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Mini-review

Role of magnesium in major depressive disorder

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Abstract

Major depressive disorder, a common and complex one, has its onset associated with many factors. Common management includes antidepressant agents, together with psychotherapy in severe cases, but a significant percentage of patients do not improve. The urgency of newer approaches is a need, and clinical trials are studying the role of magnesium in depression. However, findings are inconclusive. To evaluate the evidence about the effects of magnesium on adults with depression, a systematic review was conducted. The search was conducted using scientific records from online databases between 2000 to 2023 concerning magnesium in depression. Eight studies showed mainly positive results; three studies after magnesium add-on with traditional antidepressants, and two studies showed no improvement. The review's evidence suggested that magnesium supplementation might be effective. Therefore, further clinical trials must be designed to evaluate the efficacy of magnesium alone or in addition to other therapies following biochemical assessments.

Introduction

Depression is a readily identifiable psychological disorder compared to many psychiatric illnesses (Horwitz et al., 2016). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a patient must show one of the main symptoms of major depressive disorder: anhedonia or depressed mood and at least four secondary symptoms, which are categorized as either non-somatic or affective factors (such as feelings of worthlessness and suicidal thoughts) or somatic (such as sleep disturbances, appetite disorders, or fatigue). Crucially, these symptoms must show within a time frame of ≥2 weeks (APA, 2013; Krause et al., 2010; Elhai et al., 1012). The disorder includes two main categories: major depressive disorder, which is also mentioned as depression, and dysthymia. Depression can be recurrent and can last from months to years. Globally, depression can occur at any age, peaking in older adulthood. Here, symptoms range from mild to severe or extremely severe, and severe depression can lead to suicide (WHO, 2017).

Depression is a disease that affects people in all communities throughout the world. About 322 million people live with depression worldwide. More than 85 million (27%) people live with depression in the South-east Asia region, and it is ranked as the single largest contributor to non-fatal health loss (7.5% of all YLD). The majority of this non-fatal health loss (80%) occurred in low- and middle-income countries. Globally, the number of people living with depression increased by 18.2% from 2005 to 2015 (GBD, 2015). A National Survey of Bangladesh estimated the prevalence rate at about 6.7% and also reports that the treatment gap for adults with mental disorders is 92.3%, which means that only 7.7% receive mental health treatment (WHO, 2020). Significant proportions (16%) of rural people in Bangladesh

are suffering from mental disorders (Hosain et al., 2007). Mental illness is a taboo in Bangladeshi society. The increasing prevalence may be due to a lack of awareness, social stigma about mental health diseases, and the length of time required to get relief from symptoms. Most mental health sufferers do not seek medical help (Roth et al., 2018). So, the demand for restraining depression is rising (Marcus et al., 2012).

There are no specific laboratory investigations to diagnose major depressive disorder. Psychiatrists take the history and clinical features, and exclude other comorbid medical conditions before making the final diagnosis. Therefore, till now, the severity of clinical symptoms has been assessed by questionnaires (Lv et al., 2016).

At present, many treatment modalities remain for patients with depression, including pharmacologic, non-pharmacologic, and dietary supplements. Non-pharmacological treatments include psychotherapy, neuromodulation therapy, and transcranial magnetic stimulation. Psychotherapy reduces the risk of relapse and recurrence in major depressive disorder, either alone or in combination with antidepressants (Guidi et al., 2021). Several clinical guidelines propose psychotherapy alone or in combination with antidepressants (Qaseem et al., 2016). However, the evidence for the efficacy of neuromodulation therapy is still limited (Li et al., 2021).

Within the pharmacological approach, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are still first-line antidepressants (Li et al., 2021).

Although most of these antidepressants are usually effective, there are still some limitations, the delayed onset of action and delayed efficacy (2 weeks or more) and adverse effects (nausea or vomiting, sedation, agitation, and sexual dysfunction) that are a major reason for treatment discontinuation (Anderson et al., 2012; Bondolfi et al., 2006; Gartlehner et al., 2005). Also, failure to achieve a satisfactory response with an adequate dose and duration of treatment (Rush et al., 2006; Malhi et al., 2005; Keller et al., 1982). In addition, some patients have persistent symptoms for a long time (Keller et al., 1992).

