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Is Curcumin an Effective Treatment for Major Depressive Disorder?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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In
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Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not curcumin is an effective treatment for Major Depressive Disorder (MDD).

STUDY DESIGN: A systematic review of three peer-reviewed studies published between 2014 and 2017.

DATA SOURCES: Two of the studies were randomized, double-blind, and placebo controlled. The third study was a randomized controlled trial. All three studies were chosen due to relevance to the clinical question and if they included patient oriented outcomes. The studies were found using PubMed.

OUTCOMES MEASURED: The outcomes of the studies were measured using self-report scales on each patient's mood. The scales used were the Inventory of Depressive Symptomatology self-rated version (IDS-SR30) and the Hamilton Depression Rating Scale, 17-item version (HAM-D17).

RESULTS: The first Lopresti et al. article² found statistically significant positive changes in symptoms for patients with MDD, the sample size was not very large, which makes the study not very generalizable. The Sanmukhani study⁷ found that curcumin was as effective as fluoxetine during the range of the study, but the study only lasted six weeks. Finally, Lopresti's second published study³ found that there was not statistically significant data to support curcumin as a treatment for MDD.

CONCLUSIONS: The results of these three studies vary, showing that curcumin has the potential to be beneficial. However, further research is needed that includes larger sample sizes and longer trial durations.

KEY WORDS: Major Depressive Disorder, Curcumin, Turmeric

INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent condition in the mental health field that can severely impact a person's ability to function in their everyday life. Diagnostic criteria define MDD as having at least five symptoms of depression over the period of two weeks. Symptoms can include depressed mood, lack of interest in activities you previously enjoyed, weight change, observable slowing down of movement, fatigue, feelings of worthlessness or guilt, decreased ability to concentrate, and suicidal thoughts.¹ MDD has the potential to overwhelm and overtake a person's life, without proper intervention. While treatment options have come a long way over the years, many people struggle to find the right combination of medications, lifestyle changes, and talk therapies to help improve mood.

MDD is astonishingly common. It is estimated that 16.2 million adults in the United States had at least one major depressive episode.² This means that approximately 6.7% of all adults in the United States have suffered from the effects of depression.³ This statistic does not include the number of children and adolescents who experience MDD, which would undoubtedly greatly increase the percentage of Americans impacted by depression. According to the National Institute of Health, an estimated 3.1 adolescents from the ages of 12-17 also suffer from MDD.³

With so many millions of people needing help with MDD, it is unsurprising that the economic cost is also great. It is estimated that the total economic cost of MDD is approximately \$210.5 billion per year.⁴ It is further estimated that for every dollar spent on MDD, an additional \$1.90 is spent on related and indirect costs.⁴ While a specific number of visits for MDD is unknown, it is estimated that there are 5.7 million health care visits with a psychiatric disorder as a diagnosis.⁵ With many therapists and psychiatrists often working out of insurance networks, this could be an under-reported statistic.

The exact cause of depression is still unknown. However, it is widely considered to be related to genetic and environmental conditions. According to the Mayo Clinic, factors such as biological differences, brain chemistry, hormones, and inherited traits can contribute to onset of depression.² Because the exact cause of depression is still unknown, treatment varies in effectiveness in each individual. MDD is diagnosed according to the DSM-V and must include impairment in social, occupational, or other important areas of functioning that cannot be attributed to substance use or another medical condition.¹ Unsurprisingly, this means that depression does not look the same for every individual diagnosed with the condition, further complicating its treatment.

There are a variety of methods currently being used to treat the condition. Medications include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other atypical antidepressants.⁵ In addition to medication, MDD is often treated with psychotherapy with a mental health clinician such as a licensed clinical social worker (LCSW), a licensed professional counselor (LPC), or a clinical psychologist.²

Current treatment options are not effective for all patients and many of the medications have troubling side effects such as significant weight gain or increased suicidality.⁵ As a result, research continues to search for effective treatment outside of standard medications. Some researchers have found that curcumin can be effective in treating MDD with limited side effects.⁶ Curcumin, also known as turmeric, has been used as an Asian herbal remedy for depression and anxiety since ancient times.⁶ Research is now trying to determine the effectiveness of this method in the hopes for the most effective treatment possible.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not curcumin is an effective treatment for Major Depressive Disorder (MDD).

