THE INTEGRATIVE MANAGEMENT OF DEPRESSED MOOD

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ABSTRACT

Disorders of mood are conceptualized differently in disparate systems of medicine, although similarities in subjective reports suggest that the core symptoms of depressed mood are comparable across cultures. In North America and Europe, diverse non-conventional treatments and integrative approaches are increasingly being used in the management of depressed mood. Substantial empirical evidence supports efficacy claims of of many non-conventional biological treatments, including St. John's Wort, S-adenosyl-l-methionine (SAMe), and 5-hydroxytryptophan (5-HTP). Other non-conventional treatments, including acupuncture, bright-light exposure, mind-body or mindfulness practices, and spiritual training are difficult to evaluate using Western research paradigms, but are nevertheless gaining acceptance in Western medicine because of consistent anecdotal reports of successful outcomes in depressed mood and other mental or emotional problems. This paper reviews evidence supporting the use of non-conventional treatments, as well as combinations of non-conventional and biomedical treatments, in the management of depressed mood. Based on the available information, separate integrative treatment-planning algorithms are suggested for moderate, versus severe, depressed mood.

WESTERN PSYCHIATRIC DIAGNOSIS OF DEPRESSED MOOD

Western psychiatry describes many distinct syndromes or "sub-types" of depression, in which the core symptoms of depressed mood persist over time and occur in the context of a broader symptom pattern that may include psychosis, or lesser or greater degrees of mania (ie, euphoric or irritable mood, racing thoughts, and diminished need for sleep). For purposes of formulating an effective and safe integrative treatment plan for depressed mood, it is important to distinguish individuals who report only depressed mood from those who are depressed in the context of an underlying medical illness, or also report mania, hypomania, or psychosis. The Diagnostic and Statistical Manual, 4th edition, text-revised (DSM-IV-TR) describes two principle patterns or "disorders" of depressed mood, depending on the course and severity of symptoms: Major Depressive Disorder and Dysthymic Disorder. Western biomedical psychiatry defines Dysthymia as a symptom pattern in which chronic depressed mood of moderate intensity persists at least 2 years, together with two or more of the following symptoms: change in sleep, change in appetite, fatigue, agitation or cognitive slowing, diminished concentration, or feelings of worthlessness (but not thoughts of death or suicide). In contrast, Major Depressive Disorder is a symptom pattern in which recurring episodes of severe depressed mood (including thoughts of suicide or death) last at least 2 weeks together, with at least 5 of the above symptoms. In Western biomedical psychiatry, the diagnosis is established through history, clinical presentation, and the elimination of possible underlying or confounding medical disorders. Tables 1 and 2 show the major diagnostic criteria used in the DSM-IV for establishing Major Depressive Disorder and Dysthymic Disorder, respectively.

TABLE 1
DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER

- Five or more symptoms lasting 2 weeks or longer
- One symptom must be depressed mood or loss of interest or pleasure
- The other symptoms can include: change in sleep pattern, change in appetite, fatigue, agitation or cognitive slowing, diminished concentration, feelings of worthlessness, or thoughts of death or suicide
- Symptoms must cause significant impairment in social or occupational functioning

TABLE 2
DIAGNOSTIC CRITERIA FOR DYSTHYMIC DISORDER

- Moderately depressed mood that persists for at least 2 years prior to onset of a major depressive episode (if any)
- No history of mania or hypomania
- Two or more symptoms (see Table 1), including those in a major depressive episode (except thoughts of death or suicide), occur during an unspecified period of time

Recurring depressive episodes of variable severity and duration, interspersed with brief periods of moderate or severe euphoria or irritability and longer periods of sustained normal or "euthymic" mood, are the defining criteria for Cyclothymic Disorder and Bipolar Disorder, respectively. Symptom patterns described as psychotic disorders or personality disorders in Western psychiatry may also include depressed mood. However, in those cases, the focus of clinical attention is typically

not depressed mood. In conventional biomedical assessment and diagnosis, underlying medical problems, substance abuse, or medications identified as the cause of depressed mood are directly treated as an effort to ameliorate the patient's mood.

Depressed Mood in Diverse Healing Traditions

Many non-conventional, professional systems of medicine (eg, Chinese Medicine, Ayurveda, Kampo, etc) incorporate modalities used to treat emotional or physical symptoms commonly reported by Western patients diagnosed with Major Depressive Disorder. However, non-Western systems of medicine do not employ concepts equivalent to "depression" or "mania" in biomedical psychiatry. Other terms used to describe persisting patterns of sadness or agitation reflect alternative "ways of seeing" that are embedded in disparate non-conventional systems of medicine, and in the parent cultures from which they originate. In spite of differences in the philosophy and methods in classification, most non-Western systems of medicine endorse concepts of abnormal mood that are congruent with major diagnostic categories in Western psychiatry. Thus, treatments from diverse healing traditions address symptom patterns (experienced by patients in many regions of the world) that resemble the core experiences of Western patients who are diagnosed with disorders of depressed mood. Significantly, non-conventional treatments of depressed mood are being used at increasing rates in North America and Europe,[1-3] both alone and in combination with conventional pharmacological treatments. Integrative approaches to the management of depressed mood that have been found to be safe and effective are reviewed below.

