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EDITORIAL

A Perspective on the Emergence of Meditation Techniques for Medical Disorders

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This editorial discusses recent systematic reviews on yogic meditation techniques used for treating medical disorders and contrasts the results with two recent very large multisite state-of-the-art pharmacologic trials (one for depression,[1–4] the other for schizophrenia[5–7]) funded by the National Institutes of Mental Health (NIMH). The intent here is to put the new emerging interest in meditation techniques into a larger perspective to help clarify the need for potential novel therapies.

The review in this journal by Arias, et al. (817–832) entitled a "Systematic Review of the Efficacy of Meditation Techniques as Treatments for Medical Illness" is timely, important, and the fourth published systematic review since 2005 on yogic meditation techniques as therapies solely for specific disease states. This review does not include meditation studies on healthy subjects, nor does it focus only on a single type of meditation technique that was the focus of a recent 2004 review on hypertension,[8] or another in 2004 on all forms of complementary and alternative medicine (CAM) therapies for anxiety.[9] Arias, et al., state their interests for conducting this systematic review, writing that "meditation techniques are sought frequently by patients coping with medical and psychologic problems . . . their increasingly widespread appeal, and the potential for use as medical therapies." The authors identify 82 studies, and 20 randomized controlled trials (RCTs) met their final inclusion criteria with a total of 958 subjects (397 experimentally treated subjects and 561 control subjects). The authors state that "no serious adverse events were reported in any of the included or excluded clinical trials." And they conclude that "results support the safety and potential efficacy of meditative practices for treating certain illnesses, particularly in nonpsychotic mood and anxiety disorders." They also state that "lastly, because of possible experimenter bias, research by Maharishi Transcendental Meditation™ (TM)–associated researchers has not been included unless it was performed at a more neutral institution, and the majority of the researchers were not affiliated with the Maharishi organization." Arias et al. call TM "a commercial technique." Clearly, the only access to a TM mantra is via substantial payment by an individual. Therefore, no one outside the organization can replicate TM trials independently because the mantras are kept secret. This leaves the scientific community limited in its understanding for any potential value of TM as a therapy for medical disease states. I do not recall any pharmacologic trial in which the identity of a drug has been withheld.

Another review in 2005 focused solely on yogic meditation techniques for depression.[10] That review located five RCTs meeting their inclusion criteria. All studies showed positive results using different forms of yogic meditation, with the severity of depression ranging from mild to severe. However, the authors reported that important methodological details on randomization, compliance, and attrition rates were missing.[10] The authors reported that the only adverse effects were fatigue and breathlessness in participants in one study.[10] The researchers concluded that "overall, the initial indications are of potentially beneficial effects of yoga interventions on depressive disorders. Variation in interventions, severity and reporting of trial methodology suggests that the findings must be interpreted with caution."[10]

Two other reviews focused solely on anxiety disorders.[11,12] The first of these two[11] reviewed eight studies, all with positive results, although there were many with methodological inadequacies. The reviewers stated that "owing to the diversity of conditions treated and poor quality of most of the studies, it is not possible to say that yoga is effective in treating anxiety or anxiety disorders in general. However, there are encouraging results, particularly with obsessive compulsive disorder (OCD)."[11] The second

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review[12] on anxiety found only two RCTs eligible, given the researchers, inclusion criteria and, in one of the two (the one referred to as an "encouraging result for OCD"), the reviewers chose to ignore the significant delta or change scores used in the independent groups' *t* test,[13] and instead chose to use only endpoint analysis on the primary efficacy variable, when minor but not significantly different baseline scores were found for the two groups after initial dropouts. The endpoint analysis led to inconclusive findings. The reviewers also ignored the six within-group statistical results with various psychologic scales (including the primary efficacy variable that is the "gold standard" for OCD severity), and the intent-to-treat analyses on the primary efficacy variable, and all seven of these results showed efficacy for only one meditation protocol with all results being negative for the control meditation group. They also neglected results for phase 2 of the trial that showed at least twice the efficacy observed in pharmacologic trials. The results using the reviewers' imposed criteria conflicted with the results published in a mainstream psychiatric journal in which editorial board members specialize in OCD. Therefore, the reviewers found only one RCT showing any efficacy in treatment.[12]

All four systematic reviews of RCTs used somewhat different criteria for inclusion and exclusion and thus their conclusions varied. But perhaps the conclusion of Arias et al., that "results support the safety and efficacy for treating certain illnesses, particularly in nonpsychotic mood and anxiety disorders," is a generalization that may hold up over time.