Normal brain function and mental health rely significantly on nutrients. Vitamins and minerals play several biological functions in the human body; supplementation of these nutrients has numerous beneficial effects. It has been demonstrated that oral dietary supplements improve outcomes of hospitalized patients (Philipson et al., 2013) as well as cost-effective interventions (Elia et al., 2016). Researchers have been assessing the potential advantage of single micronutrient supplements for those with mental disorders (Firth et al., 2019) as well as the effects of overall changes to diet in psychiatric illnesses, specifically on mood disorders (Lassale et al., 2019).

Magnesium is a micronutrient required for optimal nerve transmission, is also involved in membrane phospholipids synthesis, and has an important effect on mood and brain function. Therefore, magnesium is necessary for the central nervous system to function normally (Ryan et al., 1991; Veronese et al., 2020). Furthermore, magnesium has been studied as an add-on treatment as well as a component of a high-dose supplement and enriched diet for psychiatric illness, including mood disorders (Phelan et al., 2018). However, there are often contradictory findings reported from studies on magnesium supplementation in mood disorders, possibly due to methodological variation, which includes supplementation methods (magnesium form, dosage, posology) and methods of measurement (Ordak et al., 2017).

To provide a comprehensive understanding of the association between magnesium and depression, the following questions were addressed: 1) Does magnesium supplementation effectively reduce depression symptoms? 2) If so, is it possible to determine a preferred element form, dose, or posology? To find the answer, a thorough review is conducted, analyzing all studies on magnesium supplementation administered in mood disorder patients.

Pathophysiology

Still, the exact etiology is unclear, but it is evident that major depressive disorder has multifactorial reasons, including genetic (Li et al., 2013), environmental (e.g., exposure to stressful events) and lifestyle (Gullander et al., 2014; Booij et al., 2015), social, including social and family relationships, life events, employment, and psychosocial factors such as personality and thoughts (Alvarez-Mon et al., 2021).

The most commonly accepted theory is the monoamine hypothesis. This theory proposes that a deficiency of monoamines in the brain is responsible for the development of depression. Based on this theory, different classes of antidepressants have been developed that are activated to increase the level of monoamines within the synaptic cleft (Moret and Brileyz, 2011; Hirschfeld, 2000).

Some other complex mechanisms might be associated with the pathogenesis of major depressive disorder (Racagni and Popoli, 2008). Glutamate is the main excitatory neurotransmitter in the brain. It is involved in emotional, synaptic plasticity, and cognitive processes. When glutamate binds with its receptors N-methyl-D-aspartate receptor (NMDA receptor) on the post-synaptic membrane and activates the signaling pathway. Evidence suggests that altered functioning of glutamate and depressed NMDA receptors is associated with synaptic dysfunction, excessive excitation, and