Effective Non-Conventional and Integrative Treatments of Depressed Mood

Many non-conventional treatment modalities of depressed mood have been validated by consistent positive results from controlled, double-blind studies, and in some cases by systematic reviews or meta-analyses of studies. Empirically-validated, non-conventional treatments fulfill scientific criteria for efficacy, but are not yet in widespread use in the US for a variety of reasons, including market interests and congressional lobbying of multi-billion dollar pharmaceutical companies, conservative policies of the American Psychiatric Association, inadequate post-graduate medical training in the use of non-conventional treatments in psychiatry, and other social or political factors. Accumulating data support the view that combining conventional antidepressants with certain non-conventional treatments improves mood at a more rapid rate than either kind of treatment used alone, and may improve outcome in general. Non-conventional treatments that have been studied in combination with antidepressants include exercise, bright-light exposure, somatic or mind-body techniques, and certain non-conventional biological treatments. Examples of empirically-validated, non-conventional biological treatments of depressed mood include St. John's Wort, SAMe, 5-HTP, folic acid, eicosapentaenoic acid (EPA), an Omega-3 fatty acid, and to a lesser extent, Acetyl-L-carnitine (ALC). Many placebo-controlled, double-blind studies and meta-analyses of these studies consistently show that SAMe has equivalent or superior anti-depressant efficacy compared to tricyclic antidepressants.[4] In contrast, non-conventional treatments based on putative, non-biological mechanisms of action have not been as rigorously examined by Western science, and therefore have relatively weaker scientific evidence supporting claims of efficacy. Non-biological treatments of depressed mood are nevertheless gaining acceptance because of accumulating anecdotal evidence supporting their efficacy and safety. Non-biological treatments of depressed mood include exercise and somatic and mind-body therapies, including general relaxation training,[5,6] Yoga, Tai Chi, and QiGong, as well as treatments based on empirically-validated forms of energy or information (eg, EEG biofeedback or bright-light exposure.[7,8] Spiritual healing approaches and "energy medicine" are being increasingly used to treat depressed mood in North America and Europe.[2,3] However, limited numbers of controlled trials, small study sizes, and inherent study-design problems continue to obscure understandings of putative underlying mechanisms, or efficacy of these approaches.

St. John's Wort, SAMe, 5-HTP, EPA, and ALC have been evaluated for their antidepressant efficacy alone, and in combination with synthetic antidepressants. The advantages of augmenting a synthetic antidepressant with one of these natural products include equivalent antidepressant efficacy at reduced doses of conventional antidepressants, improved tolerance and compliance, and faster response rates. More than 30 placebo-controlled trials[9-13] have verified that St. John's wort is as effective as conventional antidepressants (including imipramine, fluoxetine, sertraline, and others) for treating moderate depressed mood. Limited data suggest that higher doses of St. John's wort are effective against more severe depressed mood. A few cases of possible serotonin syndrome have been reported when St. John's wort is used in combination with a selective serotonin reuptake inhibitor (SSRI). Patients who are being treated with coumadin, protease inhibitors, SSRIs, immunosuppressive agents, and certain anti-cancer agents should be cautioned against concurrent use of St. John's wort,[14,15] which has been shown to lower serum levels

of those drugs through induction of P-450 liver enzymes.[16,17] Many studies have validated the safety and efficacy of SAMe, alone and in combination with a synthetic antidepressant.[4,18-20] Folate and B_{12} are co-factors in the synthesis of SAMe,[21] and should be taken together with SAMe. Severely depressed patients found to have low-serum folate levels are significantly less likely to respond to antidepressants,[22] so depressed patients should be encouraged to take folate. Folate alone, in doses from 200 mcg to 15mg has been shown to result in sustained improvement in depressed mood.[23,24] EPA has been shown to be effective against moderate depressed mood[25] in doses of 1, 2, or 4gm/day when used alone[26] or in combination[27] with an antidepressant. However, emerging evidence suggests that another Omega-3 fatty acid, DHA, does not appear to improve depressed mood.[28] Depressed patients taking SAMe or EPA should be monitored for signs of hypomania, which has been reported in a few cases.[29] Depressed mood also responds to 5-HTP alone, and in combination with a synthetic antidepressant.[30,31] 5-HTP crosses the blood-brain barrier, where it is converted to serotonin. Similar to SAMe and antidepressants, 5-HTP and a synthetic antidepressant potentiate each other, sometimes resulting in a more complete or rapid response.[32,33] However, when combining 5-HTP with an SSRI, the clinician should monitor the patient for signs of serotonin syndrome, although no reports of this potentially serious side effect have been reported in the peer-reviewed literature at the time of this writing. ALC has been studied in placebo-controlled, double-blind trials in severely depressed patients, elderly depressed patients, and depressed patients with dementia.[34,35] Although fewer studies have been done on ALC than on other natural products used to treat depressed mood, and no studies have compared ALC to synthetic antidepressants, results to date are promising. Table 3 summarizes the doses of non-conventional biological treatments of depressed mood, along with unresolved safety considerations associated with their use.

Chinese medical treatments of depressed mood, including acupuncture, electro-acupuncture, and certain compound herbal formulas, show promising results, although the mechanism of action remains unclear. Chinese medical treatments of depressed mood and other mental or emotional symptom patterns are reviewed in two recently published textbooks.[36,37] One large prospective, controlled study showed equivalent antidepressant efficacy of a particular electro-acupuncture protocol and amitriptyline.[38] The consistent skillful practice of Yoga,[39] QiGong, or Tai Chi[40,41] has been shown to improve overall quality of life, including indicators of moderately depressed mood. The following sections incorporate the basic concepts discussed above into specific integrative-treatment approaches for moderate and severe depressed mood.

