants at the top of the food chain. Commercial fish oils are generally derived from appropriate uncontaminated fish stocks, but attention to the label is important to assure this.

21. **FARMED FISH**: Farmed fish are becoming problematic due to the increasing use of vegetable feeds, which are rich in omega-6s but poor in omega-3s. They may also suffer from contamination, especially if animal byproducts are used for food. Reporting and regulation may eventually address these concerns, but they are not now addressed and are becoming more and more significant as a greater proportion of fish in our diet come from

aquaculture. Thus, despite the increased risk of contamination, “wild” fish are preferable until fish farm inspection reports are included on fish labels.

22. **CANNED FISH**: Canned salmon and tuna are rich in omega-3s, but the amounts vary a lot. Regular canned salmon, with skin and bones, has about 10 to 14 grams of total fat per four ounces (about ½ cup), which provides about 2,000 milligrams of omega-3s. Skinless, boneless, “premium” canned salmon has much less total fat (about three to four g per four ounces), and thus only about 650 milligrams of omega-3s.

23. **LARGE DOSAGES:** Large amounts of fish or fish oil consumption (in “Eskimo” amounts) call for greater vigilance to avoid contaminants. Greater dosages have been associated with nosebleeds or blood in the urine and call for closer monitoring to avoid serious complications such as stroke or high blood sugar. Gastrointestinal upset is common with the use of fish oil supplements, as is diarrhea, with potentially severe diarrhea at very high doses. The *Natural Standard* also documents reports of fishy aftertaste, increased burping, acid reflux/heartburn/indigestion, abdominal bloating, and abdominal pain. The *Natural Standard* recommends that gastrointestinal side effects be minimized by taking fish oil with meals and starting with low dosages. Large amounts can be taken better in two or more separate dosages.

24. **PLANT SOURCES:** Until recently, plant sources of omega 3s were discounted for use as CAM because they were so weak. Chia seeds and flax seeds contain ALA (Alpha-linolenic acid) and can be ground to get access to it, but the efficiency of converting ALA to EPA and DHA is low and varies by individual. However, recent supplements have used algal oil instead of flax seed oil, yielding up to 300 mg of combined DHA and EPA per capsule.[52] Note, however, to get the 9.6 g required to replicate Stoll’s dosage, this would require swallowing 32 large capsules of algal oil every day.

25. **DOSAGE**:

- The *Natural Standard* states that the "average" dietary intake of EPA and DHA is only 0.1 to 0.2 g per day, so omega 3 products should be counted assuming a zero baseline. The World Health Organization and governmental health agencies in "several countries" recommend consuming **0.3 to 0.5 g. per day of EPA and DHA.** If you have heart disease, the American Heart Association recommends that everyone get **one g (1,000 milligrams) per day of EPA and DHA** from fatty fish or fish oil supplements. It advises **two to four g of EPA and DHA per day from supplements for people with high triglycerides.**
- The clinical studies thus far have generally used fish oil (about 3:2 EPA to DHA). There is no clear evidence of the relative contribution of EPA and DHA to the observed outcomes. Stoll asserts that EPA appears to be "the most mood stabilizing component" in fish oil, and cites anecdotal data that suggest that too much DHA relative to EPA may actually worsen mood. [53]
- Brown *et al*. note that most consumers cannot tolerate the gastrointestinal side effects of using over 6 g. per day of omega-3 essential fatty acid. People also have a hard time with the number of pills required. However, Brown *et al.* explicitly recommend 8-10 g. per day of EPA and DHA in a 2:1 ratio for consumers who can tolerate it.[54]
- If you are healthy, the standard advice is to **eat fatty fish twice a week**. But if you don't eat this much fish, you can consider taking a fish oil supplement—500 to 1,000 milligrams per day EPA/DHA, on average. And to get 9.6 g per day, the dosage used by Stoll in his 1999 clinical trial, you would have to go on a daily ration of fatty fish. At that point, use of a fish oil supplement becomes essential.
- **Weil recommends two to four g per day of omega-3s in fish oil for prevention and treatment of depression. Stoll originally recommended one to two g per day of total omega-3s (EPA plus DHA) for health, mood or cognitive enhancement, and clinical doses of from two to five g per day. However, in his chapter in Mischoulon and Rosenbaum, Stoll upped his recommendation to between one and six g per day of EPA alone, accompanied by a lesser dose of DHA. At the top end, this would approximate the 9.6 g. per day used by Stoll in his 1999 clinical trial**. Stoll adds that: "The effective

dosage appears to be highly individualized, and if the initial target dosage is not adequately effective, **a gradual titration of the omega-3 fatty acid dosage is often required to empirically determine the optimal dosage**."[55]

- Writing in Brown *et al.* II, Mischoulon and Freeman recommend against use of omega-3s as monotherapy and counsel physician supervision for dosages of over 3g per day.[56]
- Given the wide disparity in these numbers and the gastrointestinal side effects, consultation with a health care provider seems prudent before upping the dose above one to two g. per day of combined EPA and DHA and then doing so slowly, separating and timing doses with meals.

26. **FISH OIL ISSUES**

- High quality fish and fish oil from "wild" fish low on the food chain remains the best source of omega-3 essential fatty acids. Look for the total amount of EPA and DHA on the label. It may say 1,000 milligrams of fish oil concentrate per capsule, but the small print may show only 300 milligrams of EPA and DHA (or simply "omega-3 fatty acids"), which is the key number. That would mean you need to take three capsules to get about a gram a day. Some fish oil capsules are more concentrated than others.
- There's no evidence that expensive over-the-counter fish oil brands are better than store brands—or that special marine oils such as krill, or widely promoted Norwegian or Icelandic brands, are better.[57] Claims about "molecular distillation" and other special purification processes are unverified.
- Like all over-the-counter supplements, fish oil capsules are unregulated, so you don't really know what you are getting. Still, recent tests of dozens of brands found that nearly all supplements contained the amount of omega-3 fats listed on the labels—with no significant contamination. The only regulated product is the prescription supplement, Lovaza, approved by the FDA for treating high triglycerides.
- To reduce gastrointestinal problems such as belching, take fish oil capsules with food, divide the doses among your meals, and start at a low dose and gradually increase it. Discard fish oil supplements that have a rancid smell or taste.

- Don't take cod liver oil, unless the label shows that its vitamin A content has been reduced. The oil usually contains very high levels of A, which may weaken bones and cause birth defects. Since it is made from livers, which filter out toxins, there is also greater concern about contaminants, even though the oil is supposed to be purified.

28. **FISH IS BEST.** Fish oil supplements supply omega-3s and are generally free of contaminants. But fish also contains vitamins, minerals, other fats, and other substances that may work with the omega-3s to protect the heart and overall health. Moreover, fish, which is rich in protein and low in saturated fat, can replace less-healthful foods such as red meat. As emphasized by *Berkeley Wellness*, the benefits of fish far outweigh the potential risks from contaminants, especially if you eat it in moderation (two servings a week, about 8 to 12 ounces total) and vary the types of fish. A large study in the journal ***Circulation: Heart Failure*** found that eating fried fish at least once a week was associated with a 48 percent higher risk of heart failure, so other cooking methods are preferred.[58]

29. **FISH DOSAGE:**
    - The EPA and DHA content of fish depends on the species. A good listing is found at http://fn.cfs.purdue.edu/fish4health/HealthBenefits/omega3.pdf
    - Lake Trout is the highest concentration, at 3% EPA and DHA. Atlantic salmon is almost 2%, but most fish are under 1%, meaning 100grams of fish for each gram of omega-3s. At that rate, a therapeutic dose of 6-9 grams would take a lot of fish: up to two pounds a day, so supplementation is essential.

29. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with omega-3s and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects**.**

[1] Stoll, Andrew L., M.D., *The Omega-3 Connection* (Simon & Schuster, New York 2001).

[2] Schmidt, Michael A., *Smart Fats* (Frog, Ltd., Berkeley, CA 1997), at 45.

[3]Hibbeln, J.R., "Seafood Consumption and Homicide Mortality. A Cross-National Ecological Analysis," *World Rev. Nutr. Diet*., 88:41-6 (2001).

[4] Stoll, A.L., "Omega-3 Fatty Acids in Mood Disorders: A Review of Neurobiologic and Clinical Actions," in Mischoulon and Rosenbaum*, Natural Medications for Psychiatric Disorders: Considering the Alternatives* (2002/2008), Second Edition Copyright 2008 by Lippincott Williams & Wilkins (Philadelphia), at 39-67.

[5] Stoll A.L., Severus E., Freeman M.P., Rueter S., Zboyan H.A., Diamond E., Cress K.K., Marangell L.B. "Omega-3 fatty acids in Bipolar Disorder: a Preliminary Double-blind, Placebo-controlled Trial," *Arch. Gen. Psychiatry* 56:380–1 (1999).

[6] *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown et al. II") at 19.

[7] Hibbeln,, J.R., "Fish Consumption and Major Depression," *Lancet* 351:1213 (1998)

[8] Maes, M., Smith, R., Christophe, A., Cosyns, P., Desnyder, R. & Meltzer, H., "Fatty Acid Composition in Major Depression: Decreased Omega-3 Fractions in Cholesterol Esters and Increased C20:4 Omega 6/C20:5 Omega-3 Ratio in Cholestryl Esters and Phospholipids" *Journal of Affective Disorders* 38:35-46 (1996).

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[9] Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D., "Omega-3 Fatty Acids and Mood Disorders," *American Journal of Psychiatry.* 163(6):969-78 (2006).

[10] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009), at 42.

[11] For details and citations of the studies, see Mischoulon and Rosenbaum*, op. cit.,* pp. 44 and 56-57.

[12] *Id*. at 60.

[13] Marangell, L.B., Martinez, J.M., Zboyan, H.A., Kertz, B., Kim, H.F., "A Double-blind, Placebo-controlled Study of the Omega-3 Fatty Acid Docosahexaenoic Acid in the Treatment of Major Depression," *American Journal of Psychiatry* 60:996-998 (2003).

[14]Stoll, *op. cit*., at 53-58. It should be noted that Carol A. Locke, M.D., Dr. Stoll's wife, markets (or has marketed) an omega-3 product with the brand name "Omega Brite," which contains a 7:1 ratio of EPA to DHA. Dr. Stoll's activities are more academic and are fully disclosed in his studies.

[15] Stoll, *op cit.,* at 23.

[16] Weil, *op. cit*., at 206.

[17] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 204.

[18] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 158-159.

[19] NCCAM website, http://nccam.nih.gov/health/providers/digest/depression-science.htm

[20] Appleton, K.M., Rogers, P.J. & Ness, A.R., "Updated Systematic Review and Meta-Analysis of The Effects of N-3 Long-Chain Polyunsaturated Fatty Acids on Depressed Mood," *Am J Clin Nutr.* 91(3):757-70 (2010). Epub 2010 Feb 3.

[21] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 17.

[22] Carney, R.M., Freedland, K.E., Rubin, E.H., Rich, M.W., Steinmeyer, B.C. & Harris, W.S., "Omega-3 Augmentation of Sertraline in Treatment of Depression in Patients with Coronary Heart Disease: a Randomized Controlled Trial," *JAMA* 302(15):1651-7 (2009).

[23] Lespérance, F. *et al*. "The Efficacy of Omega-3 Supplementation for Major Depression: a Randomized Controlled Trial," *J Clin. Psychiatry* 72(8):1054–1062 (2010)

[24] *Natural Standard Herb and Supplement Guide: An Evidence-based Reference*, *op. cit*., "Omega-3 Fatty Acids," at 536ff.

[25] University of California, Berkeley, School of Public Health, The Wellness Reports, *Dietary Supplements* (2010), at 28. However, a 2013 update from Berkeley Wellness examines the recent evidence:

"In 2012, two large analyses pooled data from well-designed clinical trials involving people with pre-existing heart disease or multiple risk factors. One was published in the Archives of Internal Medicine, the other in *the Journal of the American Medical Association*. They concluded that overall the evidence does not support claims that omega-3 supplements help prevent cardiovascular events.

Another large analysis of various studies, published last year in the British journal *BMJ*, looked at the link between fish consumption or omega-3 supplements and the risk of stroke. It found that the 26 observational studies suggested that higher fish intake was associated with moderately reduced stroke risk, but that the 12 clinical trials (considered the gold standard in medical research) concluded that the supplements offered no benefit. In a large trial in the *New England Journal of Medicine* in 2012, people with diabetes or prediabetes, who are at elevated risk for cardiovascular disease, took 1,000 milligrams of omega-3 supplements a day or a placebo. After an average of six years, the supplement takers were no less likely to have a heart attack or stroke or to die.

A British study in the *American Journal of Clinical Nutrition* in 2011 found that various doses of omega-3s did not help keep arteries flexible in healthy people (ages 45 to 70). Another British study, in the journal *Atherosclerosis*, similarly found no vascular benefit in people with peripheral artery disease. However, a 2012 analysis in the same journal concluded that omega-3s can improve arterial functioning.

In the newest study, published in the *New England Journal of Medicine in May*, more than 6,000 Italians at high risk for cardiovascular disease took 1,000 milligrams of omega-3 supplements a day. After five years, they did no better than a placebo group in terms of heart attacks, strokes and death rates. This was true even of people with low baseline dietary intakes of omega-3s and those not taking statins.

Critics have raised questions about some of the newer studies, saying they were not large enough to detect benefits, didn't last long enough or used omega-3 doses that were too low. Others have criticized how the studies included in the meta-analyses were selected. Had certain other studies been included, the critics say, the overall results would have been more positive. Still, benefits that are so hard to spot are likely to be quite small.

Bottom line: The proposed cardiovascular benefits of fish oil supplements now seem uncertain. Some major studies are underway and may help clarify matters. In any case, your best bet is to get your omega-3s from two or three servings of fatty fish a week. The AHA continues to advise people with heart disease or high triglycerides to consider taking the supplements, after consulting their doctors. That's still good advice if you don't eat fish, especially since some of the other proposed benefits of omega-3s may still pan out. The supplements have few, if any, serious adverse effects—unless, that is, they lead you to think you can eat an unhealthy diet or can avoid taking the statins or other drugs you may need.

The most salient point may be that in the studies from recent years, far more participants at elevated cardiovascular risk were taking "state-of-the-art" medication, such as statins and blood pressure drugs, compared to early studies. That helps explain the apparent lack of effect of the supplements. Even if omega-3s provide benefits, these would be hard to detect against the backdrop of the much larger benefits of these drugs. That could also make the supplements all the more unnecessary. (The same thing is seen in studies of low-dose aspirin, the benefits of which appear much smaller than previously estimated, now that so many high-risk people are taking statins.)"

http://www.berkeleywellness.com/supplements/other-supplements/article/omega-3-supplements-question?ap=603

[26] Hibbeln, J.R., "Long-chain Polyunsaturated Fatty Acids in Depression and Related Conditions." In: *Phospholipid Spectrum Disorder in Psychiatry*, Peet, M., Glen ,I., & Horrobin, D.F. (eds.) (Marius Press, Lancashire, UK 2000), at 195-210

[27] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 18.

[28] Birch, E.E., Garfield, S., Hoffman, D.R., Uauy, R. & Birch, D.G., "A Randomized Controlled Trial of Early Dietary Supply of Long-chain Polyunsaturated Fatty Acids and Mental Development in Term Infants," *Developmental Medicine and Child Neurology* 42(3):174-81 (2000).

[29] Mahadik, S.P., Mukherjee, S., "Free Radical Pathology and Antioxidant Defense in Schizophrenia: A Review," *Schizophrenia Research* 19:1-17 (1996); Mahadik, S.P. *et al*., "Elevated Plasma Lipid Peroxides at the Onset of Nonaffective Psychosis" *Biological Psychiatry* 43:674:679 (1998).

[30] Laugharne, J.O., *et al*., "Fatty Acids and Schizophrenia" *Lipids* 31 (Supp):S163-S165 (1996).

[31] Lake and Spiegel, *Complementary and Alternative Treatments in Mental Health Care*, *op. cit*., at 159.

[32] Freeman, M.R., Hibbeln, J.R., Mischoulon, D., *et al*. "Omega-3 Fatty Acids: Evidence for Treatment and Future Research in Psychiatry" *Journal of Clinical Psychiatry* 67:12 (2006).

[33] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 19-20.

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[35] Brown *et al., op. cit*., at 145-146.

[36] Bowman, G.L., Silbert, L.C., D. Howieson, D., Dodge, H.H., Traber, M.G., *et al*., "Nutrient Biomarker Patterns, Cognitive Function, and MRI measures of Brain Aging,"*Neurology* 78(4):241-249 (2012), Published online before print December 28, 2011, doi: 10.1212/WNL.0b013e3182436598, http://www.neurology.org/content/78/4/241 .

[37] Brown *et al., op. cit.*

[38] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 20.

[39] Newmark, S., *ADHD Without Drugs: A Guide to the Natural Care of Children with ADHD* (Nurtured Heart Publications, Tucson, AZ 2010).

[40] *Id.* at 96.

[41] One study showed that ADHD adolescents ate the same amount of omega-3 and omega-6 fatty acids as those without ADHD, yet still had less omega-3 fatty acids and more omega-6 fatty acids in their blood. Colter, A.L., Cutler, C., Meckling, K.A.., "Fatty Acid Status and Behavioural Symptoms of Attention Deficit Hyperactivity Disorder in Adolescents: A Case-Control Study," Nutr J. 7:8 (2008).

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[44] (W.W. Norton & Company New York 2012).

[45] *Id.* at 120-126.

[46] Bloch, M.H. & Qawasmi, A.,"Omega-3 Fatty Acid Supplementation for the Treatment of Children with Attention-Deficit/Hyperactivity Disorder Ssymptomatology: Systematic Review and Meta-analysis," *J Am Acad Child Adolesc Psychiatry* 50(10):991-1000 (2011). Epub 2011 Aug 12.

[47] *Id*. at 8.

[48] Brown, *et al., op. cit*., at 83.

[49] Lake and Spiegel, *Complementary and Alternative Treatments in Mental Health Care*, *op. cit*., at 160-161.

[50] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 20.

[51] *Id*. at 59.

[52] E.g., http://www.schiffmegared.com/MegaRedPlantOmega.asp

[53] Stoll, *op. cit*., at 208

[54] Brown *et al., op. cit*., at 45.

[55] *Id.* at 58.

[56] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., Brown *et al*. II, *op. cit.* at 21, citing Freeman, Hibbeln et al. (2006).

[57] http://www.berkeleywellnessalerts.com/alerts/healthy_heart/krill-oil-supplements424-1.html?ET=bwalerts:e1543:143685a:&st=email&s=EHA_121002_001

[58] http://www.berkeleywellnessalerts.com/alerts/healthy_heart/fried-fish455-1.html?ET=bwalerts:e1543:143685a:&st=email&s=EHA_121002_001

RHODIOLA ROSEA FOR STRESS AND MILD TO MODERATE DEPRESSION AND AS A POSSIBLE NEUROPROTECTANT

SUMMARY

WHAT WE KNOW

Rhodiola rosea, called rhodiola, and known as "golden root" or "arctic root" in the mountainous parts of Europe and Asia, has long been employed in Eurasian traditional medicine as a natural tonic, referred to as an "adaptogen." Rhodiola is used to promote good health, strength, endurance and physical and mental performance. Rhodiola's efficacy in treating mental health conditions isn't well-known in America because the earliest studies suffered from poor controls and generalized claims and were not done in the United States or Western Europe. However, those studies and the traditional practices that spawned them have caused people to use rhodiola to treat a wide range of conditions, such as stress, fatigue, anxiety, depression, and cognitive impairment, primarily in Eastern Europe and Asia, but increasingly in the United States and around the world.

