Before delving too deeply into the substance of this topic, I will start with a few clinical questions. First, are most of the patients you see in your practice mildly to moderately depressed or anxious, or severely depressed and/or anxious? Secondly, are we getting a clear picture about the Pharmaceutical industry’s success in providing a real difference to our patients with depression? One would certainly think that was true as he watched the commercials on the evening news. And lastly, given similar efficacy, would you choose a treatment for your patient with more side effects or less side effects?

As we ponder these questions, let’s see what the medical literature says about it. In a study looking at all the studies that were brought to the FDA regarding 4 new generation anti-depressants, published in 2008, only those patients at the upper end of the very severely depressed category seemed to receive any benefit from their drug treatment compared to placebo. We also know from the literature that remission rates (that is, those who get better) run in the 20-30% range for most studies – even when “depression care specialists” are involved in the treatment program - while most patients have either no or little improvement with anti-depressant treatment. In addition, in terms of “truth in advertising”, the very literature cited above is part of a system that must be viewed with a jaundiced eye. That is, in a recent study published in the NEJM, if one were to look at the published literature regarding anti-depressant treatments, they would find that 94% of studies were positive. However, when one includes the studies that were not published in the mix, we find that only about half of ALL the studies reveal positive results – the other half simply were not published. In a word, this is called selection bias and we are being duped by big Pharma once again.

With that as a starting point, if there were natural substances that showed results at least as good (if not superior) to standard antidepressants and anxiolytics and those substances had less side effects and were better tolerated, should we not at least give them a trial first - before using more expensive and more dangerous options – except in the more severely depressed patients?
How did the theory of serotoninergic or dopaminergic models of depression come about in the first place? Much of it began in the late 1960s and early 1970s with studies of precursor molecules such as L-tryptophan, 5-hydroxy-tryptophan, L-tyrosine, and DL-phenylalanine. Then came a number of studies looking at removing key amino acids from the diet (tryptophan and tyrosine depletion studies) and watching their effects on mood. Tryptophan depletion diets were shown to decrease levels of serotonin and have a negative effect on mood – particularly when patients had a history of depression. It was at this point that the pharmaceutical industry said a collective, “Yes! We have a winner!” and Prozac® came to market in 1987 followed by its cousin Wellbutrin® in 1989. Since then, these progenitors have been prolific to say the least. Unfortunately, much of the research on amino acid precursors and their effect on mood fell by the wayside. However, in recent years, with the advent of PET and SPECT scanning, direct measures of amino acid neurotransmitter levels in the brain has become possible. Nonetheless, until SPECT scanning becomes more commonplace and less expensive we will soldier on with assessment of neurotransmitters in urine and continue to build our clinical model around that.

In terms of treatment, 5-HTP has been used clinically for over 30 years. In addition to depression, the therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including fibromyalgia, insomnia, binge eating associated with obesity, cerebellar ataxia, and chronic headaches. 5-HTP easily crosses the blood–brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. Clinical experience has shown that when 5-HTP is used in a formula like Sanesco’s Prolent® which contains added constituents like theanine, cofactors, and enzymes, it is even more effective at raising serotonin and improving mood more quickly. There have been a number of studies recently that have even shown 5-HTP’s ability to augment the SSRIs! So we come full circle in a manner of speaking.

Inositol is another personal favorite of mine for depression, anxiety, and insomnia. Inositol or myo-inositol, a natural isomer of glucose and a precursor for the second-messenger phosphatidyl-inositol system, has previously been found superior to placebo in the treatment of depression, panic disorder, and obsessive-compulsive disorder. CSF levels of inositol have been reported to be lower than normal in depressed patients. My favorite study with inositol pitted it against fluvoxamine in panic disorder. Patients completed 1 month of inositol up to 18 g/day and 1 month of fluvoxamine up to 150 mg/day. Inositol reduced the number of panic attacks per week (mean and SD) by 4.0 (2) compared with a reduction of 2.4 (2) with fluvoxamine (p = 0.049). Nausea and...
tiredness were more common with fluvoxamine (p = 0.02 and p = 0.01, respectively) \(^7\). So in this study, the natural substance performed better and with less side effects. Sanesco’s Tranquilent\(^\text{TM}\) product uses 5-HTP and inositol in a formula with theanine to form what many of my patients call “instant Lentra\(^\text{TM}\)”.