TABLE 3
REPRESENTATIVE NON-CONVENTIONAL BIOLOGICAL AND INTEGRATIVE TREATMENTS OF DEPRESSED MOOD

Natural product	Comment
St. John's wort	• 300mg TID of 0.3% hypericin extract • caution against concurrent use with SSRI anti-depressants (eg, Paroxetine), protease inhibitors (eg, Indinavir), anti-coagulants, oral contraceptives, immunosuppressants (eg, Cyclosporin), certain anti-cancer agents (eg, etoposide); and digoxin
SAMe	• 400mg BID to 800mg TID alone or in combination with antidepressants • best bioavailability if taken before meals • caution—monitor for agitation • caution—avoid in Bipolar patients
5-HTP	• 200–600mg daily, alone or in combination with antidepressants • caution—monitor for serotonin syndrome when used in combination with SSRIs • 5-HTP is moderately sedating and is better tolerated at bedtime
Omega-3 fatty acids	• 1-9gm/day EPA fraction most effective • preliminary findings suggest efficacy alone, or in combination with conventional antidepressants • caution—may prolong bleeding time when taken with aspirin • caution—certain brands may cause hypervitaminosis A
Folate	• 800mcg to 5mg • improves mood when used alone • improves response to conventional antidepressants • may enhance antidepressant effect of SAMe
B_{12}	• 1mg/day • improves mood and enhances energy when used alone • may enhance antidepressant effect of SAMe
ALC	• 500mg to 2gm/day in divided doses • note—only studies on depressed mood in elderly or elderly with dementia • note—possibly effective in mild dementia (mechanism of action believed to involve correcting cholinergic neurotransmitter deficit in Alzheimer's)

MANAGEMENT OF MILD TO MODERATE DEPRESSED MOOD

A patient complaining of moderate depressed mood

should be considered as a candidate for alternative treatments only after possible underlying medical causes have been excluded by a psychiatrist or primary care physician. Issues of efficacy and safety should be discussed during the initial consultation. The patient should be referred to a qualified practitioner of an appropriate alternative treatment, unless his or her physician has expertise in that area. For example, a moderately depressed patient who is interested in receiving acupuncture treatment should be informed that several studies and extensive clinical experience show that acupuncture will probably be useful.[37] However, a patient complaining of severe depressed mood should not be advised to seek acupuncture treatment, on the basis of studies and case reports suggesting that severe depressed mood is seldom improved by acupuncture.

The question of combining several approaches, versus successive single treatments, in an initial integrative-treatment plan should be discussed. If the patient elects to try only one or a few approaches initially, he or she should be encouraged to explore therapies with the highest ratings of efficacy and safety. For example, aerobic exercise and improved sleep hygiene should be strongly reinforced if the patient is reluctant to take supplements or is reluctant to try mind-body practices or somatic therapies. Other therapies can then be tried if mood does not improve to a desirable degree following a reasonable investment of time and effort. It is important at the outset that the clinician and patient agree on subjective criteria for monitoring changes in mood, as well as a timeframe in which improvement is reasonably expected in response to a selected integrative-treatment plan. Such expectations are always present, and talking about them gives the patient and clinician an explicit framework in which to develop a collaborative dialog about perceived progress or delays in treatment.

Patients who request synthetic or natural product-derived antidepressant medications for depressed mood of moderate severity should be encouraged to initially try combining self-directed approaches, including improved nutrition, lifestyle changes, supplements, and mind-body practices in parallel before taking medications. Based on the available evidence, combining self-directed approaches can be reasonably expected to improve moderate depressed mood as effectively as medications, while avoiding issues of potential medication side effects, non-compliance, etc. Self-directed changes in lifestyle and nutrition also motivate the patient to pursue a range of healthy nutritional, exercise, or mind-body practices with demonstrated efficacy against moderate depressed mood. Furthermore, incompatibility issues do not arise when combining such self-directed approaches because these approaches are not potentially incompatible with other self-directed approaches or with biologically-active agents. If the patient elects to start an antidepressant after considering available evidence-based treatment options for moderate depressed mood, she should be referred to a psychiatrist or primary care physician to review appropriate medication choices and safety issues, including side effects and potential incompatibilities between antidepressants and other medications being used. Informed consent should be obtained regarding potential risks associated with the selected antidepressant and its concurrent use with other medications.

The patient should be encouraged to engage in supportive psychotherapy or cognitive-behavioral therapy directed at reducing the severity of depressive mood symptoms. Journal writing will help the patient to track progress regarding the relative effectiveness of different treatments and to provide useful feedback to the clinician. At regular (at least bi-weekly) follow-up appointments, the clinician and patient should meet to review progress or problems with the current treatment plan, and to modify the integrative-management plan if mood symptoms have not improved according to reasonable expectations within a mutually agreed-upon timeframe. In some cases, the patient will clearly not be motivated to pursue certain treatments because of side effects or other reasons. In cases where moderate depressed mood worsens or does not improve following one month of consistent self-directed efforts and appropriate somatic or mind-body treatments, it is appropriate to encourage the patient to consider biological treatment options, including synthetic psychotropic agents, natural products including certain herbals, or other natural products. Any discussion of synthetic antidepressants should always be deferred to a psychiatrist or primary care physician. Consideration of medicinal herbals, other natural products, or homeopathic preparations should be referred to qualified naturopathic physicians, herbalists, or homeopathic physicians. In all cases where biological treatments are being considered, the clinician's recommendations should be based on a thorough review of the evidence of comparative efficacy and safety of synthetic antidepressants and natural products that have been substantiated in the treatment of depressed mood. When considering biological treatments, the clinician's recommendations should take into account the patient's history of response to previous biological treatments, including reports of sensitivity to side effects when using certain synthetic or natural product-derived medicines. For example, some patients experience significant gastrointestinal distress when taking certain antidepressants (typically SSRIs), and soon discontinue their use due to such side effects. Others may report a history of agitation when taking even small doses of SAMe, or feelings of sedation or lethargy when starting a trial on 5-HTP. To minimize the

risk of an unfavorable outcome or non-compliance, it is therefore important to obtain a thorough history of treatment responses and side-effect issues associated with previous biological treatments. This information will assist the clinician in formulating an integrative plan that will most likely succeed.

