Impaired Magnesium Status and Depression

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Abstract

Magnesium (Mg) is an element present in everyday dietary plan of regular meals, but it has been shown that a large part of the population presents a low Mg status. Mg has a wide range of physiologic and protective functions within energy regulation and cellular, included neuronal, homeostasis. It obstacles excessive calcium flow into the cells, preventing cells' death, has anti-inflammatory properties, antioxidant action, and interacts with serotonin, a central neurotransmitter involved in depression pathophysiology. Epidemiologic studies have shown that low Mg status is associated with increased frequency of depression, with both cross-sectional and longitudinal designs. Promising evidence has shown that Mg has antidepressant activity similar to imipramine, and that it can be a valid supplementation to antidepressants in treatment resistant depression. However, at the present state of the art too few and small studies have investigated the role of Mg among other therapeutic means in depression, and any conclusion about its utility in clinical practice cannot be drawn. Future research should shed a light on such an important field needing more evidence.

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Magnesium • Hypomagnesemia • Depression • Depressive mood • Neurology • Psychiatry • Glutamate • NMDA • Magnesium supplementation • Epidemiology • Animal experiments

List of Abbreviations

BDNF	Brain-derived neurotrophic factor
Mg	Magnesium
NMDA	N-methyl-D-aspartate
RCT	Randomized controlled trial
RDA	Recommended daily allowance
SSRI	Selective serotonin reuptake inhibitors

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Introduction

Magnesium (Mg) plays a fundamental role in several key metabolic pathways involved in energy expenditure and physiologic cell metabolism (Volpe 2013). Its deficiency is associated with several negative health outcomes in human beings, among which metabolic disorders such as increased sugar blood levels and cardiovascular diseases widely conceived (Veronese et al. 2016). Beyond such severe and frighteningly common conditions, the role of deficiency of Mg in the development of neurological and psychiatric diseases is more complex and ultimately less clear. Mg passes the blood-brain barrier and is physiologically involved in neuron signaling and brain function at a higher order. Thus, any imbalance in Mg status may affect regular neuronal signaling and brain network, in turn possibly playing a role in the onset of neurological and psychiatric diseases, such as dementia, severe mental illnesses (including major depressive disorder, bipolar disorder or schizophrenia, suicidal behavior), and stroke. (Veronese et al. 2015b; Volpe 2013; Carl-Albrecht 2010; Ruljancic et al. 2013).

Within severe mental illness, the role of Mg deficiency in depression is still debated, with some evidences suggesting it has a role in a wide range of pathogenetic steps of mood disorders (Table 1). It was hypothesized that Mg might underpin response to treatment as well, alongside with other factors.

Table 1 Evidences regarding magnesium and psychiatric diseases (others than depression)

Condition	Reference
Premenstrual syndrome	(Pearlstein and Steiner 2000)
Attention-deficit/Hyperactivity disorder	(Kozielec and Starobrat-Hermelin 1997)
Schizophrenia	(Nechifor 2008)

In this chapter, we will discuss the possible mechanisms through which Mg deficiency underpins the development of depression, the epidemiological evidences of such a relationship, and its clinical implications.

Role of Magnesium Deficiency in Depression: Pathological and Molecular Evidences

Animal models have suggested the possible role of Mg in depression according to several pieces of evidence. To mention a couple of studies, mice receiving low Mg diet for several weeks showed enhanced depression-like behavior, as reported by their poor performance in the forced swim test (Singewald et al. 2004), and other tests with depression and anxiety-like attitudes in these animals. Similarly, in rats, Mg deficiency was associated with depression-like and anxiety-related behavior and the administration of Mg supplementations was able to improve these symptoms. (Spasov et al. 2007).

Such evidence is not surprising, and a role of Mg deficiency in depression pathogenesis is to be expected in humans as well. Actually, the role that magnesium is supposed to play in depression can be essentially summarized in three main dimensions as represented in Fig. 1.

The first we will describe is the calcium-mediated excitoxicity, the second is the relationship between Mg and serotonin, and the third is the interplay of Mg and peripheral inflammatory cytokines, alongside with oxidative stress and BDNF.

