Research to Practice

The Status of Nutraceuticals for the Treatment of Depression

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INTRODUCTION

We are all aware of the inherent challenges and limitations of the currently available prescription-based drugs for the treatment of major depressive disorder (MDD). Beyond the side-effect liability of the selective seratonin reuptake inhibitors (SSRIs) (gastrointestinal [GI] symptoms, insomnia, sexual dysfunction), there is a recognition and extensive documentation that many depressed patients do not achieve full remission of symptoms or recover full daily functioning. Consequently, augmentation strategies that add additional medications to SSRI treatments abound in clinical research and practice. Many clinicians have added naturally occurring compounds, like nutritional supplements, to this augmentation armentarium with some success. Complicating this therapeutic arena are the media and public who have often promoted nutraceuticals. In fact, the internet is laden with uncontrolled studies and testimonials, which can only obfuscate the potential benefit these agents might really offer. I thought it would be helpful to ask David Mischoulon, MD, PhD, from the Depression Clinical and Research Program (DCRP) at the Massachusetts General Hospital in Boston to discuss his perspective about the realities of treatment with nutritional supplements.

SHOULD PHYSICIANS PRESCRIBE NUTRITIONAL SUPPLEMENTS FOR THE TREATMENT OF MDD?

Dr. Mischoulon: Generally, I would say yes, with some caveats. In my opinion, the small amount of controlled clinical research that has been done is encouraging with regard to the efficacy of some nutraceuticals that have shown benign side effect profiles and limited toxicity. In fact, the most commonly used nutraceuticals appear to be better tolerated than the more standard, conventionally used antidepressants, such as SSRIs. Some of these 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. Patients with long-standing treatment-resistant depression are not likely candidates for nutraceuticals, which tend to be more effective in patients with milder forms of depressive illness. Of course, the open-label use of nutraceuticals in clinical practice can be misleading because of the high rate of placebo response. Physicians must always monitor for side effects, possible drug-drug interactions, and use their critical judgment in deciding if these agents are really making a difference.

WHICH NUTRACEUTICAL COMPOUNDS ARE THE MOST PROMISING?

Dr. Mischoulon: Studies have been most promising for S-adenosyl-methionine (SAMe), St. John's Wort (SJW), the omega-3 fatty acids, and folic acid. Of course, each compound has its own issues relative to its

safety, tolerability, and demonstrated efficacy in double-blind, randomized, clinical trials. Most of these controlled studies have been conducted in small samples of patients, have used wide-ranging doses and/or treatment delivery systems, and usually have not compared efficacy against the newer antidepressants.

WHICH NUTRACEUTICALS HAVE HAD THE MOST CONTROLLED CLINICAL RESEARCH?

Dr. Mischoulon: SAMe is among the most widely studied, with more than 45 published randomized trials. Doses used in these studies have ranged from 200 to 1600mg per day using oral, intramuscular, or intravenous routes of delivery. Overall, the bulk of data supports the use of SAMe as an antidepressant.

In fact, SAMe is frequently prescribed by physicians in parts of Europe. We are actively researching SAMe at Massachussetts General Hosptial as adjunctive therapy for MDD in one recently completed study and as monotherapy in another study. Its relative safety and lack of interactions has made it a particularly good agent for augmentation.

SJW has also been extensively studied, with about 35 to 40 published clinical trials, generally with doses from 900 to 1800mg per day. Recent comparisons against the SSRIs have yielded inconsistent findings, perhaps due in part to selection of more severely depressed samples of patients. SJW use as an augmenting agent is limited, because of interactions with other antidepressants, particularly the SSRIs.

The omega-3 fatty acids have had about 15 to 20 randomized clinical trials for depression. Although the data are promising, the studies have lacked consistent design and used relatively small samples of patients. Furthermore, the doses ranged widely from 1 to 10g per day. Given these caveats, overall omega-3 has generally been effective for unipolar depression, particular as adjunctive therapy, with increasing evidence for efficacy as monotherapy.

Folic acid is relatively understudied compared to the other agents we have discussed here. However, the few published studies of folate augmentation of standard antidepressants have all been positive, with excellent safety and tolerability.

ARE ANY NUTRACEUTICALS APPROVED BY THE FDA FOR THE TREATMENT OF MDD?