After presenting recommendations to the patient, based on the above considerations, the clinician and patient should agree on a treatment plan that does not pose safety or incompatibility issues with respect to other therapies that are currently being used. Many natural products that are beneficial for the treatment of moderate depressed mood have been shown to enhance the efficacy of antidepressant medications, including folate, thiamine and B_{12}, 5-HTP, and certain Omega-3 fatty acids (see above). Therefore, it is reasonable to expect that continued use of these natural substances, in conjunction with a synthetic antidepressant, will improve treatment response at a specified antidepressant dose. Furthermore, this integrative strategy may permit the patient to reduce the dose of his or her antidepressant with a commensurate reduction in side effects, but with no loss of antidepressant efficacy.

The Integrative Management of Severe Depressed Mood

In contrast to moderate depressed mood, the preferred initial approach to severe mood symptoms includes treatment with a synthetic antidepressant medication, along with recommendations of self-directed changes in nutrition, exercise and lifestyle, certain supplements, and a mind-body practice that fits the patient's values and beliefs. Finding out whether a patient is suicidal is the single most important concern in evaluating a patient with severe depressed mood. A patient who is actively contemplating suicide should be closely monitored for his or her safety, and accompanied to an emergency room or urgent care center for evaluation by a psychiatrist and for possible hospitalization. Patients complaining of severe depressed mood who are not actively suicidal should always be referred to a psychiatrist or primary care physician to discuss the risks and benefits of antidepressant drugs. As for the evaluation of moderate depressed mood, the initial consultation ideally includes a thorough medical, social, and psychiatric history, as well as any appropriate laboratory tests (eg, thyroid studies, electrolytes and complete blood count (CBC), liver panel, kidney function studies, and possibly serum homocysteine) to rule out underlying medical problems. A thorough history will clarify the medical and psychiatric differential diagnosis, and establish or exclude a history of mood swings, psychotic symptoms, an evolving neurologic disorder, etc. The psychiatrist or primary care physician should be proactive in making referrals to appropriate specialists if laboratory studies are abnormal. A commonly-cited example is the association between abnormal levels of thyroid hormones (elevated thyroid stimulating hormone (TSH) or low Free T-4) and persisting depressed mood. Anemias or other blood dyscrasias, electrolyte or metabolic derangements, and other markers of medical illness are often associated with reports of depressed mood. Correcting such primary medical problems often results in improved mood. Evolving neurological symptoms, or a known history of cancer or heart disease, warrant automatic referrals to specialists in these areas of Western medicine prior to the consideration of alternative treatments.

Assuming that primary medical causes of severe depressed mood have been excluded, follow-up appointments should be scheduled at least weekly after the patient has started a recommended antidepressant. The patient should be given clear instructions to contact the nearest emergency room or call "911" in the event of recurring suicidal thoughts or a suicide plan. Assuming that underlying medical problems and comorbid psychiatric symptoms have been ruled out, it is appropriate to consider certain non-conventional treatments in combination with antidepressants. When the patient elects to try non-conventional approaches, he or she should be encouraged to use only those that have been demonstrated to be effective in the treatment of severe depressed mood (see Table 3). It is important that the alternative practitioner or psychiatrist who is carefully managing the patient's care should obtain the patient's consent to exchange information with other clinicians and therapists who are working with the patient. The integrative-treatment plan should be reviewed and modified as needed at each session until the most effective combination of conventional and non-conventional treatments is determined.

In cases of severe depressed mood where there is minimal improvement after a period of time in which it is reasonable to expect change, or in cases where symptoms worsen, it is appropriate to review and clarify both the medical and psychiatric differential diagnoses, possibly including referrals to medical specialists, to rule out confounding or undiagnosed medical or neurological disorders that may be interfering with treatment response, including, for example, hypothyroidism, other endocrinological disorders, degenerative neurological disorders, cancer, and others. As in the management of moderate depressed mood, it is important to invite the patient who is severely depressed to participate in all treatment decisions in order to improve clinician-patient alliance and enhance compliance. It has long been established[42] that the perception of control and autonomy significantly improves outcomes in severely depressed patients.

Moderate Depressed Mood: Case Presentation

Mary is a 37-year old single parent of two small children. She has been working part-time as a waitress to support her family since separating from her husband, John, 8 months ago. Mary receives monthly child support and qualifies for food stamps to help out with grocery bills because of her fixed limited income. She has no serious medical problems, maintains a healthy lifestyle, and exercises when possible, though during the past few months has experienced "less energy for exercise" and has gained 5 pounds. Before the separation, she did not drink or use drugs, but in recent weeks she has had a glass of wine almost nightly, and recently told a friend "it doesn't do much for me anymore." In the past month, she has had trouble falling asleep, and often wakes up during the night "worrying about the money situation." She recently started seeing a psychologist on a weekly basis "to find out what is happening to me" after a friend expressed concern that she had been "blue too long." Mary had never been depressed before, nor is there any family history of depression or other major psychiatric or neurological disorders. Her therapist has provided support and encouragement while teaching Mary cognitive skills addressing "the negative self-talk that seems to be in my head." Her therapist has found no evidence of suicidal thoughts, and Mary's concentration and short-term memory are not impaired. Sleep continues to be a problem, and she describes "always feeling tired." The psychotherapist decides to refer Mary to a psychiatrist for consultation and treatment.

During the initial consultation, the psychiatrist confirms that Mary has not experienced previous episodes of depressed mood, mania, or hypomania, and that her mood symptoms have continued at their present baseline for approximately 2 months. He also confirms the absence of suicidal thoughts or a suicide plan. He notes insomnia with middle awakening, chronic fatigue, decreased activity with weight gain, and moderate alcohol use. Mary is aware of the risk of using increasing amounts of alcohol to "ease my pain" and to improve sleep, and agrees to make efforts to avoid drinking, especially when alone at night. For purposes of establishing the most appropriate integrative treatment plan, Mary's symptoms are viewed as a persisting pattern of moderate depressed mood. An integrative treatment plan is formulated, irrespective of whether the particular Western psychiatric diagnosis is Dysthymic Disorder or Adjustment Disorder with depressed mood, as long as moderately depressed mood is the core symptom.