We will know more about this topic when a new project in progress (tentative completion date December 31, 2006) is completed. The project is entitled "Evidence Report on the Effectiveness of Meditation in Healthcare." The National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) has spent $325,000 to support a systematic review of all meditation studies on both healthy subjects and disease states, and to also assess preclinical meditation studies that may lead to findings that help differentiate the effects, mechanisms, and potential benefits of various meditation techniques. The NCCAM project is being conducted by an experienced team at the University of Alberta Evidence-Based Practice Center, Alberta, Canada, with the advice of a technical expert panel on meditation. The Alberta center was chosen by the Agency for Healthcare Research and Quality for conducting this review and meta-analysis.

So what we see is a recent increase of interest in the potential therapeutic value of meditation techniques by professionals in professional institutions. No doubt, there are at least two reasons for this interest. The first is that the use of meditation techniques are unquestionably as Arias et al., state showing "increasingly widespread appeal and for their potential use as medical therapies." The second reason may be the disappointment with pharmaceuticals for treating psychiatric disorders, which is now more obvious given the recent results of what are probably the two largest, most expensive, expertly designed and conducted multisite clinical trials ever funded by the NIMH. The first trial is "The Sequenced Treatment Alternatives to Relieve Depression (STAR*D)" study, which had three levels (level 1 [1], level 2 [2, 3], and level 3 [4]), and was conducted over 6 years at a cost of $35 million. As of July 14, 2006, there were 40 publications listed on PubMed from STAR*D. The primary motive for STAR*D was that many depressed patients do not respond adequately to the first drug treatment. And, therefore, what to do next was unclear, as there was an absence of empirical research.[14] Previously, most trials, many of which were funded by the pharmaceutical industry, focused on "uncomplicated, nonchronic major depression; in this respect, they often do not reflect the clinical 'real world'"[14] STAR*D was designed to treat more typical outpatients with much less restrictive inclusion/exclusion criteria, that included other psychiatric and medical comorbidities, and with outcomes focused on remission rather than just a decrease in symptom severity, which is typical of pharmaceutical-industry studies.[14]

In Level 1 of STAR*D, with 4790 patients screened, there were

> 2,876 outpatients available for analysis who were given citalopram [a selective serotonin reuptake inhibitor (SSRI)] with a mean dose of 41.8 mg/day and patients were assessed for remission rates (≤7 on the Hamilton Depression Ratings Scale (HAM-D) as the primary outcome, or a score of ≤5 on the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) (secondary outcome). Response was defined as ≥50% reduction in QIDS-SR scores. . . . Remission rates were 28% (HAM-D) and 33% (QIDS-SR). The response rate was 47% (QIDS-SR). . . . Citalopram was selected as a representative SSRI given the absence of discontinuation symptoms, demonstrated safety in elderly and medically fragile patients, once-a-day dosing, few dose adjustment steps, and favorable drug-drug interaction profile.[1]

Level 2 of STAR*D included patients who could not tolerate citalopram or did not go into remission and they had the option of switching to another drug (sustained-release bupropion, sertraline, or venlafaxine extended-release), or augmentation of citalopram with bupropion sustained-release, buspirone, or talk therapy. Detailed results are summarized below for Level 2 (not including talk therapy), however, the study authors concluded: "After unsuccessful treatment with an SSRI, approximately 1 in 4 patients had a remission of symptoms after switching to another antidepressant."[2]