MENTAL HEALTH IMPLICATIONS

Studies document rhodiola's impact on an individual's overall general physical and mental health. Rhodiola can be used to reduce stress, combat fatigue, increase mental performance and improve physical and mental fitness and resilience.

Stress, Neuroprotection and Mild to Moderate Depression

Three of the sources consulted for this outline (most of which ignore rhodiola) concur that rhodiola is a promising and relatively benign treatment for a number of mental health

conditions, including stress, neuroprotection ("cognitive stimulation" and improvement in "cognitive deficiencies" and memory) and mild to moderate depression. The *Natural Standard* mildly but decisively dissents, finding these claims unsubstantiated. All other claims (below) are promising but unproven.

Bipolar Disorder

Two sources warn against rhodiola use in persons with bipolar disorder. But some experts (Brown *et al.*) believe, based on clinical experience, that moderate doses of rhodiola can be helpful in persons with bipolar disorder who are taking mood stabilizers and whose mood swings are primarily depressive with only occasional mild hypomanic symptoms. This requires working closely with a physician if there is any chance of bipolar "cycling."

Adjunctive Use

When combined with tricyclic antidepressants, rhodiola use has been associated with reduction of antidepressant side effects, particularly sedation fatigue and sexual dysfunction, as well as an improvement in depressive symptoms. Brow*n et al*. state that they use rhodiola as an adjunctive treatment in depression because it "increases mental and physical energy" and "improves mood and stress tolerance."

Anxiety

Brown *et al.* note that rhodiola also can be useful in the treatment of anxiety, and a recent open-label study supports this use.

Chronic Fatigue Syndrome, Fibromyalgia Syndrome, and ADHD

Brown *et al.* add that their clinical experience shows rhodiola to be beneficial in chronic fatigue syndrome and fibromyalgia syndrome. It is also a useful adjunctive treatment in attention deficit disorder (ADHD), since it activates cognition and tends to improve accuracy, alertness and attention.

Exhaustion, Decreased Motivation, Daytime Sleepiness, Decreased Libido, Sleep Disturbances, and Cognitive Complaints

Iovieno *et al*. state that rhodiola is effective in treating physical deficiencies such as exhaustion, decreased motivation, daytime sleepiness, decreased libido, sleep disturbances, and cognitive complaints such as concentration deficiencies, forgetfulness, decreased memory, susceptibility to stress, and irritability.

Alleviation of Side Effects of Psychotropic Medication

In Brown *et al.* II, Panossian asserts, based on one small study, that rhodiola can relieve side effects of psychotropic drugs used to treat schizophrenia.

DRUG INTERACTIONS AND SIDE EFFECTS

Drug Interactions

- If you are considering continuing the use of rhodiola with psychotropic drugs, you should definitely consult with the prescribing physician, even though there are no documented interactions except for MAOIs. Brown *et al.* advise against use of rhodiola with MAOIs.
- Rhodiola may add to the stimulant effects of caffeine; it also may augment antianxiety, antibiotic, antidepressant medications.
- Rhodiola may affect platelet aggregation in higher doses.
- Rhodiola may interfere with birth control pills.
- Rhodiola may interfere with diabetic or thyroid medication.

Side Effects

- Generally uncommon and mild.
- May include allergy, irritability, insomnia, increased blood pressure, and chest pain.
- Most frequent side effects (according to Brown *et al*) are activation, agitation, insomnia, anxiety, and occasional headache.

- Evidence for the safety and appropriateness of rhodiola use during pregnancy and lactation is not currently available, and rhodiola is therefore not recommended for pregnant women or during breastfeeding. Likewise, safety and dosages for children have not been demonstrated. Brown and Gerbarg note that rhodiola has been used in small doses for children as young as 10 years of age without adverse effects but emphasize that dosages for children (8-12 years old) must be small and carefully titrated to avoid overstimulation.

CONCLUSION

Rhodiola is a very promising treatment for stress and mild to moderate depression and as a neuroprotectant and is promising for a number of other mental health conditions. The risk of drug interactions and side effects is minimal, but consumers using antianxiety, antibiotic, or antidepressant medications, birth control pills, or diabetic and thyroid drugs should consult with the prescribing physician. Rhodiola is just becoming known in America, and is being popularized by experts like Brown, Gerbarg, Mischoulon, and Weil. Although much more study is needed, it appears to have a promising future in low-risk mental health treatment and self-care.

OUTLINE

1. *Rhodiola rosea* (hereinafter "rhodiola") is widely distributed at high altitudes in the mountainous regions of Europe and Asia, where it is known as "golden root," "arctic root," "roseroot," or "Aaron's rod." It also is found in North America. The roots of the plant have been used for centuries in the traditional medicine of Asia, Scandinavia, and Eastern Europe as a health-enhancing supplement stimulating the nervous system, enhancing physical and mental performance, and alleviating fatigue, psychological stress, and depression.

2. **PREPARATION:** Rhodiola extract is mainly used in the form of capsules or tablets, though tinctures are also available. The capsules and tablets contain 100, 150, or 180 mg of

a standardized amount of 3 percent rosavins and 0.8–1 percent salidroside because the naturally occurring ratio of these compounds in *Rhodiola rosea* root is approximately 3:1. Rhodiola is obtained by drying and grinding the root. It contains many biologically active substances. Its stimulating and adaptogenic properties are attributed to p-tyrosol, salidroside, rosavins, and additional phenolic compounds.

Specific neurochemical mechanisms have been documented for some but not all of the bioactive compounds. The combined effects differ from the effects of isolated components. Rhodiola extracts are standardized for both rosavins and salidroside. The standardized Swedish Herbal Institute formula, SHR-5, is commonly used in the newer studies of depression, cognitive function and fatigue.

3. **ESTABLISHED USES:** Soviet studies have led to wide use of rhodiola in Russia, the former Soviet Union, and Scandinavia to combat stress, fatigue, anxiety, depression, and cognitive impairment, including brain injury, and to promote strength, endurance, and physical and mental performance.

4. **EFFICACY: STRESS, NEUROPROTECTION AND MILD TO MODERATE DEPRESSION: Three of the sources consulted for this outline concur that rhodiola is a promising and relatively benign treatment for a number of mental health conditions, including stress, neuroprotection ("cognitive stimulation" and improvement in "cognitive deficiencies" and memory) and mild to moderate depression.** The *Natural Standard* mildly but decisively dissents.

   - Rhodiola has long been classified by Soviet researchers as an "**adaptogen**," a substance that nonspecifically increases the resistance of an organism to a variety of chemical, biological, and physical stressors.
   - The Soviet Union began testing rhodiola as far back as the 1960s for enhancement of mental and physical performance, aiming at military, space exploration, and sports applications. According to Brown *et al*., Soviet scientists found that rhodiola was

effective for: "cognitive stimulation with emotional calming; enhanced learning and memory; and increased accuracy in mental performance for prolonged periods of time."[1] Rhodiola was found to **protect against physical stresses, fatigue, cold, heat, toxins, and radiation. Studies of uncertain methodological rigor found that rhodiola "enhanced intellectual work capacity, abstract thinking, and reaction time."**[2]

- In a 2002 review (the first review of rhodiola in English) and in their 2004 book*, The Rhodiola Revolution*,[3] Brown and Gerbarg state that **the primary clinical uses of rhodiola are for cognitive disorders, memory and performance under stress.** However, based on trials conducted in the former Soviet Union beginning in 1987 and their own clinical practice, they note that rhodiola **also can be useful in the treatment of depression.** A recent small open-label study showed promising results for the use of rhodiola for **anxiety**, but the size and open label study design preclude any conclusion at this point except for the usual need for more study.[4]
- In Brown *et al.* II, Panossian, A.G. asserts that rhodiola studies have shown a "significant antidepressant effect."[5]
- The randomized study conducted by Darbinyan *et al*. and published in 2001 assessed "fatigue and mental performance" (associative thinking, short-term memory, concentration, speed of audio-visual perceptions, and other parameters defined as a "Fatigue Index") in a group of 56 young, healthy physicians on night duty receiving a low-dose treatment of SHR-5 rhodiola (**170 mg per day**). The tests were performed before and after night duty during three two-week periods in a double-blind cross-over trial. **A statistically significant improvement in fatigue and mental performance was observed in the treatment group during the first 2 weeks**. By 6 weeks, however, the effect appeared to be lost. Iovieno *et al*. speculate that the effect decline could be due to the relatively short-term benefit of use of SHR-5, or to the low dose used, or the cross-over design of the study.[6] Brown and Gerbarg add that the dosage used in this study was sub-therapeutic -- about half of the recommended dose. They state that in their clinical experience, some people are able to continue taking rhodiola in

therapeutic doses for many years with good response, while others may need to take "holidays" of from 2 to 4 weeks to restore effectiveness.

- In a second study, 40 medical students were randomized to receive either a low dose of SHR-5 (**100 mg per day**) or placebo for 20 days during a stressful examination period. Subjects receiving rhodiola demonstrated **significant improvements in physical fitness, mental fatigue, psychomotor performance and general well-being**. They also reported improvement in sleep patterns, reduced need for sleep, greater mood stability, and a greater motivation to study.[7] (Spasov *et al*., 2000).
- Fintelmann and Gruenwald's 2007 open label study of "Vigodana" (a German vitamin and mineral tonic[8] containing rhodiola)[9] showed it to be associated with a statistically significant (P<.001) improvement in physical and cognitive deficiencies. The treatment was rated as "good" by over 80% of physicians and subjects. More research is needed, but the use of rhodiola for cognitive disorders is certainly promising. This treatment cannot yet be treated as fully evidence-based, but, in light of a benign side-effect profile, it may be appropriate to use rhodiola for prevention and treatment of cognitive impairment as the evidence is accumulated.

5. **DEPRESSION: THE 2007 DARBINYAN *ET AL.* STUDY: There is only one randomized study investigating the antidepressant effect of rhodiola monotherapy in people with depression.** Darbinyan *et al*. (2007)[10] conducted a 6 week double-blind, placebo-controlled pilot study with 89 persons diagnosed with **mild to moderate depression**. The research subjects were randomized to receive placebo or SHR-5 at two different doses (**340 or 680 mg per day**). The efficacy of SHR-5 was assessed on the basis of specific subgroup scores of the Hamilton Rating Scale for Depression (HAM-D). Although qualified by the researchers as "**modest but significant**," the results were impressive, with **equivalent results at both doses**:
    - **Group A (340 mg): from 24.52 to 15.97 (p<0.0001)**
    - **Group B (680 mg): from 23.79 to16.72 (p<0.0001)**
    - **Group C (placebo): from 24.17 to 23.41 (p=0.3306)**

No side effects were reported.

- A **recent article by Iovieno, *et al*. (2011) describes rhodiola as part of the "next wave of natural antidepressants,**" based on the 2007 Darbinyan study cited above.
- **Weil concurs that: "If you experience mental fog and fatigue along with mild to moderate depression, you might consider a trial of rhodiola**."[11]

6. **DISSENT:** Although the *Natural Standard* acknowledges the use of rhodiola as an "adaptogen" for "mental performance," it rates the use as "**C**," "**unclear scientific evidence for this use**." It states: "Preliminary clinical evidence suggests that rhodiola may benefit learning, memory and mental performance," but it deems the data "insufficient" to make a recommendation. The *Natural Standard* does not even mention use of rhodiola for stress or depression.

7. **SUGGESTED BUT UNPROVEN USES: ANXIETY, ATTENTION DEFICIT DISORDER (ADHD), CHRONIC FATIGUE SYNDROME, FIBROMYALGIA SYNDROME:** As described above, recent evidence, suggests that rhodiola may be a promising treatment for **anxiety**. Brown *et al.* also state **that rhodiola can be helpful in the treatment of attention deficit disorder (ADHD), chronic fatigue syndrome and fibromyalgia syndrome**, since it activates cognition and tends to improve accuracy, alertness, attention, and energy, but clinical study is needed to validate these clinical observations. Given the relatively small risk, people may reasonably decide to give rhodiola a try in the absence of conflicting information.

8. **SUGGESTED BUT UNPROVEN USES: BIPOLAR DISORDER:** Russian researchers warned against rhodiola use in persons with bipolar disorder ("manic-depressive illness"). **Rhodiola has not been studied in bipolar depression**, and Iovieno *et al* advise caution in patients with bipolar spectrum disorders because of its activating effect, which could increase the **risk of "cycling." However, Brown *et al.* believe, based on their clinical experience, that "[rhodiola] can be quite helpful in [persons with bipolar disorder] on mood stabilizers whose mood swings are primarily depressive with only occasional mild hypomanic**

symptoms."[12] This requires working closely with a physician if there is any substantial risk of bipolar cycling

9. **SUGGESTED BUT UNPROVEN USES: ADJUNCTIVE USE FOR DEPRESSION:** Only very small, old and generally not well-controlled Soviet studies have thus far documented the **antidepressant effect of rhodiola as an adjunct to synthetic antidepressants**. These studies suggest that **when combined with tricyclic antidepressants, rhodiola use was associated with a marked reduction in medication side effects as well as an improvement in depressive symptoms**.[13] Brow*n et al*. state that they use rhodiola **as an adjunctive treatment in depression** with all classes of antidepressants except MAOIs, **because it "increases mental and physical energy" and "improves mood and stress tolerance."** People should consult with their prescribing physician before attempting such adjunctive use. Further studies of Rhodiola as an adjunct to all classes of antidepressants would be worthwhile. **Brown *et al.* advise against use of rhodiola with MAOIs**

10. **SUGGESTED BUT UNPROVEN USES: EXHAUSTION, DECREASED MOTIVATION, DAYTIME SLEEPINESS, DECREASED LIBIDO, SLEEP DISTURBANCES, AND COGNITIVE COMPLAINTS:** Iovieno *et al.* concur that rhodiola is effective **for improving physical and cognitive deficiencies such as exhaustion, decreased motivation, daytime sleepiness, decreased libido, sleep disturbances, and cognitive complaints such as concentration deficiencies, forgetfulness, decreased memory, susceptibility to stress, and irritability**.

11. **SUGGESTED BUT UNPROVEN USES: ALLEVIATION OF SIDE EFFECTS OF PSYCHOTROPIC MEDICATION:** In Brown *et al.* II, Panossian, A.G. asserts that rhodiola studies have shown "alleviat[ion of] psychotropic side effects in subjects [with schizophrenia]."[14]

12. **DRUG INTERACTIONS**
    - **No data are available concerning efficacy, safety and pharmacological interaction of rhodiola used in combination with SSRIs.**

- **Rhodiola does not appear to interact with other medications such as warfarin (Coumadin) and theophylline, as many CAM treatments for d**epression do, and can be of value in patients who take multiple drugs. However, Brown and Gerbarg caution that in some people doses above 600 mg per day of rhodiola can affect platelet aggregation. Thus, when rhodiola is used with anti-coagulants, bleeding and clotting times should be tested and doses adjusted as needed.
- Brown *et al*. caution that people should restrict their consumption of caffeine while on rhodiola, since the stimulant effect can be additive. The *Natural Standard* cautions of a broader risk of additive effects, but the clinical data are not available to demonstrate a significant risk at this point. Brown *et al.* also caution that, although no unwanted pregnancies have been reported, rhodiola **may impair the effectiveness of birth control pills** and may restore or "normalize" the menstrual cycle.
- The *Natural Standard* warns that rhodiola may lower blood sugar levels and cautions that persons with diabetes or taking blood sugar lowering medications should monitor and adjust dosages accordingly. Brown and Gerbarg observe minimal hypoglycemic effects and suggest monitoring for people who are insulin dependent or unstable diabetics.
- Rhodiola may augment the effects of antianxiety, antibiotic, antidepressant, anticancer, antioxidant, exercise performance-enhancing and cognitive-enhancing treatments. Rhodiola may also normalize thyroid function and reduce the necessary dose of synthetic thyroid replacement medication. It can further enhance the effects of other treatments for erectile dysfunction**.** In animal studies, rhodiola showed no significant effects on the metabolism or serum levels of theophylline or warfarin or on the anticoagulant activity of warfarin, indicating that it is not likely to significantly interfere with medications metabolized by the CYP450 enzyme systems.[15] There are no reported cases of bleeding attributable to rhodiola.
- Brown and Gerbarg caution that these are concerns about potential rhodiola interactions with drugs are mostly theoretical and have not been documented to occur

in humans. In particular, as addressed under adjunctive use, the addition of rhodiola to antidepressants other than MAOIs is a promising practice.

13. **SIDE EFFECTS**

- **According to Iovieno *et al*., Rhodiola appears to have an excellent safety profile**. Side effects are **uncommon and mild**, and can include allergy, irritability, insomnia, fatigue (not seen by Brown and Gerbarg), and unpleasant sensations, especially at high doses. An increase in irritability and insomnia within several days has been reported in some individuals at doses of 1500 – 2000 mg per day of rhodiola extract, which would be an excessive dose.
- **According to Brown *et al*, the most frequent side effects of rhodiola are activation, agitation, insomnia, anxiety, and headache.** Bruising, increased blood pressure, heart palpitations and chest pain are cited by Brown *et al*. as uncommon.
- Rhodiola is best absorbed when taken on an empty stomach 30 minutes before meals, and **should be taken early in the day** and around noon to avoid interference with sleep. If adverse effects on sleep occur, a smaller dose with very gradual increases can be suggested.
- **According to Brown *et al*., rhodiola (by itself) does not cause addiction, habituation or withdrawal symptoms.**
- Although it has not been clinically linked with cancer risk, in light of its estrogen-like effects, Brown *et al*. advise that women with a personal or family history of breast cancer should be informed that the possibility of increased risk for estrogen-sensitive breast cancer has not yet been adequately investigated. Brown and Gerbarg add that rhodiola shows anti-cancer effects in clinical practice, in studies of human cancers transplanted into animals and in a few small human pilot studies.
- The *Natural Standard* warns that rhodiola may lower blood sugar levels and may cause increased heart rate, irregular heart beats, salivation, and hormonal (estrogen-like) side effects. Brown and Gerbarg have not observed drops in blood sugar, irregular heartbeats or increased salivation in their clinical practice. Although orally ingested

rhodiola was found to bind to estrogen receptors, it did not activate them, nor did it increase serum estradiol levels in rat studies.[16]

- Evidence for the safety and appropriateness of rhodiola use during pregnancy and lactation is not currently available, and rhodiola is therefore not recommended for pregnant women or during breastfeeding. Likewise, safety and dosages for children have not been demonstrated. Brown and Gerbarg note that rhodiola has been used in small doses for children as young as 10 years of age without adverse effects but emphasize that dosages for children (8-12 years old) must be small and carefully titrated to avoid overstimulation. They recommend starting with a dose of about 6 mg per day.[17]

14. **DOSAGE:** It is important to find a *Rhodiola rosea* root extract that contains at least 1% salidriside and 3% rosavins. The standardized Swedish Herbal Institute formula, SHR-5, contains 4% rosavins. Brown *et al*. state that they have recommended doses of **50-600 mg per day of rhodiola to help assuage the symptoms of chronic fatigue syndrome and fibromyalgia syndrome, 200-400 mg per day for adjunctive use for depression, up to 750 mg per day if rhodiola is used alone for depression**, and up to 900 mg in some cases. Brown and Gerbarg add that **maximum effectiveness in adults generally occurs on dosages of between 150 and 600 mg per day.** The table in the Brown *et al.* text shows a larger range of dosages for depression ranging from 150 to 900 mg per day, making **titration with the guidance of a physician essential, especially if other antidepressants have been or will be used concurrently to treat the depression, as will often be the case.** Brown and Gerbarg state that here is no rationale for dosages in excess of 900 mg per day.