Of course, Lentra\(^\text{TM}\) is Sanesco’s GABA formula. GABA is another very important quasi-amino acid that plays an important role in depression, anxiety, and insomnia. Numerous studies have shown that inadequate GABA activity or low levels of GABA have been associated with anxiety, depression, insomnia, panic disorder, migraine headaches, and epilepsy \(^8\). Historically, it has been assumed that GABA is neither well absorbed from the GI tract, nor does it cross the blood-brain-barrier with much gusto. So we have typically used precursor and cofactor substances to raise levels of GABA. Items such as theanine, Lactium\(^\text{TM}\) (a milk peptide), glutamine, and even inositol have been used in formulas. Lactium\(^\text{TM}\) is a French Canadian nutraceutical and is a key ingredient in Lentra\(^\text{TM}\). Valeric acid found in valerian root, acts in a similar way to valproic acid in that it primarily is believed to be a GABA reuptake inhibitor and thus keeps what GABA is available - around longer. Lately, I have come to appreciate a newer form of GABA called PharmaGABA\(^\text{TM}\), through a process developed by the Japanese. PharmaGABA\(^\text{TM}\) is a natural form of GABA produced with the help of Lactobacillus hilgardii – a beneficial lactic acid bacteria used in the making of the traditional Korean vegetable dish known as kimchi. PharmaGABA\(^\text{TM}\) is apparently absorbed much better and has stronger affinity for the GABA receptors than GABA products that have been used in the past.

Another kingpin in the struggle with depression is folic acid – specifically L-methylfolate (MTHF). There is a substantial body of literature suggesting that depression is associated with folate deficiency. A recent meta-analysis of 11 studies which included over 15,000 patients found a significant relationship between the risk of depression and low folate status \(^9\). A number of studies have shown that at least one third of depressed patients have low folate levels. In addition, patients using anti-depressants who are folate deficient, experience a later onset of action, less improvement, more severe episodes, and higher chances of relapse.

Why is this a big concern? Because 7 out of 10 people with depression may have a specific genetic factor (a polymorphism in the MTHFR enzyme) that limits their ability to convert folic acid or folate from the diet to L-methylfolate. \(^10\) This conversion is important because L-methylfolate is the only form of folate used by the brain to correct the neurotransmitter imbalances linked to depression. A recent study showed that L-methylfolate plus an antidepressant at treatment onset was more effective in improving depressive symptoms within 60 days than antidepressant monotherapy, led to major symptomatic improvement more rapidly than SSRI/SNRI monotherapy, and was better tolerated \(^11\).

Further, MTHF is a regulator of BH4 - a critical cofactor of tryptophan hydroxylase and tyrosine hydroxylase which are the key enzymes that metabolize tryptophan to 5-HTP, phenylalanine to tyrosine, and tyrosine to dopamine. Finally, MTHF crosses the BBB, but plain folic acid does not.

Another trimonoamine modulator is SAMe (S-adenyl methionine). SAMe acts as a major methyl donor for the synthesis of monoamines. Low levels of SAMe have been reported in the CSF of depressed patients. SAMe has been studied in over 45 randomized trials and 11 placebo-controlled trials with n = 40 to 100. SAMe is consistently more effective than placebo and is effective as standard anti-depressants.

SAMe has also been shown to augment the action of SSRIs. In a very recent clinical trial, 73 patients with severe depression who had failed an SSRI trial underwent DBPC study with SAMe 800mg bid or placebo added to their regimen. Response was more likely with SAMe (36.1%) Vs. placebo (17.6%) as was remission 25.8% Vs. 11.6%. Differences were clinically significant and clinically meaningful \(^12\). So once again we see the importance of the critical cog of methylation in the folate cycle and in the production of monoamines.
However there are a few concerns about SAMe – not about its safety and efficacy, but about its production. In 2000, an independent lab study revealed that over half of the SAMe samples tested contained significantly less SAMe than was claimed. It is also difficult to synthesize and have it remain stable as it is easily oxidized. The above mentioned independent lab report also noted that in some cases, the milligram amount of SAMe was based upon the weight of the salt rather than the active SAMe portion. That is, 200mg of SAMe tosylate disulfate contains only 100mg of active SAMe. Here it must be stressed to know your supplier and that the quality control on the product you chose is sound. Sanesco literally shopped the world in order to find the top quality ingredients found in its methylation formula, MethylMax®.

In terms of its safety, SAMe has been studied for over 30 years, no known drug interactions occur with SAMe, and it is extremely well tolerated. It should be noted however, that bipolar patients who take SAMe should be on a concurrent mood stabilizer. Of course, this is true with just about any antidepressant.