Level 3 included patients who could not tolerate treatment or, again, did not achieve remission at Level 2 and

they were randomly assigned to mirtazapine or nortriptyline.[4] Menza summarized: "In Level 3, 114 patients were randomly assigned to mirtazapine (up to 60 mg/day) and 121 to nortriptyline (up to 200 mg/day) for up to 14 weeks of treatment. Remission rates did not differ between the treatment options: 12.3% with mirtazapine and 19.8% with nortriptyline. In addition, the treatments did not differ in tolerability."[14]

Menza wrote about STAR*D in an editorial in the *American Journal of Psychiatry*[14]: "So what were the results, and what have we learned that we did not already know? The overall remission rate in Level 1 (all patients taking open-label citalopram) was 27.5%. No surprise here, as clinical trials with antidepressants typically report remission rates of 30% or less." For Level 2, Menza wrote that

> remission rates did not differ significantly among the three antidepressant switch strategies: 21.3% with bupropion sustained-release, 18.1% with sertraline, and 24.4% with venlafaxine extended-release. Level 2 remission rates were also similar across drug augmentation strategies: 29.7% achieved remission with citalopram plus bupropion sustained-release, and 30.2% achieved remission with citalopram plus buspirone, but buspirone was not tolerated as well as bupropion. Here, we do have some surprises and, perhaps, new clinical guidance. . . . STAR*D suggests that our clinical practice of switching to another class of antidepressant may not be any more effective than switching to another SSRI. While this may be counterintuitive, and we would like to see replication of the finding, it does give some pause to our current thinking.[14]

STAR*D is invaluable because it examines the "real world" and what can be expected with SSRIs for response and remission and it lends appropriately to the generalizability when conducted by the most highly trained psychiatrists. "But in the end," Menza noted, "this first wave of data from STAR*D will not greatly affect the prescribing practices of most clinicians."[14]

The second NIMH trial was also a very complex trial of gargantuan proportions. "The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)" study was also designed as a multilevel trial to compare the effectiveness and tolerability of antipsychotic drugs. CATIE was conducted over a 5-year period at a cost of $42.6 million.[5] The design[15] for CATIE and methods and rationale[16] have been described. As of July 14, 2006, there were 45 CATIE publications on PubMed.

CATIE was conducted to compare the effectiveness and tolerability of most of the actively marketed second-generation antipsychotics with that of a typical first-generation antipsychotic, in this case perphenazine. The first level of the trial[5]

> included 1493 schizophrenic patients (mean age 40.6 yrs, 74% male, 40% nonwhite and 12% Hispanic, average length of illness of 14.4 yrs) at 57 U.S. sites comparing olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), and risperidone (1.5 to 6.0 mg per day) for up to 18 months. Ziprasidone (40 to 160 mg per day) was later included after FDA approval. . . . Overall, 74 percent of patients discontinued the study medication before 18 months (1061 of the 1432 patients who received at least one dose): 64 percent of those assigned to olanzapine, 75 percent of those assigned to perphenazine, 82 percent of those assigned to quetiapine, 74 percent of those assigned to risperidone, and 79 percent of those assigned to ziprasidone. The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine ($p < 0.001$) or risperidone ($p = 0.002$) group, but not in the perphenazine ($p = 0.021$) or ziprasidone ($p = 0.028$) group. The times to discontinuation because of intolerable side effects were similar among the groups, but the rates differed ($p = 0.04$); olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for extrapyramidal effects.
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> The CATIE Level 1 authors concluded:
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> The majority of patients in each group discontinued their assigned treatment owing to inefficacy or intolerable side effects or for other reasons. Olanzapine was the most effective in terms of the rates of discontinuation, and the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone. Olanzapine was associated with greater weight gain and increases in measures of glucose and lipid metabolism.[5]

Tamminga commented about Level 1: "That first report thus also showed once again the stark reality of antipsychotic drugs—their therapeutic limitations and their problematic side effects, especially the metabolic effects."[17]

