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**What are the effects of curcumin, whether alone or in conjunction with alternative therapy,  
on major depressive disorder?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

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, whether alone or in conjunction with alternative therapy, has an effect on Major Depressive Disorder (MDD).

**Study Design:** Systematic review of 3 primary studies, published between 2013 and 2016.

**Data Sources:** Three randomized control trials (RCT), two of which were double blind. These studies were found using Cochrane Systematic Reviews and PubMed.

**Outcomes Measured:** Outcome for all three articles are symptomatic changes of MDD. The outcomes measured were Patient-Oriented Evidence that Matters (POEMS) and were assessed using various self-rated tools.

**Results:** All three studies demonstrated an improvement in depressive symptoms compared to placebo or other control groups. In Lopresti, Maes et al., curcumin has a significant effect on symptoms compared to placebo ( $p=0.045$ ).<sup>1</sup> In Sanmukhani et al., an improvement was seen in the group receiving curcumin, although not statistically significant ( $p=0.58$ ).<sup>2</sup> Lastly, Lopresti, Drummond compared placebo to low-dose curcumin, high-dose curcumin, and low-dose curcumin combined with saffron. In this study, drug treatment with curcumin had a positive effect on patients with depression ( $p=0.012$ ), although there was no difference between the differing curcumin doses or curcumin/saffron combination.<sup>3</sup>

**Conclusions:** Curcumin does appear to be safe and effective for adults suffering from MDD. Two out of the three trials included in this systematic review were able to show significant data in support of the positive effects of curcumin. The use of curcumin for symptomatic relief in MDD is promising, however, more RCT must be done to support this.

**Keywords:** curcumin, depression, major depressive disorder

## **INTRODUCTION**

Major depressive disorder is a mental health condition that is characterized by chronic depressed mood and/or loss of interest in activities and hobbies. Oftentimes, there may be accompanying low self-esteem, decreased energy, fatigue, and non-specific pain. It was initially thought that a disturbance in the level of serotonin was the major cause of MDD, however, it is now known that there are many other dysregulations that contribute, such as, dysregulation in the hypothalamic-pituitary-adrenal axis, activation of immune-inflammatory pathways, mitochondrial dysfunction, and neuroprogression.<sup>1</sup>

MDD affects individuals worldwide and is a cause of impaired functional capacity which can lead to suicides.<sup>2</sup> It affects approximately 6-8 percent of adults each year with a lifetime prevalence of 15-20%.<sup>3</sup> Because MDD is only a small aspect of mental health disorders, there is not an exact number of yearly healthcare visits. However, according to the CDC, the percent of physician office visits with depression indicated on the medical record is 10.4%, It is estimated that a total of \$210.5 billion are spent per year for MDD patients.<sup>4, 5</sup>

There are several traditional methods that are used to treat MDD. Specific prescription medications include, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), dopamine reuptake blockers, and tricyclic antidepressants. Cognitive behavioral therapy and electroconvulsive therapy is sometimes used in conjunction. Because the disease is chronic, patients must be on long term treatment, however, pharmacological therapy has significant adverse reactions and side effects. Additionally, some patients may be resistant to these medications. Therefore, a safer alternative is being searched for.<sup>2</sup> Curcumin is the major active ingredient in turmeric (*Curcuma longa*), which is often used as a southeast Asian cooking spice. It is a potent antioxidant that can lower markers of antioxidant

stress, act as a COX-2 inhibitor, and lower pro-inflammatory cytokines.<sup>1</sup> Additionally, it can affect the hypothalamic-pituitary-adrenal axis and influence monoamine transmission through its effects on serotonergic and dopaminergic activity.<sup>1</sup>

## **OBJECTIVE**

The objective of this selective EBM review is to determine “what are the effects of curcumin, whether alone or in conjunction with alternative therapy, on major depressive disorder?”