METHODS

The three studies analyzed in this review were found via PubMed, using keywords major depressive disorder, curcumin, and turmeric. All three studies were randomized and controlled trials (RCT). Two of the studies were double blind. The studies examined whether or not curcumin can be effective in treating MDD. The population included patients that are aged eighteen years-old or older and have been diagnosed with major depressive disorder. The intervention used in the studies was high-dose curcumin extract (500mg BID). The interventions were compared to visually matched placebos. In one study, Curcumin was also compared to outcomes of treatment with another medication, 20mg of fluoxetine.⁶ Outcomes were measured by several symptoms scales, including the Inventory of Depressive Symptomatology self-rated version (IDS-SR30) and the Hamilton Depression Rating Scale, 17-item version (HAM-D₁₇).

All of the reviewed studies were published in English and were found using keywords “curcumin,” “turmeric,” and “major depressive disorder.” Studies were excluded if they included patients under the age of eighteen. The statistics used included ANOVA, p-values, and changes in mean from the baseline. The specific characteristics and demographics from the three studies can be found in Table 1.

OUTCOMES MEASURED

The outcomes measured varied by each study, but all three were patient oriented (POEMS). Sanmukhani et al.⁶ measured improvements in depressive symptoms through the use of the Hamilton Depression Rating Scale, 17-item version (HAM-D₁₇). In the Lopresti and

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interven- tions
Lop- resti, 2017 (1)	Double blind RCT	111	18- 65	Patients aged 18 to 65 years who met the DSM-IV criteria for current MDD with an IDS-SR ₃₀ score of 18 or greater.	Patients with other psychiatric disorders, a high risk of suicide, or other medical illnesses; were pregnant, lactating or intended to fall pregnant; had an infection or illness over the past month, were currently taking any antiplatelet or anticoagulant medications; or had been diagnosed with any coagulation disorder.	12	high-dose curcumin extract 500 mg BID VS Visually matched placebo
<u>Lop- resti</u> , 2014 (2)	Double blind RCT	56	18- 65	Patients aged 18 to 65 years who met the DSM-IV criteria for current MDD with an IDS-SR ₃₀ score of 14 or greater.	Patients with other psychiatric disorders, a high risk of suicide, or other medical illnesses; were pregnant, lactating or intended to fall pregnant; had an infection or illness over the past month, were currently taking any antiplatelet or anticoagulant medications; or had been diagnosed with any coagulation disorder.	4	curcumin extract 500 mg BID VS Visually matched placebo BID
San- muk- hani, 2014 (3)	Double blind RCT	60	>18	Patients over 18 who met the DSM-IV criteria for MDD and score more than seven on Hamilton Depression Rating Scale, 17-item version (HAM-D ₁₇) (Hamilton, 1960).	Patients with other psychiatric disorders, suicidal ideation, schizophrenia, mental retardation, cognitive impairment, other uncontrolled organic disease, abnormal laboratory tests, history of seizure disorder (other than febrile), unstable thyroid disorder or known allergy or hypersensitivity to the study medications; and who had failed to respond to at least two adequate antidepressant therapies in the past or had taken any antidepressant or investigational new drug in last 30 days or currently receiving psychotherapy specifically designed to treat depression.	9	curcumin 1,000 mg (500 mg BID) VS fluoxetine 20 mg daily VS curcumin 1,000 mg (500 mg BID) and fluoxetine 20 mg daily

Drummond study,⁷ improvements in depressive symptoms were measured with the Inventory of Depressive Symptomology self-rated version (IDS-SR₃₀). The third article by Lopresti, Maes, et al.⁸ also used the IDS-SR₃₀ to measure changes in depressive symptoms. This study also used the

Spielberger State-Trait Anxiety Inventory (STAI), which is a self-report tool for assessing anxiety.⁸

RESULTS

This review consists of three randomized and controlled studies that measured the mean change from baseline on self-report scales of depressive symptoms. Two of the studies also included placebos. All studies included both men and women who were eighteen years or older.