Moderate Depressed Mood: Analysis and Treatment Plan

After reviewing his findings with Mary, the psychiatrist suggests that a combination of lifestyle changes, a suitable mind-body practice, and supplements is a reasonable first-tier integrative approach to her symptoms. Mary recalls that she once enjoyed practicing Tai Chi, and is encouraged to resume her practice with a local teacher she knows about. She remembers "how much more energy I had" when she followed a healthy diet, and commits to "reforming the way I eat!" The psychiatrist briefly reviews the evidence in favor of thiamine and folate for improved energy and depressed mood, and also recommends that Mary increase her current doses of quality brands of vitamins C and E, with the goal of improving general mental functioning. Ginseng tea and other ginseng preparations are mentioned as safe approaches to managing fatigue. Basic strategies in sleep hygiene are briefly discussed, and melatonin (3mg) is recommended. The use of simple relaxation techniques, including deep breathing and taking time to listen to soothing music, is encouraged. The psychiatrist presents the option of an antidepressant and reviews reasonable synthetic and natural product-derived alternatives, but in view of Mary's relatively mild symptoms and the absence of a history of previous depressive episodes, does not recommend that an antidepressant be taken at this stage of treatment. Mary concurs with the psychiatrist, stating that she does not wish to take medication at this time. The psychiatrist suggests that they re-visit this option in the future if her mood does not improve substantially, or worsens, over the ensuing 4 weeks. She is encouraged to continue in psychotherapy in order to actively work on issues of abandonment and self-esteem, to practice cognitive approaches aimed at diminishing negative self-talk, and to keep a journal of progress or obstacles encountered while getting started with the selected treatment plan. The psychiatrist and Mary schedule two follow-up appointments at 2-week intervals, and agree to phone contact between sessions in the event of worsening depression.

When Mary returns in 2 weeks, she appears more rested and immediately comments that she has stopped drinking entirely. She is praised for making this choice, and remarks that taking 3mg of melatonin "solved the whole sleep problem!" After putting her boys to bed, she sometimes takes a bath by candlelight while listening to her favorite jazz CDs. She has forgotten to take the recommended vitamin supplements, but has used ginseng tea during the early afternoon with some improvement in energy. She has purchased an automatic rice cooker and has substituted high-energy bars for chocolate "to avoid sugar rushes." Mary has not found the time to exercise as much as she would like, but has started to "bring more music into my life," including some of her favorite jazz works while "being a mom at home." Mary is encouraged by the rapid improvement in her mood and overall level of wellness, and ascribes these to changes in diet, her

"self-work," and her growing Tai Chi practice. At the end of the session, the psychiatrist praises Mary's efforts and emphasizes that her progress has resulted from positive lifestyle changes and continuing psychological work. Mary is very encouraged by these comments and is empowered by the fact that she "didn't need" to take an antidepressant. Both feel that the next appointment can be safely delayed a month, and agree to phone contact in the event of recurring depression.

One month later, Mary continues to do well. She remains optimistic and encouraged by her progress, and has remained abstinent from alcohol, with the exception of an occasional glass of wine. She has stopped going to psychotherapy, but still works on her self-talk, and has continued with her Tai Chi practice. She takes B vitamins, as well as C and E, but no longer requires melatonin to sleep. She is able to find time to exercise aerobically every other day, and continues to take baths while listening to jazz before going to sleep. After encouraging Mary to continue pursuing a healthy lifestyle, and briefly commenting on "warning signs" of recurring depression that would justify on-going treatment, the psychiatrist tells her that treatment is unnecessary at present, but suggests a follow-up appointment in 2-3 months "to touch base." The psychiatrist invites Mary to schedule an earlier appointment, if needed, for recurring depressed mood, and the appointment ends with a smile and a handshake.

Severe Depressed Mood: Case Vignette

Paul is a 57-year old married, semi-retired broker with a complicated medical history, including coronary artery disease, non-insulin dependent diabetes, and recently diagnosed basal-cell carcinoma on the back of his neck. He is a recovering alcoholic and has been sober for 11 years. Recently he has "been less interested" in attending AA meetings or "doing anything else social." He has three grown children, including a 32-year old daughter who lives nearby and is newly-divorced with two small children. His activities on free days include golfing, gardening and taking his two grandchildren to get ice cream. He sometimes becomes tearful when watching television shows, and recently started to cry during a commercial advertising long-distance telephone service "because it reminded me of how far away I am from my son in Nebraska." Paul first experienced severe depressed mood at the age of 18, soon after leaving home to start college. At that time, his symptoms included persistent feelings of hopelessness and worthlessness, severe daytime fatigue, loss of appetite, and frequent thoughts of suicide. He was not abusing alcohol at that time. There were no manic symptoms during the first episode, or subsequently. Paul did not seek help at that time, and recalls "gutting it out" and eventually feeling better after several months. Afterwards, his mood was "okay" for three years, when suddenly he felt like he was "hit by a truck" with severe depressed mood and suicidal thoughts. Paul finally agreed to see a psychologist at the student health center, where he was diagnosed with Major Depressive Disorder. The psychologist referred him to a family practice doctor at the clinic, who started him on Prozac. In spite of "feeling dizzy" and experiencing diminished libido, Paul continued taking Prozac "because I knew I had to," and his mood improved dramatically in about 6 weeks on a dose of 20mg. After 1 year, he discontinued Prozac because of unresolved side-effects. After a 2-year period of normal mood, Paul became depressed within months after moving to New York City to begin a new job as a stock broker. He soon found a psychiatrist who started him on Zoloft, 100mg, but his mood continued to worsen and he was eventually hospitalized for 3 days because of intrusive suicidal thoughts. While hospitalized, he was started on Lithium carbonate and continued on Zoloft, which was increased to 200 mg. Following discharge, his mood continued being "okay" and he reported fewer side effects than on Prozac. His biggest concern was a 30-pound weight gain during the first 3 months on Lithium, and "the tremor and nausea were also annoying." However, he continued on both drugs. After 3 years, against his psychiatrist's advice, Paul decided to stop taking Lithium, but continued on Zoloft. He continued a grueling daily routine as a Wall Street broker, and exercised less and less over the ensuing years. His psychiatrist eventually tried Paxil, Serzone, Wellbutrin, Effexor, Trazadone, and most recently, Celexa on him. Paul was unable to take Effexor for more than a few days because of severe headaches. He was recently started on Mirtazapine, and has experienced carbohydrate cravings that sometimes "wake me up and send me to the fridge…I can't resist them..." Although his mood improved on some antidepressants, he said he hasn't felt like his old self in years. About two years ago, soon after being diagnosed with heart disease and "wanting to take better care of my life and my wife," Paul found a part-time opportunity at a brokerage in the suburbs, near his daughter's home. He was able to negotiate an early retirement agreement with the Wall Street firm where he had risen to full-partner status, and confidently left "the fast lane" with a sizeable pension and the promise of "golf and grandchildren four days a week." Soon after settling in his new home, Paul's daughter told him about a local clinic where both conventional and non-conventional treatments were available. Paul was intrigued by the idea of combining different kinds of medicine, and after his frustrating experiences with conventional treatments of depressed mood, was open to new approaches.