Level 2 had two parts (1) (N = 444) comparing the tolerability of olanzapine, quetiapine, risperidone and ziprasidone with individuals who had stopped their Level 1 medications for tolerability side-effects,[6] and (2) (N = 99) comparison of efficacy of a first-generation antipsychotic (clozapine) with second-generation antipsychotics in individuals who had stopped their phase 1 medications for poor efficacy.[7] Level 2, part 1, showed that

> The time to treatment discontinuation was longer for patients treated with risperidone (median: 7.0 months) and olanzapine (6.3 months) than with quetiapine (4.0

months) and ziprasidone (2.8 months). Among patients who discontinued their previous antipsychotic because of inefficacy (N = 184), olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among those who discontinued their previous treatment because of intolerability (N = 168).[6]

The authors concluded that, for Level 2, part 1, "risperidone and olanzapine were more effective than quetiapine and ziprasidone as reflected by longer time until discontinuation for any reason."[6]

For Level 2, part 2, "median time until treatment discontinuation for any reason was 10.5 months for the clozapine-treated patients, 2.7 months for the olanzapine-treated patients, 3.3 months for the quetiapine-treated patients, and 2.8 months for the risperidone-treated patients."[7] Time to discontinuation because of inadequate therapeutic effect was significantly longer for clozapine than for olanzapine, quetiapine, or risperidone. At 3-month assessments, Positive and Negative Syndrome Scale total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone but not olanzapine. The authors concluded: "For these patients with schizophrenia who prospectively failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another newer atypical antipsychotic. Safety monitoring is necessary to detect and manage clozapine's serious side effects."[7]

In sum, for CATIE, the medications were comparably effective but had very high rates of discontinuation (averaging 74%) because of the inability to control symptoms or intolerable side-effects. Tamminga commented that "the side effect outcomes are staggering in their magnitude and extent and demonstrate the significant medication burden for persons with schizophrenia."[17] In addition, olanzapine was associated with less hospitalization as a result of psychotic relapse but patients on olanzapine also experienced substantially more weight gain and metabolic changes that are now referred to as "metabolic syndrome."[18,19] This new but controversial syndrome includes insulin resistance, abdominal obesity, low levels of high-density lipoprotein cholesterol, high levels of triglycerides and hypertension. Individuals with metabolic syndrome have a two-to-threefold increase in cardiovascular mortality and a twofold increase in all-cause mortality.

It also turns out that the cheaper first-generation antipsychotic (perphenazine) worked about as well and was tolerated about as well as the newer antipsychotics. And clozapine showed nearly a threefold increase in time until drug discontinuation compared to the three new antipsychotics olanzapine, risperidone, and quetiapine. The researchers stated: "This study strongly confirms what we have seen before, that clozapine is our most effective drug for schizophrenic psychosis."[17]

The results of STAR*D and CATIE clarify a great deal now about pharmacologic treatment for depression and schizophrenia. And clearly, the one unequivocal finding is that any new treatment modalities, especially those without side-effects, now must be pursued rigorously and vigorously for the treatment of both depression and schizophrenia and all psychiatric disorders. What we do not know, perhaps with the exception from an early result for treating OCD,[13] is how well the various meditation techniques will compare in clinical trials with discrete psychiatric disorders. To date, I am aware of only one RCT that has compared two different meditation protocols using experts for the respective yogic meditation techniques.[13] I believe it is timely and very important to compare TM,[20] the Relaxation Response,[21] Mindfulness Meditation,[22] Kundalini Yoga meditation techniques,[23–25] and other yogic meditation techniques from various lineages[26] in RCTs for psychiatric disorders with the groups run by the best experts in the field (similar to STAR*D and CATIE), and to use all the blinding possible for assessment. One can only imagine that the costs would be considerable compared to current NCCAM and NIMH funding levels now designated for these areas. But in time these efforts may well prove to be worth the expense. One final comment: In the system of Kundalini Yoga as taught by Yogi Bhajan, supposedly there are disorder-specific meditation techniques for the treatment of various psychiatric disorders,[27] and one disorder-specific technique, to date, has shown efficacy for treating OCD.[13]

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