Mg is a natural calcium antagonist. For this effect, Mg acts blocking the voltage-dependent N-methyl-D-aspartate (NMDA) channel (Fig. 1), which in turn physiologically regulates the entrance of calcium into the neuron (Iseri and French 1984). Physiologic Mg levels are believed to have neuroprotective properties leading to a reduction in the neuron death (Alzheimer 2012; Sobolevskii and Khodorov 2002). Such a beneficial action is supported by the fact that Mg deficiency damages neurons through the excessive opening of NMDA-coupled calcium channels leading to an excessive intraneuronal mitochondrial concentration of calcium, which finally activates some calcium-dependent enzymes regularly silenced in normal conditions. This excitotoxic pathway results in a series of mechanisms (e.g., cytoskeletal breakdown, failure to generate ATP, and production of free radicals) ultimately leading to neuronal death (Durlach et al. 1997). Another effect of Mg deficiency in the development of depression is probably linked to L-glutamate, which in turn can furtherly boost a calcium-mediated neuronal excitoxicity (Mark et al. 2001).

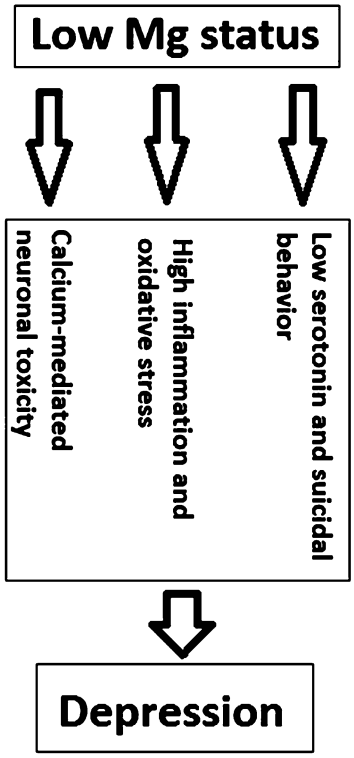

Fig. 1 Role and pathways of magnesium deficiency in depression

From a clinical perspective, as happens for ketamine's antidepressant activity, such a NMDA receptor blockade may result in a mood improvement, and theoretically this is the case also of Mg.

In particular it has been suggested that such low Mg levels' detrimental effects on mood disorders may be localized in particular in hippocampus (Durlach et al. 1997).

Secondly Mg seems to be implicated in the metabolism of different neurotransmitters involved in the pathogenesis of depression (Szewczyk et al. 2008; Durlach et al. 1997), and evidence showing a correlation between platelet magnesium, platelet serotonin, and suicidal behavior in a population of patients with depression furtherly supports a close Mg-serotonin interplay with clinical implications (Ruljancic et al. 2013). Such an interaction plays at a central level as well, as shown in animal models where the forced swim test performance is linked to serotonin receptors and is improved by concomitant administration of Mg and antidepressants (Cardoso et al. 2009). Moreover, Mg has shown to protect neurons in the cerebellum from hypoxic damage through an increase in BDNF (Golan et al. 2004).

Third, a subclinical Mg deficiency status has been demonstrated to be associated with chronic inflammatory state (Nielsen 2014), and Mg seems to able to decrease inflammatory cytokines. More in detail, in vivo Mg has shown to induce a decrease in TNF-alpha and IL-6, in vitro to reduce inflammatory cytokines' genes and

proteins (Sugimoto et al. 2012), and low Mg status has been associated with oxidative stress in subjects with type 2 diabetes mellitus (Araujo Sampaio et al. 2014). In other words, Mg deficiency seems to be associated with an increased inflammatory state and oxidative stress level (as shown by the increased levels of oxidative stress markers, e.g., lipid, protein, and DNA oxidative modification products). Finally, other research has suggested a potential relationship between Mg deficiency and reduction in antioxidant barriers (Zheltova et al. 2016). Since both inflammation (Kohler et al. 2017) and oxidative stress (Black et al. 2015) play a role in the development of depression, it is possible that deficiency in Mg contributes to depressive mood through affecting these pathways.