Last, but certainly not least, is St. John’s Wort (or also known as Hypericum perforatum) – or just Hypericum. It is one of the oldest and most highly investigated medicinal herbs in the world. Hypericum is thought to have reuptake inhibition of serotonin, norepinephrine, and dopamine. It may also have some MAO inhibition characteristics, but the concentration of these substances in the herb are felt to be so low as to not contribute too much of its activity.

Randomized clinical trials show that Hypericum extracts are more effective than placebo and similarly effective as standard antidepressants while having better tolerability in the acute treatment of major depressive episodes. Adverse events are uncommon and mild – most commonly gastrointestinal upset. In over 3200 patients only 1.5% stopped taking the drug because of side effects. There have been no reports of overdose in the literature. There may be some minor increases in sensitivity to UV light, however no reports of phototoxicity have been noted in the literature at usual dosage ranges. 17 cases of psychosis have been reported in the literature from patients taking Hypericum. Finally, bipolar patients should be advised to use Hypericum only with a concurrent mood stabilizer.

The main safety concern with Hypericum is the now fairly long list of drug-drug interactions. Hypericum extracts are powerful activators of the cytochrome P450 enzyme 3A4. A number of reviews have been written underscoring these interactions. Perhaps the main interactions that the clinician will encounter are decreased activity of warfarin, BCPs, theophylline, digoxin, protease inhibitors relevant to HIV-infected individuals, cancer patients on chemotherapy, and transplant patients on immunosuppressives like cyclosporin. It is also not wise to combine Hypericum with SSRIs because of the risk of serotonin syndrome.

The intake of fish could be considered a dietary measure which we will speak to briefly next. But the amounts of omega-3 oils from fish that we consume has dropped so dramatically over the last century, as we have seen a shift from omega-3 to omega-6 oils, that adding fish oil to a therapeutic regimen has actually become necessary. Not only have omega-3 oils been found to improve mood, they are powerfully anti-inflammatory and may help address the pro-inflammatory state we find ourselves in as a result of our dietary choices (namely the increase in sugar and grains).

There have been about 20 controlled trials and a number of open studies that suggest that giving omega-3 oils as a supplement can yield antidepressant and/or mood stabilizing effects. Fish oils have also been used as an adjunctive treatment for depression. A recent randomized, placebo-controlled study of 70 depressed patients who had initially failed their standard antidepressant regimen received 1 g/d of EPA for 12 weeks in addition to their drug therapy and showed significantly higher response rates (53%) to the combination therapy than subjects who used the placebo (29%) and drug combination. Higher doses of the fish oil did not make much difference.
Perhaps it stands to reason that omega3s will improve brain function and mood. What is the brain made of? To oversimplify, it is made of fat, cholesterol, and phospholipids. So if we don’t have the right types of fats in our membranes and in our brain cells, we will not do well. Bipolar patients seem to do well with fish oil as well. Studies show that bipolar patients may have significantly longer durations of remission on fish oil vs. placebo although this has not been consistent in all studies. A recent Cochrane review revealed that most of the benefit from fish oil in bipolar patients is on the depression symptoms rather than the manic phase.

Lastly, a recent report showed that omega-3 and fish oil supplements do not cause increased bleeding during surgery. In a study involving 95 consecutive patients who underwent posterior-only lumbar decompression surgery, supplementation with omega-3 fatty acids (stopping 2.3 days before surgery) was not found to increase intraoperative blood loss or postoperative bleeding in any way. In fact, subjects in the control group, who did not receive omega-3 fatty acid supplements prior to surgery had greater blood loss (154 vs. 138 mL), though this amount was not significant. In addition, there were two complications related to bleeding in the control group, as compared to zero on the omega-3 group. It looks like there will need to be more studies before we can recommend patients not stop their omega-3s before surgery, but this preliminary study is quite compelling.

Lifestyle factors and diet are also paramount in managing depression. A good B-complex seems like a reasonable addition to any regimen for depression as B6 (P5P) and B12 are major cofactors in many of the enzymes used in production of neurotransmitters. In addition, vitamin D is also very important and plays a significant role in mood. A literature search of peer-reviewed mood disorder research studies that measured serum 25-hydroxyvitamin D (25(OH)D) levels in women showed that four of six studies reviewed revealed significant results, with all four showing an association between low 25(OH)D levels and higher incidences of four mood disorders: premenstrual syndrome, seasonal affective disorder, non-specified mood disorder, and major depressive disorder.

