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File: ■ Turmeric (*Curcuma longa*)
■ Curcumin
■ Major Depressive Disorder

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RE: Clinical Trial Demonstrates that a Standardized Curcumin Product Is Efficacious in Treating Major Depressive Disorder

Sanmukhani J, Satodia V, Trivedi J, et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. *Phytother Res*. 2013; [epub ahead of print]. doi: 10.1002/ptr.5025.

Depression affects many people throughout the world and can be the cause of disruptive health problems, and can even lead to suicide. Although standard pharmaceutical treatments exist, chronic use of them may result in adverse effects. Botanicals may provide therapeutic options for depression with greater tolerability. Curcumin, a compound found in turmeric (*Curcuma longa*) root, has been shown to alleviate depression previously; suggested mechanisms include impacts on neurotransmitters and the potentiation of other antidepressant pharmaceuticals. This 6-week, randomized, controlled trial investigated curcumin, the standard antidepressant fluoxetine, and a combination of both treatments in patients suffering from major depressive disorder (MDD).

Patients diagnosed with MDD were recruited at Sir Takhtasinhji General Hospital in Bhavnagar, Gujarat, India. Patients were older than 18 years of age, had access to a caregiver, and rated higher than 7 on the Hamilton Depression Rating Scale (17-item version; HAM-D_{17}). This scale rates symptoms of depression, and total scores of 0-7 are considered normal. Those suffering from other severe mental illness, including those with suicidal tendencies, seizures, thyroid disorders, or allergies to the study treatments, were excluded. Those for whom at least 2 other antidepressants had failed to work, those who had taken antidepressants or an "investigational" drug within 30 days prior to the study, and those who were participating in therapy were excluded. Included female patients were using contraception and were not pregnant at the time of the study's beginning.

Curcumin (50-mg capsules) was procured from Arjuna Natural Extracts; Kochi, Kerala, India. Capsules were standardized to contain 88% curcuminoids and 7% volatile oils, and the daily dose of curcumin was 1000 mg. Fluoxetine (20-mg capsules of Flunil-20®) was obtained from Intas Pharmaceuticals; Ahmedabad, Gujarat, India. The fluoxetine

dosage was 20 mg per day. Prior to being randomly assigned, patients were subjected to physical and psychiatric exams, laboratory parameters, and vital sign measurements. Patients were randomly assigned to groups taking either fluoxetine only, curcumin only, or both fluoxetine at 20 mg/day and curcumin at 1000 mg/day, for 6 weeks. Curcumin was administered twice daily, 12 hours apart, in 500-mg doses taken after breakfast and dinner. During the first 2 weeks of the study, paracetamol and benzodiazepines were permitted to treat headaches and insomnia, respectively. At 2, 4, and 6 weeks into the study, parameters were measured.

The primary outcome was the HAM-D_{17} score, followed by the mean change in the score and the remission rate. Secondary outcomes included patients' rate of response on the Clinical Global Impression-Improvement (CGI-I) assessment scale and scores on the Clinical Global Impression-Severity of Illness (CGI-S) scale. The CGI-I is a 7-point scale where 1 means "very much improved" and 7 means "very much worse"; and the CGI-S is a 7-point scale where 1 means "normal/not at all ill" and 7 means "extremely ill." Safety was assessed by treatment-emergent adverse events (TEAEs), the measurement of vital signs, and physical exams during clinical visits. Laboratory parameters were also measured at the end of the study. Those with a HAM-D_{17} score of ≤ 7 were considered to be in remission; a 50% decline in HAM-D_{17} scores as compared with baseline scores constituted a response. According to the CGI-I scale, a score of 1 or 2 indicated a response. Efficacy and tolerability were classified as "excellent, good, fair, or poor." Pill counting was done to assess compliance.

Of the patients recruited, 60 were enrolled and were randomly assigned to the 3 groups (n=20 per group). Overall, there were no "major" deviations or violations of the protocol. Because of either loss to follow-up or withdrawal due to adverse effects (fluoxetine group), 45 patients completed the study, with 16 in the fluoxetine group, 14 in the curcumin group, and 15 in the combination group for the per-protocol analysis (the intention-to-treat [ITT] population was n=17 in the fluoxetine group, n=16 in the curcumin group, and n=18 in the combination group). According to the HAM-D_{17}, a greater response to treatment in the ITT population was observed in the combination group compared to the curcumin group and the fluoxetine group; this was not significantly different (77.8% vs. 62.5% and 64.7%, respectively; P=0.58).

At the end of the study, the mean changes in the HAM-D_{17} scores in the ITT population were not significantly different between the combination group (-14.8; 95% confidence interval [CI]: -17.6, -12.0) and the fluoxetine group (-14.0; 95% CI: -18.2, -9.8) or the curcumin group (-12.6; 95% CI: -15.8, -9.5; P=0.77). This was also true of the rate of remission (P=0.58), and the results were the same in the per-protocol analysis. The efficacy rating was either "excellent" or "good" for 70.5% of those in the fluoxetine group, 75% of those in the curcumin group, and 83.3% of those in the combination group; there were no significant differences between them (P=0.66).

TEAEs were observed in 2 patients in the fluoxetine group, 2 in the curcumin group, and 5 in the combination group. Adverse effects were classified as "mild" and included gastritis, giddiness, hot flashes, nausea, photosensitivity, and mouth ulcers. No significant differences were seen at the end of the study as compared to baseline in patients' laboratory or physical parameters. Although tolerability was rated as "excellent" for 82.3% of those in the fluoxetine group and 87.5% of those in the curcumin group as compared with 66.6% of those in the combination group, these differences were not significant (P=0.30).

This study showed curcumin to have similar efficacy as fluoxetine. It is suggested that curcumin's bioactivity may be due to effects on neurotransmitters such as serotonin, or the concurrent potentiation of antidepressant pharmaceuticals. This study also shows curcumin to be well tolerated, with no serious adverse effects. It is discussed that curcumin's bioavailability was improved through the addition of curcuminoids and volatile oils, although this additive process is not described in the methods. Discussed shortcomings of this trial include the intentionally small sample size and the absence of a placebo group. Also, patients were not blinded to the treatments. A future, double-blind, placebo-controlled clinical trial will likely confirm curcumin as a good candidate for the treatment of MDD, both alone and in combination with standard treatments.

—Amy C. Keller, PhD