Epidemiological Evidences of Magnesium Deficiency and Depression

Mg deficiency is largely present in the general population (Veronese et al. 2014) and some individuals (such as diabetic subjects) are particularly prone to this condition (Veronese et al. 2016). Some research suggests that optimal Mg levels are associated with healthy life (Veronese et al. 2015a). However, despite such an important role of Mg and physical and mental well-being, more than half of the American individuals do not reach the suggested RDA for Mg (Whang 1987). Since several conditions associated with Mg deficiency (poor nutrition, gastrointestinal and renal diseases, insulin resistance and/or type 2 diabetes, alcoholism, stress, and certain medications) are also associated with depression (Serefko et al. 2016), the interest on Mg status in populations is increasing, and given the above-mentioned mechanisms, Mg deficiency as a putative risk factor for depression has been object of growing interest.

Table 2 summarizes the findings of epidemiological studies regarding Mg deficiency and depression in human beings. In a systematic review, Derom et al. found that a higher dietary intake of Mg is probably associated with lower prevalence and incidence of depression (Derom et al. 2013), suggesting a protective role of Mg. However, the same authors failed to find any significant association between other estimates of Mg status (e.g., blood and cerebrospinal levels) and the presence of

Table 2 Epidemiological evidence of Mg deficiency in depression

	Association	References
Dietary	Mg deficiency is associated with higher prevalence and incidence of depression	(Derom et al. 2013)
Serum/ plasma	Less evident association between Mg deficiency (hypomagnesemia) and depression	(Derom et al. 2013; Cheungpasitporn et al. 2015)
Other measurements	Not consistent results regarding cerebrospinal fluid Mg status, analyzed through phosphorous nuclear magnetic resonance spectroscopy, seems to be lower in depressed people	(Derom et al. 2013; Eby and Eby 2010)

depression. These latter findings are surprising and are in contrast with other investigations which reported that cerebrospinal Mg is probably low in both treatment-resistant suicidal depression and in patients that have attempted suicide (Eby and Eby 2010). Consistently with an association between depression and Mg deficiency, other investigations reported that serum Mg levels are lower in depressed people compared to healthy controls (Levine et al. 1999; Joffe et al. 1996). As evidence accumulated enough across years, other researchers recently and definitively confirmed a possible role of low Mg levels in predicting depression showing that hypomagnesemia increased the presence of depression of about 34% in a meta-analysis including almost 20,000 participants, with a low heterogeneity of results (Cheungpasitporn et al. 2015). Such an increased risk, even if with a statistically marginal significance, survived after sensitivity analysis according to cross-sectional study or longitudinal design (Cheungpasitporn et al. 2015).

While a magnesium deficiency may be considered among the causes that contribute to depression, it cannot be said on the other hand, at the present state of evidence, that a low Mg status should be expected in all subjects with depression. More probably, a subgroup of depression cases may have Mg deficiency as a contributing factor to onset or maintenance of the disease.

Moreover, beyond serum Mg levels, brain magnesium has been found low in depressed subjects as well, using neuroimaging techniques, such as phosphorous nuclear magnetic resonance spectroscopy (Eby and Eby 2010). However, the most consistent evidence regards in fact the association between low dietary Mg intakes and depression, or blood levels of Mg and depression, while other estimates of Mg (such as blood) are less used for epidemiological purposes, thus limiting any conclusion on the relationship between brain Mg and depression.

Clinical Implications of Mg Deficiency in Depression

Figure 2 summarizes the clinical implications of Mg deficiency as risk factor for depression. Animal and in vitro models suggest a relevant role of Mg deficiency for the development of depression, with response to antidepressants and anxiolytics drugs in response to experimentally induced Mg deficiency states (Szewczyk et al. 2008). Also, in these laboratory studies such a response to psychopharmacologic agents is augmented by Mg administration, suggesting an interaction between Mg, antidepressants, and anxiolytics (Szewczyk et al. 2008).

Data involving human subjects show similar results about the potential implications of Mg use as a therapeutic mean for depression. Mg supplementation should be considered as a safe intervention, with used doses in clinical trials ranging from 300 mg to 4 gr die (Du et al. 2016). Its use has been tested in a limited, but meaningful number of studies.