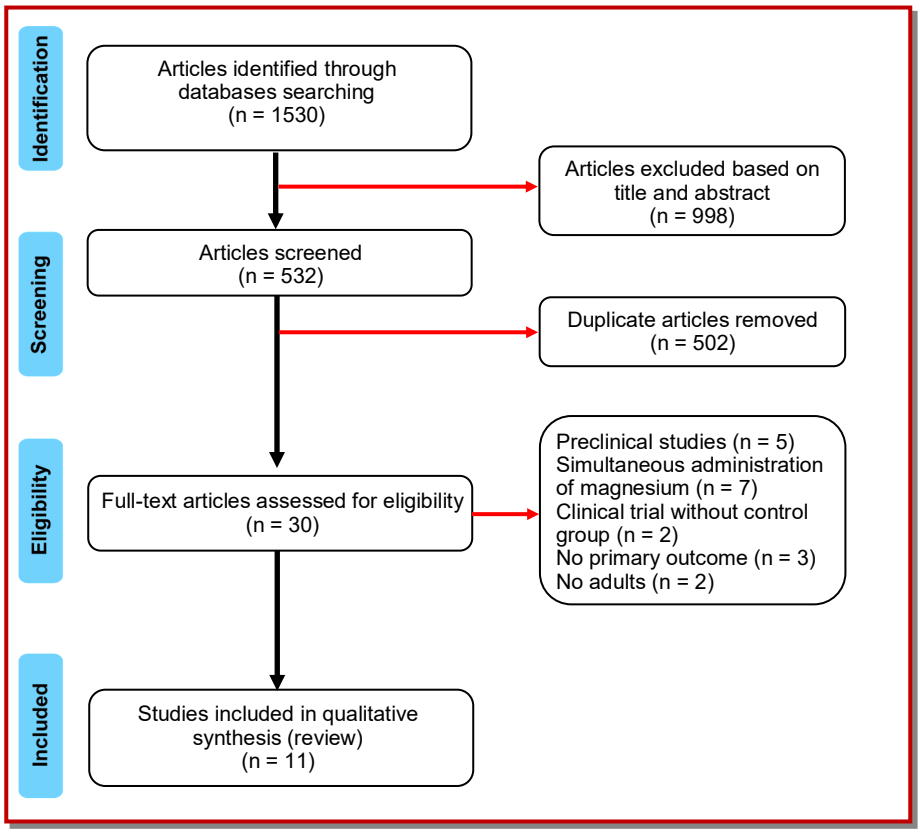

Figure 1: Flow diagram for the selection process for articles in this review

neuronal cell death, which ultimately leads to behavioral disorders, depression, and other mood disorders (Gray et al., 2015; Chandley et al., 2014; Serefko et al., 2013). Some research showed that a brain-derived neurotrophic factor (BDNF) (Zhang et al., 2019, oxidative stress (Bajpai et al., 2014), circadian rhythms, and melatonin (Hale et al., 2010) have relevance in the onset and development of major depressive disorder.

Magnesium for brain and psychiatric disorders

The second most prevalent cation, magnesium, mostly remains intracellular and serves as a cofactor for more than 300 metabolic reactions. All human cells need magnesium to function properly, protect against excessive neuronal excitation, and neuromuscular coordination in the nervous system (Kirkland et al., 2018). Additionally, it has a role in myelination (Seyama et al., 2018), proliferation of neural stem cells (Ang et al., 1995), growth of neurites (Kronbauer et al., 2017), synaptic development and maintenance (Sun et al., 2016), neuronal transmission (Stangherlin et al., 2018), and in the regulation of cholinergic, serotoninergic, and dopaminergic transmission (Spasov et al., 2009). The main dietary sources of magnesium are whole grains, nuts, green leafy vegetables, and fish. Magnesium is absorbed from the gastrointestinal tract and excreted through the kidneys (Jahnen-Dechent and Ketteler, 2012).

Though the exact mechanism of antidepressant activity of magnesium is yet unknown, it is likely to be mediated by a variety of mechanisms. NMDA receptor blockade seems to be the key mechanism (Pochwat et al., 2014). As magnesium blocks calcium channels in the NMDA receptor, a low level of magnesium leads to high calcium and glutamate levels, resulting in a deregulated function of the synapses, which consequently leads to depression (Serefko et al., 2013; Castilho et al., 1999).

Magnesium is likely safe when taken orally in an appropriate dosage regimen. Sometimes, it may cause headaches, stomach upset, nausea, vomiting, diarrhea, and constipation. These adverse effects can be overcome by taking it after the meal (Guerrera et al., 2009). For adults, the recommended dietary allowance (RDA) is 310-320 mg for women and 400-420 mg for men daily. Oral magnesium intake is safe when taken at a lower level than the upper tolerable limit. The upper tolerable limit for adults is 350 mg per day of elemental magnesium (Food and Nutrition Board, 1997).