## **METHODS**

This selective EBM review analyzed 3 randomized control studies that evaluated the aforementioned objective. The population criteria included males and females over the age of 18 who are suffering from MDD. All three RTCs used curcumin as the main intervention compared to placebo or another control group. Two of the three trials (Lopresti, Drummond and Sanmukhani et al.) had multiple arms in their studies and further evaluated the combination of curcumin with other therapy options. The outcomes measured in all three RTCs were symptomatic changes of MDD using various self-rating tools such as, Inventory of Depressive Symptomatology self-rated score (IDS-SR<sub>30</sub> score), Spielberger State-Trait Anxiety Inventory tool (STAI tool), and Hamilton Depression Rating Scale (HAM-D<sub>17</sub> scale).

Keywords used to search for the articles included, “curcumin”, “depression”, and “major depressive disorder”. All articles were found on PubMed and published in the English language. Types of studies searched included only RTCs that were POEMs, included human species data, and originally published in a peer reviewed journal within the last 10 years. Any studies that

were found on the Cochrane database or previously published by a student were excluded. Other exclusion criteria included patients not suffering from MDD or were being evaluated for MDD and another concurrent disease. Summary of statistics used were relative risk reduction (RRR), absolute benefit increase (ABI), numbers needed to treat (NNT), p-value, and ANOVA F-score. The demographics and characteristics of the individuals included in these studies are displayed in Table 1.

Table 1: Demographics &amp; Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Lopresti, Drummond <sup>3</sup> (2016)	Randomized Double Blind Placebo Controlled	123	18-65	Males and females meeting the DSM-IV criteria for MDD and had an IDS-SR <sub>30</sub> score greater than or equal to 18	Psychotic d/o, bipolar, OCD, PTSD, eating d/o, substance abuse, suicidal, diabetes, AI, CVD, HTN, neurodegenerative, fibromyalgia, asthma, currently pregnant, breastfeeding, infection/illness in the last month, coag d/o	186	High dose and low dose curcumin (250 mg and 500 mg)  and  saffron/curcumin combination (250 mg of curcumin and 15 mg of saffron)
Sanmukhani et al <sup>2</sup> (2013)	Randomized Controlled Trial	45	>18	psychiatry outpatients of Sir Takhatsinhji General Hospital in Gujarat India. Individuals scored >7 on Hamilton Depression Scale	suicidal, schizophrenic, schizoaffective, or other psychotic disorders, mental retardation, cognitive impairment, bipolar disorder. Abnormal lab tests, h/o seizure, thyroid disorder, allergy, failed at least 2 adequate antidepressant therapies or taken any antidepressant in the last 30 days, or are currently receiving psychotherapy	15	500 mg curcumin BID  and  curcumin/fluoxetine combo (500 mg curcumin + 20 mg fluoxetine)
Lopresti, Maes et al <sup>1</sup> (2014)	Randomized double-blind placebo controlled study	52	18-65	DSM-IV criteria for current major depressive disorder and (IDS-SR <sub>30</sub> ) score $\geq 14$ .	psychotic d/o, bipolar, OCD, PTSD, eating d/o, substance abuse, high risk of suicide, diabetics, AI diseases, CVD, HTN, neurodegenerative disorders, fibromyalgia, asthma, smokers, pregnant, had suffered an illness in past month, any coagulation disorder	25	Curcumin 500mg BID

## **OUTCOMES MEASURED**

All outcomes measured were POEMs and reflected the efficacy of curcumin on MDD symptoms. All three RTCs used self-rating tools in which the patients are asked to rate their depressive symptoms based on the DSM-IV criteria for major depressive episode (inability to sleep, sexual dysfunction, loss of interest in activities, self-esteem, etc.) In Lopresti, Drummond, outcomes were measured using IDS-SR<sub>30</sub> score and STAI tool.<sup>3</sup> In Sanmukhani et al., outcomes were measured using the HAM-D<sub>17</sub> scale, and Lopresti, Maes et al. used IDS-SR<sub>30</sub> and STAI tool.<sup>2,1</sup> All RTCs did a baseline analysis using the self-rated tools as well as reanalyzed at various times throughout the study.