One randomized controlled trial (RCT) compared Mg efficacy with imipramine 50 mg, in 23 adults with depression, and hypomagnesemia and type 2 diabetes mellitus, showing equivalent efficacy between the two interventional arms (Barragan-Rodriguez et al. 2008). Another recent cross-over placebo-controlled

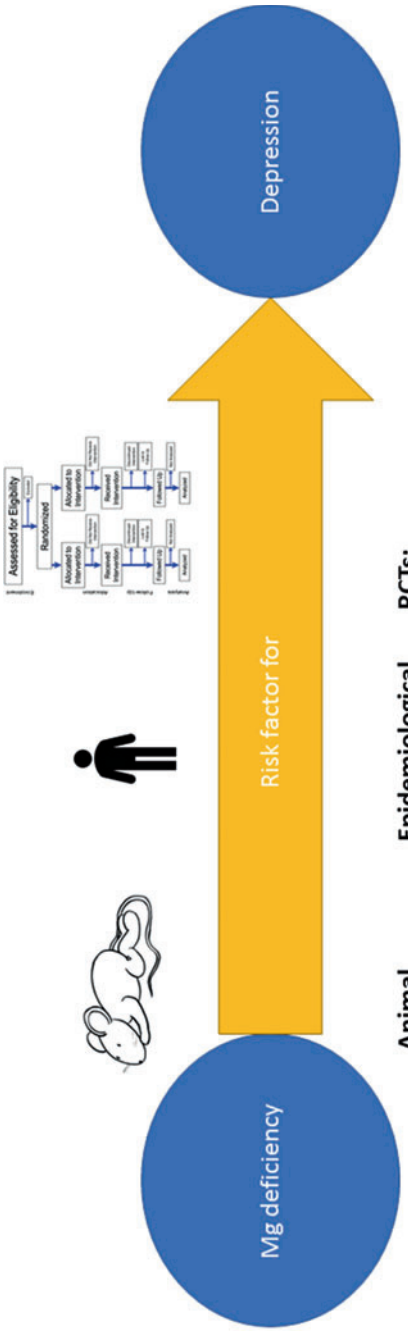

Fig. 2 Clinical implications of magnesium deficiency in depression

study assessing Mg impact on depressive symptoms in treatment resistant depression, showed a correlation of 4 mg of Mg infusion and Patient Health Questionnaire-9 scoring, but not of Hamilton Rating Scale for Depression, after 7 days of treatment (Mehdi et al. 2016). A further investigation on a small group of patients described a notable response rate in patients with treatment resistant depression concomitantly treated with probiotics and Mg in addition to SSRI (selective serotonin reuptake inhibitors) (Bambling et al. 2017). Overall, however, a small total sample size and a limited number of studies have assessed effects of Mg on depression to draw any definitive conclusion.

It cannot be excluded that a subgroup of patients with low serum Mg may benefit the most from Mg supplementation, but whether routine Mg serum levels' first line screening are warranted or not in patients with depression is still a question to be addressed. Mg serum levels assessment, however, should be considered among concomitant factors maintaining depressed mood in cases showing partial or no response at all to standard antidepressant treatment instead. Vice versa patients with low Mg state should be monitored for an increased risk of depression, and Mg integration in those cases should be warranted as a preventive mean against mood disorders (Table 3).

Magnesium and Antidepressants

A different perspective should be used to evaluate concomitant administration of Mg and antidepressants. In this context, the association between Mg and medications is complex and may differentially affect drugs' efficacy according to the used compound, even beyond antidepressants class and depression (Eby and Eby 2006). For example, it was demonstrated that Mg supply decreased the intensity of morphine-induced physical drug dependence (Nechifor 2008), and that lithium, neuroleptics, and benzodiazepines treatment may require lower doses when supplemented with Mg in bipolar affective disorders (Heiden et al. 1999). Mg is supposed to play its antidepressant activity and to interact with antidepressants as NMDA antagonist, through GSK-3 inhibition, and boosting serotoninergic action rather than noradrenergic action of antidepressants (Szewczyk et al. 2008), as shown in Fig. 3. Such an interaction, has also shown to correlate with the risk of suicidal behavior, with low platelet serotonin and magnesium levels are present with higher frequency when self-harming occurs. Other specific data regarding antidepressants are, however, needed.

