Magnesium Supplementation and the Reduction of Depressive Symptoms in Adults

Introduction

Depression is a serious health problem in the United States with the CDC reporting 11.5% of adults experiencing mild symptoms, 4.2% experiencing moderate symptoms, and 2.8% experiencing severe symptoms in 2019.[1] Due to many challenges faced during the Covid-19 pandemic, these numbers skyrocketed. According to published research, depression increased three-fold during the pandemic and is estimated to be the leading cause of disease burden by 2030.[2] While depression symptoms can vary from mild to severe, merely having depression increases the risk of death by suicide with the more severe cases being the most at risk.[3] It is vital for those experiencing depression symptoms to seek medical and psychiatric help immediately. Numerous medications are on the market to treat depression and are usually recommended in conjunction with psychotherapy.[3] These medications, however, do not come without side effects ranging from nausea and weight gain to insomnia and heart problems.[4] One promising alternative to these medications to relieve depressive symptoms is magnesium supplementation.

Magnesium plays a vital role in many systems of the body via enzymatic activity, DNA replication, and the synthesis of nucleic acids and proteins.[5] In addition, magnesium is involved in neurotransmission and therefore linked to the pathology of neurological diseases such as Alzheimer's disease and Parkinson's disease.[5] Due to these roles, scientists began to wonder if magnesium could also play a role in psychological disorders such as anxiety and depression. Consequently, animal trials were embarked upon which demonstrated magnesium to have antidepressant effects.[6] The combination of previous hypotheses and the success of the animal

trials, led scientists to initiate human experiments to assess the efficacy of magnesium on the relief of depressive symptoms. The purpose of this paper is to review a portion of the research conducted on this subject and to answer the question, does supplemental magnesium improve the symptoms of depression in adult humans?

Methods

To unearth research related to magnesium supplementation and relieving depression symptoms, scholarly databases were used such as PubMed and the University of North Florida's online library. "Magnesium and depression", "magnesium in the treatment of depression", and "magnesium supplementation, supplements, and/or use and depression, depressive disorders, and mood disorders" were key words and phrases used to find published articles. Materials were further specified by publication date, 2010-2021, as well as type of trial. While randomized controlled clinical trials are the gold standard and the goal for finding research for this review, two articles herein are crossover-controlled trials while the other two are placebo controlled clinical studies. In addition, each article was peer reviewed, and the hypothesis was tested on adult human subjects rather than animals.

Main Findings

As mentioned above, depression is a major health concern, and one that is escalating quickly. Because treatment options for depression can be limited by cost, availability, efficacy, and side effects, it is important for scientists to seek beneficial alternatives.[7] Tarleton et al set out to examine whether supplementation with oral magnesium (Mg) chloride would improve depressive symptoms in those experiencing mild-to-moderate symptoms.[7] One hundred and twenty-six adults who scored a 5-19 on the Patient Health Questionnaire (PHQ-9) participated in this twelve-week blocked, randomized, cross over trial. Groups were randomized into either immediate or delayed treatment. During the six-week active treatment portion, subjects were

given tablets of magnesium chloride and instructed to take 500 mg daily for a total of 248 mg elemental magnesium per day. Magnesium chloride was chosen for this trial due to the high bioavailability and tolerability in comparison to other magnesium salts. Assessment of depressive symptoms was completed bi-weekly via phone calls during which changes in the PHQ-9 were documented; these assessments were also completed during the six-week non-treatment portion of the study. The primary outcome was the net difference in depressive symptoms from baseline to the end of each treatment period. Calculations showed a net improvement of depressive symptoms during the supplementation period of -6 points on the PHQ-9 scale, with the patients reporting differences within the first two weeks. Strengths of this trial include the PHQ-9 questionnaire being used which is a clinically validated questionnaire with high sensitivity. In addition, the paired analysis allowed each subject to serve as his/her own control which minimized variance and improved statistical power. Patients were enrolled over an entire year which controlled for seasonal effects. Lastly, patients were randomized into treatments groups, adherence was high, and the withdrawal rate was low. Weaknesses of this trial are the lack of a placebo group, and the randomization that was not blind to the subjects or the research group.[7]

