Ask the Expert

Depression and Dysthymia

What role should natural products play as augmentation therapies for major depressive disorder?

Reply from David Mischoulon, M.D., Ph.D.

For individuals with major depressive disorder (MDD), it is both a good and bad time to be depressed. There there are at least two dozen FDA-approved antidepressants on the market, not to mention mood stabilizers and atypical antipsychotics that also carry indications for depression. Yet as we learn more about antidepressants, the evidence suggests that these agents may not be as effective as we once thought. Many individuals do not respond well to standard antidepressants, and many who do respond will eventually relapse.

When faced with a patient with treatment-resistant depression, psychiatrists will often add a secondary agent to boost the effect of the original antidepressant. For example, a patient with limited response to an SSRI may benefit from the addition of bupropion, since their different mechanisms of action may synergize for a more robust effect. Studies such as STAR*D have supported augmentation and combination strategies for patients who do not respond completely to an initial antidepressant. What role might natural products have in this particular strategy?

Natural products are appealing in large part for their easier accessibility, better tolerability, and fewer stigmas than standard antidepressants. But efficacy and safety are less established, and toxic reactions have occurred when some of these products are taken in excessive doses, for longer than recommended periods, or in combination with other drugs. There is also a fair amount of variability in purity and quality of these agents, particularly those from herbal sources that contain many potentially active ingredients, and this can have an impact on efficacy as well as tolerability. Finally, these products are generally not covered by insurance, and many are expensive.

There are currently three natural products that have a fairly strong body of evidence in support of their antidepressant activity: St. John's wort (*Hypericum perforatum*), *S*-adenosyl methionine (SAMe), and omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). All have been studied as monotherapy for depression. Omega-3s also have a substantial number of clinical trials examining their efficacy for augmentation of standard antidepressants. There are, however, few published clinical trials of SAMe augmentation for antidepressant partial responders. St. John's wort presents more limited options for combination therapy because of the risk of adverse interactions. The evidence for all these will be reviewed.

There are about 40 published clinical trials of St. John's wort monotherapy for depression, with evidence generally supporting efficacy, although recent studies have produced mixed results. For example, two high-profile, large-scale, multisite randomized trials from the early 2000s did not demonstrate any significant advantage for St. John's wort over placebo. While these trials may have been limited by low assay sensitivity, underdosing of active drugs, and greater severity of depression compared with earlier European studies, their impact on the popularity of St. John's wort was notable. Recent meta-analyses generally caution about the overall mixed

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findings, particularly in comparisons against selective serotonin reuptake inhibitors (SSRIs).

Recommended doses of St. John's wort range from 900–1800 mg/day, though different preparations may vary substantially due to standardization to different active ingredients, such as hypericin or hyperforin; head-to-head comparisons are, unfortunately, lacking. Tolerability is quite good, although adverse reactions have been documented, including potentially toxic adverse interactions with different medications. In particular, the combination of St. John's wort with SSRIs has been shown to result in serotonin syndrome, a potentially fatal reaction. For this reason, patients should be cautioned not to combine St. John's wort with SSRIs. The risk of interactions with other antidepressants is not clear, but overall St. John's wort is best limited to monotherapy for depression.

There are over 30 published clinical trials of omega-3s for depression, usually involving combinations of EPA and DHA at different ratios and total doses. Studies overall support antidepressant efficacy, both as monotherapy and as augmentation of standard antidepressants. A recent meta-analysis by Sublette and colleagues supported EPA as more antidepressogenic than DHA, given that preparations comprising EPA at 60% or greater, relative to DHA, produced more robust antidepressant effects.

Omega-3s appear to have no significant interactions with other drugs (except possibly anticoagulants), which makes them well suited for combination therapy in treatment-resistant depression. Doses of about 1000 mg/day are recommended for unipolar depression, conservatively at ratios of at least 3:2 in favor of EPA. It must be noted that many commercially available "fish oil" preparations may not specify amounts or ratios of EPA and DHA. Consumers and physicians should read labels carefully and select preparations that disclose specific content. There are various Internet sites that provide information about the contents and quality of various natural products, although these sites should also be perused with caution.

SAMe has been extensively studied, with about 45 clinical trials that collectively support efficacy for monotherapy of MDD. There are very few combination studies, however. One such study suggested that the combination of SAMe plus a tricyclic antidepressant (TCA) was effective and safe, and might even work faster than TCA therapy alone. Two studies from our group, one open and one placebo-controlled, found benefit for partial responders to SSRIs and SNRIs. Recommended doses are usually between 800–1600 mg/day, although certain patients may require higher doses to attain the full effect. Tolerability is good, with mild gastrointestinal upset as the most commonly reported side effect. SAMe is best absorbed when taken on an empty stomach. Early preparations of SAMe were unstable and often degraded quickly on the shelf; nowadays, stabler salt forms of SAMe (e.g., tosylate and butanedisulfonate) have longer shelf lives, and blister packs may also provide stability.

Folic acid forms also have growing evidence as adjunctive antidepressants, with recent investigations focusing on 5-methyl tetrahydrofolate (5-MTHF; Deplin). Other natural products such as 5-hydroxy tryptophan (5-HTP), chromium, inositol, and Rhodiola, are often used by themselves or in combination with standard antidepressants, but evidence for these is more limited, and so these products should be recommended with greater caution.

Given the seriousness of untreated depression, and the relatively limited data on the optimal role of natural agents in the psychiatrist's armamentarium, we do not recommend that depressed patients self-medicate. The best recommendation for a patient with MDD that is not responding adequately to a standard antidepressant is to discuss the matter with their prescribing physician and review more established second-line strategies such as dose increases, combination and augmentation, and the addition of psychotherapy. Natural products may be considered when deemed safe, and patients who are prone to side effects may be particularly good candidates. Caution is required with bipolar patients because of the risk of cycling. Likewise, pregnant women need to be carefully advised, as the risks these products may pose to an unborn child remain to be elucidated.

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