15. **RESEARCH**: Long-term outcomes -- benefits and liabilities from continuing treatment with rhodiola and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects. Although consumer use of rhodiola has become common, American academic studies and literature have not kept pace.

[1] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009), at 160-161.

[2] *Id.*

[3] Rodale Press, Emmaus, PA (2004).

[4] Bytstritsky, A., Kerwin, L. & Feusner, J.D., "A Pilot Study of Rhodiola rosea (Rhodax) For Generalized Anxiety Disorder," *Journal of Alternative and Complementary Medicine* 14(2):175-180 (2008).

[5] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 54.

[6] Darbinyan, V., Kteyan, A., Panossian, A., Gabrielian, E., Wikman, G. & Wagner, H., "Rhodiola rosea in Stress-induced Fatigue – A Double-blind Cross-over Study of a standardized Extract SHR-5 with a Repeated Low-dose Regimen on the Mental Performance of Healthy Physicians During Night Duty," *Phytomedicine* 7:365-371 (2000).

[7] Spasov, A.A., Wikman, G.K., Mandrikov, V.B., Mironova, L.A. & Neumoin, W., "A Double-blind Placebo-controlled Study of the Stimulating and Adaptogenic Effect of Rhodiola rosea SHR-5 Extract on the fatigue of Students Caused by Stress during an Examination Period with a Repeated Low-dose Regimen," *Phytomedicine* 7:85-89 (2000).

[8] In addition to rhodiola, the proprietary formula includes roseroot, vitamin E, vitamins B6 and B12, folate and magnesium.

[9] Fintelmann, V. & Gruenwald, J., "Efficacy and Tolerability of a *Rhodiola Rosea* Extract in Adults With Physical and Cognitive Deficiencies," *Advances in Therapy* 24(4):929-939 (2007).

[10] Darbinyan, V, Aslanyan, G, Amroyan, E, Gabrielyan E, Malmström, C & Panossian, A., "Clinical Trial of Rhodiola Rosea L. Extract SHR-5 in the Treatment of Mild to Moderate Depression," *Nord. J. Psychiatry.* 61(5):343-8 (2007). All further references to Darbinyan *et al*. are to this study.

[11] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 116.

[12] *Id*.

[13] Brichenko,V.S., Kupriyanova, I.E., Skorokhadova, T.F., "The Use of Herbal Adaptogens Together with Tricyclic Anti-depressants in Patients with Psychogenic Depressions," in Goldberg, E.D. (Ed.) *Modern Problems of Pharmacology and Search for New Medicines*, vol. 2 (Tomsk State University Press, Tomsk, Russian Republic, former Soviet Union, 1986); Brichenko, V.S.and Skorokhodova,T.F., "Herbal Adaptogens in Rehabilitation of Patients with Depressions," in*: Clinical and Organizational Aspects of Early Manifestations of Nervous and Mental Diseases* (Barnaul 1987).

[14] Brown *et al*. II at 54.

[15] Gerbarg, P.L., Brown, R.P., "Phytomedicines for Prevention and Treatment of Mental Health Disorders," *Psychiatric Clinics of North America* 35(1):_____(2013); Panossian, A., Hovhannisyan, A., Abrahamyan, H., *et al*. "Pharmacokinetic and Pharmacodynamic Study of Interaction of Rhodiola Rosea SHR-5 Extract with Warfarin and Theophylline in Rats," *Phytother Res* 23(3):351–7 (2009).

[16] Eagon, P. K., Elm, M. S., Gerbarg, P. L., Brown, R. P., Check J. J., Diorio, G. J.& Houghton, Jr. F., "Evaluation of the medicinal botanical Rhodiola rosea for estrogenicity" [Abstract], *American Association of Cancer Research* ____:_____ (2003).

[17] Brown, R.P. and Gerbarg, P.L., *Non-drug Treatments for ADHD* (W.W. Norton & Company, New York, 2012), at 65.

ST. JOHN'S WORT FOR MILD TO MODERATE DEPRESSION

SUMMARY

WHAT WE KNOW

One of the most well-known and studied CAM treatments, St. John's wort is widely used throughout the U.S. and Europe to treat mild to moderate depression.

MENTAL HEALTH IMPLICATIONS

Eight sources agree: St. John's wort can help with mild to moderate depression.

It is used extensively by prescription in Germany, where randomized studies have shown the proprietary Schwabe St. John's wort formula to be effective in moderate to severe depression. Mischoulon and Rosenbaum suggest that it may be a promising practice for severe depression.

Although many people use St. John's wort as long-term treatment, there is little evidence of long-term safety or efficacy. All of the clinical studies have been short (24-26 weeks at the most), and most have been small.

Another source (Brown *et al*). notes that St. John's wort also can be a useful treatment for somatoform disorder (somatization disorder and hypochondria) and seasonal affective disorder.

SIDE EFFECTS & DRUG INTERACTIONS

If you are considering continuing the use of St. John's wort with psychotropic drugs, you should **definitely** consult with the prescribing physician. People with complex medical conditions should insist on careful monitoring while taking St. John's wort.

Side Effects

- May trigger "cycling" in people with bipolar disorder.

- Other common side effects, such as nausea, loose stools, and sun sensitivity, are easily addressed by taking food with each dose and using sunscreen.
- There are insufficient data available at this time to recommend use of St. John's wort by children or during pregnancy or breast-feeding.

Drug Interactions

St. John's wort has serious potential interactions with many prescription medications, including antidepressants, birth control medications and others**. The use of St. John's wort should always be discussed with the prescribing physician.**

CONCLUSION

St. John's wort is a commonly-taken and well-supported treatment for mild to moderate depression. It may have other benefits, but also has serious risks of drug interactions. Adjunctive use with antidepressants requires caution and strict coordination with the prescribing physician. Long-term use also requires consultation with a health care practitioner.

OUTLINE

1. *Hypericum perforatum*, commonly called St. John's wort, hypericum, Klamath weed, or goat weed, is a perennial plant with yellow flowers whose medicinal uses were first recorded in ancient Greece. It is the most studied and one of the most popular CAM products used for mental health conditions. It is a common roadside plant throughout the United States, Europe and Asia and has a long history of folk use in many cultures. The prevalent name St. John's wort apparently refers to John the Baptist, as the plant blooms around the time of the feast of St. John the Baptist in late June in the northern hemisphere.

2. Research on St. John's wort has be hampered by the intermittent course of most depression (its tendency to come and go), variability in the quality of extracts, use of low doses of the

antidepressants used as active controls for comparison, and lack of research on the risk of serotonin syndrome when St. John's wort is combined with other anti-depressants. Serotonin syndrome is a serious condition defined by muscle rigidity, fever, confusion, increased blood pressure and heart rate, and coma. See Major Risks, below.

3. **PREPARATION:** The flowering tops of St. John's wort are used to prepare teas and tablets containing concentrated extracts. There is no standardized extract of St. John's wort, but Mischoulon and Rosenbaum report that most studies use a formula of 0.3% hypericin or hyperforin (the actual active ingredient is unknown), and the Schwabe company has recently tested its proprietary St. John's wort formula (WS 5570) with success in treating more severe depression. It is urgent that more testing be done and that a standardized non-proprietary extract be developed for further study. *Berkeley Wellness* cautions that formulas vary widely in the amount and bio-availability of hypericin or hyperforin and that contaminants can be a problem.

4. **POTENTIAL USES:** According to NCCAM, St. John's wort is used for severe depression, anxiety, and sleep disorders, though the available evidence supports only its use for mild to moderate depression. A few randomized controlled studies show beneficial effects of John's wort for treatment of somatization disorder (similar to hypochondria, transferring emotional conditions to physical symptoms) and seasonal affective disorder. It has also been tested (unsuccessfully) for use to relieve irritable bowel syndrome.

5. **EFFICACY**: **MILD TO MODERATE DEPRESSION: Eight sources consulted for this outline agree that St. John's wort is better than placebo and possibly as effective as tricyclic antidepressants and SSRIs in treating short-term mild to moderate depression.**
   - Fugh-Berman and Cott found St. John's wort to be an evidence-based treatment for mild to moderate depression, relying principally on a 1996 meta-analysis evaluating twenty-three randomized trials of St. John's wort (of which twenty were double-blind) involving 1757 patients with mild to moderate depression.[1] "**Improvement in depressive**

symptoms (usually measured by the HAM-D or Clinical Global Impression scale) was observed in all groups. In 15 placebo-controlled trials, St. John's wort was found to be significantly more effective than placebo. In eight treatment-controlled trials (i.e., trials contrasting St John's wort with an active clinical agent), clinical improvement in those receiving St. John's wort did not differ significantly from those receiving tricyclic antidepressants."[2]

- Brown *et al.* note that **recent studies support the efficacy of St. John's wort in treating mild to moderate depression**. However, they do not recommend it as a first line treatment because of the incidence of phototoxicity (1%) and the risk of medication interactions. However, they note that **people with a history of good response to low-dose SSRIs but intolerable side effects such as weight gain or sexual dysfunction, would be better candidates for St. Johns wort**.[3]
- Mischoulon and Rosenbaum are more positive: **St. John's wort, "has demonstrated superior efficacy to placebo and equal efficacy to low dose tricyclic antidepressants in most of the older controlled trials, but has had more mixed results against the SSRIs and placebo in some of the newer, large-scale studies. The most recent studies have generally shown St. John's wort to be more effective than placebo, equal to antidepressants, and able to prevent depressive relapses."**[4]
- **However, they conclude that: "Because the literature as a whole suggests that St. John's wort may be less effective in cases of more severe or more chronic depression, the best candidates for St. John's wort may be those with milder and more acute forms of depression**."[5]
- Lake and Spiegel (by Yee, Yee and Naing) concur that there is "compelling evidence" for the use of St. John's wort in mild to moderate depression, terming studies in more serious depression "inconclusive."[6]
- The *Natural Standard* concurs that: "**Numerous studies report St. John's wort to be more effective than placebo and equally effective as tricyclic antidepressant drugs in the short term treatment of mild to moderate major depression (1-3 months.)**"[7] The focus on short-term use is significant. One of the most significant research gaps is lack of

information on longer-term use of St. John's wort. Although many people use St. John's wort as long-term treatment, there is little evidence of long-term safety or efficacy. The clinical studies have been short (24-26 weeks at the most), and most have been small. The one exception, the 2002 NIMH/NCCAM Hypericum Depression study, was inconclusive.

- *Berkeley Wellness'* 2010 review of Dietary Supplements confirms the **"consensus" that St. John's wort, "works better than a placebo [and at least as well as tricyclic anti-depressants or SSRIs] in treating people with mild to moderate depression, at least in the short term**."[8]
- *Consumer Reports* found St. John's wort to be, "**likely effective for improving symptoms of some forms of depression.**" The significance of the Consumer Reports reference is that St. John's wort was one of only 11 popular supplements that: "**have been shown to likely be safe for most people and possibly or likely to be effective in appropriate doses for certain conditions**."[9]
- The Mayo Clinic states that, "St. John's wort **is effective in treating mild to moderate depression and [is] relatively safe. … It has been shown to be as effective as some prescription antidepressants and with fewer side effects**…. Its drawback -- and the reason [that Mayo] gave it a yellow light instead of a green -- is that it interacts with many medications and has caused serious side effects."[10]
- The National Center for Complementary and Alternative Medicine addressed St. John's wort in its October, 2012 Clinical Digest:

> St. John's wort has been used for centuries for mental health conditions and is widely prescribed for depression in Europe. There is public interest in the United States as well, and many people come to NCCAM's Web site seeking information on St. John's wort for depression, consistently making it one of the top five search terms every month. However, **current evidence for using St. John's wort for depression is not conclusive**, and the herb can have serious side effects. It is also important to note that in the United States, the Food and Drug Administration has not approved its use as an over-the-counter or prescription medicine for depression.[11]

6. **SEVERE DEPRESSION**

- **Despite conflicting clinical evidence, Mischoulon and Rosenbaum express hope that St. John's wort may eventually be found effective in moderate to severe depression. But this hope is not shared by the other sources.** *Berkeley Wellness Reports* is more pessimistic, stating flatly that studies do not support the use of St. John's wort for severe depression, depression of long duration, or bipolar disorder. The *Natural Standard* describes the scientific evidence for use of St. John's wort for moderate to severe depression as "unclear" and "speculative," and the Mayo Clinic focuses on the negative studies, counseling the use of stronger medications. Even Consumer Reports limits its endorsement to "some forms" of depression, presumably excluding moderate to severe symptoms.
- **2002 NIMH/NCCAM HYPERICUM DEPRESSION STUDY.** The most important reasons why it is so difficult to evaluate the effectiveness of St. John's in severe depression is that preparations of the drug are not standardized and severe depression is notoriously subject to spontaneous remission, as illustrated by the **high placebo response (32%) in the landmark 2002 NIMH/NCCAM Hypericum Depression study**, which **compared to a 24% remission rate for St. John's wort and sertraline (Zoloft) and thus cast doubt on the efficacy of St. John's wort in moderate to severe depression**.[12]
- With regard to the 2002 NIMH/NCCAM Hypericum Depression study, **Mischoulon and Rosenbaum point out that a 32% placebo remission rate is, in and of itself, a statistical anomaly, and that the occasional high spontaneous remission rate of depressive symptoms, especially in people with moderate to severe depression, makes it difficult to assess the efficacy of mental health interventions. Thus, according to Mischoulon, the emphasis in the 2002 study should have been on the significant finding of equivalency of efficacy between St. John's wort and sertraline (Zoloft), a well-recognized antidepressant, more than on the difference between both and the high placebo remission rate found in the study. However, the 2002 study had a negative effect on public perception, casting doubt on all depression medications, herbal and**

synthetic, and effectively confining advocacy of St. John's wort to people with mild to moderate depression.

- The *Natural Standard* endorses the use of St. John's wort only for **mild to moderate depression,** which it ranks as **"A," "Strong scientific evidence for this use."** It relegates all other uses to category C, "Unclear scientific evidence for this use." These include anxiety disorder, moderate to severe depressive disorder, obsessive-compulsive disorder, seasonal affective disorder, and social phobia.
- The Schwabe study published in 2005[13] is the most persuasive evidence that St. John's wort may be effective for more severe depression. It used doses of 1800 mg per day of the Schwabe St. John's wort formula (WS 5570) compared to 40 mg daily of paroxetine (Paxil) in 251 participants with moderate to severe depression. Over a six-week period, **HAM-D scales decreased by a mean of 14.4 for the St. John's wort formula group and 11.4 for the paroxetine group, a significant improvement in effectiveness over the SSRI**. In the continuation phase (after successful acute treatment), both the St. John's wort formula and the SSRI group had similar continued efficacy and similar improvements in HAM-D scores, without statistically significant differences in continuation phase outcomes or relapse prevention.[14] **71% of patients with moderate to severe oppression responded to the Schwabe St. John's wort formula, in comparison to only 60% given paroxetine (Paxil).**
- **Thus, according to Mischoulon and Rosenbaum there may be a role for St. John's wort in the treatment of more severe depression**, although the difference between German and American studies remains striking, and more studies will be needed to bridge the gap. In particular, the use of different formulas makes it difficult to compare results. The studies have generally used a 0.3% hypericin or hyperforin, but the actual active ingredient is unknown, and proprietary mixes are not disclosed. Among other initiatives to clarify the research record, the Schwabe formula should be further tested in cases of moderate to severe depression to determine whether the company's positive results can be replicated.

- **Brown *et al.* II** (by Sarris)**, while agreeing that St. John's wort is not a first-line treatment for severe depression, concedes that at least one study does support such use if medications are ineffective or poorly tolerated and no suicidal thinking is evident.**[15]

7. **SUGGESTED BUT UNPROVEN USES: SEASONAL AFFECTIVE DISORDER: Based on a few randomized studies,** Brown *et al*. also recommend St. John's wort for seasonal affective disorder. However, the studies show no incremental benefit over light therapy alone. Other uses, including **anxiety, perimenopausal mood disorders, premenstrual syndrome, and fibromyalgia**, have been proposed, but neither Brown *et al*. nor Brown *et al*. II nor Lake and Spiegel recommend using St. John's wort for any of these uses. The relative risks St. John's wort compared to other CAM remedies weigh against experimentation outside of clinical studies.

8. **ADJUNCTIVE USE - CAUTION: Brown *et al.* recommend that: "St. John's wort can be useful for mild depression, combined with other treatments, when there is need for an incremental boost in antidepressant effect, if there is seasonal affective disorder, or when somatic symptoms are prevalent."**[16] **But see MAJOR RISKS below, concerning the danger of serotonin syndrome. Adjunctive use of St. John's wort is not yet evidence-based, drug/herb interactions must be monitored and studied, and caution is advised. People considering using St. John's wort together with an antidepressant or other prescription medicine are strongly advised to do so ONLY under a physician's supervision. See Drug Interactions below for more information.**

9. **NEGATIVE EVIDENCE**
   - According to *Berkeley Wellness*, a well-designed 2010 study found St. John's wort ineffective to relieve **irritable bowel syndrome**. According to Brown *et al.* II, high-quality clinical trials have ruled out use of St. John's wort for **ADHD, obsessive- compulsive disorder and social phobia.**

- *Berkeley Wellness* cites negative evidence concerning the use of St. John's wort for treatment of **severe depression, depression of long duration, bipolar disorder, anxiety, obsessive-compulsive disorder, seasonal affective disorder, sleep disorders, or premenstrual syndrome**. Brown *et al.* disagree concerning **seasonal affective disorder**. Existing evidence does not resolve this controversy.

10. **MAJOR RISKS**

- The **risks of serotonin syndrome in people already taking medication for depression are significant.** Serotonin syndrome is a condition defined by tremor, muscle rigidity, fever or drop in body temperature, confusion, increased blood pressure and heart rate, and coma. Using St. John's wort with MAOIs may also increase the risk of severely increased blood pressure. These symptoms may occur in people taking St. John's wort with SSRI antidepressants such as fluoxetine (Prozac) or sertraline (Zoloft) or with monoamine oxidase inhibitors (MAOIs) such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate).
- **Likewise, the risk of triggering cycling (speeding up the depression/mania cycle) in people with bipolar illness is severe**. These two risks make it imperative that people who have already been under physician treatment, and especially people already taking psychotropic medication, get physician advice before using St. John's wort. Use of a mood stabilizer may reduce this risk.