A second study was conducted assessing the supplementation of magnesium on the symptoms of depression in those with treatment-resistant depression.[8] In this crossover trial, twelve subjects were randomized into two groups, one of which received an infusion of 4g magnesium sulfate in 5% dextrose while the other group received a placebo infusion consisting of 5% dextrose only for a total of 8 days with treatments given on days 1, 2, 7, and 8. This treatment period was followed by a five-day washout period before the subjects exchanged treatment groups. Both the participants and the researchers were blind to who was receiving treatment and who was receiving the placebo. Baseline assessments were taken and then repeated on treatment days. The Hamilton Rating Scale for Depression (HAM-D) and the

Patient Health Questionnaire-9 (PHQ-9) were used to set the baseline for each patient as well as monitor symptoms throughout the trial. The magnesium sulfate infusion was well tolerated with no adverse effects reported. The strengths of this study are that it was double-blind, placebo controlled, and it employed the use of HAM-D and PHQ-9 which are both strong indicators of depression and are utilized by clinicians. After analyzing the data, Medhi et al noted no changes in depressive symptoms immediately following infusions and no significant differences from baseline to completion of trial with only a -0.17 decrease in PHQ-9 scores and no notable change in HAM-D scores.[8]

Rajizadeh and a research team conducted a trial to determine the impact of magnesium oxide supplementation on depression in patients who presented with a magnesium deficiency.[5] Sixty participants, aged 20-60, were enrolled in this double-blind trial and were randomized into two groups, one of which received two 250mg magnesium oxide tablets daily for eight weeks while the other group received a placebo. Depression status was measured under the supervision of a psychiatrist utilizing the Beck Depression Inventory-II Questionnaire while magnesium serum levels were assessed via photometric method post centrifugation. The strengths of this study are randomization, placebo controlled, double-blind, the length of the trial, and a fairly large sample size with similar health status since they all began the trial with a magnesium deficiency. At the end of the trial, 88.5% of the patients receiving the magnesium supplement saw an increase in serum magnesium levels as well as a statistically significant decline in depressive symptoms at 15.85 reduction on the Beck Depression Inventory-II Questionnaire.[5]

In 2018, a trial was conducted to test whether supplementation with magnesium aspartate had an impact on depression.[6] This trial differs from those above because magnesium was supplemented in addition to the administration of fluoxetine which is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Thirty-seven participants who met the

criteria of either having an ICD-10-codable depressive episode or major depression as defined in DSM-IV were randomized into either the treatment or placebo group with both the researchers and subjects being blinded to this selection. Over the course of eight weeks, patients received 10-40mg fluoxetine daily in addition to 40mg of magnesium equivalent to 3.30 mEq of magnesium aspartate or placebo supplementation three times a day. Psychometric scales employed during this trial were the Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression Scale (CGIS); treatment was considered effective with a 50% reduction in baseline HDRS score. The strengths of this trial include use of a placebo, double-blind, and utilization of HDRS and CGIS as they are considered clinically applicable and accurate scales. At the end of the trial, seventeen participants had received the magnesium treatment with a baseline HDRS score of 30.5. Fifteen of these seventeen participants saw a 50% improvement in HDRS scores while eleven of the twenty participants in the placebo group saw the same change. Due to these facts, the research team reported no statistical significance in the intervention group. Overall, there were no statistically significant differences noted from baseline to completion of the trial between the magnesium treatment group and the placebo group.[6]