Magnesium has been suggested as a potential antidepressant in many previous preclinical and clinical studies (De Souza et al., 2000, Camardese et al., 2012). An earlier cross-sectional report showed a relationship between lower intake of magnesium and depression (Tarleton et al., 2015). This observation was supported

by a prospective study and clinical trials (Tarleton et al., 2017; Bagis et al., 2013). However, some other trials observed no changes following magnesium supplementation (Mehdi et al., 2017; Fard et al., 2017).

Because of these inconsistent findings, it is still unclear how magnesium acts as an antidepressant. Therefore, addressing this widespread and rapidly expanding issue, an integrated approach toward major depressive disorder is essential. In this regard, the current review investigates the role of magnesium as a possible therapeutic agent in major depressive disorder patients, the rationale of use, the state of ongoing preclinical and clinical trials, and discusses future research directions.

Materials and Methods

Search strategy

For reporting the systematic reviews, the PRISMA protocol was followed. A search was conducted using PubMed database, MEDLINE, Scopus, PsychINFO, and Wiley-Blackwell Cochrane Library from 2000 to 2023 to analyze the role of magnesium in depression. Relevant papers of reported trials and observational studies that fulfilled the review criteria were selected. Studies with patients receiving magnesium treatment either alone or in combination with other strategies, such as non-pharmacological (physical exercise, psychotherapy) or antidepressants, and studies compared with placebo or pharmacotherapy alone, are considered for review.

Papers were reviewed by using the following search strategy: the terms associated with the intervention ("magnesium or Mg2+", "oral magnesium", "magnesium treatment", "mineral", "multi-mineral", "micro-minerals", "trace element"), terms relating to the outcome ("mood", "mood disorder", "depression", "psychiatric disorders", "psychotic disorders", "mental diseases") and terms related to the study design ("randomized control trial", "randomised control trial", "randomized controlled trial", "randomised controlled trial", "placebo-controlled", and "clinical trial").

Inclusion criteria

Every study that met the following criteria was included: 1) case reports, case series, observational studies, clinical trials (randomized and non-randomized), 2) studies included adult patients with depression, 3) studies that provided various forms of magnesium supplements (magnesium chloride, magnesium gluconate, magnesium glycinate, magnesium aspartate, magnesium oxide, magnesium sulfate, and 4) studies of minimum 1-week intervention duration.

Exclusion criteria

To minimise selection bias and heterogeneity followings are excluded from this review: 1) studies not assessed the magnesium's effect as primary outcome, 2) clinical trials without a control or placebo group, 3) *in vivo* (animal) and in vitro pre-clinical studies, 4) case-control studies, cohort studies, 5) systematic reviews and/or meta-analyses, 6) studies include children or adolescents' participants, and 7) unpublished studies and gray literatures.

Reviews and meta-analyses were searched to identify the current literature on magnesium research and neurological diseases. A detailed description of the recent studies is given as an update.

Data extraction

The following data were extracted that included studies: first author's surname, publication year, demographic features (mean age and sex), sample size, study design, type and dosage of magnesium supplement, duration of intervention, depression scale used, mean depression score changes with their SDs for the intervention and control groups, and direction of evidence.

Results

Study selection

Searching various databases, 1530 citations are identified. After the removal of duplication, a total of 532 records were screened. After the first screening, 502 records were excluded based on the title and abstract. 32 full-text articles were finally assessed for eligibility. 21 articles were excluded after the second screening procedure for the following reasons: 6 studies were preclinical; 7 studies administered other nutrients with magnesium simultaneously; 2 trials had no control group; 4 studies did not evaluate the effect of magnesium treatment as a primary outcome; and 2 studies did not evaluate depression in the adult sample. Finally, 11 articles in total were selected as eligible for this review. A summary of the methods for the identification and inclusion of studies is shown in Figure 1 (PRISMA diagram) (Moher et al., 2009).