In the study by Sanmukhani et al., sixty patients were randomized into three different treatment groups.⁶ The first group received fluoxetine (20mg) as treatment for depression and the second group received curcumin (1000mg). All sixty participants were diagnosed with MDD. The study lasted six weeks and forty-five patients completed the trial, with no significance in variance of dropout rate in each group.⁶ Nine patients did not attend a single follow-up visit, leaving 51 patients included in the analysis (n=17, fluoxetine; n=16, curcumin; n=18, fluoxetine and curcumin).⁶

The HAM-D₁₇ scores were analyzed at the end of the second, fourth, and sixth weeks. Outcomes showed similar results in treatment outcomes for the treatment groups. The mean change in HAM-D₁₇ scores from the baseline at the end of the trial was -14.0 for the fluoxetine group, -12.6 for the curcumin group, and -14.8 for the fluoxetine and curcumin combination group.⁶ With all groups showing “excellent efficacy,” the investigators found no statistical difference in the three treatment groups (p=0.66).⁶

There were several patients who experienced treatment emergent adverse effects (TEAEs). Five patients in the combination group, two patients in the fluoxetine group, and two patients in the curcumin group reported these effects. TEAEs included gastritis, giddiness, hot flushes, photosensitivity, and nausea. The medications were still considered to be well-tolerated

because all TEAEs were mild and there was no significant difference in vital signs, physical examination, or laboratory tests from the baseline. The fluoxetine group and curcumin group had higher proportion of “excellent” tolerability than the combination group, but the difference was not statistically significant ($P = 0.30$)⁷.

Table 2: Efficacy of Curcumin in Comparison with Fluoxetine in the Treatment of Major Depressive Disorder, as measured by mean change in baseline from HAM-D₁₇, conducted by Sanmukhani et al.⁶

Study: Sanmukhani et al. ⁶	P
Efficacy of Curcumin in comparison with Fluoxetine for treatment of MDD	0.77

The results of the Lopresti and Drummond study⁷ was randomized, double-blind, and placebo-controlled. The study comprised of 160 participants, all of whom received the placebo for one week. Participants were excluded if they also had a psychotic disorder, bipolar disorder, comorbid obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, chronic fatigue syndrome, fibromyalgia, any substance abuse disorder, or if they had a high risk of suicide.⁷ Patients were also excluded if they suffered from medical illnesses such as diabetes, autoimmune issues, cardiovascular disease, hypertension, or asthma.⁷

The participants were split into four trial groups: a placebo group, a low dose of curcumin, a high dose of curcumin, and a combination dose of curcumin and saffron. All pills looked identical and participants were not told which treatment they would be receiving. 111 participants completed the 12-week study, with no statistically significant in any one group. No participants dropped out due to adverse side effects.⁷

The results from this study were measured by mean change from the baseline reading of the Inventory of Depressive Symptomatology self-rated version (IDS-SR₃₀). The researchers

found that the IDS levels changed for all four groups, but only for the first four weeks for the placebo group. The mean change from the baseline group for the placebo was -8.91 and the high-dose curcumin was -11.72.⁷ This means that the difference between the placebo and curcumin is small, at 2.81. While the study demonstrates a statistically significant effect treating MDD with curcumin per the p value, the magnitude of baseline in IDS score is not large.⁷

Table 3: Efficacy of Curcumin in Comparison with Placebo in the Treatment of Major Depressive Disorder, as measured by mean change in baseline from IDS-SR₃₀ conducted by Lopresti, Drummond⁷

Study: Lopresti, Drummond ⁷	P
Efficacy of Curcumin in comparison with Placebo for treatment of MDD	<0.001

The third study of this review was also randomized, double-blind, and placebo controlled. Lopresti et al.⁸ used the IDS-SR₃₀ to measure change in depressive symptoms over the course of 8 weeks. 56 individuals participated in this study, both men and women from ages 18-65 were included. All participants were diagnosed with MDD according to DSM-IV criteria and had a baseline IDS-SR₃₀ score of less than or equal to 14.⁸ Participants were excluded if he or she was also diagnosed with a psychotic disorder, bipolar disorder, comorbid obsessive compulsive disorder, or posttraumatic stress disorder. Patients were also excluded if they have substance abuse conditions, high risk for suicide, or have certain medical conditions. Excluded medical conditions included diabetes, autoimmune disease, cardiovascular disease, hypertension, neurodegenerative disorders, chronic fatigue syndrome, fibromyalgia, were pregnant, or were currently breastfeeding. A participant was also excluded if he or she has suffered an infection or illness in the past month, were currently taking anticoagulant medications or had an anticoagulant disorder.⁸