Severe Depressed Mood: Analysis and Treatment Plan

During the initial appointment, a nurse practitioner trained in Western psychiatry and acupuncture takes a thorough medical, psychiatric, and social history, including a detailed review of Paul's treatment-response history to antidepressant drugs and side-effect issues. Paul reports that he is taking Mirtazipine (15mg at night), but notes recent weight gain due to "a ravenous appetite" since starting that medication 6 months earlier. He is concerned that he has been eating too many sweet foods that have been increasing his blood-sugar readings. The nurse practitioner assesses Paul's current mood as moderately depressed, using DSM-IV criteria, and confirms the absence of suicidal thoughts. She also confirms that the most recent episode of severely depressed mood was about two years ago. They review the effectiveness and side effects of medications used to manage his diabetes and heart disease, and discuss Paul's medical history in detail, including a recent recommendation from his endocrinologist to increase his oral hypoglycemic agent because of poorly-controlled blood sugars. The nurse practitioner takes this opportunity to talk about well-documented relationships between both of Paul's medical disorders and depressed mood. She also notifies Paul of mood-worsening side effects described in the Physician's Desk Reference (PDR) for a newly-prescribed, anti-hypertensive medication. Paul experiences some relief in realizing that his medical problems and medications are probably contributing to his depressed mood, and realizes that by improving his general health he will gain back some control over his depressed mood. Paul asks for advice on "an approach to depressed mood…without all the side-effect problems." He describes disappointment and frustration over incomplete responses to medications and his apparent sensitivity to side effects. The nurse practitioner reviews lifestyle changes and alternative therapies that are known to contribute to improved mood, alone or when used together with antidepressants. Paul realizes that he has never been told about non-conventional treatments by his doctors, and so has never previously tried any of them. "I thought all that stuff was nonsense!" he says.

The nurse practitioner outlines an integrative-treatment plan that combines an antidepressant with lifestyle changes, exercise, supplements, and a mind-body practice. She invites Paul to actively participate in shaping the plan. Paul is pleased to have an opportunity to take responsibility for improving his health, saying, "The Doc never asked me what I thought before." The nurse practitioner recommends modifications in lifestyle, emphasizing improved diet, and addressing his poorly-controlled diabetes and a consistent exercise plan. Paul has not been physically active since his teens, but realizes that his diabetes, heart disease, and depressed mood will benefit from improved nutrition and a consistent daily-exercise program. The nurse practitioner advises Paul to obtain a medical release from his internist before starting to exercise, and suggests that he begin physical training under supervision. They discuss the importance of a stress-management program that fits with Paul's values and beliefs. Paul agrees to start a routine of listening to relaxing music on a daily basis.

The nurse practitioner discusses rational, integrative, medication strategies that address Paul's depressed mood, emphasizing that many reasonable options have not been explored, such as certain synthetic antidepressants and natural substances including SAMe, Omega-3 essential fatty acids, 5-HTP, and certain vitamin supplements, especially folate, B_6, B_{12}, E and C. Paul has recently read a newspaper article about the health benefits of SAMe and Omega-3 fatty acids, and expresses interest in trying one or both of these. The nurse practitioner briefly reviews the documented safety of SAMe in patients with heart disease. Reported side effects of SAMe are briefly discussed, including mild agitation or sedation and gastrointestinal distress during the initial weeks of treatment. The nurse practitioner uses the clinic's computer to refer to an expert database (Natural Medicines Comprehensive Database), and confirms the absence of reported interactions between SAMe and Remeron or Paul's other medications. She documents this fact in the intake note. As Paul has never tried alternative treatments, the nurse practitioner advises a "conservative approach," starting SAMe at 200mg daily, and increasing the dose every few days to the recommended therapeutic range (1200 to 1600mg) for depression, while monitoring for side effects. He is also advised to hold the dose when improved mood lasts at least one week. Paul is advised to continue on Remeron until it is clearly evident that he is able to tolerate SAMe and that it is effective. Paul agrees with these recommendations, and signs a release authorizing the nurse practitioner to notify his psychiatrist of the new plan. The nurse practitioner briefly goes over some basic cognitive-behavioral therapy approaches to depressed mood, including reframing and using distraction and self-affirmations to "help get through hard days." She suggests that Paul begin a daily relaxation program, starting with simple breathing techniques. In the final minutes of the first appointment, the nurse practitioner summarizes her assessment and goes over the initial treatment plan. She gives Paul a handwritten note listing the treatments they have agreed to begin. A routine follow-up appointment is scheduled in 3 weeks, with the understanding that Paul should call for an earlier appointment if there are problems taking the SAMe or if his symptoms worsen before then.