Study characteristics

Table I provides a summary of the nine RCTs' characteristics. One study was published from the UK, one from Poland, two from the USA, and five studies from Iran. These trials were published in between 2016 and 2023. Two studies were solely conducted on female subjects (Abiri et al., 2022; Fard et al., 2016), and the rest of the seven were conducted on both genders. The sample size of these RCTs was 12–90, which, in total sample size was 464 adults. The participants of these studies had an age between 20 to 60 years. The total duration of the intervention was from 1 to 8 weeks. These RCTs had 40–500 mg of different types of magnesium daily interventions. Only one study used the parenteral form, and the rest of the studies used the

Table I

Summary of clinical trials investigating the effects of magnesium supplementation on depression

Author, Year	Gender, Sample size, Mean age (y)	Study design	Baseline depression	Depression scale	Antidepressant usage	Intervention		Duration (week)	Outcomes (score changes)		Direction of evidence
						Treatment group	Control group		Treatment group	Control group	
Sultana and Rahman (2023)	♂/♀: Inter: 45, Con: 45, 30	Randomized, double-blind, parallel	Moderate-major	DASS-21	Different SSRIs	200 mg/day magnesium glycinate	Placebo	8	−17.0 ± 5.1	−19.3 ± 3.5	Positive
Abiri et al., (2022)	♀: Inter: 26, Con: 25, 34	Randomized, double-blind, parallel	Mild-moderate	BDI II	No	250 mg/day magnesium oxide	Placebo	8	−1.6 ± 1.1	−0.4 ± 0.8	Positive
Tarleton et al., (2017)	♂/♀: 57 IT: 55, DT: 57, 52	Randomized, open-label, cross-over	Mild-moderate	PHQ-9	No	IT- 500 mg/day MgCl2	DT- 500 mg/day MgCl2	6	IT group: -6.3 ± 4.6	DT group: -6.3 ± 5.4	Positive
Fard et al., (2016)	♀: Inter: 33, Con: 33, 26	Randomized, triple-blind, parallel	Major/PD	MDSS	No	320 mg/day magnesium sulfate	Placebo	8	−1.4± 1.7	−0.4 ± 1.3	Negative
Mehdi et al., (2017)	♂/♀: Inter: 6, Con: 6, 46	Randomized, double-blind, cross-over	Mild-moderate /TR	HAM-D	No	4 g magnesium sulfate saluted in 5% dextrose infused in 4 h	Placebo: 5% dextrose infused in 4 h	1	−0.8 ± 1.0	−4.83 ± 1.0	
	♂/♀: Inter: 6, Con: 6								−3.1 ± 1.0	−1.3 ± 1.0	
Rajizadeh et al., (2017)	♂/♀: Inter: 26, Con: 27, 20-60	Randomized, double-blind, parallel	Mild-moderate	BDI II	Some subjects	500 mg/day magnesium oxide	Placebo	8	−15.6 ± 8.9	−10.4 ± 7.9	Positive
Ryszewska-Pokraśniewicz et al., (2018)	♂/♀: Inter: 17, Con: 20, 48	Randomized, parallel	Major	HAM-D	Fluoxetine	40 mg/day magnesium aspartate	Placebo	8	−19.2 ± 1.0	−17.1 ± 1.0	Unclear
Afsharfar et al., (2021)	♂/♀: Inter: 19, Con: 21, 20-60	Randomized, double-blind, parallel	Mild-moderate	BDI	No	500 mg/day magnesium oxide	Placebo	8	−3.5 ± 4.6	−0.6 ± 3.7	Positive
Nazarinasab et al., (2022)	♂/♀: Inter: 30, Con: 30, 38	Randomized, double-blind, parallel	Major	BDI	Different SSRIs	250 mg/day NR	Placebo	6	−19.2 ± 2.2	−16.7 ± 2.1	Positive

PD, Postpartum depression; TR, Treatment-resistant; IT, Immediate treatment; DT, Delayed treatment; BDI, DASS-21, Depression, Anxiety and Stress Scale - 21 Items; PHQ, Patient Health Questionnaire; Beck's depression inventory; MDSS, Mean depression symptom score; HAM-D, Hamilton depression rating scale; SSRI, Selective serotonin reuptake inhibitors; NR, Not reported