Of the 56 participants, there were four drop-outs, three from the active treatment group and one from the placebo treatment group. Reasons for withdrawal included an unexpected trip overseas, increased digestive complaints in one person in the curcumin group, and two people did not consistently take the medications (one from each group).⁸ The participant that withdrew had a pre-existing digestive complaint. With this exception, there were no severe adverse events reported and there was no significant difference in reported adverse events between the placebo and curcumin groups.⁸

When the full 8 weeks of treatment are taken into account, there was no statistically significant difference between the IDS values in the placebo and curcumin groups. However, ANOVA analyses revealed some differences if the data was separated into two groups: baseline to week 4 and weeks 4 to 8. All IDS values decreased in baseline to week 4. However, only the curcumin group continued to decrease in weeks 4 to 8. The placebo group did not have significant changes in the latter half of the study.⁸ The study also measured anxiety through the STAI questionnaire. STAI values showed the same trend as the IDS values, in that the placebo had no significant changes in the second half of treatment. However, when the study is looked at as a whole, there was not a statistical difference between treatment groups.

Table 4: Efficacy of Curcumin in Comparison with Placebo in the Treatment of Major Depressive Disorder, as measured by mean change in baseline from IDS-SR₃₀ and STAI anxiety measures, conducted by Lopresti et al.⁸

Study: Lopresti et al. ⁸	P
Efficacy of Curcumin in comparison with Placebo for treatment of MDD	0.189

DISCUSSION

Major Depressive Disorder accounts for a large portion of adults on disability in the United States³ and effective treatment methods can often be elusive. This selective evidence-based medicine review aimed to explore whether or not Curcumin could be one such effective treatment method. The research reviewed showed some promise, especially when Lopresti et al.⁸ compared their data in two halves, separating the first 4 weeks from the final 4 weeks. The other two studies did not conclusively disprove curcumin as an effective treatment, further showing the promise of this proposed intervention. Sanmukhani et al. also showed that there was no statistically significant difference between curcumin and the more mainstream treatment of Fluoxetine⁶ over the six-week trial.

One limiting factor to cost efficiency in choosing curcumin is the bioavailability and absorption rates. According to the NIH, curcumin has relatively poor absorption abilities and low bioavailability, which are both issues that would need to be addressed in mass producing curcumin as an insurance-covered medication.³ Overall, it was found that curcumin was well-tolerated by all participants. Participants included men and women from ages 18-65. MDD also impact children and adolescents, leading to the need for further research to be applicable to all ages.

Limitations

Sanmukhani et al.'s study did not include a placebo group, making it impossible to compare the trial groups to a non-active treatment group.⁶ Another consideration of this study is the small sample size as well as the duration of the study. The number of participants was less than 60 which makes generalizing the results difficult and potentially inaccurate. Because Fluoxetine, an SSRI, can take up to six weeks to observe positive changes, the short duration of the study may overestimate the comparative effectiveness of curcumin. While the small sample

size did show promise in the effectiveness of curcumin in comparison to fluoxetine, more research is needed.

The Lopresti and Drummond study also had a small sample size, limiting the significance of the results.⁷ Furthermore, this study's trial length was relatively short, which also limited the study's ability to find statistically significant results. If the study had been larger and longer, it might have yielded more fruitful results. The third study of this review, Lopresti et al.,⁸ also had a relatively small population size. However, the longer length of the study yielded more significant results. Furthermore, both Lopresti studies reported that the participants in the trial mainly consisted of individuals who have had multiple depressive episodes. This could indicate that the patients are treatment resistant. Therefore, further research on individuals closer to initial onset of symptoms may see more promising results. Overall, all three studies found that further research is warranted as their limited initial results were promising in supporting the use of Curcumin in treatment of MDD.

CONCLUSION

The results of the three reviewed studies were inconclusive as to whether or not curcumin is an effective treatment for Major Depressive Disorder. Sanmukhani et al. found that curcumin was no different than fluoxetine in the treatment of MDD.⁶ The other two studies found that curcumin was not different enough from the placebo to be statistically significant. However, curcumin cannot be ruled out as an effective treatment for MDD because the insignificant differences could be attributed to study length and size. Therefore, it is important to continue research into the efficacy of Curcumin for the treatment of Major Depressive Disorder.

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