Table 3 Questions still open regarding magnesium and depression.

1. Should serum magnesium levels be assessed in all depressed individuals?
2. What is the precise role of magnesium in depression?
3. Can magnesium supplementation improve depressive symptoms?
4. Should magnesium supplementation be used as add-on therapy in depression?

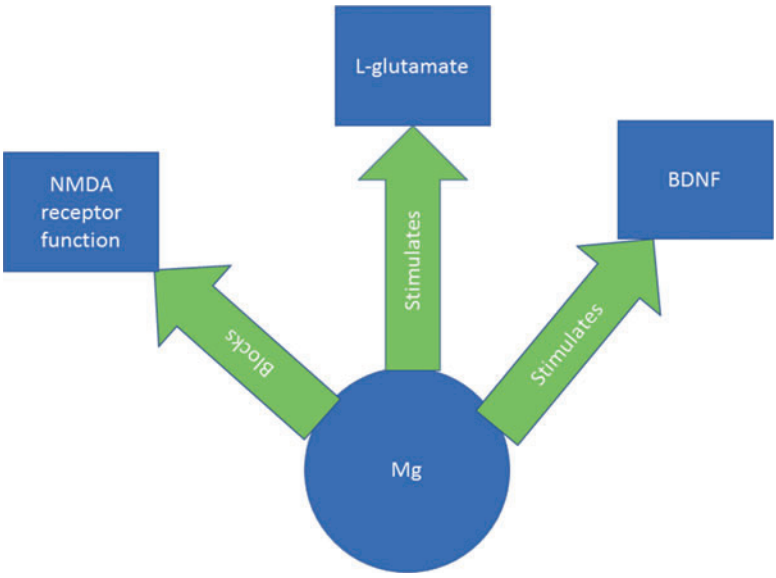

Fig. 3 Mechanisms of Mg action as antidepressant

Conclusion

Mg deficiency is a common condition in general population. The impact of this condition in the development of depression is probably important, but still too few studies use dietary Mg as proxy for Mg status. In the future more observational studies are needed to better characterize the relationship between Mg and depression, which ideally assess Mg status with more precise, valid and reliable methods than Mg dietary intake. The same is for the role of Mg supplementation of antidepressant treatment in patients suffering from depression. While promising evidence is available already, more studies should address several questions, with larger samples. In particular, it is still unclear whether Mg improves depressive symptoms in specific population such as patients with hypomagnesemia or treatment resistant depression only, or conversely if it may be a valid treatment coadjuvant for the whole population affected by depression.

Policies and Protocols

In this chapter, we have summarized the role of magnesium in depression. We have started describing the relevance of magnesium in cellular and neuronal homeostasis, and in a wide range of severe conditions. Secondly, we have focused on depression and described the possible mechanisms that may underpin a role of poor magnesium

status in increasing the risk of depression, identifying three main pathophysiologic domains. Then, we have moved to epidemiologic data supporting an association between depression and low magnesium status. Finally, we have summarized what is the state of the art of the efficacy evidence of magnesium in several depression figures, such as depression in presence of hypomagnesemia, and treatment resistant depression. We have ultimately concluded that evidence is not enough at the present time to confirm or exclude any relevant role of magnesium among treatment means for depression.

We suggest that more studies in the future focus on magnesium supplementation of depression treatment, and in particular that trials with specific features are needed. First of all trials should include larger sample sizes, and have a randomized double-blinded design, to minimize any possible risk of bias. Moreover, studies should focus on specific populations, in order to answer the question whether magnesium is helpful in treating depressive symptoms in case of hypomagnesemia only, or if its properties are useful in amplifying antidepressants' action in any figure of depression, regardless the magnesium state.