11. **DRUG INTERACTIONS**

- **The potential drug interactions with St. John's wort are many and serious.** This alone caused the Mayo Clinic to give St. John's wort a **yellow caution light**, saying, "You shouldn't take St. John's wort if you take prescription medications. It's also important to talk to your doctor before taking St. John's wort. If you have a more severe form of depression, you may need a stronger medication."[17] **All of the cited sources urge caution in the use of St. John's wort if any other medications are being taken and counsel physician advice.**

- Mischoulon and Rosenbaum detail the gradually developing concern over drug-drug interactions with St. John's wort: "These interactions, occurring largely via the liver enzyme CYP-450-3A4, have resulted in decreased activity of several drugs, including warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, and irinotecan HCl injection (Camptosar)."[18]
- The *Natural Standard* states that: "St. John's wort interferes with the way the body processes many drugs using the liver's cytochrome P450 enzyme system. As a result, the levels of these drugs may be increased in the blood in the short term (causing increased effects or potentially serious adverse reactions) and/or decreased in the blood in the long term (which can reduce the intended effects)."[19] Examples of medications that may be affected in this matter include: carbamazapine, cyclosporine, which prevents the body from rejecting transplanted organs, irinotecan (Camptosar) and possibly other drugs used to treat cancer, midazolam, nifedipine, theophylline (dimethylxanthine), fenprocoumon (Marcoumar, Marcumar**),** statins, anesthetics (undefined, presumably general), anticoagulants like warfarin (Coumadin) and related anticoagulants, and human immunodeficiency virus drugs such as nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, indinavir (Crixivan) and possibly other drugs used to control HIV infection.
- **The US Food and Drug Administration suggests that people with HIV/AIDS taking protease inhibitors or on NNRTIs avoid taking St. John's wort.**
- **Extreme caution is urged for cancer patients receiving chemotherapy and for transplant and other patients who take immunosuppressive drugs.**
- **It must be presumed that, given the popularity of St. John's wort, many people are combining it with standard antidepressants without telling their doctors. Clinicians should advise their patients not to combine St. John's wort with tricyclic antidepressants, SSRIs or MAOIs, because anecdotes of "serotonin syndrome" have been reported, presumably related to St. John's wort's MAOI activity. See Major Risks, above.** In addition, when combined with certain antidepressants, St. John's wort may

increase side effects such as nausea, anxiety, headache, and confusion. Using St. John's wort with MAOIs may also increase the risk of severely increased blood pressure.

- **Mischoulon and Rosenbaum report 17 cases of psychosis resulting from St. John's wort, of which 12 involved mania or hypomania, adding: "Clinicians should therefore advise bipolar patients to use St. John's wort only in combination with a mood stabilizer."[20] People with bipolar illness who take St. John's wort should be carefully monitored, in view of the risk of cycling (speeding up the depression/mania cycle).**
- **St. John's wort can interact with birth control pills, but this interaction is controversial**, with three recent (2003-2008) studies finding no reduced contraceptive effect and two showing lowered contraceptive efficacy.[21] The frequency of interaction is difficult to estimate, and a sixth recent study describes it as "unpredictable." One report mentioned eight cases of interaction, but the rate is unknown. **In summary, there appears to be a potential interaction that decreases biologic activity of oral contraceptives, but this may vary depending on the birth control pill formulation and the St. John's wort formulation (hypericin or hyperforin content) and possibly other factors. The studies are limited by small samples, but this is more than just anecdotal evidence. How likely a woman is to become pregnant from this interaction remains unclear, but there is enough evidence to warrant caution. There is a clear risk of breakthrough bleeding from this interaction.**
- All of the sources urge caution in the use of St. John's wort if ANY other medications are being used. The list of additional potential drug interactions includes:
  - digoxin (digitalis) or digitoxin which strengthen heart muscle contractions
  - loperamide (Immodium) (Probably uncommon)
  - triptan-type headache medications such as naratriptan (Amerge), rizatritan (Maxalt), COX-2 inhibitor drugs like rofecoxib (Vioxx) (Probably uncommon)
  - non-steroidal anti-inflammatory drugs like ibuprofen (Motrin) (Probably uncommon)
  - St. John's wort has been shown to decrease the concentrations of imatinab, omeprazole, tolbutamide, caffeine, dextromethorphan, fexofenadine, cimetidine,

voriconazole, and other medications. This may require adjustments to maintain an effective dose.

- The *Natural Standard* advises caution if benzodiazepine tranquilizers, opioids, or P-glycoprotein regulated drugs are taken with St. John's wort.

12. **SIDE EFFECTS**

- Brown *et al*. conclude that: "**Our view of data from 35 double-blind randomized trials found that dropout and adverse effects for patients receiving St. John's wort were similar to placebo, lower than with older antidepressants, and slightly lower than with SSRIs.**"[22]
- In Brown *et al* II, Sarris concluded more broadly, based on a review of 16 post-marketing studies (34,834 subjects), that St. John's wort is "ten-fold safer than synthetic antidepressants."[23]
- However, it must be kept in mind that clinical trials often do not include patients with co-existing medical or psychiatric disorders who may be on other medications. In real life clinical practice, many people are taking additional medications for co-morbid medical conditions. Therefore, one cannot always generalize the findings from even a randomized study to the potential risks to patients being treated outside of a research trial.
- Generally, Mischoulon and Rosenbaum report, use of St. John's wort by itself creates few dangers, and adverse events are relatively "**uncommon and mild"** for persons who are screened under the above criteria of risk, **somewhat similar but milder than SSRIs**.
- The *Natural Standard* states that St. John's wort is **generally well tolerated for up to three months.** The **most common adverse effects include gastrointestinal upset, skin reactions, fatigue/sedation, restlessness or anxiety, sexual dysfunction, dizziness, headache, and dry mouth.** Studies suggest that **side effects occur in 1 to 3% of patients and** that **this percentage is similar to placebo (and less than standard antidepressant drugs).** [24]

- There are insufficient data available at this time to recommend use of St. John's wort by children or during pregnancy or breast-feeding.
- The list of all of the many observed side effects of St. John's wort includes:
  - sensitivity to sunlight (danger of severe sunburn), rare, under 1% risk, and generally in light-skinned people or with use of antibiotics or birth control pills. **Nonetheless, persons using St. John's wort should use sunscreen and other protection outdoors.**
  - gastrointestinal symptoms including nausea, loose stools, constipation and heartburn/gastric upset. **Persons using St. John's wort should take it with food.**
  - anxiety
  - dry mouth
  - dizziness
  - fatigue/sedation
  - headache
  - sexual dysfunction/disinterest (including impotence)
  - confusion
  - insomnia
  - bruxism (teeth clenching)
  - vivid dreams
  - restless legs
  - tingling
  - suicidal and homicidal thoughts. Mischoulon and Rosenbaum report 17 cases of psychosis, but lesser disturbance is difficult to quantify. **If these thoughts persist, get help.**

13. **DOSAGE:** The typical dose for mild to moderate depression is **900 mg per day** standardized to contain 0.3% hypericin or hyperforin and split in three dosages. **Brown *et al*. note that treating severe depression may require doses of up to 1,800 mg. per day for 6-12 weeks. At these higher doses, Saint John's wort causes more side effects, similar to Zoloft and increases the risk of interactions with medications. This is twice the dosage used in most**

of the cited studies, but because of the many different preparations of Saint John's wort, dosages are not truly comparable. Lake and Spiegel and Brown *et al*. II (through Sarris, J.) recommend dosages of 300 mg three times per day. In the absence of a standardized formulation, dosages can only be considered as approximations.

14. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with St. John's wort and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects.

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[3] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009) at 33.

[4] Nierenberg, A.A., Lund, H.G. & Mischoulon, D., "St. John's Wort: A Critical Evaluation of the Evidence for Antidepressant Effects," in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008) at 35.

[5] *Id.*

[6] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 97.

[7] *Natural Standard Herb and Supplement Guide: An Evidence-based Reference*, "St. Johns wort," at 684-686.

[8] Berkeley (University of California) Wellness Reports – *Dietary Supplements* (2010 and 2011 editions), "St. John's wort" at 51/51.

[9] Consumer Reports, "Dangerous Supplements," published by Consumers Union, September, 2010 at 16-20.

[10] *The Mayo Clinic Guide to Alternative Medicine 2011* (Time Home Entertainment, Inc., New York 2010) at 60.

[11] http://nccam.nih.gov/health/providers/digest/depression-science?nav=cd

[12] Hypericum Depression Trial Study Group, "Effect of Hypericum Perforatum (St. John's wort) in Major Depressive Disorder: A Randomized Controlled Trial," *JAMA* 287:1807-1814 (2002). On the two primary outcome measures, neither sertraline nor H perforatum was significantly different from placebo. The random regression parameter estimate for mean (SE) change in HAM-D total score from baseline to week eight (with a greater decline indicating more improvement) was -9.20 (0.67) (95% confidence interval [CI], -10.51 to -7.89) for placebo vs. -8.68 (0.68) (95% CI, -10.01 to -7.35) for H perforatum (P =.59) and -10.53 (0.72) (95% CI, -11.94 to -9.12) for sertraline (P =.18). Full response occurred in 31.9% of the placebo-treated patients vs 23.9% of the H perforatum-treated patients (P =.21) and 24.8% of sertraline-treated patients (P =.26). Sertraline was better than placebo on the CGI improvement scale (P =.02), which was a secondary measure in this study. Adverse-effect profiles for H perforatum and sertraline differed relative to placebo. http://www.ncbi.nlm.nih.gov/pubmed/11939866

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[14] *Id.*

[15] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 67.

[16] *Id.*

[17] Mayo Clinic, *op. cit.*

[18] Mischoulon and Rosenbaum, *op. cit*. at 34.

[19] *Natural Standard Herb and Supplement Guide: An Evidence-based Reference*, "St. Johns wort," at 685

[20] Mischoulon and Rosenbaum, *op. cit*. at 34.

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S-ADENOSYL-L-METHIONINE (SAM-E) FOR DEPRESSION AND TO ENHANCE THE EFFECTIVENESS OF CONVENTIONAL ANTI-DEPRESSANTS AND AS A POSSIBLE NEUROPROTECTANT

SUMMARY

WHAT WE KNOW

S-adenosyl-L-methionine (commonly called "SAM-e") is a naturally-occurring chemical component present in all cells of the body where it is essential in more than 200 metabolic pathways. SAM-e has been approved as a prescription drug for depression in Germany, Italy, Spain, and Russia, and has been in use in Europe for over three decades. It is available without a prescription in the United States and some other countries.

MENTAL HEALTH IMPLICATIONS

SAM-e appears to be an effective treatment for depression: Five of seven sources agree, and the two others say it's promising. SAM-e can be used alone or in conjunction with other antidepressants. Since its side effects are less than those of many antidepressants, SAM-e is better tolerated by many people: It works more rapidly and does not cause weight gain, sexual dysfunction, sedation, or cognitive interference. One leading researcher (Brown *et al*.) calls SAM-e a "first line CAM treatment" for mild, moderate, or even severe depression.

Recent studies have shown promising potential for treatment of dementia, but those studies are preliminary and small. Experts have suggested that SAM-e may also help address ADHD.

SIDE EFFECTS

- There are few side effects of SAM-e.
- It is better tolerated than other antidepressants by older people and by people on

medications that compromise liver function.

- Mild nausea is the most common side effect and can be alleviated by taking SAM-e with food.
- Like any other activating anti-depressant, SAM-e can worsen underlying agitation, panic, or anxiety. Accompanying use of a mood stabilizer is essential if there is any indication of mania or bipolar disorder. In the absence of bipolar symptoms, a calming agent can be used to deal with any undesirable activating effects of SAM-e.
- SAM-e has not been studied in children or in pregnant or breast-feeding women. Accordingly, although there are no contraindications, it cannot be recommended.

DRUG INTERACTIONS

- There are no known drug interactions with SAM-e.
- In fact, SAM-e may help prevent other drugs from interacting with the liver.

CONCLUSION

More like a vitamin than a drug, SAM-e is a natural metabolite that the body needs more of as we age or if we become ill. SAM-e is generally safe and evidence-based for the treatment of depression. It is also a promising neuroprotectant and may be helpful in treating ADHD. If it were not for the expense and the lack of insurance reimbursement, it would be preferred over most prescription antidepressants.

OUTLINE

1. S-adenosyl-L-methionine (commonly called "SAM-e"), a naturally-occurring metabolite engaged in over 200 essential chemical reactions within all cells of the body, was discovered in 1952. SAM-e is safe both short and long-term because it is a substance that the body needs more of as we age or if we get ill. It is more like a vitamin or an amino acid than a drug.

2. It has been approved as a prescription drug for depression in Germany, Italy, Spain and Russia, and has been in use in Europe for over three decades. It was released in the United States for non-prescription sale in 1999. SAM-e participates in the synthesis of many essential molecules, including the neurotransmitters norepinephrine, dopamine and serotonin, which are implicated in major depression. SAM-e has an important role in the structure of the lipid bilayer in cell membranes, perhaps altering their electrical properties to facilitate transmission. This in turn appears to affect mood.

3. **EFFICACY**

4. **MONOTHERAPY FOR DEPRESSION**

- **Five of the seven sources that address SAM-e agree that SAM-e can be as effective as tricyclic anti-depressants and SSRIs and that it is better than placebo in treating depression. Berkeley Wellness and the Mayo Clinic agree that SAM-e is a promising treatment for depression but caution that long-term benefits and risks are unknown. See below.**
- **A 1994 meta-analysis by Bressa, G.M., assembled** data from twenty-five double-blind studies (fourteen against tricyclic antidepressants and eleven against passive placebo). **The anti-depressant response rate ranged from 17% to 38% better for SAM-e than for placebo. SAM-e was significantly more effective than passive placebo and "equivalently effective to and typically better tolerated than" tricyclic anti-depressants in the treatment of depression.**[1]
- Fugh-Berman and Cott concluded that **use of SAM-e for depression and for some other symptoms of mental disorder is supported by a basic neurobiological rationale and by some clinical evidence.** It functions as a methyl group donor, similar to folate, described in another chapter of this outline.
- A **2002 review** by Brown *et al.* found **SAM-e to be safe and effective for treatment of major depression.** They reviewed sixteen open trials, thirteen double-blind, placebo-controlled studies and nineteen double-blind controlled trials in comparison to standard anti-depressants.[2]
- According to Brown *et al*., SAM-e is **as effective as traditional antidepressants for depression.** A history of a good response to tricyclic antidepressants would "weigh … heavily" in favor of using SAM-e by itself. **Brown *et al.* consider SAM-e to be a "first line CAM treatment" for mild, moderate or severe depression.**[3]
- **A 2002 review by NCCAM, published by the AHRQ, concluded that:**

    - "Compared to placebo, treatment with SAM-e was associated with an improvement of approximately 6 points in the score of the Hamilton Rating Scale for Depression. (This degree of improvement is clinically significant and is equivalent to a partial response to treatment.)

    - Compared to treatment with conventional therapy, SAM-e was not associated with a statistically significant difference in outcomes."[4]
- Mischoulon and Rosenbaum cite the history of over 40 small clinical studies confirming the efficacy of IV and IM administration of SAM-e monotherapy, beginning in 1973, concluding that "parenteral [used by injection, bypassing the stomach and entrails] SAM-e appears to be an effective anti-depressant." In the absence of comparative studies, they question the efficacy of oral dosing and the appropriate dose. However, they note that in the 2010 adjunctive use trial cited below, in which Dr. Mischoulon participated, oral SAM-e was used, with a coating to avoid loss of potency when taken by mouth.
- Mischoulon and Rosenbaum cite **four double-blind studies using oral dosages of 1,600 mg per day** that **found improvement** in depressive symptoms over placebo. The only study that found no greater effect than placebo was flawed by exposure to air of an older form of SAM-e that oxidized and became ineffective (Fava, *et al*. (1992).[5] Mischoulon and Rosenbaum suggest that Fava *et al*.'s older preparation of the drug (later found to degrade substantially in the gut) and the low (400 mg per day) dosage may have contributed to the lack of effect in the 1992 study.
- **Mischoulon and Rosenbaum recommend oral SAM-e monotherapy for mild to moderate depression, for persons who are intolerant of standard anti-depressants, and for those whose depression has proven unresponsive to a series of anti-depressant trials. They also caution that use of a mood stabilizer is essential if there is any indication of mania or bipolar disorder. They are silent on adjunctive use, although the subsequent 2010 article co-authored by Mischoulon (below) supports adjunctive use.**
- **Lake and Spiegel** (through Settle, J.E.) **conclude that SAM-e is one of the most thoroughly studied dietary supplements," and that recent studies have "la[id] to rest charges of inconclusive data."[6] They affirm SAM-s's efficacy for mild to severe depression.**

- **Consumer Reports lists SAM-e as one of eleven "supplements to consider**," stating that it is, "**likely effective in reducing symptoms of major depression**."
- **Berkeley Wellness and the Mayo Clinic take a more conservative position, stating that the real risks and benefits are still not established. Berkeley does add that:** "Some studies show that **SAM-e might be an effective treatment for depression, with fewer side effects than anti-depressant drugs**."
- The Mayo **Clinic gives SAM-e a green light of approval but** states equivocally that: "SAM-e **has promise as an effective treatment for depression…, but the long-term benefits and risks are still unknown**….[I]t's best to consult your doctor before trying SAM-e. Two drawbacks are the inconsistent quality and high price…." "…[M]ost of the studies were poorly designed. Large-scale, controlled studies are needed…."
- Weil cites with approval the 2010 Papacostas, Mischoulon, Shyu, Alpert & Fava study cited below under adjunctive use and states generally that SAM-e "works quickly, often lifting mood within days rather than weeks [as is often the case with prescription antidepressants.]"[7] He says unequivocally that: "You can use SAM-e with prescribed antidepressants (and other medications)."[8]
- The Berger *et al.* study, with over 20,000 participants, is a larger scale validation of safety [not efficacy, since the focus of the study was on arthritis] than can be obtained for most nutriceuticals.[9]

5. **ADJUNCTIVE USE FOR DEPRESSION**

- **Brown *et al*. suggest that SAM-e is also "quite useful" in augmenting the effect of other antidepressants, including MAOIs, SSRIs, SNRIs, and tricyclics.** Brown *et al*. do not specify a recommended dose for augmentation, but rather suggest starting with 200-400 mg per day and increasing the dose every 3-7 days as tolerated until a response is achieved. They point out that there is a wide range in dose requirements for response depending on the medication being augmented and the characteristics of the people receiving treatment.

- **Confirming this suggestion, a 2010 clinical trial by Papacostas, Mischoulon, Shyu, Alpert & Fava found that SSRI non-responders improved significantly when SAM-e was added to the SSRI dose. The trial had 73 subjects, selected because their HAM-D scores had failed to improve on SSRIs alone. Subjects were given oral dosages of SAM-e 1,600 mg per day (a severe depression monotherapy dose) split into two doses of 800 mg each, to supplement a long list of SSRIs, including fluoxetine, citalopram, paroxetine, escitalopram, sertraline, duloxetine and venlafaxine, at manufacturer-specified minimum dosages. HAM-D response and remission rates for the SAM-e group were 36.1% and 25.8% respectively, compared to 17.6% and 11.7% for the placebo group. Translating that into people, six people treated with placebo responded and four remitted; in contrast, of the people receiving SAM-e supplementation, 18 responded and 14 remitted.**[10]
- Additional studies should help in determining optimal doses, safety for long-term use, effectiveness in preventing relapses, and appropriate protocols for complementary use with other anti-depressant drugs.
- **Thus, use of SAM-e as an adjunctive treatment to tricyclics, SSRIs and MAOIs appears to hold promise.** Doses will vary depending on the dose and effect of the antidepressant and the individual's characteristics Larger and longer term studies are needed to confirm and extend the evidence of efficacy and absence of significant adverse drug interactions. Other potential drugs with which SAM-e might be used adjunctively remain to be tested. As with any combination treatment, adjunctive SAM-e therapy should be tried under close supervision with the prescribing physician.