Getting adequate sunlight during our 9-5 workdays can be a challenge at best. People are simply indoors much more these days and are exposed to artificial light more and more. Plus, when we are able to move outside, we often cover up or use heavy doses of sun block to prevent the harmful effects of sunlight. However, sunlight and natural spectrum light can have a powerful effect on mood. This probably occurs for at least two reasons. First, we know that exposure to sunlight increases our production of vitamin D, which as stated above, can be an important determinant of mood. Also, it looks like sunlight improves our production of serotonin and increases serotonin turnover in the brain. The production and turnover of serotonin is lowest in winter as the days are shortest during that time of the year.

Physical exercise is also a potential treatment for depression and anxiety. A great number of studies describe an association of physical activity and general well-being, mood and anxiety. Although in many of the meta-analyses, it is pointed out that there are methodological problems with many of the studies. In a recent study, Blumenthal et al. reported that in adults with major depression, the efficacy of exercise seems generally comparable to antidepressant medication and both tend to be better than placebo. Also, exercise seems to compare quite favorably with standard psychotherapy of MDD and there have actually been a few studies that have evaluated their relative efficacy. In one study, running appeared to be just as effective as psychotherapy. It should be noted that patients with panic disorder or panic attacks, should be informed that in rare cases exercise-associated bodily sensations may trigger panic attacks, despite an anxiolytic activity of acute and long-term exercise.

For a brief explanation of what might be the reason for improvement of mood with exercise, there are a number of possibilities. One might be the social support – particularly of people who run or exercise together in groups. There is an increased self efficacy, or a sense of mastery, as well as changes in self-concept that may be responsible for the therapeutic efficacy of exercise. In addition, neuroendocrine changes may also be the reason. Some of these include increased central norepinephrine neurotransmission, changes in the HPA axis with exercise, as well as increased serotonin synthesis and metabolism. Most of us think about serotonin as it relates to mood only, but serotonin is responsible in part for our axial posture. Indeed, simply the firing of motor neurons (particularly in a repetitive manner) such as walking, running, or swimming, results in increased release and synthesis of serotonin in the brain. The effect of sustained exercise is also known to contribute to the production of b-endorphins.
Diet is the last aspect of this summary of adjuncts and alternatives to standard antidepressants that will be explored. Since L-tryptophan is an essential amino acid, it would stand to reason that a diet high in tryptophan might protect against depression or aid in the treatment of depression or anxiety. Well, there actually has been a study looking at this and there is indeed a negative association between dietary tryptophan and suicide rates.

As nice as it might be to open a roadside stand that sells turkey and banana sandwiches with a glass of milk on the side in an effort to raise tryptophan levels and keep the world from going over the edge, unfortunately it looks like that purified tryptophan increases brain serotonin, but foods containing tryptophan do not. However, α-Lactalbumin, a minor constituent of milk, is one protein that contains relatively more tryptophan than most proteins. Acute ingestion of α-lactalbumin by humans has been shown to improve mood and cognition, at least in some circumstances, presumably owing to increased serotonin.

One substance that may not increase production of serotonin, but certainly has an impact on serotonin is sugar or refined carbohydrates of all kinds. Many of us know patients who have been on the Adkins diet (or some other similar very low carbohydrate diet) who have experienced lowered mood. This is because carbohydrate consumption – acting via insulin secretion and the “plasma tryptophan ratio” - increases serotonin, making us feel better, at least temporarily. As sugar levels rise, so does serotonin. It is this author’s clinical supposition that as insulin pours out to maintain glucose homeostasis, and sugar enters the cell, serotonin may “leak” out of the synapse and be lost. When this happens time and time again as the blood sugar spikes and crashes, low serotonin may result. I believe this is precisely why we see so many patients with low serotonin when we test and why we see so many patients taking antidepressants like SSRIs. At least part of the explanation may lie in the fact that Americans eat approximately 150 pounds of sugar per person per year. That is obviously quite an assault on our serotonin synthesis and metabolism machinery.

I would be remiss to not include at least a nod to what I feel is a most crucial piece in bringing depressed and anxious patients to a higher level of wellness. That is, whatever therapy is chosen for the patient “to take” there is an equally, if not more important therapy “to share” and that is the mental health support piece. Counseling for depression administered during depressive episodes has been shown to be effective in reducing subsequent relapse and recurrence. Patients who recover following treatment of acute depression by counseling subsequently show less relapse or need for further treatment than do patients who recover following treatment with antidepressant medication and are then withdrawn from medication. Counseling “works” presumably by helping the patient acquire skills that allow them to change their thinking and the way they view their concerns that confer some protection against future bouts of depression or anxiety. An outgrowth of counseling theory is Mindfulness-based CBT (MCBT). MBCT aims at developing participants’ awareness of, and changing their relationship to, unwanted thoughts, feelings, and body sensations, so that participants no longer avoid them or react to them in an automatic way but rather respond to them in an intentional and skillful manner.