Dr. Mischoulon: No. However, one preparation of omega-3 (Omacor) has been approved by the FDA for the treatment of hypertriglyceridemia and 5-methyltetrahydrofolate (MTHF) as Deplin has been approved as a prescription drug for folate supplementation. However, to date there are no approvals for the treatment of depression.

WHAT ARE THE SIDE EFFECTS AND RISKS ASSOCIATED WITH NUTRACEUTICALS?

Dr. Mischoulon: As I mentioned earlier, as a group of agents the nutraceuticals are more benign than conventional antidepressants like fluoxetine or escitalopram. However, each nutraceutical has its own unique liabilities. SAMe may be the most benign of all but it can cause occasional GI side effects. On the other hand, omega-3 can cause more troublesome GI upset at higher doses and has a fishy taste. Some reports have suggested that folate supplementation may be associated with elevated homocysteine levels and perhaps an increased risk of colon cancer, though the evidence overall suggests safety for most people. SJW has been associated with serotonin syndrome when used with SSRIs, and its induction of the 3A4 pathway may cause drug-drug interactions and render some concomitant medications ineffective. SJW also carries a risk of phototoxicity, and therefore, people who use SJW should beware of excessive exposure to the sun.

WHAT IS THE AVAILABILITY OF SAMe, OMEGA-3, AND MTHF?

Dr. Mischoulon: All of these nutritional supplements are available in health food stores. But, health food stores are not pharmacies. The manufacture and control of nutritional supplements is not a well-regulated area compared to that of FDA-approved drugs. For instance, there are many different brands of SJW available in health food stores that vary in price and may vary in potency. In fact, the potency of each nutritional product can vary greatly regardless of the stated dose on the packaging, as there is often high variability in the manufacturing process that affects bioavailability and metabolism. Herbal medicines in particular can have multiple ingredients beyond the single agents we have been discussing, which are not necessarily what a depressed patient needs to be taking.

WHAT IS ON THE HORIZON FOR NUTRACEUTICALS IN PSYCHIATRY?

Dr. Mischoulon: There are a few natural medications that have been studied for anxiety and insomnia. These include kava and valerian, as well as melatonin. Valerian and melatonin have a relatively large number of clinical trials to support their efficacy, but there are fewer studies of kava, about which there have been growing concerns regarding liver toxicity in the past few years. Ginkgo biloba has a large number of clinical trials supporting its efficacy in controlling symptoms of early

dementia. Regarding depression, there is continued interest in a number of potential natural antidepressants, including 5-hydroxytryptophan, inositol, rhodiola, and chromium, among others. But evidence for these nutraceuticals is very preliminary and these products should therefore be used with caution.

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FINANCIAL DISCLOSURES: Dr. Targum is on the consulting staff of the department of psychiatry at Massachussetts General Hospital and is an executive-in-residence at Oxford Bioscience Partners (Boston, MA) where he works with start-up CNS companies. Currently, Dr. Targum is chief medical officer at Methylation Sciences Inc., Chief Medical Advisor at Prana Biotechnology Ltd., and Senior Medical Advisor at BrainCells Inc. In addition, he is the founder and chief scientific officer at Clintara LLC and clinical advisor to Nupathe. Dr. Targum has equity interests in BrainCells Inc., Clintara LL, SmartCells, Methylation Sciences Inc, United BioSource Corporation (UBC), and Prana Biotechnology Ltd. Within the past year, Dr. Targum has received consultation fees from BrainCells Inc., Clintara LLC, Methylation Sciences Inc., and Prana Biotechnology Ltd. At different times during the past 10 years, Dr. Mischoulon has received support from the following companies: Lichtwer Pharma GmbH, Bristol-Meyers Squibb Company, Cederroth, Laxdale (Amarin), Nordic Naturals, Swiss Medica, Ganeden, Pamlab, Pfizer, Virbac, and Back Bay Scientific. Dr. Mischoulon has also received support from Reed Medical Education (a company working as a logistics collaborator for the Massachussetts General Hospital (MGH) Psychiatry Academy). The education programs conducted by the MGH Psychiatry Academy were supported through Independent Medical Education (IME) grants from pharmaceutical companies co-supporting programs along with participant tuition. For 2008, those companies included Astra Zeneca, Eli Lilly, Bristol-Meyers Squibb, Forest Laboratories, Inc., Janssen Pharmaceuticals, and Pfizer.

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