6. **NEUROPROTECTION**

- Recent U.S. studies have shown promising evidence of effectiveness of SAM-e in protecting the aging brain.
- Brown and Gerbarg cite three small but **promising recent** studies of the use of SAM-e for treatment and prevention of dementia, using a complex nutriceutical formulation including folate (vitamin B9) (400 micrograms), vitamin B12 (6 micrograms), vitamin E

(30 IU), N-acetyl cysteine (600 mg), acetyl-L-carnitine (500 mg), and 400 mg of SAM-e.[11] As stated in the Chan, Paskavitz, Remington, Rasmussen, & Shea study, "Preclinical studies … demonstrate that the constituents of this formulation provide neuroprotection against oxidative stress, decrease PS-1 expression, γ-secretase[12] activity, Abeta generation and tau phosphorylation, increase GSH, ATP, and acetylcholine, compensate for ApoE deficiency, prevent cognitive decline, and decrease aggression. These are the principal clinical markers of dementia.

- The initial two nutriceutical formulation studies, first, an open label study of people with early Alzheimer's Disease and second, double-blind and placebo-controlled study of people without dementia, showed **significant improvement in cognitive performance and lessening of behavioral difficulties in all age cohorts below age 74.** Of course, variations in the nutriceutical formulation might or might not change these results, and differential studies are needed, but the studies as a whole point to a promising avenue for supplementation with SAM-e in combination with other nutrients.
- Chan *et al.* found improved performance of the **early Alzheimer's** group against historic placebo groups in both the Neuropsychiatric Inventory (NPI) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADSC-ADL) measurements. The preliminary findings also demonstrated NPI performance, "**apparently equivalent to that of individuals receiving donepezil and apparently superior to that of individuals receiving galantamine or placebo**."[13]
- Chan *et al*. suggest that SAM-e may be the most important constituent of the formulation, but they stress that: "the impact of simultaneous administration of multiple agents provided superior neuroprotection."[14] Remington, Chan, Paskavitz & Shea [15] took the next step and did a small double-blind, placebo-controlled trial of the same neutriceutical formulation with SAM-e on 12 institutionalized patients diagnosed with **moderate- to late-stage Alzheimer's Disease**. Participants receiving the formulation demonstrated a clinically significant delay in decline in the Dementia Rating Scale and clock-drawing test as compared to those receiving placebo. Institutional caregivers reported approximately 30% improvement in the Neuropyschiatric Inventory

and maintenance of performance in the Alzheimer's Disease Cooperative Study-Activities of Daily Living for more than 9 months. This formulation holds promise for delaying the decline in cognition, mood, and daily function that accompanies the progression of Alzheimer's disease, and may be particularly useful as a supplement for pharmacological approaches during later stages of this disorder.[16]

- An Italian review of omega-3 essential fatty acids and SAM-e recommended dual supplementation (**with nutriceuticals added) for "very mild"** Alzheimer's disease and mild cognitive impairment (Panza *et al*., epub 2006).[17]
- .In Brown *et al*. II, Bottiglieri states that even without other nutriceuticals, there is "significant" evidence that SAM-e can, "improve measures of cognitive function as well as mood and speed of mental processing."[18]
- Further research on the potential use of SAM-e for neuroprotection in combination with other nutrients could be extremely beneficial.

7. **SUGGESTED BUT UNPROVEN USES: ADHD:** Brown and Gerbarg cite one 4-week open-label study of eight men with adult attention deficit hyperactivity disorder that **showed significant improvement in measures of ADHD as well as mood in 75% of the subjects**.[19] Brown and Gerbarg recommend SAM-e in ADHD if there has been an incomplete response to other medications, stimulants are not well-tolerated or have lost effectiveness over time, or the person is experiencing depression as well as ADHD.[20]

8. **DRUG INTERACTIONS**
   - Brown *et al.* state that there are **no proven reported adverse reactions with other medications** and that SAM-e protects the liver from the adverse effects of other medications. Studies have demonstrated that SAM-e can improve liver function in patients with gallstones, infectious hepatitis, alcohol-related liver disease, or elevated liver enzymes due to medication toxicity.[21] Thus, SAM-e can safely augment the beneficial effects of other anti-depressants. According to Brown *et al*., it has an electroencephalogram profile similar to tricyclic anti-depressants and is the only

adjunctive medication that has been found safe and effective in combination with monoamine oxidase inhibitors.[22]

- The 2010 study co-authored by Mischoulon (cited above) showed the safety of using SAM-e as an adjunct to SSRIs.
- The Mayo Clinic says that SAM-e can react with antidepressants, but no other source agrees with that caution. See Adjunctive Use for Depression above.
- *Consumer Reports* lists a risk of a toxic reaction when taken with the cough suppressant dextromethorphan, certain (undefined) anti-depressants, narcotic pain relievers or levodopa (for Parkinson's disease**). Brown, Gerbarg and Mischoulon all dissent from the concern expressed about adjunctive use (see discussion above under that title) and levadopa. Brown et al. assert that SAM-e is beneficial in Parkinson's disease. Levodopa depletes SAM-e causing depression and other problems.[23] Administration of SAM-e counteracts some of the adverse effects of levodopa. It does not interact adversely.**

9. **SIDE EFFECTS**

- In Brown et al. II, Bottigleri states the most obvious advantage of SAM-e: "Unlike many prescription antidepressants, SAM-e does not cause weight gain, sexual dysfunction, sedation, or cognitive interference."[24]
- SAM-e is **activating**, and can exacerbate underlying agitation, panic or anxiety, like any other activating anti-depressant. Brown *et al*. emphasize that SAM-e is most effective against enervating depression: It helps to energize persons whose depression is characterized by low energy, low motivation, tiredness, and hypersomnia. For the same reason, according to Brown *et al*., if depression is accompanied by anxiety or agitation, it may be necessary to use benzodiazepine, buspirone, or another anxiolytic for two to three weeks, until the activating effects of the SAM-e are subside.
- In Brown *et al.* II, Bottigleri cautions that people who are sensitive to the activation produced by SAM-e may need to use a "calming agent" until jitters, agitation and anxiety subside.

- Because of its activating effects, SAM-e generally should not be taken after 4 p.m.
- All of the sources warn that **SAM-e can induce mania in persons with bipolar disorder**. Thus, bipolar disorder needs to be ruled out or controlled before initiating use of SAM-e. A careful psychiatric evaluation is the appropriate way to make this diagnosis
- **Mild and transient anxiety, insomnia, loose bowels and heartburn are the only physical effects** noted by Fugh-Berman and Cott.
- Brown *et al.* cite **"mild nausea"** as the most common side effect of SAM-e. Related symptoms like loose bowels, flatulence and abdominal pain can also occur. Although SAM-e is best taken with an empty stomach, about 20-30 minutes before breakfast or lunch. If nausea is problematic, it may be alleviated by eating a small snack right before taking SAM-e. Persistent irritable bowel effects, nausea or diarrhea may require discontinuation of SAM-e treatment. Occasionally, patients complain of a headache.
- As side effects, *Consumer Reports* lists gastro-intestinal symptoms, dry mouth, headache, mild insomnia, anorexia, sweating, dizziness, anxiousness and nervousness, especially in "high doses" (undefined).
- **According to Brown *et al*., SAM-e has far fewer side effects than other anti-depressants, works more rapidly, and does not cause weight gain or sexual dysfunction. SAM-e does not cause sedation or cognitive interference, making it preferable to many other treatments for depression. It is also better tolerated by elderly people and by people on medications that compromise liver function.**
- **Lake and Spiegel assert flatly that SAM-e presents "no known medical risks."[25]**
- **Mischoulon and Rosenbaum describe the potential benefits of orally-administered SAM-e for depression, including ease of administration and lack of sexual and weight-gain side effects, as well as a shortening of the latency (delay) of the anti-depressant effect of the drug.**
- If SAM-e is combined with a nutriceutical formulation, the side effect and drug interactions of the other constituents must be considered as well. Folate and omega-3 essential fatty acids are dealt with in separate chapters of this outline.

- SAM-e has not been studied in children or in pregnant or breast-feeding women. Accordingly, although there are no contraindications, it cannot be recommended.

10. **DOSAGE**

- Fava *et al.*'s 1995 study used **400 mg per day of injected SAM-e**, but there is no standard IV or IM dose, and oral medication is now the dominant form, with a stomach-acid-resistant covering to slow damage through the digestion process.
- Brown *et al*. recommend an **oral dosage of 400 to 600 mg per day for mild depression, 600 to 1,200 mg per day for moderate depression, 1,200 to 1,600 mg per day for severe depression, and 1,600 to 2,400 mg per day for very severe treatment-resistant depression.** Weil concurs. However, they all caution that consumers who are elderly or frail, or have significant medication sensitivities, significant anxiety, serious gastrointestinal problems, or other serious medical conditions, should work up to these dosages. Starting with a dose as low as 200 mg. per day, Brown *et al.* recommend increasing the dose to the recommended range as long as the medication is well tolerated, over a period of days or weeks. Brown *et al.* note that dosages above 1,600 mg. per day have not been tested in clinical trials, but are sometimes necessary for response.
- In Brown *et al*. II, Bottiglieri states that his review of the clinical trials suggests that the lowest effective oral dose is **800 mg per day for mild to moderate depression and 1600 mg per day for severe depression.**
- For **dementia**, the three cited trials used **400 mg per day** as part of the nutriceutical tonic. In Brown *et al*. II, Bottiglieri states that **400 mg of SAM-e alone, 3 times a day** for 3-5 months, can, "improve measures of cognitive function as well as mood and speed of mental processing."[26]
- All SAM-e products must list the amount of SAM-e in each tablet. Pharmaceutical grade SAM-e is available without a prescription. The two pharmaceutical grade brands are Donamet and SAMYR. They are well regulated by the European equivalent of the FDA. Also, ConsumerLab.com posts reviews of other SAM-e brands including analysis of the

number of milligrams of active product in each brand. Consumers should be wary of purchasing "bargain brands," because they are often of poor quality with less active ingredients.

- Brown, Gerbarg and Bottiglieri stress that because SAM-e is easily oxidized, oral doses should be purchased only in blister packs that isolate each pill. They should not be stored in the refrigerator to avoid condensation within the blister pack.

11. **RESEARCH:** Long-term studies with tracking of side effects are needed to confirm and extend the positive findings of SAM-e research, particularly in the areas of medication augmentation and neuroprotection. Since many doctors are not yet familiar with SAM-e, dissemination of information about its safety and efficacy is needed. SAM-e has been used by hundreds of thousands of people and many of these have taken it for 10 years, some for 20 years. No long-term adverse effects have appeared. If anything, it has long-term health benefits. The fact that there was a well-done, closely monitored for side effects, 3-year study of SAM-e in 20,000 people should be considered a sufficiently long-term trial.

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[12] The best-known substrate of gamma secretase is amyloid precursor protein, a large integral membrane protein that, when cleaved by both gamma and beta secretase, produces a short amino acid peptide called amyloid beta whose abnormally folded fibrillar form is the primary component of amyloid plaques found in the brains of Alzheimer's disease patients.

[13] *Id*. at 577.

[14] *Id.* at 579.

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[20] Brown, R.P. & Gerbarg, P.L., *Non-Drug Treatments for ADHD* (W.W. Norton and Company, New York 2012), at 126-129.

[21] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009), at 20.

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[25] Lake and Spiegel, *op. cit*. at 120.

[26] *Id.*

TRYPTOPHAN/5-HYDROXY-L-TRYPTOPHAN (5-HTP) FOR ANXIETY, FOR DEPRESSION AND TO ENHANCE THE EFFECTIVENESS OF CONVENTIONAL ANTI-DEPRESSANTS

SUMMARY

WHAT WE KNOW

Tryptophan, an amino acid, is a precursor of serotonin and has been used since the 1970s to increase brain levels of serotonin. **5-HTP (5-hydroxy-L-tryptophan)** is a modern variant, now extensively marketed in the United States. Before it was temporarily banned by the FDA (from 1989-2002), tryptophan was successfully used to supplement standard tricyclic antidepressants. It has been used successfully with MAOIs. Two meta-analyses, in 2004 and 2006, showed modest support for the use of 5-HTP as an adjunctive treatment for depression. Earlier studies had shown modest effectiveness for anxiety. As with tryptophan, the clinical activity of 5-HTP is believed to result primarily from its ability to act as a precursor of serotonin synthesis and increase central nervous system levels of serotonin.

MENTAL HEALTH IMPLICATIONS

Depression and Anxiety

There are insufficient data to recommend use of tryptophan or 5-HTP, but there is enough promise to merit further research and cautious experimentation if standard treatments for depression or anxiety are ineffective or poorly tolerated. Mischoulon concludes that it is one of the safer of the natural products available for mood disorders, and previous evidence is supportive of its use for depression and anxiety. Mischoulon says that though it appears to act like an SSRI, he still would like to see a new wave of more rigorous research with current preparations before he proceeds to recommend it on the same platform with the better-tested

SSRIs. Despite these evidentiary concerns, 5-HTP has been used clinically for over 30 years for the treatment of a wide variety of conditions, including:

- fibromyalgia,
- insomnia,
- binge eating associated with obesity,
- cerebellar ataxia, and
- chronic headaches.

There is some risk, but it appears to be manageable.

DRUG INTERACTIONS

Interaction with psychotropic drugs has been tested and appears generally safe, but no reported studies have been conducted with SSRIs. Thus, consumers should consult with the prescribing physician before using 5-HTP if they are currently being treated with a psychotropic drug, especially an SSRI.

SIDE EFFECTS

The most common reported adverse effects are gastrointestinal, including nausea, vomiting, and diarrhea. Sedation is also a concern. These side effects are usually moderate and often abate or disappear once a steady dosage is achieved**.** Less common side effects may include headache, insomnia, and palpitations. Studies have shown no sign of toxicity. Generally, oral 5-HTP has been well tolerated. 5-HTP has not been studied in children or in pregnant or breast-feeding women. Accordingly, although there are no contraindications, it cannot be recommended.

CONTAMINATION

Contaminated tryptophan caused an epidemic of eosinophilia-myalgia syndrome (EMS) that peaked in 1989. One researcher cautions that absent testing, tryptophan cannot be presumed to be safe, but others advise that while prescription tryptophan is now safe, consumers should be careful about purchasing non-prescription tryptophan. Thus, there is some risk of

contamination with both tryptophan and 5-HTP, and consumers should buy these supplements only from reputable sources.

CONCLUSION

Promising, but not yet proven. With the exception of adjunctive use, which needs to be under physician supervision, 5-HTP is a reasonable choice if other treatments prove ineffective or are poorly tolerated.

OUTLINE

1. **Tryptophan**, an amino acid, is a precursor of serotonin and **has been used since the 1970s to increase brain levels of serotonin**. Small, mostly uncontrolled studies have shown positive effects in some depressed patients, but others have not. The reason proposed for the equivocal effects is that tryptophan by itself may be insufficient to boost serotonin levels. On the other hand, using tryptophan (or its active, metabolized form, 5-HTP) as an adjunct to supplement standard antidepressants has been more successful. Tryptophan was banned by the FDA from 1991-2002. 5-HTP has been found effective for relief of anxiety in preliminary double-blind studies.

2. **5-HTP (5-hydroxy-L-tryptophan)** is a modern variant, now extensively marketed in the United States. 5-HTP is created in the body from tryptophan and in turn is used by the body to create serotonin. 5-HTP may thus offer the advantage of bypassing the conversion process, which requires the enzyme tryptophan hydroxylase, which in turn can be affected by stress and other factors. Supplemental 5-HTP is created from the seeds of the *Griffonia simplicifolia* plant and is often combined with St. John's wort.

3. **EFFICACY**: **MONOTHERAPY AND ADJUNCTIVE USE FOR ANXIETY AND DEPRESSION: There are insufficient data to recommend use of tryptophan or 5-HTP, but there is enough promise to merit further research and to advise consumers using tryptophan or 5-HTP of the promising evidence that exists.** Though the list of noted drug interactions and side effects is still short, it will grow longer as we learn more about 5-HTP and tryptophan. So a consumer must decide whether to take 5-HTP or tryptophan now because it is promising, or later, when science knows enough to make the call and more information is available. If you are under a physician's care, and especially if you are taking psychotropic medicine, you definitely should talk with your medical doctor before trying adjunctive supplementation with 5-HTP or tryptophan.
    - **Although only five of eleven controlled studies showed statistically significant improvement**, according to Brown *et al*., **increasing numbers of consumers are using 5-HTP as a treatment for depression.**
    - **Lake and Spiegel** (through Settle, J.E.) **cite the double-blind study by Kahn et al. (1985, 1987), which showed significant improvement in anxiety symptoms, but not depression** 5-HTP was as good as clomipramine (Anafranil) for anxiety, but less effective for depression.[1]
    - As early as 1976, Walinder *et al*.[2] found that 24 depressed patients started on clomipramine (Anafranil), an older tricyclic antidepressant, improved more rapidly with tryptophan supplementation. There are also considerable data suggesting that tryptophan depletion can increase depressive symptoms in patients with major depression and seasonal affective disorder. Subsequent reversal of depression with intravenous tryptophan supports the notion of an antidepressant effect. No interaction was noted with tricyclic anti-depressants.
    - Lake and Spiegel (through Settle, J.E.) state flatly that the existing research on 5-HTP is flawed by small sample sizes, uncontrolled study conditions and heterogeneous study populations. Reports of a 20% relapse rate after the first month of treatment makes longer studies essential in assessing the efficacy of 5-HTP.

- According to Iovieno *et al*. (Iovieno, N., Dalton E. D., Fava, M. & Mischoulon, D., "Second-tier Natural Antidepressants: Review and Critique," *Journal of Affective Disorders* 130(3):343-57 (2011)), **5-HTP has been used clinically for over 30 years for the treatment of depression.** Most studies of the use of 5-HTP for depression were conducted 20 or more years ago, at a time when there was a great interest in the serotonin hypothesis of depression. Its use declined dramatically when tryptophan was banned, but it is making a strong comeback.
- Iovieno *et al.* describe all of the old studies and conclude that "**results from the published trials suggest that 5-HTP may have some efficacy in the treatment of depression** and may deserve to be evaluated in more rigorous studies in order to conclusively establish its effectiveness, **both as monotherapy and as augmentation**."[3] However, they warn, the older research is defective. A 2002 systematic review of published clinical trials in which 5-HTP and L-tryptophan were used in depression found that only two of the 108 examined trials were of sufficient quality to meet the inclusion criteria for a meta-analysis.
- **Mischoulon concludes that tryptophan/5-HTP is one of the safer of the natural products available for mood disorders, and previous evidence is supportive of its use for depression and anxiety, but "larger and more rigorous studies are needed to clarify its place in the psychiatric armamentarium." Mischoulon says that though it appears to act like an SSRI, he still would like to see a new wave of more rigorous research with current preparations before he proceeds to recommend it on the same platform with the better-tested SSRIs.**
- **Before it was banned by the FDA (from 1991-2002), tryptophan was successfully used to supplement standard tricyclic antidepressants. Two meta-analyses**, in 2004[4] and 2006,[5] **showed modest support for the use of 5-HTP as an adjunct to tricyclic anti-depressants in the treatment of depression.** As with tryptophan, the clinical activity of 5-HTP is believed to be primarily due to its ability to act as a precursor of serotonin synthesis and increase central nervous system levels of serotonin.