Summary Points

1. Magnesium is an important physiologic regulator of cellular homeostasis, including neurons.
2. Low magnesium status is frequent.
3. Low magnesium status is involved in several severe medical conditions, such as diabetes and cardiovascular disease.
4. Low magnesium status can contribute to depression pathogenesis or maintenance through calcium-mediated cellular toxicity, disruption of inflammatory cytokines homeostasis, and impaired serotonin balance.
5. Low magnesium status increases the risk of depression, and can be frequent in a population affected by depression.
6. Several animal studies suggest that hypomagnesemia leads to depression.
7. Several animal studies suggest that magnesium supplementation has antidepressant activity.
8. Several animal studies suggest that magnesium supplementation amplifies the action of antidepressants according to behavioral tests.
9. Preliminary evidence suggests a role of magnesium supplementation in improving depression in patients with hypomagnesemia.
10. Studies in humans are too few and with small sample sizes to draw any definite conclusion about the role of magnesium in depression, regardless the magnesium status.
11. Further studies are needed to better characterize the role of magnesium in treating depression, with larger sample sizes, randomized double blind design, and subjects with either low or normal magnesium state.

References

Alzheimer C (2012) Molecular and cellular biology of neuroprotection in the CNS. New York, NY: Springer Science & Business Media

Araujo Sampaio F, Monte Feitosa M, Hermes Sales C, Costa E, Silva DM, Climaco Cruz KJ, Oliveira FE, Colli C, Do Nascimento Marreiro D (2014) Influence of magnesium on biochemical parameters of iron and oxidative stress in patients with type 2 diabetes. Nutr Hosp 30:570–576

Bambling M, Edwards SC, Hall S, Vitetta L (2017) A combination of probiotics and magnesium orotate attenuate depression in a small SSRI resistant cohort: an intestinal anti-inflammatory response is suggested. Inflammopharmacology 25:271

Barragan-Rodriguez L, Rodriguez-Moran M, Guerrero-Romero F (2008) Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. Magnes Res 21:218–223

Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BW (2015) Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 51:164–175

Cardoso CC, Lobato KR, Binfare RW, Ferreira PK, Rosa AO, Santos AR, Rodrigues AL (2009) Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium. Prog Neuropsychopharmacol Biol Psychiatry 33:235–242

Carl-Albrecht H (2010) Cerebrospinal fluid magnesium level in different neurological disorders. Neurosci Med 1:60

Cheungpasitporn W, Thongprayoon C, Mao MA, Srivali N, Ungprasert P, Varothai N, Sanguankeo A, Kittanamongkolchai W, Erickson SB (2015) Hypomagnesaemia linked to depression: a systematic review and meta-analysis. Intern Med J 45:436–440

Derom M-L, Sayón-Orea C, Martínez-Ortega JM, Martínez-González MA (2013) Magnesium and depression: a systematic review. Nutr Neurosci 16:191–206

Du J, Zhu M, Bao H, Li B, Dong Y, Xiao C, Zhang GY, Henter I, Rudorfer M, Vitiello B (2016) The role of nutrients in protecting mitochondrial function and neurotransmitter signaling: implications for the treatment of depression, PTSD, and suicidal behaviors. Crit Rev Food Sci Nutr 56:2560–2578

Durlach J, Bac P, Yasui M, Strong MJ, Ota K, Verity MA (1997) Mechanisms of action on the nervous system in magnesium deficiency and dementia. In: Miner metal neurotoxicology. CRC Press, Boca Raton, pp 201–210

Eby GA, Eby KL (2006) Rapid recovery from major depression using magnesium treatment. Med Hypotheses 67:362–370

Eby GA, Eby KL (2010) Magnesium for treatment-resistant depression: a review and hypothesis. Med Hypotheses 74:649–660

Golan H, Kashtuzki I, Hallak M, Sorokin Y, Huleihel M (2004) Maternal hypoxia during pregnancy induces fetal neurodevelopmental brain damage: partial protection by magnesium sulfate. J Neurosci Res 78:430–441

Heiden A, Frey R, Presslich O, Blasbichler T, Smetana R, Kasper S (1999) Treatment of severe mania with intravenous magnesium sulphate as a supplementary therapy. Psychiatry Res 89:239–246

Iseri LT, French JH (1984) Magnesium: nature's physiologic calcium blocker. Am Heart J 108:188–193

Joffe RT, Levitt AJ, Young LT (1996) The thyroid, magnesium and calcium in major depression. Biol Psychiatry 40:428–429

Kohler CA, Freitas TH, Maes M, De Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctot KL, Carvalho AF (2017) Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 135:373