After 3 weeks Paul returns, frustrated that "nothing

is working" and that he's "going downhill fast." He complains of feeling sad most of the time, continues to crave sweets, and remarks that over-eating and weight are still problems. He denies suicidal thoughts, but feels demoralized and appears anxious. He has not kept up a regular exercise program, saying "I'm worried that my heart won't be able to handle the work." He has been listening to music several times a day and has been working in his garden, sometimes many hours a day. "I'm really getting a workout in the garden!" he says. The nurse practitioner encourages him for finding a creative and enjoyable way to exercise. Paul has also started taking a vitamin B-complex, but has not purchased the other recommended vitamin supplements. Although he found SAMe at a local health-food store, he has not increased his dose as they had discussed, and takes only 200mg in the morning. On questioning Paul about possible reasons for his resistance to beginning these treatments, the nurse practitioner confirms (from his reply) that Paul has a strong need for independence: "I don't want to be needing all these pills for the rest of my life!" The nurse praises Paul's efforts to exercise and improve his diet, and he is reminded that improvements in his physical health will improve his depressed mood. The nurse practitioner also reminds Paul that when he reaches an adequate dose of SAMe, assuming there are no significant side-effect problems and his mood improves, it will be reasonable to consider discontinuing the Remeron in consultation with his psychiatrist, which will take away his night-time cravings, resulting in weight loss. He is told that improved control over eating and weight will improve both his diabetes and hypertension. Paul is also encouraged to start taking the recommended doses of quality brands of vitamins C and E. It is suggested that Paul return in 1 week, but he is hesitant to "return too soon." They agree on a routine follow-up appointment in 2 weeks.

At the second return appointment, Paul appears brighter and is noticeably more rested. He seems calmer and appears to have lost some weight. He has been using basic techniques in cognitive therapy to "avoid going into the gloomy thoughts." Paul smiles at the nurse practitioner as he explains that his internist has given him "a clean bill of health" to exercise, and he has been riding a bicycle almost everyday during the past 2 weeks. He comments that "the vitamins seem to give me more energy," and he's raised his SAMe dose according to the plan. At 400mg he experienced mild restlessness, which subsided after 1 week at that dose. He currently takes 400mg before breakfast and lunch as recommended for maximum absorption, without side effects. He has experienced a consistent improvement in mood after taking this dose (800mg/day) for about 1 week. About a week ago, he met with his psychiatrist and they decided it was okay to discontinue the Remeron to see how Paul would do without it. His positive mood has continued since going off Remeron, and he noticed an immediate reduction in craving sweets. The change in appetite, combined with regular exercise, has resulted in a 5-lb weight loss over the past 3 weeks. His most recent blood-pressure reading was moderately lower than before, and his internist is considering taking him off the oral hypoglycemic agent if he continues to exercise, manage his diet well, and lose weight. Paul continues to enjoy music everyday, and is also playing golf. He agrees to return every 2 months, or more often if his mood worsens. He plans to continue exercising and listening to relaxing music while taking SAMe and vitamins. As he leaves, Paul states "My big goal in life now is to take as few pills as possible from here on out!" He thanks the nurse practitioner for helping him to move toward his goal of increased autonomy, while improving his physical and mental health.

Summary

Mental or emotional symptoms are conceptualized in many different ways, depending on the system of medicine within which a patient is evaluated. Western biomedicine views depressed mood as a biological disorder caused by changes in certain neurotransmitters. In contrast, non-Western systems of medicine attribute depressed mood to patterns of energetic imbalance. Different ways of seeing implicit in disparate systems of medicine have resulted in diverse non-conventional or integrative treatments of depressed mood. Substantial research and clinical evidence suggest that many non-conventional biological treatments mitigate symptoms of moderate or severe depressed mood. These treatments include St. John's wort, S-adenosyl-l-methionine (SAMe), and 5-hydroxytryptophan (5-HTP).

Most non-biological alternative treatments are effective against moderate depressed mood only, and are more difficult to evaluate using standard Western experimental methods. Many of these treatments are widely used in Western countries on the basis of consistent reports of positive outcomes. These treatments include acupuncture, bright-light exposure, mind-body or mindfulness practices, and spiritual training. Based on my own clinical experience and a critical review of the medical literature, separate integrative strategies incorporating different combinations or sequences of conventional and non-conventional treatments are suggested for the management of moderate versus severe depressed mood.

References

1. Unutzer J, Klap R, Sturm R, et al. Mental disorders and the use of alternative medicine: results from a national survey. *Am J Psychiatry*. 2000;157(11):1851-1857.
2. Kessler R, Soukup J. The use of complementary and alternative