## **RESULTS**

In Lopresti, Maes et al., seventy-seven people were initially screened for the study and fifty-six met the criteria to join. A placebo and curcumin treatment group were created with twenty-eight individuals in each. Fifty-two people ultimately completed 8 weeks – 4 dropped out, one from the placebo and three from the curcumin group. Over the 8 weeks, 500mg curcumin capsules were given BID to the treatment group, and an identical looking pill containing cellulose was given to the placebo group. This review will focus on IDS-SR<sub>30</sub> score between weeks 4 and 8. There was a significant change in IDS-SR<sub>30</sub> score between weeks 4 and 8 for those receiving the curcumin treatment,  $p=0.045$ . Between these weeks, ANOVA F score was 4.22, which is a large treatment effect due to statistical significance. Additional ANOVA analyses revealed that IDS-SR<sub>30</sub> scores improved in both the placebo and treatment group in the first 4 weeks, but only continued to improve during the last 4 weeks in the treatment group. There were no significant changes in STAI scores over the full 8 weeks (baseline-week 4,



p=0.516; week 4-week 8, p=0.097; baseline-week 8, p=0.358). Adverse events were monitored and there were no significant differences between the placebo and treatment group, as shown in Table 2.<sup>1</sup>

Table 2- List and frequency of adverse events reported by participants.<sup>1</sup>

<b>Complaint</b>	<b>Curcumin</b>	<b>Placebo</b>
<b>No adverse events</b>	16	14
<b>Digestive: bloating, nausea, diarrhea</b>	7	6
<b>Respiratory- breathing problems</b>	0	1
<b>Dermatology- dry skin, flaking skin</b>	3	2
<b>Neurology- headaches, dizziness</b>	2	2
<b>Pain- joint pain, back pain, neck pain</b>	2	4
<b>Cardiovascular- racing heart, chest pain</b>	2	0
<b>Vision- sore eyes, dry eyes, blurry vision</b>	3	0
<b>Auditory- ringing in ears</b>	1	2
<b>Oral- dry mouth, sore gums</b>	2	2

Sanmukhani et al. did a 3-armed study and compared 500 mg BID of curcumin, 20 mg Fluoxetine, and 20mg Fluoxetine + 500 mg BID curcumin. Sixty patients were split with 20 patients in each group. Forty-five patients completed the full 6 weeks. At the end of the study, the number of patients who responded to treatment (response is defined as 50% reduction in HAM-D<sub>17</sub> scores compared to baseline) in the fluoxetine + curcumin group was 77.8% compared to the fluoxetine group of 64.7%.<sup>2</sup> Table 3 summarizes these statistics. The numbers needed to treat (NNT) value is 8, meaning that for every 8 patients with MDD being treated with 20mg of

fluoxetine + 500 mg BID of curcumin, 1 more patient will have an improvement in their depressive symptoms compared to fluoxetine alone. This study also evaluated treatment emergent adverse events (TEAEs) to prove safety of curcumin. The most common adverse event recorded was gastritis, which was reported in all three groups studied. All TEAEs were mild and all medications were very well tolerated.<sup>2</sup>

Table 3- Comparison between combination group and fluoxetine alone.<sup>2</sup>

Control event rate (CER)	Experimental event rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	95% CI; p value
0.647	0.778	0.202	0.131	8	0.58