Kozielec T, Starobrat-Hermelin B (1997) Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD). Magnes Res 10:143–148
Levine J, Stein D, Rapoport A, Kurtzman L (1999) High serum and cerebrospinal fluid Ca/Mg ratio in recently hospitalized acutely depressed patients. Neuropsychobiology 39:63–70
Mark LP, Prost RW, Ulmer JL, Smith MM, Daniels DL, Strottmann JM, Brown WD, Hacein-Bey L (2001) Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. Am J Neuroradiol 22:1813–1824
Mehdi S, Atlas SE, Qadir S, Musselman D, Goldberg S, Woolger JM, Corredor R, Abbas MH, Arosemena L, Caccamo S (2016) 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. doi:10.1111/pcn.12480
Nechifor M (2008) Interactions between magnesium and psychotropic drugs. Magnes Res 21:97–100
Nielsen FH (2014) Effects of magnesium depletion on inflammation in chronic disease. Curr Opin Clin Nutr Metab Care 17:525–530
Pearlstein T, Steiner M (2000) Non-antidepressant treatment of premenstrual syndrome. J Clin Psychiatry 61(Suppl 12):22–27
Ruljancic N, Mihanovic M, Cepelak I, Bakliza A, Curkovic KD (2013) Platelet serotonin and magnesium concentrations in suicidal and non-suicidal depressed patients. Magnes Res 26:9–17
Serefko A, Szopa A, Poleszak E (2016) Magnesium and depression. Magnes Res 29:112–119
Singewald N, Sinner C, Hetzenauer A, Sartori SB, Murck H (2004) Magnesium-deficient diet alters depression-and anxiety-related behavior in mice – influence of desipramine and Hypericum perforatum extract. Neuropharmacology 47:1189–1197
Sobolevskii AI, Khodorov BI (2002) Blocker studies of the functional architecture of the NMDA receptor channel. Neurosci Behav Physiol 32:157–171
Spasov AA, Iezhitsa IN, Kharitonova MV, Kravchenko MS (2007) Depression-like and anxiety-related behaviour of rats fed with magnesium-deficient diet. Zhurnal vysshei nervnoi deiatelnosti imeni IP Pavlova 58:476–485
Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez Kitchen CM, Funderburg N, Mesiano S, Bernstein HB (2012) Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. J Immunol 188:6338–6346
Szewczyk B, Poleszak E, Sowa-Kucma M, Siwek M, Dudek D, Ryszewska-Pokrasniewicz B, Radziwon-Zaleska M, Opoka W, Czekaj J, Pilc A, Nowak G (2008) Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. Pharmacol Rep 60:588–589
Veronese N, Berton L, Carraro S, Bolzetta F, De Rui M, Perissinotto E, Toffanello ED, Bano G, Pizzato S, Miotto F, Coin A, Manzato E, Sergi G (2014) Effect of oral magnesium supplementation on physical performance in healthy elderly women involved in a weekly exercise program: a randomized controlled trial. Am J Clin Nutr 100:974–981
Veronese N, Zanforlini BM, Manzato E, Sergi G (2015a) Magnesium and healthy aging. Magnes Res 28:112–115
Veronese N, Zurlo A, Solmi M, Luchini C, Trevisan C, Bano G, Manzato E, Sergi G, Rylander R (2015b) Magnesium status in Alzheimer's disease: a systematic review. Am J Alzheimers Dis Other Demen 31:208–213
Veronese N, Watutantrige SF, Luchini C, Solmi M, Sartore G, Sergi G, Manzato E, Barbagallo M, Maggi S, Stubbs B (2016) Effect of magnesium supplementation on glucose metabolism in people with or at risk of diabetes: a systematic review and meta-analysis of double-blind randomized controlled trials. Eur J Clin Nutr 70:1354–1359
Volpe SL (2013) Magnesium in disease prevention and overall health. Adv Nutr (Bethesda) 4:378S–383S
Whang R (1987) Magnesium deficiency: pathogenesis, prevalence, and clinical implications. Am J Med 82:24–29
Zheltova AA, Kharitonova MV, Iezhitsa IN, Spasov AA (2016) Magnesium deficiency and oxidative stress: an update. Biomedicine 6:20