- In their 2006 meta-analysis cited above, Turner and colleagues concluded that 5-HTP supplementation deserves reconsideration as an anti-depressant, but that **it is premature to recommend its widespread clinical use until more extensive clinical trials further address its efficacy and safety, especially in adjunctive use with SSRIs.**
- **Iovieno *et al*. concur, stating that in the absence of any studies of modern anti-depressants, 5-HTP should be "used with caution" as an adjunct to SSRI or MAOI treatment (due to the risk of serotonin syndrome) and that "vigilance" is necessary if 5-HTP is used in monotherapy or adjunctive treatment with tricyclics.**
- **Brown *et al*. II, through Akhondzadeh, Gerbarg, P.L. and Brown, R.P., reviewed 27 studies of 5-HTP treatment for depression and found only five showed statistically significant results over placebo. They conclude that, "limited evidence supports the use of 5-HTP as augmentation to antidepressant medications."[6]**
- There are no adequate, well-controlled trials on the use of 5-HTP or tryptophan in children or in pregnant or lactating women, nor any systematic studies evaluating long-term side effects.

4. **SUGGESTED BUT UNPROVEN USES: FIBROMYALGIA, INSOMNIA, BINGE EATING ASSOCIATED WITH OBESITY, CEREBELLAR ATAXIA, AND CHRONIC HEADACHES: According to Iovieno *et al*., 5-HTP has been used clinically for over 30 years** for the treatment of a wide variety of conditions, including **fibromyalgia, insomnia, binge eating associated with obesity, cerebellar ataxia, and chronic headaches**. There are no published studies of these uses, with the exception of Lake and Spiegel's reference to insomnia treatment. Lake and Spiegel state that, "doses up to 600 mg have been shown to be effective in treating insomnia but may increase the incidence of vivid dreams."[7] They recommend 100-300 mg 30-45 minutes before bedtime for insomnia.

5. **DRUG INTERACTIONS:** There is concern about the possibility that combining tryptophan or 5-HTP with any psychotropic drug, especially an MAOI or SSRI antidepressant, may cause serotonin syndrome. This syndrome is characterized by hypertension, hyperthermia,

flushing, hyperreflexia, dizziness, disorientation, and myoclonus. Serotonin syndrome may theoretically occur with any drug that affects the serotonin system. However, Iovieno *et al.* report that **serotonin syndrome has never been reported in humans in association with 5-HTP, either as monotherapy or in combination with other medications, including TCAs, MAOIs and tryptophan** (citing Alino *et al*., 1976; Das *et al*., 2004; Kline and Sacks, 1980; Nardini *et al*., 1983; Nicolodi and Sicuteri, 1996; & Quadbeck *et al*., 1984).[8] Alino *et al.* specifically found therapeutic efficacy in augmenting MAOIs with 5-HTP. This list is incomplete. The *Natural Standard* does not review tryptophan or 5-HTP.

6. **SIDE EFFECTS:** The most common adverse effects reported by Iovieno *et al*. are gastrointestinal and include nausea, vomiting, and diarrhea. Lake and Spiegel also caution that 5-HTP may cause sedation. **Generally, oral doses of 200–300 mg per day of 5-HTP have been well tolerated.** Gastrointestinal effects are usually moderate and often abate or disappear once a steady dosage is achieved, and Lake and Spiegel recommend an enteric coating to minimize gastrointestinal side effects**.** A study comparing 5-HTP to 5-HTP plus a peripheral decarboxylase inhibitor (PDI) found that gastrointestinal side effects were dose-dependent and occurred more frequently in patients receiving 5-HTP alone. Less common side effects may also include headache, insomnia, and palpitations. Available studies have shown no sign of toxicity.[9] 5-HTP has not been studied in children or in pregnant or breast-feeding women. Accordingly, although there are no contraindications, it cannot be recommended.

7. **CONTAMINATION:**
    - Contaminated tryptophan caused an epidemic of eosinophilia-myalgia syndrome (EMS) that peaked in 1989. More than 1500 cases were reported by 1998, including 27 deaths. Most patients had arthralgia (73%), rash (50%), cough or dyspnea (59%), peripheral edema (59%) elevated aldolase levels (46%) and elevated liver function tests (43%). Neuropathy or neuritis was seen in 27%.

- Almost all cases for which information was available involved tryptophan manufactured by Showu Denko, a company that had recently changed both its manufacturing process and the strain of bacillus used to manufacture tryptophan. Fugh-Berman cautions that absent testing, tryptophan cannot be presumed to be safe. Lake and Spiegel report one case of EMS in 5-HTP, for which the contaminant was found. Brown and Gerbarg respond that prescription tryptophan and 5-HTP dispensed in the United States is free from contamination, but consumers should be careful about purchasing non-prescription supplements.
- Because of its chemical and biochemical relationship to tryptophan, the safety of 5-HTP has been questioned. However, excluding the one established contamination case, according to a 2004 review by Das *et al.,* no definitive case of toxicity had emerged despite the worldwide usage of 5-HTP for last 20 years, with the possible exception of one unresolved case of a Canadian woman.[10]
- According to Iovieno *et al*., writing in 2010, several other cases of EMS-like syndromes have since been reported in people taking 5-HTP, but the substance was not analyzed.
- According to the Das *et al.* and Iovieno, *et al.* reviews, extensive analyses of several sources of 5-HTP have shown no toxic contaminants similar to those associated with tryptophan nor the presence of any other significant impurities, with the exception of a single study that showed very small amount of toxic chemical in 5-HTP in lab analysis**.** But the quality control issue remains. Thus, there is some risk of contamination with both tryptophan and 5-HTP, and consumers should buy these supplements only from reputable sources.

8. **DOSAGE: Because the half-life of 5-HTP is just 2-5 hours, it should be taken in divided dosages throughout the day, at least 20 minutes before meals.** The "average" dose of **5-HTP** cited by Brown *et al*. is **200-300 mg. per day**, in divided dosages. Iovieno *et al*. agree. Lake and Spiegel recommend a **maximum of 150 mg**. Brown *et al*. found that the doses of 5-HTP used in the reviewed studies ranged from 20 to 3250 mg per day, more often from

200 to 300 mg per day, with dose scheduling ranging two- to four-times per day. Their recommended dosing frequency was **three times per day**.

9. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with 5-HTP or tryptophan and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects. The studies are all old, small, and short-term. Despite its popularity, 5-HTP is truly an orphan supplement. Research needs to consider long-term as well as short-term effects and needs to catch up with consumer use. Prompt government and academic attention are required.

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[1] Lake, J.A. and Spiegel, D., *Complementary and Alternative Treatments in Mental Health Care*, American Psychiatric Publishing, Inc., Washington (2007), at 135.

[2] Walinder, J., Skott, A., Carlsson, A., Nagy, A. &, Bjorn-Erik, R., "Potentiation of the Antidepressant Action of Clomipramine by Tryptophan," *Arch. Gen. Psychiatry* 33:1384 –9 (1976).

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[4] Das, Y.T., Bagchi, M., Bagchi, D. & Preuss, H.G., "Safety of 5-HTP," *Toxicology Letters* 150(1):111-122 (2004).

[5] Turner, E.H., Loftus, J.M. & Blackwell, A.D., "Serotonin à la Carte: Supplementation with the Serotonin Precursor 5-HTP," *Pharmacology and Therapeutics* 109(3):325-338 (2006).

[6] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 31.

[7] Lake, J.A. and Spiegel, D., *op. cit*. at 136.

[8] Turner *et al, op. cit.* at 351.

[9] Das, *et al*., *op. cit*. (2004)

[10] Das, Y.T., Bagchi, M., Bagchi, D. & Preuss, H.G., "Safety of 5-hydroxy-L-tryptophan," *Toxicol Lett* 150(1):111-22 (2004).

VALERIAN FOR SLEEP DISORDERS

SUMMARY

WHAT WE KNOW

Valerian has long been used for sleep disorders and anxiety and has also been used for other conditions, such as headaches, depression, menopausal symptoms, sedation, irregular heartbeat, and trembling. The research is not yet good enough to confirm those claims.

But the risk is minimal.

MENTAL HEALTH IMPLICATIONS

Research suggests that valerian may be helpful for sleep disorders, but there is not enough evidence from well-designed studies to confirm this. Three of the eight sources discussing valerian decline to recommend its use for sleep disorders, citing inadequate evidence, despite its traditional use in the United States, Europe and Japan. Brown *et al* II's 2013 statement would raise the dissent to 50% -- 4 of 8. In the sleep laboratory, the effects of valerian were not significantly different from those of placebo, and a 2007 meta-analysis concluded that no rigorous studies had found any significant effect of valerian on sleep.

There is not enough scientific evidence to determine whether valerian works for anxiety (the sources are split 3 to 3 on the use of valerian for anxiety) or for other conditions, such as headaches, depression, menopausal symptoms, sedation, irregular heartbeat and trembling.

Despite the lack of persuasive clinical evidence of efficacy in treating insomnia, sleep quality remains to be studied, and subjective reports still hold out hope. Valerian may not be ideal for acute treatment of insomnia, but some evidence and analysis suggests that it may be effective in the promotion of natural sleep after several weeks of use. Since it appears relatively safe as long as drug interactions are avoided, valerian may be a CAM support to help with sleep even if it can't cure chronic insomnia.

DRUG INTERACTIONS

The *Natural Standard* cautions that valerian may increase the amount of drowsiness brought on by other drugs or herbs. *Berkeley Wellness* specifically counsels that valerian not be taken with alcohol, tranquilizers or barbiturates. Valerian interacts with anesthetics and so must be discontinued before surgery.

SIDE EFFECTS

Valerian can cause mild side effects, such as occasional gastrointestinal effects, headaches, dizziness, excitability, uneasiness, unsteadiness, low body temperature, tiredness the morning after its use, and a “hangover” from large doses. Similarly, "valerian withdrawal" may occur if the consumer stops using the drug suddenly after long-term high-dose use. This may entail confusion and rapid heartbeat. Valerian is classified by the FDA as "generally regarded as safe," and some researchers refer to valerian as “quite safe.” Long-term use may result in insomnia. Slight reductions in concentration and ability to perform complicated thinking may occur for few hours after taking valerian. Use caution if driving or operating heavy machinery.

Brown *et al*. caution against use of valerian in pregnancy or in association with hepatic disease. Safety for children has been more studied but is still controversial. Accordingly, it cannot be recommended. In the absence of a standard extract, no recommendation can be made on dosage.

CONCLUSION

Promising, but not yet proven. The split of the sources confirms that this is a controversial supplement, even though it appears benign (except for the odor and taste).

OUTLINE

1. Valerian**,** *Valeriana officinalis,* is a plant native to Europe and Asia; it is also found in North America. Valerian has been used as a medicinal herb since at least the time of ancient Greece and Rome. Its therapeutic uses were described by Hippocrates, and in the 2nd century, Galen prescribed valerian for insomnia. Valerian is commonly referred to as all-heal or garden heliotrope.

2. Valerian is an odoriferous, popular European botanical medicine used for its mild sedative and tranquilizing properties. The German Commission E recommends 2 to 3 g of the dried root one or more times a day for "restlessness and nervous disturbance of sleep."

3. Valerian has long been used for sleep disorders and anxiety.

4. **EFFICACY: SLEEP DISORDERS: Research suggests that valerian may be helpful for sleep disorders, but there is not enough evidence from well-designed studies to confirm this. Three of the eight sources discussing valerian decline to recommend its use for sleep disorders, citing inadequate evidence, despite its traditional use in the United States,**

Europe and Japan. In the sleep laboratory, the effects of valerian were not significantly different from those of placebo, and a 2007 meta-analysis concluded that none of the rigorous studies found any significant effect of valerian on sleep.

- In recommending valerian, **Fugh-Berman and Cott relied on two studies suggesting that valerian can induce sleep.** Both valerian preparations produced a significant decrease in subjectively evaluated sleep latency scores and improved sleep quality.
- However**, in the sleep laboratory, the effects of 900 mg of valerian were not significantly different from those of placebo**, a finding that they suggest may be explained by the stressful sleep environment obscuring the mild hypnotic action of valerian.[1]
- **Brown *et al.* cite a 2006 meta-analysis of 16 valerian studies that concluded that it might improve sleep without causing side effects**.[2] Thus, they list valerian for use with insomnia. They point out that the valerian has a cumulative effect over time, and maximal benefit may not be achieved for two weeks. However, Brown *et al*. II cite the 2010 systematic review by Fernandez-San-Martin et al. that showed subjective improvement in sleep quality but little objective evidence of improvement in sleep problems.[3]
- Mischoulon and Rosenbaum extensively critique the existing clinical trials, beginning with the failure to standardize a valerian extract, different doses and dosing schedules, short terms of treatment, and the blend of symptomatic and non-symptomatic individuals in the sample. In one suggestive study, 121 people with significant sleep disturbance responded initially the same as to placebo, but after four weeks, and the valerian-treated group had a significantly better overall response.[4] This leads to the suggestion that longer and larger trials of symptomatic people could give a better idea of the drug's potential in treating sleep disorders. Although it may not be as effective as benzodiazepines for treatment of acute conditions, **Mischoulon and Rosenbaum suggest that valerian may be effective in the promotion of natural sleep after several weeks of use.**

- **However, Mischoulon and Rosenbaum emphasize the 2007 meta-analysis by Taibi *et al*.**,[5] with a subtitle that summarizes the evidence to date: "**safe but not effective**." The analysis included 37 studies, of which 29 were placebo-controlled. **None of the rigorous studies found any significant effect of valerian on sleep**.[6]
- **Lake and Spiegel** (in the Ayurveda discussion authored by Prathikanti)**, state that seven randomized, placebo-controlled studies support use of valerian for the treatment of insomnia.**
- The ***Natural Standard*** is quite negative about the use of valerian for insomnia, qualifying it as **"C," "unclear scientific evidence for this use."** The *Natural Standard* recounts the history of valerian use in the United States from the mid-1800s to our era, when it has been replaced by sedatives and analgesics. It remains popular in North America, Europe and Japan.
- **The Mayo Clinic gives valerian a green light**, and stating that: **"Valerian appears to be beneficial for insomnia … and is generally safe at recommended doses**." However, the clinic recommends using valerian in short courses of treatment, "no more than a few weeks at a time."
- **Weil recommends** valerian pills or capsules for insomnia.[7]
- ***Berkeley Wellness***, while discussing the positive trials, concludes that, "**there is inadequate scientific evidence to show the efficacy of valerian in treating … insomnia**." *Berkeley Wellness* concludes in particular that it has yet to be shown that valerian affects the "quality" of sleep, for which a sleep laboratory would be required.
- Valerian's safety during pregnancy and breast-feeding is unknown. Brown *et al*. caution against use in pregnancy or in association with hepatic disease. Safety for children has been more studied but is still controversial.

5. **SUGGESTED BUT UNPROVEN USES: ANXIETY, HEADACHES, DEPRESSION, MENOPAUSAL SYMPTOMS, SEDATION, IRREGULAR HEARTBEAT, AND TREMBLING**
   - **Brown *et al*., Brown et al. II, Mayo and Weil all support the use of Valerian for mild anxiety. Mischoulon and Rosenbaum, the *Natural Standard*, and *Berkeley Wellness* do**

not. Brown *et al.* cite a 2002 randomized, controlled study which showed improvement only on the "psychic factor" on the Hamilton Anxiety Scale.[8] The abstract concluded: "Although the principal analysis (HAM-A between group comparison) found negative results, the preliminary data obtained in the present study suggest that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety."

- There is not enough scientific evidence to determine whether valerian works for other suggested conditions, such as headaches, depression, menopausal symptoms, sedation, irregular heartbeat and trembling.
- The ***Natural Standard*** is quite negative about the use of valerian for "anxiety disorder, depression, menopausal symptoms and sedation," qualifying all as **"C," "unclear scientific evidence for this use."**

6. **DRUG INTERACTIONS:**
   - The *Natural Standard* cautions that valerian may increase the amount of drowsiness brought on by other drugs, although it cautions, "this is an area of controversy." Examples include benzodiazepines and other tranquilizers such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. In one human study, a combination of valerian and the beta blocker drug propranolol (Inderal) reduced concentration levels more than valerian alone. Agitation, anxiety and self injury were reported in one consumer who took valerian with fluoxetine (Prozac) for a mood disorder. The person was also drinking alcohol, so causality is difficult to assign. In theory, valerian may also interact with anti-seizure medications, although there are no human data to that effect. Valerian may also increase the amount of drowsiness caused by some herbs or supplements, including St. John's wort and kava.
   - *Berkeley Wellness* specifically counsels that valerian not be taken with alcohol, tranquilizers or barbiturates. Valerian interacts with anesthetics and so must be discontinued before surgery.

7. **SIDE EFFECTS**
    - Valerian can cause **mild side effects**, such as occasional gastrointestinal effects, headaches, dizziness, excitability, uneasiness, unsteadiness, low body temperature, tiredness the morning after its use,[9] and a “hangover” from large doses. Similarly, "valerian withdrawal" may occur if the consumer stops using the drug suddenly after long-term high-dose use. This may entail confusion and rapid heartbeat. These symptoms may improve with the use of benzodiazepines such as lorazepam (Ativan). Valerian is classified by the FDA as: "**generally regarded as safe**," and Fugh-Berman and Cott refer to valerian as “**quite safe**.” Slight reductions in concentration and complicated thinking may occur for few hours after taking the drug. Use caution if driving or operating heavy machinery, since valerian can cause “impaired vigilance” for a few hours after ingestion, according to Lake and Spiegel. Long-term use may result in insomnia.
    - **Toxic reactions from valerian are rare** but may include blurred vision and dystonia (a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures).
    - Valerian has an unpleasant taste and odor. One advantage of valerian over other sedatives and hypnotics is that there have been no reported cases of valerian habituation or abuse and only one case of possible withdrawal symptoms.

8. **CONCLUSION: Since it appears relatively safe so long as drug interactions are avoided, valerian may be a CAM support to help with sleep even if it can’t cure chronic insomnia.**

9. **DOSAGE**: The *Natural Standard* states that doses range from **400 to 900 mg per day** of aqueous or aqueous-ethanol extract, corresponding to 1.5 to 3 g of the drug, taken 30 to 60 minutes before going to bed. But the “recommended dose” listed by Mischoulon and

Rosenbaum is lower, **between 450 and 600 mg per day**, presumably in pill or capsule form, approximately two hours before bedtime. Valerian has historically been used in the form of a tea, involving 1.5 to 3 g of the roots steeped for 5 to 10 minutes in 150 mm of boiling water. However, this formulation has not been studied. Doses of 300-1,800 mg per day have been taken by mouth in capsule form. Dosage is difficult to determine for the tea or the tincture. *Berkeley Wellness* states that because the active ingredient(s) have not been isolated and extracts are so different, no dosage can be recommended.

