Are Nutritional Supplements Ready for Prime Time?

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Over the past 20 years, there has been a surge of clinical trials examining the safety and efficacy of natural compounds for psychiatric indications. These studies have produced encouraging evidence for several putative antidepressants such as *S*-adenosyl-L-methionine (SAMe), St. John's wort (SJW), the omega-3 fatty acids, and folic acid.[1–6]

There are about 45 published randomized controlled trials (RCTs) of SAMe monotherapy against placebo or tricyclic antidepressants (TCAs). While generally suggestive of safety, superiority over placebo, and comparable efficacy to the TCAs, the studies are limited by small samples, wide-ranging doses of 200–1600 mg/day, and different delivery systems (oral, intramuscular, and intravenous), as well as premature decomposition of some of the early oral forms of this agent.[1,2] There is 1 positive open study of SAMe augmentation,[7] and no comparisons against newer antidepressants.

SJW, at doses between 900–1800 mg/day, has also performed well against placebo and TCAs in about 35 to 40 published RCTs,[3,4] many of which are limited by small samples, shorter-than-optimal treatment periods, and a lack of rigorous diagnostic instruments. Recent comparisons with selective serotonin reuptake inhibitors (SSRIs) have been plagued by inconsistent data, with active comparators often proving no more effective than placebo as well as SJW[3,4]; these trials are therefore of limited use and cannot be taken as a clear indication of efficacy.

The omega-3 fatty acids have had a smaller, but generally positive, body of about 15–20 RCTs suggesting efficacy for unipolar depression, particularly as adjunct therapy, and mixed results in bipolar disorder.[5] An encouraging meta-analysis of 8 omega-3 RCTs for depression was limited by its combination of augmentation and monotherapy trials and inclusion of 3 bipolar samples.[5] As with lithium and thyroid augmentation, most of these studies were not large, and there was a wide range of omega-3 preparations and doses (1–10 g/day). Overall, the data suggest a signal, but the quality of the studies and lack of consistent design remain troublesome.

Folic acid supplementation has been shown to benefit depressed people with folate deficiencies,[6] but only 3 published clinical trials have examined folate administration in normofolatemic depressed patients.[8] A double-blind RCT[9] showed beneficial effects of 500 μg/day of folate augmentation in 127 fluoxetine partial responders. Alpert and colleagues[10] found similar benefits in an open trial with 22 SSRI partial responders receiving 15–30 mg/day of folinic acid augmentation. A third study of 96 subjects with mild-to-moderate dementia and depression found no significant difference between 50 mg/day of 5-methyltetrahydrofolate (MTHF) augmentation versus trazodone 100 mg/day.[11] These mostly encouraging findings require replication in larger samples to increase their generalizability.

One particularly appealing quality of nutraceuticals is their relatively benign toxicity profile. These agents generally have fewer and less frequent side effects than their U.S. Food and Drug Administration (FDA)–sanctioned counterparts, and toxic reactions are relatively rare.[12] However, with increasing use of these agents, we have learned that they should be used with greater caution. For example, SJW has caused serotonin syndrome in combination with SSRIs, and its induction of the 3A4 pathway may render certain concomitant drugs ineffective, resulting in potentially tragic consequences, such as transplant rejection.[4] The omega-3s have been linked to bleeding,[5] and both SJW and the omega-3s, as well as SAMe, have been associated with cycling in bipolar individuals.[4,5] Folate preparations and SAMe appear less prone to adverse effects and interactions,[6,12,13] and perhaps for this reason they are finding a niche as antidepressant augmentation therapy.[6–13]

Should Nutraceuticals Be Prescribed More Often?

Given the encouraging findings of efficacy, benign side effect profiles, and limited toxicity, should physicians be prescribing these agents more regularly? Some preparations of omega-3 (Omacor) and MTHF (Deplin) are approved by the FDA for hypertriglyceridemia and folate supplementation, respectively (though not yet for any psychiatric indication), which suggests that these products are gaining credibility among clinicians. However, the lack of fully convincing efficacy data in psychiatric populations remains their primary downside, and is probably the greatest obstacle to acceptability by the medical establishment at large. Yet, as we learn more about the apparently limited efficacy of standard antidepressants,[14,15] the differences between these natural agents and their FDA-approved counterparts may prove not so large after all.