Lopresti and Drummond did a four-arm study comparing high dose curcumin (500 mg), low dose curcumin (250 mg), low dose curcumin + saffron, and placebo. 33 patients were placed in the high dose curcumin, 28 in the low dose curcumin, 26 in low dose curcumin + saffron, and 36 in placebo (n=123). All were placed on placebo for a week prior to being divided into treatment groups. Ultimately, 49 people were dropped from the study, leaving a total of 111 participants who completing the full 12 weeks. This review will focus on IDS scores. There was a significant reduction in scores in all groups, except scores only decreased in the first 4 weeks in the placebo group. When comparing all active treatment groups to placebo, there was a significant change in IDS score from baseline to 12 weeks,  $p=0.031$ .<sup>3</sup> Direct comparison of IDS response rates of high dose curcumin and placebo is seen in Table 4. The NNT value is 7, meaning that for every 7 patients with MDD being treated with 500 mg curcumin, 1 more patient will have an improvement in their depressive symptoms compared to placebo. Lopresti and

Drummond also analyzed adverse events. The high dose curcumin group reported the most adverse events, although there were of minor severity. The most common complaint was diarrhea and spicy aftertaste.<sup>3</sup>

Table 4- Comparison between high dose curcumin and placebo.<sup>3</sup>

<b>Control event rate (CER)</b>	<b>Experiment event rate (EER)</b>	<b>Relative benefit increase (RBI)</b>	<b>Absolute benefit increase (ABI)</b>	<b>Number needed to treat (NNT)</b>
0.13	0.28	1.15	0.15	7

## **DISCUSSION**

Two out of the three RCTs incorporated in this paper showed a statistically significant decrease in depression symptoms in patients suffering from MDD who were treated with curcumin. Additionally, all three RCTs found that curcumin was a safe intervention with minor adverse events. Other studies that were done on animal models proved it to be safe even at supra-therapeutic doses.<sup>2</sup> Curcumin is widely available in the United States and does not require a prescription. The most common method is one to three capsules of 500 mg.<sup>6</sup> It is often used as a natural supplement for ulcers, analgesic effects, and to relieve flatulence.<sup>6</sup> However, because of the widespread availability of curcumin, it is difficult to assess the purity and composition of the capsules being sold. Consequently, the bioavailability of these products is questionable. Additionally, curcumin is not FDA approved to attest to its efficacy and safety. Therefore, efficacy and safety is limited to a few clinical trials and it is challenging to determine interaction with other medications or health conditions. Contraindications to use include allergies, pregnancy, breast feeding, and those with gallstones or bile duct obstructions.<sup>6</sup>

Weaknesses of all three RCTs were small sample sizes, which limits the reliability of the findings. Lopresti, Maes et al. and Sanmukhani et al. both had less than 100 participants. Additionally, Sanmukhani et al. and Lopresti, Drummond had losses to follow-up greater than 20%, meaning that all subjects who entered the trial were not accounted for and attributed at its conclusion. Sanmukhani et al. also did not use a placebo and also did not have a double-blind study.

Other limitations of this analysis are the lack of RCTs that evaluate the effects of curcumin on humans. There are many trials of curcumin results on other animals, such as rats, but very little on humans. Therefore, the search was limited and only included the three RCTs that existed and met all inclusion criteria. Two out of the three studies were by the same research group which limited the diversity and methods used to analyze treatment effect. Lastly, since the studies only showed significant data after several weeks of treatment, a longer follow up time is needed to evaluate the full effects of curcumin. Future studies should include a larger patient population as well as longer follow up time.

## **CONCLUSIONS**

These three chosen studies show that curcumin is a safe and effective treatment option for patients who suffer from MDD. No serious life-threatening reports were made during the trials and there is evidence to show that curcumin is safe at supra-therapeutic doses even up to 8 g/day.<sup>2</sup>

The evaluation of holistic medication on MDD is still underway and the research is still fairly new. Due to the limited amount of studies and small sample sizes, more studies must be done to further compare curcumin to other drugs as well as evaluate it over a longer time. Since

curcumin is a natural spice and not FDA approved, it is imperative to confirm its all-around safety, especially when taken with other drugs for unrelated diseases. Many patients who suffer from depression have other coexisting medical diagnoses and may be taking other medications. In order to fully establish curcumin as safe monotherapy for MDD, future studies should include drug interactions with other common medications.

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