10. **RESEARCH:** Long-term outcomes -- benefits and liabilities from continuing treatment with valerian and comparative assessment with other drugs -- require further investigation, as do the systematic tracking, reporting and quantification of adverse effects.

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[1] "Dietary Supplements and Natural Products as Psychotherapeutic Agents," by Adriane Fugh-Berman, M.D. (of Georgetown Medical School) and Jerry M. Cott, Ph.D. (of the National Institutes of Health) (1999), *Psychosomatic Medicine* 61:712-728 (1999), at 720

[2] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton & Company, New York 2009) at 129, citing Bent, S., Padula, A,. Moore, D., Patterson, M., & Mehling, W., "Valerian for Sleep: a Systematic Review and Meta-analysis," *American Journal of Medicine*, 119(12):1005-1012 (2006).

[3] Muskin, P.R., Gerbarg, P.L., and Brown, R.P., *Complementary and Integrative Therapies for Psychiatric Disorders,* Psychiatric Clinics of North America, copyright Elsevier, Inc., Philadelphia (2013) ("Brown *et al*. II") at 87.

[4] Vorbach, E.U., Gortelmayer, R., Brunning, J., "Therapie von Insomnien: Wirksamkeit Vertraglichkeit eines Badrian-Preparates," *Psychoparmakotherapie* 3:109-115 (1996).

[5] Taibi, D.M., Landis, C.A., Petry, H., Vitiello, M.V., "A Systematic Review of Valerian as a Sleep Aid: Safe but Not Effective," *Sleep Medicine Review*, 11:209-230 (2007).

[6] Mischoulon, D., "Herbal Remedies for Anxiety and Insomnia: Kava and Valerian," in *Natural Medications for Psychiatric Disorders: Considering the Alternatives,* co-edited by David Mischoulon, M.D. and Jerrold F. Rosenbaum, M.D. (both of Harvard Medical School) (Lippincott, Williams and Wilkins, Philadelphia 2002/2008), at 119-139.

[7] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 117, 207 & 212.

[8] Andreatini, R, Sartori, V.A., Seabra, M.L. & Leite, J.R., "Effect of Valepotriates (Valerian Extract) in Generalized Anxiety Disorder: a Randomized Placebo-controlled Pilot Study," *Phytother Res.* 16(7):650-4 (2002).

[9] *Valerian root (Valeriana officinalis).* In: Blumenthal M, Goldberg A, Brinckman J, eds.*, Herbal Medicine: Expanded Commission E Monographs.* Newton, MA: Lippincott Williams & Wilkins; 2000:394–400. Awang D.V.C., Leung A.Y. "Valerian" in: Coates, P., Blackman, M., Cragg, G., et al., eds*., Encyclopedia of Dietary Supplements (*Marcel Dekker, New York 2005) at 687–700.

YOGA FOR DEPRESSION, SCHIZOPHRENIA, ANXIETY, PTSD AND ADHD AND MEDITATION FOR ALL FORMS OF STRESS

SUMMARY

WHAT WE KNOW

It will come as no surprise that **yoga and meditation** —which come in many variations—have long been acknowledged as allies in mastering the mind and coping with stress. Science is increasingly validating those claims, especially for depression, schizophrenia, anxiety, PTSD (post-traumatic stress disorder), and ADHD (attention deficit hyperactivity disorder). Mind-body techniques are difficult to evaluate as CAM treatments because it is not possible to double-blind the clinical trials, but single-blind trials, open-label studies, and studies of comparative responses to mass trauma provide a substantial scientific basis for recommending yoga as a CAM treatment. Over 600 research studies on one form of meditation, Transcendental Meditation, indicate the positive effects of this stress reducing technique.

Yoga and meditation are described separately in this outline, but it should be recognized that anxiety, stress and attention problems can interfere with a person's ability to meditate, and yoga and other physical disciplines, including exercise and other CAM treatments, can help bring about the relaxation response achieved through meditation. In addition, meditation is an integral part of yoga and difficult to separate out.

MENTAL HEALTH IMPLICATIONS

In addition to the expected benefits that come with exercise or relaxation, experts suggest that yoga and meditation may help facilitate psychotherapy.

Yoga

Studies have shown that yoga can have positive benefits for people with several types of mental health conditions, including depression, ADHD, anxiety, schizophrenia and PTSD.

Meditation

Meditation is especially beneficial for reducing stress. Studies show it can also reduce depression and anxiety, and help people manage chronic pain.

DRUG INTERACTIONS.

No drug interactions have been identified with yoga and meditation.

SIDE EFFECTS

The rapid yoga breathing in more strenuous types of yoga may affect people with bipolar disorder, psychosis or anxiety. Extra caution is advised in people with these symptoms.

Like all exercise programs, yoga can cause people to have asthma attacks, pull muscles, or exacerbate existing medical conditions. People with chronic medical conditions and those who are pregnant should talk with a doctor before taking up a yoga program. In fact, anyone looking to start an exercise program for the first time should talk to a professional.

A well-trained yoga instructor is an invaluable aid in helping people get maximum benefit from yoga.

CONCLUSION

Stretching, breathing, relaxation and exercise are good for almost everyone. Yoga and meditation can benefit people who have mental health conditions, as well as those who do not.

OUTLINE

YOGA

1. *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* Brown *et al.*'s book which serves as a major source for this outline, has a major focus on yoga and other "mind-body techniques," including breathing exercises, multiple schools of yoga and meditation, and specialized physical disciplines like Tai Chi,[1] Qigong[2] and Aikido.[3] Brown *et al.* is the only consulted source that attempts to describe the science supporting these traditional

disciplines for the calming of the mind in the interest of enlightenment, promoting mental wellness and healthier understandings of suffering and mortality as a path to spiritual insight.

2. Yoga breathing exercises are a particularly powerful tool, amplified in Brown and Gerbarg's 2012 book, *The Healing Power of the Breath* (Shambhala Boston 2012). Brown and Gerbarg recommend "coherent breathing" and breath counting, as does Weil, who outlines his technique in four simple rules: (1) put your attention on your breath; (2) Try to make your breathing deeper, slower, quieter, and more regular; (3) Let your belly expand with each inhalation; and (4) Practice exhaling more air with each breath.[4] The Mayo Clinic recommends "relaxed breathing" for anxiety and stress.

3. The Mayo Clinic and Weil strongly recommend yoga and tai chi, and Weil devotes special attention to Mindfulness Based Stress Reduction, described below under meditation, which combines yoga postures, breathing and meditation. Weil's recommendations, and the science that supports them, are gathered there. Mayo observes that, in addition to relief from anxiety and stress: "Some clinical research shows that yoga can improve some measures of cognitive function and decrease symptoms of depression."

4. Mind-body techniques are difficult to evaluate as CAM treatments because it is not possible to double-blind the clinical trials, but single-blind trials, open-label studies, and studies of comparative responses to mass trauma provide a substantial scientific basis for recommending yoga as a CAM treatment. Brown *et al*., who have used yoga techniques extensively in mass disaster situations,[5] also have developed a neurophysiological model to explain how these practices affect mental health in modern scientific terms. It is hypothesized that stress induces imbalance of the autonomic nervous system with decreased parasympathetic nervous system and increased sympathetic nervous system activity, under-activity of the inhibitory transmitter GABA, and increased allostatic load.

Thus, yoga practices are effective when they correct underactivity of the parasympathetic nervous system and GABA system through stimulation of the vagal nerves and reduce alostatic load. Depression, epilepsy, PTSD and chronic pain all respond to vagal nerve stimulation and to pharmaceuticals that improve brain GABA activity. They also show improvement in response to yoga practices. [6]

5. Hatha Yoga[7] (in the US commonly called "yoga"), as it originated in India, consists of a system of spiritual, moral and physical practices. Two central and common aspects of yoga practice today are physical postures (asanas) and breathing exercises (pranayamas). These breathing exercises aim to focus the mind, facilitate relaxation and enhance wellness. Evidence suggests that these practices result in physiological effects such as increased parasympathetic drive, **calming of stress response systems**, release of hormones, and modulation of thalamic generators. The thalamus (located in the third ventricle of the brain) plays a critical role in the anatomy of mood and emotion.

6. **EFFICACY**: **A review of the literature evaluating the different forms of yoga suggests potential beneficial effects for depressive disorders, anxiety, stress reduction and general well-being.** As stated by Brown *et al*., the most "authoritative" source, "both optimistic and cautious," is Pilkington, Kirkwood, Rampes. & Richardson, "Yoga for Depression: the Research Evidence" (2005).[8] However, the underlying trials were small and uncontrolled.

7. **DEPRESSION**
   - As of 2005, there were five randomized controlled trials of the use of yoga to alleviate depression, each of which examined different forms of yoga interventions and in which the severity of the condition ranged from mild to severe. All trials reported positive findings, but methodological details such as method of randomization, compliance and attrition rates were missing. No adverse effects were reported with the exception of fatigue and breathlessness in participants in one study. The Pilkington *et al.* summary concludes: "**Overall, the initial indications are of potentially beneficial effects of yoga**

interventions on depressive disorders. Variation in interventions, severity and reporting of trial methodology suggests that the findings must be interpreted with caution. Several of the interventions may not be feasible in those with reduced or impaired mobility. Nevertheless, further investigation of yoga as a therapeutic intervention is warranted."[9]

- In 2007, a team from Harvard and Boston University led by Chris Streeter, M.D. (of B.U.), conducted a pilot "open-label" study of eight experienced yoga practitioners practicing the Ashtanga, Bikram, Iyengar, Kripalu, Kundalini, Power and Vinyasa forms of yoga. The yoga practitioners were evaluated against a group of 11 people who read popular magazines and fiction. The control group experienced no changes on gamma-aminobutyric acid (GABA) levels (a neurotransmitter implicated in depression). In contrast, **the brains of the yoga practitioners showed an average GABA rise of 27%, with more experienced practitioners showing greater rises, up to 80% in one case**.[10] Streeter asserted: "I am quite sure that this is the first study that's shown that there's a real, measurable change in a major neurotransmitter with a behavioral intervention such as yoga."[11]
- The ABC news article quoting Streeter demonstrates the controversy about the importance of GABA, which is seen by some as a minor neurotransmitter compared to dopamine (DA), norepinephrine (noradrenaline), epinephrine (adrenalin), histamine or serotonin. This concern is answered by Streeter, Gerbarg, Saper, Ciraulo & Brown, in the review cited in endnote 5.
- The Streeter and colleagues study is cited with approval in **Broad's 2012 book, *The Science of Yoga: The Risks and the Rewards*.[12]** Broad **stresses that despite the lack of randomized, double-blind studies, "Many people have looked to their own experience on such matters and found that, overall, yoga lifts their emotional life."[13]**
- Amy Weintraub's book, *Yoga for Depression: A Compassionate Guide to Relieve Suffering through Yoga* (Norton, New York 2012), is recommended by Brown, Gerbarg and Broad, and may be consulted for specific yoga techniques helpful in coping with depression.[14]

- The 2005 Lavey *et al.* 113-subject open-label trial showed the potential efficacy of yoga in improving the mood of psychiatric inpatients.[15] Participants completed the Profile of Mood States (POMS) prior to and following participation in a yoga class (45 minutes, once a week). Analyses indicated that participants reported significant improvements on all five of the negative emotion factors on the POMS, including tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment. There was no significant change on the sixth POMS factor, vigor-activity. Improvements in mood were not related to gender or diagnosis. The abstract concluded: "**The results suggest that yoga was associated with improved mood, and may be a useful way of reducing stress during inpatient psychiatric treatment**."[16]

13. **SCHIZOPHRENIA**

- Similarly, Yoga has been used to **lessen the effects of schizophrenia**. In a 2007 randomized, observer-blind trial cited with approval by Brown and Gerbarg, over 4 months, subjects in the yoga group had significantly less psychopathology than those in the physical training (exercise) group at the end of four months. They also had significantly greater social and occupational functioning and quality of life. Subjects in the yoga group significantly improved in negative symptoms (p= 0.001) and socio-occupational functioning (p = 0.006) over the physical training group, without significant differences in positive symptoms and depression scores.[17] The exercise group improved less.

13. **ANXIETY AND PTSD**

- **van der Kolk,** who founded The Trauma Center in Brookline, MA, has reported dramatic results in the use of yoga for treatment of PTSD:

  "People with PTSD lose their way in the world. Their bodies continue to live in an internal environment of the trauma. We all are biologically and neurologically programmed to deal with emergencies, but time stops in people

who suffer from PTSD. That makes it hard to take pleasure in the present because the body keeps replaying the past. If you practice Yoga and can develop a body that is strong and feels comfortable, this can contribute substantially to help you to come into the present."[18]

- **Appropriately taught yoga and other mind-body relaxation techniques appear to reduce stress and PTSD. A 2004 open-label Albanian study of Kosovo refugees showed the effectiveness of an eight-week mind-body skills program that included meditation, biofeedback, movement, guided imagery, breathing techniques, autogenic training, psycho-education about stress, and group discussions of their experiences.** Scores on an Albanian version of the PTSD Reaction Index were significantly reduced after the skill program and remained reduced at the nine- and 15-month follow ups.[19]
- Four small 2004 Australian open-label studies of Iyengar Yoga provided to Vietnam veterans with longstanding diagnoses of PTSD showed that the postures improved depression scores, but: "**the addition of yoga breathing (particularly Ujjayi) and Ham Su meditation significantly reduced symptoms of PTSD, including anxiety, insomnia, flashbacks, and anger outbursts**."[20]
- An unpublished 2005 Australian single-blind (the rater was ignorant of the subjects' treatment or wait list status), randomized, wait list-controlled study of a five-day course of Sudarshan Kriya Yoga (in which Brown and Gerbarg participated, and that was cited with approval by Broad) showed a **significant reduction in the Clinician Administered PTSD Scale for the yoga group** over the wait list group ($p = 0.007$).[21]
- In a 2011 review, Gerbarg and Brown with Wallace examined the "evidence and insights" from a series of mass disaster interventions. Reviewing Gordon's experience treating PTSD in Kosovo, Gaza and Israel, and in American veterans, and Gerbarg's and others' studies of flood victims in Bihar and after the Asian Tsunami, genocide in Rwanda and Sudan, and the 2010 earthquake in Haiti, Gerbarg, Wallace and Brown concluded that, "**mind-body practices have been shown to reduce symptoms of anxiety, depression and PTSD in survivors of mass disasters**."[22]

- "When designed to accommodate local cultural traditions, the nature of the trauma, and long-term sustainability," Gerbarg and colleagues concluded, "**mind-body programs can meet the urgent need for immediate psychological relief** post-disaster as well as during the recovery years…[Survivors participating in such programs] forge bonds within their community to solve problems collectively, rather than resorting to violence for self-preservation. Mind-body practices not only serve disaster survivors but also provide tools to ameliorate the stress of trauma exposure among service providers. As safe, simple, adaptable, and cost-effective interventions, mind-body techniques support individual and community-wide wellness, essential for healing and reconstruction post-disaster."[23]
- In a 2012 study, Katzman *et al.* tested a multi-component, yoga-based, breath intervention program as an open-label adjunctive treatment in people suffering from severe, treatment-resistant generalized **anxiety disorder. Significant reductions occurred in the pre- and post-intervention mean HAM-A total score** (t=4.59; P<0.01) and psychic subscale (t=5.00; P≤0.01). The response rate was 73% (21 out of 29 subjects, defined as a decrease ≥50% on the HAM-A) and remission rate of 41% (12 out of 29 subjects, defined as a HAM-A score ≤7).[24]

8. **ADHD**

- Brown and Gerbarg's 2012 book on ADHD reviews Jensen and Kenny's 2004 open-label study, Haffner, Roos, Goldstein, Parzer,and Resch's randomized 2006 study and the YES! studies still in process, that showed the effectiveness of a program of yoga breathing, yoga postures, meditation, and interactive discussion and group processes on Identity Conflict Resolution, Self Esteem, and the Modified Anger Coping, Planning and Concentration Scale, Distractibility Scale, and Irritability Scale.[25] They conclude that "**while additional studies are needed, encouraging preliminary data support the use of yoga, a low-risk intervention, as an adjunctive treatment for ADHD**."

9. **FACILITATE PSYCHOTHERAPY:** Brown *et al*. describe six ways that yoga, in addition to reducing stress and promoting healing, can facilitate psychotherapy:
    - When people in treatment acquire tools like yoga for reducing anxiety, they are better able to tolerate the painful memories and emotions that arise during therapy sessions as well as in their outside daily life.
    - Yoga philosophy and techniques are compatible with most psychotherapeutic approaches in that they teach nonjudgmental awareness and dispassionate observation of thoughts, feelings, and sensations.
    - By practicing yoga, people learn how to observe themselves, how to direct their attention, and how to shift their awareness between experiencing emotions and observing from a safe distance.
    - If treatment has been blocked by emotional numbing, repression, suppression, denial, dissociation, or isolation of affect, yoga can sometimes move the treatment forward. Yoga can "improve cognitive-emotional integration" and bring unconscious content into consciousness.
    - Introducing mind-body techniques can strengthen the therapeutic alliance by empowering the individual to deal directly with stress and reducing dependence on the therapist or medication. It is an essential building block of recovery to use tools like yoga and meditation to support development of mastery and independence.
    - As a person engages in yoga practices, greater awareness, access to memories, and new insights often emerge. The therapist can use this material and validate the person under treatment in an active and collaborative rather than passive or inferior role in the process.[26]

7. SIDE EFFECTS AND DRUG INTERACTIONS

- Brown *et al*. caution that some physical conditions limit practicing yoga and other mind-body techniques. Pregnancy, uncontrolled hypertension, a recent heart attack or serious heart disease, seizure disorders, migraine headaches, chronic obstructive pulmonary

disorder (COPD), asthma, and physical injuries are all contraindications for rapid or forceful yoga breathing. They recommend slow, gentle yoga breathing practices as being both safe and effective. Physical injuries and disabilities may limit the asanas (postures) that can be practiced or sustained and will require more careful preparation and practice. **A skilled and sensitive teacher is important to avoid injury and make progress.**

- People with bipolar disorder may be triggered to become manic, particularly from Bhastrika, Kapalabhati, Kundalini, or rapid-cycle breathing. Even slow Ujjayi or alternate nostril breathing may induce mania in some people.[27] Brown *et al*. state that yoga can be useful in treating bipolar conditions if the people under treatment can learn to slow down their breath rate whenever they notice themselves becoming agitated, with the help of an appropriate teacher.
- Because rapid yoga breathing can lower serum lithium levels, people being treated with lithium alone should not attempt it. People taking lithium with other mood stabilizers should be sure that their lithium levels are checked and adjusted to take into account any effects from rapid yoga breathing.[28]
- Severe character disorders and psychosis may make group yoga practice inadvisable, and rapid yoga breathing can be abused by people experiencing psychotic states seeking to further alter their consciousness. It is better to avoid yoga if the mental health condition is that severe. However, as cited above, careful yoga techniques have been shown to help in reducing stress during inpatient psychiatric treatment and lessening the effects of schizophrenia. A skilled practitioner can be helpful in setting a pace and scope of yoga practice suited to the individual.
- **Brown *et al*. state that anxiety disorders and post-traumatic stress disorder can respond to yoga breathing if the person undergoing the treatment is well-prepared and sensitively coached.** At pp. 110-111, they give detailed recommendations to avoid triggering a panic attack and to assist in recovery if needed. Obviously, this requires special training and sensitivity on the part of the yoga instructor.