Discussion and Conclusion

Based on the above research, the supplementation of magnesium in relation to the improvement of depressive symptoms is inconclusive. Two of the above studies reported a decrease in depression,[5,7] while two of the studies did not.[6,8] This is less concerning than the lack of consistency across the studies regarding type and dosage of magnesium, duration of treatment period, sample of participants, and type of psychometric scale used to monitor depressive symptoms. Tarleton et al supplemented their subjects with 500mg of Mg chloride for six weeks,[7] while Rajizadeh et al utilized 500mg of Mg oxide for eight weeks,[5] an infusion of 4g of Mg sulfate was administered for eight days in the Mehdi trial,[8] and 120mg of Mg aspartate

was given daily for eight weeks in the remaining trial.[6] In addition, the participants for each study were not a cohesive sample, the subjects of one trial presented with mild-moderate depression,[7] in another, subjects were diagnosed with treatment resistant depression,[8] in the third, patients with depression also presented with a magnesium deficiency,[5] and in the last trial, patients were diagnosed with major depressive disorder and were dosed with fluoxetine in addition to the Mg during the trial.[6] While there was some crossover in psychometric scales used in the studies, there was still variation from the PHQ-9 scale[7] to the HAMD scale[6,8], with one study using neither of these.[5] One factor that was consistent throughout all the trials was tolerance of the various Mg supplements; the subjects reported no adverse side effects which is important for future research to proceed. Prospective studies should begin by using the same variation of magnesium as well as choosing one category of depressive patient and employing the use of the same psychometric scale. In addition, more research should be completed to investigate what dosage of magnesium provides a therapeutic effect so researchers can utilize that dosage across future trials.

As mentioned above, the incidence rate of depression is climbing rapidly with grave implications for those suffering as well as for the disease burden in America. Proving the efficacy of magnesium supplementation in the treatment of depression could decrease the need of medications which would in turn decrease cost to consumers and the healthcare system in addition to alleviating side effects associated with depression medications. It is therefore vital that scientists perform cohesive research on the subject so an irrefutable conclusion can be drawn.

References:

1. Villarroel MA, Terlizzi EP. Symptoms of depression among adults: United States, 2019. Center for Disease Control and Prevention website. https://www.cdc.gov/nchs/products/databriefs/db379.htm. Published September 2020. Accessed March 8, 2021.

2. Ettman CK, Abdalla SM, Cohen GH. Prevalence of depression symptoms in US adults before and during the Covid-19 pandemic. *JAMA Netw Open*. 2020; 3 (9): e2019686. Doi: https://doi.org/10.1001/jamanetworkopen.2020.19686

3. Does depression increase the risk for suicide? U.S Department of Health and Human Services website. https://www.hhs.gov/answers/mental-health-and-substance-abuse/does-depression-increase-risk-of-suicide/index.html. Updated September 16, 2014. Accessed March 8, 2021.

4. Antidepressants: get tips to cope with side effects. Mayoclinic website. https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20049305. Published September 12, 2019. Accessed March 8, 2021.

5. Rajizadeh A, Mozaffari-Khosravi H, Yassini-Ardakani M, Dehghani A. Effect of magnesium supplementation on depression status in depressed patients with magnesium deficiency: a randomized, double-blind, placebo-controlled trial**.** *Nutrients.* 2017; 35: 56-60. Doi: https://doi.org/10.1016/j.nut.2016.10.014

6. Ryszewska-Pokrasniewicz B, Mach A, Skalski M, et al. Effects of magnesium supplementation on unipolar depression: a placebo-controlled study and review of the importance of dosing and magnesium status in the therapeutic response. *Nutrients.* 2018; 10(8):1014. Doi: https://doi.org/10.3390/nu10081014

7. Tarleton EK, Littenberg B, MacLean CD, Kennedy AG, Daley C. Role of magnesium in the treatment of depression: a randomized control clinical trial. *PLoS One*. 2017; 12 (6): e0180067. Doi: https://dx.doi.org/10.1371%2Fjournal.pone.0180067

8. Mehdi SM, Atlas SE, Qadir S, et al. Double-blind, randomized crossover study of intravenous infusion of magnesium sulfate versus 5% dextrose on depressive symptoms in adults with treatment-resistant depression. *Psychiatry Clin Neurosci*. 2017; 71 (3): 204-211. Doi: https://doi.org/10.1111/pcn.12480