Biofeedback techniques and constructs such as HeartMath® are other non-drug adjunctive therapies that show great promise. A growing body of research indicates that autonomic function is altered in depression and anxiety, as evidenced by impaired baroreflex sensitivity, changes in heart rate, and reduced heart rate variability (HRV). In a recent study, researchers used heart rate variability (HRV) biofeedback to treat moderate to severe depression. At follow up BDI (Beck Depression Inventory) was found significantly decreased as compared to baseline conditions in patients with depression. In addition, depressed patients had reduced anxiety, decreased heart rate and increased HRV after conduction of biofeedback. Increasing awareness and obtaining adequate counseling are key determinants to achieving remission from depression and anxiety and can be integral to human growth and potential.

In conclusion, in light of the fact that there is such a small (if any) difference between placebo and drug treatment in any case except the most severely depressed patients, the fact that the majority of patients with depression and many with severe anxiety are not responsive to their prescribed drug treatments, the fact that as physicians we get such incredibly biased information from research performed by the pharmaceutical industry – then add to this the fact that many natural remedies are safer, less expensive, and at least as effective as their drug counterparts,
shouldn’t we at least consider giving these natural therapies a try first – before resorting to drug treatment? To quote an excerpt of an article published in Psychiatry in 2009, “The most commonly used nutraceuticals appear to be better tolerated than the more standard, conventionally used antidepressants, such as SSRIs. Some of the nutritional supplements can be used in patients who have achieved only partial treatment response to standard antidepressant medications and may offer additional clinical benefit without increasing the side effect burden.”

**To me, this is the essence of Integrative Medicine.** We do the best thing for our patients using ALL the tools in our toolkit to come up with therapeutic recommendations that may include either/or, or both conventional and non-conventional treatments.

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**A Practical “Tool” For An Integrative Approach**

One of the clinical “tools” available to practitioners considering the natural therapy options discussed by Dr Watkins is Sanesco’s Communication System Management (CSM) model. The CSM model is a clinical system designed to help you to assess, monitor, and correct key neurotransmitter imbalances that may be associated with your patients’ symptoms of anxiety and depression. *The CSM model includes three integrated components.*

- The CSM model utilizes a **noninvasive lab assay** measuring neurotransmitter and adrenal hormone levels to establish baseline levels of a patient’s biochemistry. Subsequent testing is used as an effective tool for monitoring treatment.
- As a model of individualized medicine, CSM includes patient-centered analysis of symptoms and lab results. With oversight by Sanesco’s Medical Board, highly trained clinical staff correlates 48 patient-reported symptoms, current dietary and lifestyle factors, supplement and medication intake, to the reported lab results; generating a comprehensive “**Correlation Analysis**” report. This Correlation Analysis report provides you with extensive patient specific information to help you open the window to your patient’s neuroendocrine system.
- The third component of the CSM model is using the **nutraceutical supplements** discussed in Dr Watkins’ monograph. Sanesco’s Targeted Nutritional Therapy products are safe and effective options for restoring some of the biochemical imbalances that may be associated with anxiety and depression, as well as other symptoms related to neuroendocrine system function.

Sanesco developed this “CSM” model in collaboration with a team of medical doctors, naturopathic doctors, nutritionists, and researchers. The goal was to provide a practical science-based individualized approach for looking at the key contributors to potential underlying causes of chronic symptoms.

Sanesco provides complimentary training to practitioners on the three components of this model through its **CSM Certification Program.** This exclusive program includes one-to-one interactive training sessions, live webinars, a self-tutorial library, and much more. Contact a Sanesco representative to **enroll today - Call 866.670.5705 and Press “2”**

*The above statements have not been evaluated by the FDA. The products mentioned above are not intended to diagnose, treat, cure or prevent any disease.*

*Not all of the nutraceutical products mentioned in this monograph are distributed by or sold by Sanesco International. Contact a Sanesco representative for more information.*

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Sanesco International is a research-driven company helping practitioners in assessing, monitoring, and correcting neurotransmitter and adrenal hormone imbalances affecting HPA-T axis function.

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