Table II

Summary of other studies investigating the effects of magnesium supplementation on depression

Author, Year	Sample size, age range (y)	Study design	Baseline depression	Depression scale	Antidepressant usage	Intervention	Duration (week)	Outcomes	Direction of evidence
Noah et al. (2021)	132, 18-50	Randomized, single-blind, parallel	Normal-Extremely severe	DASS-42	No	300 mg/day magnesium lactate dehydrate	8	Depression scores reduced from moderate to normal (≤9)	Positive
Eby and Eby (2006)	Male/female: 4, 23-59	Case series	Major depression	Not reported		125–300 mg magnesium glycinate and turbinate with each meal and at bedtime	1	Rapid recovery	Positive

DASS-42, Depression Anxiety Stress Scale 42 items

oral form. Studies used magnesium aspartate (1 study), magnesium glycinate (1 study), magnesium sulfate (2 studies), magnesium chloride (2 studies), and magnesium oxide (2 studies). One study did not specify the type of magnesium supplement that was administered. All studies used a parallel design, except two studies (Mehdi et al., 2017; Tarleton et al., 2017), which was a crossover design and study. Four studies used BDI for assessment, two studies used HAM-D, one study used MDSS, one study used PHQ-9, and one study used DASS-21. The baseline severity of depression was mild to moderate in five studies, while in three other studies, participants had severe depression.

Table II summarizes the two studies other than clinical trials. One study is a case series, and another is a post-hoc analysis of an RCT. Case series published from the UK and post-hoc analysis published from the USA in 2006 and 2021, respectively. The case series was published in 2006 and the post-hoc analysis was published in 2021. The sample size was 4 in the case series and 132 in post-hoc analysis. The participants of these studies had an age between 18 to 59 years. These studies had 125-300 mg of different types of oral magnesium daily interventions. One study used magnesium glycinate and another used magnesium lactate dehydrate. The total duration of the intervention was 1 week in the case series and 8 weeks in the post-hoc analysis. The baseline severity was major depression in the case series, and while in the post-hoc analysis, participants had normal to extremely severe depression.

Depressive symptoms

There was a large variation between measures of depression, with a total of five different measures. Out of these, seven clinical trials found evidence of improvement in depression symptoms, but only two trials (Fard et al., 2016 and Mehdi et al., 2017) that used the MDSS and HAM-D depression scale, respectively, found no evidence of improvement. Those participants who have a low depression score at baseline (Abiri et al., 2022; Tarleton et al., 2017; Rajizadeh et al., 2017; and Afsharfar et al., 2021) showed more improvement in depression score than the participants with major or resistant depression. Four studies found a benefit of magnesium supplementation with antidepressants; on the other hand, one study found no significant superiority of antidepressant treatment augmentation with magnesium supplementation on depressive symptoms (Ryszewska-Pokraśniewicz et al., 2018). Also, found longer duration intervention improves symptoms more than the shorter (Mehdi et al., 2017) intervention period. In contrast, evidence of rapid recovery was also found shorter duration intervention of 7 days in a case series (Eby and Eby, 2006).

Discussion

Depression is a mood disorder that adversely affects both health and functioning. Several therapeutic options for treating depression are being explored; those target the neurotransmitter system outside of the standard monoamine hypothesis. Current treatments are limited due to delayed efficacy, unwanted adverse effects, and acceptability by the patients (Li et al., 2021). Several studies have investigated a link between depression and magnesium. Numerous prior studies, including preclinical, case-control, and cohort proposed magnesium as a potential antidepressant (De Souza et al., 2000; Camardese et al., 2012; Tarleton et al., 2015). In many clinical trials, the existing antidepressants have been shown to have a lack of efficacy, as well as the connection between magnesium intake and antidepressant effects (Tarleton et al., 2017; Rajizadeh et al., 2017). Unfortunately, studies administering magnesium as a therapeutic option did not show significant results consistently. To clarify this issue, in this review, all studies that evaluate the effect of magnesium in depressed patients are included. A total of 11 (eleven) studies were analyzed, including nine RCTs in which magnesium was administered either as monotherapy or as an add-on therapy.