therapies to treat anxiety and depression in the United States. *Am J Psychiatry*. 2001;158(2):289-294.
3. Druss B, Rosenheck R. Use of practitioner-based complementary therapies by persons reporting mental conditions in the United States. *Arch Gen Psychiatry*. 2000;57:708-714.
4. Bressa GM. S-adenosyl-l-methionine (SAMe) as an antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand*. Suppl 1994;154:7-14.
5. Murphy GE. Carney RM, Knesevich MA, Wetzel RD, Whitworth P. Cognitive behavior therapy, relaxation training, and tricyclic antidepressant medication in the treatment of depression. *Psychol Rep*. 1995;77(2):403-420.
6. Blumenthal JA, Babyak MA, Moore KA , et al. Effects of exercise training on older patients with major depression. *Arch Intern Med*. 1999;159(19):2349-2356.
7. Levitt AJ, Joffe RT, Kennedy SH. Bright light augmentation in antidepressant nonresponders. *J Clin Psychiatry*. 1991;52(8):336-337.
8. Brown MA, Goldstein-Shirley J, Robinson J, Casey S. The effects of a multi-modal intervention trial of light, exercise, and vitamins on women's mood. *Women Health*. 2001;34(3):93-112.
9. Linde K, Ramirez G, Mulrow C, et al. St. John's wort for depression—an overview and meta-analysis of randomized clinical trials. *BMJ*. 1996;313(7052):253-258.
10. Vorbach EU, Hubner WD, Arnoldt KH. Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine: randomized double-blind study with 135 outpatients. *J Geriatr Psychiatry Neurol*. 1994;Suppl 1:S24-28.
11. Kim HL, Streltzer J, Goebert D. St. John's wort for depression: a meta-analysis of well-defined clinical trials. *J Nerv Ment Dis*. 1999;187(9):532-538.
12. Schrader E. Equivalence of St. John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol*. 2000; 15(2):61-68.
13. Vorbach EU, Arnoldt KH, Hubner WD. Efficacy and tolerability of St. John's wort extract LI 160 versus imipramine in patients with severe depressive episodes according to ICD-10. *Pharmacopsychiatry*. 1997;30(Suppl 2):81-85.
14. Ernst E. St. John's wort supplements endanger the success of organ transplantation. *Arch Surg*. 2002;137(3):316-319
15. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. *J Geriatr Psychiatry Neurol*. 1999;12(1):7-10.
16. Roby CA, Anderson GD, Kantor E, Dryer DA, Burstein AH. St. John's wort: effect on CYP3A4 activity. *Clin Pharmacol Ther*. 2000;67(5):451-457.
17. Broughton A, Denham A. Hypericum and Drug Interactions. *Eur J Herb Med.* 2003;5(2):19-25
18. Janicak PG, Lipinski J, Davis JM. "S-adenosylmethionine in depression: a literature review and preliminary report. *Ala J Med Sci*. 1988;25(3):306-313.
19. Kagan BL, Sultzer DL, Rosenlicht N, Gerner RH. Oral S-adenosylmethionine in depression: a randomized double-blind, placebo-controlled trial. *Am J Psychiatry*. 1990;147(5):591-595.
20. Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H. Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. *Psychiatry Res*. 1992;44(3):257-262.
21. Fava M, Borus J, Alpert J, et al. Folate, Vitamin B-12, and homocysteine in major depressive disorder. *Am J Psychiatry*. 1997;154:426-428.
22. Reynolds EH, Preece JM, Bailey J, Coppen A. Folate deficiency in depressive illness. *Br J Psychiatry*. 1970;117(538):287-292.
23. Bottiglieri T, Hyland K, Laundy M, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet*. 1990;336(8730):1579-1580.
24. Crellin R, Bottiglieri T, Reynolds EH. Folates and psychiatric disorders: their clinical potential. *Drugs*. 1993;45(5):623-636.
25. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry*. 2002;59(10):913-919.
26. Su K, Huang S, Chiu C, Shen W. Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13(4):267-271.
27. Nemets B, Stahl Z, Belmaker RH. Addition of Omega-3 fatty acids to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002;159:477-479.
28. Marangell LB, Martinez JM, Zboyan HA, et al. A Double-blind placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*. 2003;160(5):996-998.
29. Carney MWP, Martin G, Bottiglieri T, et al. Switch mechanism in affective illness and S-adenosylmethionine. *Lancet*. 1983;1(8328):820-821.
30. Birdsall TC. 5-Hydroxytryptophan: a clinically effective serotonin precursor. *Altern Med Rev*. 1998; 3(4):271-280.
31. Byerley WF, Judd LL, Reimherr FW, Grosser BI. 5-Hydroxytroptophan: a review of its antidepressant efficacy and adverse effects. *J Clin Psychopharmacol*. 1987;7(3):127-137.
32. Van Praag HM, van den Burg W, Bos ER, Dols LC. 5-Hydroxytryptophan in combination with clomipramine in "therapy-resistant" depression. *Psychopharmacologia*. 1974;38(3):267-269.
33. Mendlewicz J, Youdim MB. Antidepressant potentiation of 5-Hydroxytryptophan by L-deprenil in affective illness. *J Affective Disorders*. 1980;2:137-146.
34. Bella R, Biondi R, Raffaele R, Pennisi G. Effect of acetyl-L-carnitine on geriatric patients suffering from dysthymic disorders. *Int J Clin Pharmacol Res*. 1990;10(6):355-360.
35. Tempesta E, Casella L, Pirrongelli C, et al. L-acetylcarnitine in depressed elderly subjects: a cross-over study vs placebo. *Drugs Exp Clin Res*. 1987;13(7):417-423.
36. Allen J, Schnyer R, Hitt S. The efficacy of acupuncture in the treatment of major depression in women. *Psychol Sci*. 1998;9(5):397-401.
37. Flaws B, Lake J. Book II: Ch 1, 5 In: *Chinese Medical Psychiatry: A Textbook and Clinical Manual*. Boulder, CO: Blue Poppy Press; 2001.
38. Luo H, Meng F, Jia Y. Clinical research on the therapeutic effect of electro-acupuncture treatment in patients with depression. *Psychiatry Clin Neurosci*. 1998;52 (Suppl):S338-340.
39. Janakiramaiah N, Gangadhar BN, Murthy PJ, et al. Antidepressant efficacy of Sudarshan Kriya Yoga in melancholia: a randomized comparison with electroconvulsive therapy and imipramine. *J Affect Dis*. 2000;57:255-259.
40. Tang C, Wan J, Lu Z. Effects of QiGong and Taijiquan on reversal of aging process and some psychological functions. 3rd National Academy Conf. on Qigong Science. 1990.
41. Wang J. Psychological effects of Qigong. 1st World Conf. Acad Exch Med. 1997.
42. Antonovsky A. *Health, Stress and Coping*. San Francisco, CA: Josey-Bass & Co; 1979.

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