MEDITATION

8. Meditation is even more difficult to evaluate since the definition is extremely diffuse, and in principle it can aid in coping with any stressful mental health condition. All meditation disciplines make spiritual claims, and some emphasize meditation as a way of coping with suffering, but Transcendental Meditation ("TM") makes extensive scientific claims on the web, claiming that, "[s]tudies have found that the TM technique reduces anxiety, depression, and even symptoms of post-traumatic stress disorder….

9. Over 600 research studies on TM indicate the positive effects of this stress reducing technique, for example:
   - Faster recovery from stress
   - Decreased anxiety and insomnia
   - Reduced substance abuse
   - **Decreased depression**
   - Reduction in high blood pressure"[29]

10. The 20 studies cited for TM's efficacy in treating mental health conditions are all at least 13 years old, often not fully randomized and suffer from other methodological concerns common with studies of mind-body CAM techniques, but are certainly suggestive. See http://www.tm.org/research-on-meditation

11. A 2006 Cochrane Collaboration review determined that **the small number of reliable TM studies do not allow any conclusions to be drawn about the efficacy of meditation therapy in reducing anxiety**, except that TM is comparable to other relaxation therapies.[30]

12. The Dalai Lama has encouraged research in "mindfulness and contemplative neuroscience,"[31] through his Mind and Life Institute, http://www.mindandlife.org/, and has a special interest in research focused on the origins and practice of compassion. His credo is

that empirical evidence must triumph over scriptural authority, and that research can only reinforce the power of meditation.

13. These studies all bear watching, as the research proceeds. There is a dearth of research on the use of meditation for psychiatric diagnoses, but a broad consensus that mindfulness can be very helpful in developing the "emotional resilience" to cope with depression.[32]

14. *Berkeley Wellness* recently summarized the meditation data:

    "Subjecting meditation to scientific testing is a challenge. States of mind are hard to measure. And other forms of relaxation training (for instance, progressive muscle relaxation, biofeedback, and stress management) may be just as useful.

    Still, research over the past 30 years suggests that mindfulness meditation may help in conditions such as insomnia, chronic pain, psoriasis, fibromyalgia, and **some psychiatric disorders. It has been shown to alter aspects of the immune, nervous, and endocrine system and produce changes in areas of the brain associated with memory, learning, and emotion. Research suggests it may be particularly useful in helping people adhere to medical treatment and cope with pain, as well as reduce anxiety and depression associated with illness." [33]**

15. Yoga and meditation are described separately in this outline, but it should be recognized that anxiety, stress and attention problems can interfere with a person's ability to meditate, and yoga and other physical disciplines, including exercise and other CAM treatments, can help bring about the relaxation response achieved through meditation.

16. **SOFT BELLY:** Gordon, whose 2008 comprehensive guide to alternative approaches to mental health care is called simply *Unstuck*, has a more mundane and secular approach. He calls therapeutic meditation "**soft belly**." As described by Gordon, soft belly is a biologically powerful concentrative meditation, grounded in slow, deep breathing. When you do soft

belly, you simply allow your belly to rise with the in breath and fall with the out breath, while you focus on the image of a soft, relaxed belly. According to Gordon, when your belly is soft, all of the other muscles in your body begin to relax as well. Thus, "soft belly can help quiet the mental and physical agitation, the persistent fight-or-flight response, and the chronic stress, [as well as the] exhaustion, hopelessness, and self-condemnation, when we are depressed."[34]

17. In addition to TM, Gordon, whose book is a compendium of contemporary integrative medical approaches to mental health and substance use conditions, refers readers to numerous retreat opportunities, his own Center for Mind-Body Medicine, www.cmbm.org , and the following traditional meditation resources:
    - The Independent Meditation Center Guide, www.gosit.org
    - Vipassana Meditation, www.dhamma.org
    - Shambhala, www.shambhala.org
    - Tai Chi, www.americantaichi.net
    - Qigong, www.nqa.org and www.qigonginstitute.org, and
    - Osho/Rajneesh, www.osho.com

18. **THE RELAXATION RESPONSE:** Benson, of the Harvard Medical School, calls this important technique for self-calming "**the relaxation response**," after his 1975 book of that title, and explains it on his website:

Steps to Elicit the Relaxation Response

The following is the technique reprinted with permission from Dr. Herbert Benson's book, The Relaxation Response, pages 162 – 163

1. *Sit quietly in a comfortable position.*
2. *Close your eyes.*
3. *Deeply relax all your muscles, beginning at your feet and progressing up to your face. Keep them relaxed.*
4. *Breathe through your nose. Become aware of your breathing. As you breathe out, say the word, "one"*, silently to yourself. For example, breathe in… out…, "one", in… out… "one", etc. Breathe easily and naturally.*
5. *Continue for 10 to 20 minutes. You may open your eyes to check the time, but do not use an alarm. When you finish, sit quietly for several minutes, at first with your eyes closed and later with your eyes opened. Do not stand up for a few minutes.*
6. *Do not worry about whether you are successful in achieving a deep level of relaxation. Maintain a passive attitude and permit relaxation to occur at its own pace. When distracting thoughts occur, try to ignore them by not dwelling upon them and return to repeating "one."*

Note: With practice, this response should come with little effort. Practice the technique once or twice daily, but not within two hours after any meal, since the digestive processes seem to interfere with the elicitation of the relaxation response.

* or any soothing, mellifluous sound, preferably with no meaning. or association, to avoid stimulation of unnecessary thoughts.[35]

19. Benson ushered in a new era of understanding in the field of mind-body medicine. Coining the term "relaxation response," which the Mayo Clinic calls the "rest and digest" response, Benson identified the body's physiological reaction that is the exact opposite of, and necessary complement to, the stress (fight-or-flight) response. This is a secular concept of meditation. In the four decades since that initial discovery, Benson and his colleagues have established a therapy to counteract the harmful effects of stress. They have explored how the relaxation response, the power of expectation and belief, and other mind-body phenomena can produce healing in your own body. Benson's studies of the relaxation response show that the core of meditational practices is the same, and that the pervasive stress of modern life can be counteracted by self-discipline and self-calming.

20. In *Relaxation Revolution*, Benson and Proctor contend that we have the ability to self-heal diseases, prevent life-threatening conditions, and supplement established drug and surgical procedures with mind-body techniques. In a special "treatment" section, Benson and Proctor describe how these mind body techniques can be applied—and are being applied—to treat a wide variety of conditions, including anxiety and depression. The proof will have to be weighed by others, and the jury is certainly out, but the lack of an identifiable risk of harm may make the question of efficacy moot. Relaxation certainly works for many people.

21. **OPEN FOCUS:** Similarly, Fehmi, developed the secular concept of "open focus." During the 1970s Fehmi developed and recorded a series of exercises that involved imagining space in various contexts and successfully talked subjects into the synchronous-alpha state. The strong correlation between observed brain wave type (alpha, beta, theta) and the way the subject was attending became obvious. Was the mode of attending perhaps the

fundamentally important thing, with brain waves secondary? *The Open-Focus Brain* is Fehmi's affirmative answer to that question.[36]

22. **MINDFULNESS BASED STRESS REDUCTION (also called Mindfulness-Based Cognitive Therapy)**: Starting in 1979, Kabat-Zinn[37] developed the Mindfulness Based Stress Reduction (MBSR) program at the University of Massachusetts Medical Center. MBSR brings together mindfulness meditation and yoga in an 8-week intensive training that meets on a weekly basis. Mindfulness practice seeks to cultivate greater awareness of the unity of mind and body, as well as of the ways that unconscious thoughts, feelings, and behaviors can undermine emotional, physical, and spiritual health. The mind is known to be a factor in stress and stress-related disorders, and meditation has been shown to positively affect a range of autonomic physiological processes, such as lowering blood pressure and reducing overall arousal and emotional reactivity. http://www.mbct.com/

23. The MBSR program started in the Stress Reduction Clinic at the University of Massachusetts Medical Center in 1979 and is now offered in over 200 medical centers, hospitals, and clinics around the world, including some of the leading integrative medical centers such as the Scripps Center for Integrative Medicine, the Duke Center for Integrative Medicine, and the Jefferson-Myrna Brind Center for Integrative Medicine. MBSR/MBCT work is based on an active partnership in a participatory form of medicine, one in which patient/clients take on significant responsibility for doing a certain kind of interior work in order to tap into their own deepest inner resources for learning, growing, healing, and transformation.

24. The National Institutes of Health's National Center for Complementary and Alternative Medicine has provided a number of grants to research the efficacy of the MBSR program in promoting healing. Completed studies have found that activity levels and feelings of self esteem increased for a majority of participants. For more information on these studies, see http://www.umassmed.edu/Content.aspx?id=41286. Recent studies have validated MBSR/MBCT for prevention of relapses in recurrent depression, equivalent to

antidepressant therapy.[38] One recent MBSR study showed **greater gray matter concentration for meditators** in the right anterior insula and in the left inferior temporal gyrus and right hippocampus.[39]

25. Similarly, the 2005 Lazar *et al*. study cited by Gordon and Benson was a breakthrough, in that it found that a portion of **the cerebral cortex of "regular meditators"** (engaged in Buddhist-inspired Insight Meditation, http://www.dharma.org/) **was thicker than those of the control group**.[40] The abstract expands on the potential significance of the findings:

    "Previous research indicates that long-term meditation practice is associated with altered resting electroencephalogram patterns, suggestive of long lasting changes in brain activity. We hypothesized that meditation practice might also be associated with changes in the brain's physical structure. Magnetic resonance imaging was used to assess cortical thickness in 20 participants with extensive Insight meditation experience, which involves focused attention to internal experiences. Brain regions associated with attention, interception [perception of sensations from inside the body] and sensory processing were thicker in meditation participants than matched controls, including the prefrontal cortex and right anterior insula. Between-group differences in prefrontal cortical thickness were most pronounced in older participants, suggesting that meditation might offset age-related cortical thinning. Finally, the thickness of two regions correlated with meditation experience. **These data provide the first structural evidence for experience-dependent cortical plasticity associated with meditation practice."**[41]

26. Weil expresses this same radical thought in asserting that **"learning to change our ways of thinking and perceiving can actually change the function and structure of our brains."[42] In integrative medicine, the brain is not primary, as it has become under the medical model. The mind can heal the brain.**

27. No side effects of meditation have been documented, but lack of skill could cause increased anxiety and is certain to result in boredom and discontinuation of meditation practice. As

with yoga, the help of an insightful and cheerful guide(s) and of supportive companions on the way is helpful if not, for most of us, essential.

[1] For a recent *Berkeley Wellness* review of the benefits of Tai Chi, see http://www.berkeleywellnessalerts.com/alerts/womens_health/tai-chi-health-benefits443-1.html?ET=bwalerts:e1502:143685a:&st=email&s=ERA_120811_001 A new study, published in the *Journal of Alzheimer's Disease*, included 120 healthy older people in China. Those who practiced tai chi three times a week for 40 weeks showed increases in brain volume, as seen on MRI, as well as improvements on several tests of memory and learning, compared to those not doing the exercise who had normal age-related brain shrinkage. Previous research has shown that aerobic activity is good for the brain, but this study suggests that a more gentle form of exercise is also beneficial.

[2] See recent fibromyalgia trial, http://nqa.org/2012/08/a-randomized-controlled-trial-of-qigong-for-fibromyalgia/

[3] http://en.wikipedia.org/wiki/List_of_martial_arts .

[4] Weil, A., *Spontaneous Happiness* (Little, Brown and Company, New York 2011), at 146-147.

[5] Gerbarg practices integrative psychiatry, combining standard and complementary treatments. Her research focuses on mind-body practices for reducing the effects of stress and trauma, particularly in survivors of mass disasters, including the Asian Tsunami, 9/11 World Trade Center attacks, 2010 earthquake in Haiti, genocide in Sudan and Rwanda, Gulf Horizon Oil Spill, and veterans.

[6] Streeter, C.C., Gerbarg, P.L., Saper, R.B., Ciraulo, D.A. & Brown, R.P., "Effects of Yoga on the Autonomic Nervous System, Gamma-Aminobutyric Acid, and Allostasis in Epilepsy, Depression, and PTSD," *Medical Hypotheses* (2012) doi:10.1016/j.mehy.2012.01.021.

[7] Hatha Yoga may be viewed as a subdivision of Raja Yoga, which is the yoga system that most emphasizes meditation. Of the Eight Limbs of Raja Yoga, the two limbs that are emphasized in Hatha Yoga are (3) Asana & (4) Pranayama. Hatha Yoga was intended as a practice to lead one eventually to be fit to practice Raja Yoga. This is clearly stated in the 1st verse of the Hatha Yoga Pradipika. While it is true that when we say the word "yoga" in the US, we mean Hatha Yoga, Hatha is a much more recent (not so ancient) way of practicing Yoga. Its spiritual and moral practices are emphasized in Raja Yoga.

[8] Pilkington, K., Kirkwood, G., Rampes, H. & Richardson, J., "Yoga for Depression: the Research Evidence," *J Affect Disord*. 89(1-3):13-24. Epub (2005).

[9] http://www.ncbi.nlm.nih.gov/pubmed/16185770 .

[10] Streeter, C.C., Jensen, J.E., Perlmutter, R. M., *et al*., "Yoga Asana Sessions Increase Brain GABA Levels: A Pilot Study," *Journal of Alternative and Complementary Medicine* 13(4):419-426. See also, Streeter, C.C., Whitfield, T.H., Owen, L., et al., "Effects of Yoga versus Walking on Mood, Anxiety, and Brain GABA Levels: A Randomized Controlled MRS Study," *Journal of Alternative and Complementary Medicine*,16(11):1145-52 (2011).

[11] http://abcnews.go.com/Health/Healthday/story?id=4507486&page=1#.UCkYLfZlRGg

[12] Simon & Schuster, New York (2012).

[13] *Id*. at 79.

[14] *Id.* at 79-80. See also the forthcoming *Yoga Skills for Therapists: Mood Management Techniques to Teach & Practice* (Norton, New York 2012).

[15] Lavey, R., Sherman, T., Mueser, K.T., Osborne, D.D., Currier, M. & Wolfe R., "The Effects of Yoga on Mood in Psychiatric Inpatients," *Psychiatr Rehabil J.* 28(4):399-402 (2005).

[16] http://www.ncbi.nlm.nih.gov/pubmed?term=lavey%20yoga .

[17] Duraiswamy, G., Thirthalli, J., Nagendra, H.R. & Gangadhar, B.N., "Yoga Therapy as an Add-on Treatment in the Management of Patients with Schizophrenia--a Randomized Controlled Trial," *Acta Psychiatr Scand*. 116:226-32 (2007). http://www.nimhans.kar.nic.in/yoga/abst10_1.pdf

[18] http://www.traumacenter.org/clients/MagInside.Su09.p12-13.pdf ; Van der Kolk, B.A., "Clinical Implications of Neuroscience Research in PTSD," *Annals of the New York Academy of Sciences* 1071:277-93 (2006).

[19] Gordon, J.S., Staples, J.K., Blyta, A. & Bytyqi, M., "Treatment of PTSD in Postwar Kosovo High School Students Using Mind-body Skills Groups: A Pilot Study," *Journal of Trauma and Stress* 17(2):143-147 (2004).

[20] *How to Use Herbs, Nutrients & Yoga in Mental Health Care,* by Richard P. Brown, M.D. (of Columbia University College of Physicians and Surgeons), Patricia L. Gerbarg, M.D. (of New York Medical College), and Philip R. Muskin, M.D. (of Columbia as well) (W. W. Norton and Company, New York, 2009) at 99; Carter, J.J., Gerbarg, P.L., Brown, R.P & Ware, R., "Multi-component Yoga Breath Program for Vietnam Veteran PTSD: Randomized Controlled Trial," *International Journal of Yoga Therapy* 16:49-57 (2009).

[21] Brown, R.P. and Gerbarg, P.L., "Sudarshan Kriya Yogic Breathing in the Treatment of Stress, Anxiety and Depression," *Journal of Alternative and Complementary Medicine* 11(1):189-201 (2005); "A Controlled Breathing Course for Social & Emotional Health for Vietnam Veterans With Chronic PTSD-RCT" (unpublished), presented to the American Psychiatric Association at [INSERT NEEDED] on [INSERT NEEDED], http://clinicaltrials.gov/ct2/show/NCT00256477 .

[22] Gerbarg, P.L., Wallace, G. & Brown, R.P., "Mass Disasters and Mind-Body Solutions: Evidence and Field Insights," *International Journal of Yoga Therapy* 21:23-34 (2011).

[23] *Id*. at 32.

[24] Katzman, M.A., Vermani M., Gerbarg, P.L., Brown, R.P., Iorio, C., Davis, M., Cameron, C. & Tsirgielis, D., "A Multicomponent Yoga-based, Breath Intervention Program as an Adjunctive Treatment in Patients Suffering from Generalized Anxiety Disorder with or without Comorbidities, *Int'l. J Yoga* [serial online] 5:57-65 (2012). http://www.ijoy.org.in/article.asp?issn=0973-6131;year=2012;volume=5;issue=1;spage=57;epage=65;aulast=Katzman

[25] Brown, R.P. & Gerbarg, P.L., *Non-Drug Treatments for ADHD* (W.W. Norton and Company, New York 2012), at 208-209.

[26] Brown *et al., op cit.* at 113-114. Dr. Gerbarg's chapter, "Yoga and Neuro-Psychoanalysis." was published in *Bodies In Treatment: The Unspoken Dimension* edited by Frances Sommer Anderson (The Analytic Press, Hillsdale, N.J. 2007).

[27] *Id.* at 109.

[28] *Id.*

[29] http://www.tm.org/inner-peace Extensive citations to research do not examine it critically.

[30] Krisanaprakornkit, T., Krisanaprakornkit, W., Piyavhatkul, N. & Laopaiboon, M., "Meditation Therapy for Anxiety Disorders," prepared and maintained by the Cochrane Collaboration and published in *The Cochrane Library*, issue 1, no. 004998 (2006).

[31] http://www.brighamandwomens.org/about_bwh/publicaffairs/news/publications/DisplayBulletin.aspx?articleid=5592

[32] Weil, *op. cit.,* at 70.

[33] http://www.berkeleywellnessalerts.com/alerts/womens_health/510-1.html?ET=bwalerts:e1654:143685a:&st=email&s=ERA_130105_001

[34] The list of sources covers pp. 390 and 395-396 of Gordon's book, *Unstuck*, by James S. Gordon, M.D. (The Penguin Press, New York 2008). Quotation at 34.

[35] http://www.relaxationresponse.org/steps/

[36] *The Open-Focus Brain: Harnessing the Power of Attention to Heal Mind and Body*, by Les Fehmi and Jim Robbins, Trumpeter Books / Shambhala (2007). Http://Www.Openfocus.Com/

[37] Http://En.Wikipedia.Org/Wiki/Jon_Kabat-Zinn; See *The Mindful Way Through Depression: Freeing Yourself from Chronic Unhappiness*, by J. Mark G. Williams, John D. Teasdale, Zindel V. Segal & Jon Kabat-Zinn. Guilford Press, 2007.

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[41] http://www.ncbi.nlm.nih.gov/pubmed/16272874

[42] Weil, *op. cit*., at 64.