Consistent with this study, a review article found that magnesium was useful in reducing depression (Serefko et al., 2013). Another review stated that magnesium has a good potential to have an effect on depression (Kirkland et al., 2018). A review in 2020 evidenced that magnesium supplementation may be beneficial (Botturi et al., 2020). Additionally, magnesium supplementation showed a significant decrease in depression scores, suggesting that magnesium supplementation could have a beneficial effect in the treatment of depression (Moabedi et al., 2023).

A clinical trial that evaluated the effect of oral magnesium chloride supplementation showed a reduction in depression scores 6 weeks later (Tarleton et al., 2017). A trial that investigated the effect of oral magnesium oxide supplementation on magnesium-deficient major depressive disorder patients demonstrated similar findings and reported significant benefits from consumption (Rajizadeh et al., 2017). A study that investigated the effect of supplemental oral magnesium oxide for 8 weeks conducted on 61 females found a significant reduction in depression score using the BDI II scale (Abiri et al., 2022). Another trial conducted on 40 depressed subjects provided oral magnesium oxide for 8 weeks showed improved BDI test score (Afsharfar et al., 2021).

A clinical trial of eight weeks of oral magnesium glycinate supplementation with antidepressants on 90 patients with mild to moderate depression revealed a reduction in depression symptoms with the DASS-21 scale (Sultana and Rahman, 2023). A randomized trial on 60 major depressive disorder patients administering magnesium supplements with SSRI improved depression symptoms after 6 weeks with the Beck II test (Nazarinasab et al., 2022).

One trial observed no changes with HAM-D following supplementation of magnesium sulfate infusion for 1 week to 12 mild to moderate or treatment-resistant depression; this dissimilarity was probably due to short -duration supplementation and a smaller sample size (Mehdi et al., 2017). Eight weeks magnesium supplementation on 66 patients with postpartum depression demonstrated similar results that magnesium did not reduce depressive symptoms assessed with the MDSS scale (Fard et al., 2016). Similarly, no difference was seen between the groups using the HAM-D scale after 8 weeks of magnesium aspartate supplementation compared to placebo in one trial; likely due to the smaller sample size, which was in total 37 (Ryszewska-Pokrasniewicz et al., 2018).

A case series showed a very interesting result: a rapid recovery (within 7 days) from depression symptoms in response to magnesium treatment in the form of glycinate and taurinate at a dose of 125-300 mg (Eby and Eby, 2006). Another post-hoc analysis of an RCT on 132 patients administered oral magnesium lactate dehydrate for 8 weeks found a meaningful clinical benefit of depression measured with DASS-42 (Noah et al., 2021). Moreover, a two-week randomized trial in 23 elderly type 2 diabetes patients associated with hypomagnesemia who became newly diagnosed with depression, showed that magnesium chloride treatment is equally effective as that of imipramine (Barragan-Rodriguez et al., 2008). One study found a decrease in symptoms of depression in patients with fibromyalgia after magnesium citrate treatment (Bagis et al., 2013).

Those trials showed positive evidence that used their dosage form of magnesium- magnesium oxide, chloride, and glycinate in a dose from 250-500 mg/day in an oral formulation, which was within the RDA for adults, and for 6-8 weeks. Those trials showing negative evidence could be due to the use of the dosage form of magnesium sulfate and aspartate for a short duration (1 week).

The current systematic review revealed mainly positive findings, although they were conducted in diverse populations and used various tools to measure symptoms.

Conclusion

The current review showed positive evidence supporting the beneficial role of magnesium in reducing depression symptoms. Clinical trials of longer follow-up with biochemical evaluation are needed to expand the current understanding of magnesium's effects on

depression as a monotherapy or add-on treatment.

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Ethical Issue

Not applicable

Conflict of Interest

Authors declare no conflict of interest

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