Safety and tolerability. Apart from the SJW-related drug-drug interactions, the natural products reviewed here are better tolerated than standard agents. Omega-3s may cause gastrointestinal upset and fishy taste at higher doses, though less so at the more common dose of 1 g/day.[5] SAMe is very safe, is well tolerated except for occasional gastrointestinal upset, and has no associated hepatotoxicity.[1,2,12,13] The same can be said for folate and MTHF.[6,8,12,13] None have been strongly associated with the more bothersome antidepressant-related side effects, such as sexual dysfunction and weight gain.[12] That said, many of these products have not been subjected to the same level of rigorous and systematic testing for toxicity as the FDA-approved drugs, and as such may harbor unknown dangers.

Efficacy. Most comparative studies suggest that these natural agents are superior to placebo and are as effective as some standard antidepressants, mostly TCAs, although comparisons with the newer antidepressants are sorely lacking and the published ones have yielded mixed and inconclusive evidence.[4] There is also debate about adequacy of dosing and particular brands, given the high variability of manufacturing procedures and the many potentially active chemicals in herbal medicines.[4] This, too, dampens the enthusiasm for nutraceuticals versus standard antidepressants.

Accessibility. While easily obtainable over the counter, nutraceuticals can prove expensive, since they are not covered by insurance.[16] SAMe tends to be the most costly, since it is relatively newer in the U.S.[13] The MTHF preparation sold under the brand name Deplin, while it may be covered by some insurance plans, will most likely be costly for those without coverage; other forms of folate are more affordable, though perhaps less able to cross the blood-brain barrier.[6] There are many brands of omega-3s and SJW available, and these tend to vary in price, but out-of-pocket expenditure remains an obstacle for many consumers. However, with insurance carriers increasingly reluctant to cover brand-name antidepressants, clinicians often have to prescribe older generic drugs that may have more bothersome side effects; this may encourage consumers to spend the money for natural products if their tolerability is better. Still, it is hard to beat the $20 monthly copayment for registered drugs.

The Right Medication for the Right Patient

Despite their higher cost and potential hazards, nutraceuticals remain extremely popular in the U.S. and worldwide.[16–18] When considering the sales figures and usage patterns for these agents,[17–19] some might argue that nutraceuticals are already in "prime time," whether they are ready or not. In carefully selected patients, and with thoughtful consideration on the clinician's part, natural remedies can indeed be of great value. We have previously offered a set of guidelines for clinicians,[20] suggesting that the best candidates for nutraceuticals may be those at both extremes of the illness severity spectrum. People with mild illness and a strong interest in natural products may have nothing to lose by trying a nutraceutical—for example, a patient with a first depressive episode, relatively mild symptomatology, and no significant family history. At the other extreme, patients for whom everything else has failed may want to try these agents as a last resort, or as an alternative to more aggressive interventions such as electroconvulsive therapy. However, the more refractory patients are the hardest to treat, and natural remedies seem to work better in people with milder and less chronic forms of illness.[20] Patients with longstanding resistant depression, for example, are usually not prime candidates for nutraceuticals.

Regarding specific types of use, most of these agents, with the exception of SJW, can be safely combined with other antidepressants,[4] and the research generally supports augmentation.[4–7,9–11] The omega-3s, SAMe, and MTHF could be used in partial responders to standard agents, since their benign toxicity profiles would allow patients to obtain additional antidepressant benefit without increasing the side effect burden or risk of drug-drug interactions. Augmentation could therefore represent an excellent niche for many of these agents.

Finally, given that many nutraceuticals have various health benefits, they might be investigated for prophylaxis or maintenance in selected populations. For example, in healthy people with a family history of depression, a daily omega-3 dose not only might provide the well-documented cardiovascular benefit,[21] but may theoretically protect them from developing depression. Folate supplementation also has multidimensional health benefits, in addition to protecting against depression.[22] Patients with arthritis who are at risk of depression might consider SAMe for pain relief.[23] However, the appropriateness of prophylaxis—as opposed to maintenance—in mood disorders is not well established, and when such an approach is considered, the usual arguments apply: if you want to prevent illness, why not use something tried, true, and safe?

Conclusions

Nutraceuticals continue making inroads into general acceptability by the medical establishment. But before we promote the nutraceuticals reviewed here to "prime time" and begin recommending them as a first-line therapy for most cases of depression, we need more well-designed, adequately powered efficacy studies, including comparisons with standard agents, and continued investigation into their safety.

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Drs. Mischoulon and Fava have financial associations with many companies that produce psychoactive pharmaceutical agents; these include consultancies, receipt of research grants and honoraria, participation in advisory boards, equity holdings, and patents.

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