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Effects of Magnesium on Immune Response in Treatment-Resistant Depression

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ABSTRACT

Depression is an ill-defined mood disorder despite global *prevalence. Within this population is a treatment-resistant subgroup challenged by ineffective treatment options that are perhaps resultant of past attachments to conventional paradigm. Increasing studies describe an exacerbation of depression by chronic stress starting at an early age due to trauma, suggesting a closer look at the developing immune system. Basic nutrition is required for normal immune function; nutrient deficiencies are a common finding in depressed subjects. Adequate levels of magnesium (Mg) promote positive effects in treatment-resistant depression (TRD)—observations corroborated by evidence demonstrating its roles in symptomatic improvement, depressed cytokine production, and interactions with the pathobiological components of depression. The current review supports Mg as a potential safe and accessible orthomolecular treatment for TRD. Future work designed to validate these results, and careful attention to the immune system functioning in children, in contrast to adults, are appropriate next steps as the inflammation incited by childhood maltreatment may be a major genetic pushbutton in the development of TRD.*

INTRODUCTION

Depression is a prevalent systems-level disability that widely overlaps or is comorbid with other disease states—mental and physical. Accordingly, multiple brain regions, pathways, and signaling molecules appear to be involved (Miller & Raison, 2016; Williams et al., 2016). Treatment-resistant depression (TRD) comprises a third or more of the depressed population. Reduced—it is the failure to achieve complete remission following adequate antidepressant therapy (Chamberlain et al., 2019; Fava, 2003; Gaynes et al., 2013). TRD patients are at high risk for physical and mental comorbid states, disease severity, and no effective treatment options (Eby III & Eby, 2010). Discord across research groups has slowed the advancement towards more definitive criteria for TRD due to aspects involving research design, lacking treatment response metrics, low inter-clinician reliability, and comorbidity—factors that perpetuate ambiguity around the predictors for TRD (Chamberlain et al., 2019; Gaynes et al., 2013). This review takes a broad look at immune system function in TRD with a special consideration towards magnesium (Mg) as an effective orthomolecular adjunct or treatment option for TRD within a Westernized population predisposed to malnutrition.

CURRENT INTERVENTION

Depression gives rise to several neuroanatomical changes including negative volume and activity shifts in the hippocampus and prefrontal cortex (PFC), and hypertrophy of the amygdala (Pittenger & Duman, 2008; Zarate et al., 2013). Conventional antidepressant therapies focused on the molecular approach to disease and treatment—selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOIs), are based on the monoamine hypothesis and rely on increasing the synaptic availability of several key neurotransmitters—norepinephrine, serotonin, and dopamine, and promoting neurogenesis (Koo et al., 2010; Lacasse & Leo, 2005). Generally, only short-term antidepressant use seems to be effective, producing marginally significant effect sizes when compared to placebo and in certain cases of depression following weeks of treatment (Cipriani et al., 2018). Further, these antidepressants

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not only come with undesired side effects—cognitive impairments (Sayyah et al., 2016) and persistent sexual dysfunction (Csoka et al., 2008), as examples, but can remain long after discontinued use alongside symptomatic return (Cipriani et al., 2018; Davies & Read, 2019). The discovery of fast-acting antidepressants, such as ketamine or scopolamine (Berman et al., 2000; Wohleb et al., 2017), have lifted conservative eyes onto alternative pathways that can pause and reverse the injuries and brain changes governed by depression.

ORIGINS AND EPIGENETICS

Mental illness often presents in early life (Kessler at al., 2010; Kim-Cohen et al., 2005). The main predictor of well-being in adults is childhood emotional health and stability (Cabaj et al., 2014; Kessler et al., 2010). In other words, childhood trauma increases the risk of adult mental health disorders, including depression, and seems to be a primary feature of TRD (Sachs-Ericsson et al., 2007; Williams et al., 2016). The diathesis stress model describes the increased risk for depression when an individual has a history of maltreatment and expresses two short alleles for the serotonin transporter gene (5-HTTLPR), rather than two long or one long plus one short allele (Caspi et al., 2003). This model has been examined in the context of generational stress, gender differences, and chronic stress leading to depression (Liu & Alloy, 2010).

Pathogen host defense (PATHOS-D) hypothesis

Within the modern gene pool are common, pro-inflammatory alleles linked to increased risk for depression (Raison & Miller, 2013). The persistence of depression risk alleles in the human genome is at odds with Darwinian evolution. Depression impairs reproduction and survival by its maladaptive effects on social functioning. In earlier times, infection led many humans to death before adulthood, therefore genetic alleles that promoted protective pro-inflammatory mechanisms were strongly selected for (Fumagalli et al., 2011; Gurven & Kaplan, 2007; Miller & Raison, 2016). The pathogen host defense (PATHOS-D) hypothesis suggests that these alleles, in connection to the immunological and behavioural responses to a wide scope of environmental threats, persist to enhance survival as they have for antecedent generations (Miller & Raison, 2016; Raison & Miller, 2013).

Cytokine hypothesis

The reliable use of cytokines to induce or reverse depressive symptoms has gained much attention. Individuals at high risk for depression are consistently found to have higher levels of inflammatory markers when compared to low-risk individuals in a variety of populations including youth, chronic pain, and breast cancer patients (Kim et al., 2013; Kovacs et al., 2016; Raison et al., 2010; Tartter et al., 2015). Further, the height of the inflammatory response to a psychosocial stressor corresponds well to predictions of later depression development (Aschbacher et al., 2012; Pace et al., 2006; Quinn et al., 2020). Growing studies support the role of low-grade systemic inflammation in the pathogenesis of depression—namely TRD, psychosis, and other neuropsychiatric disorders (Chamberlain et al., 2019; Dantzer et al., 2008; Khandaker et al., 2015; Metcalf et al., 2017; Michopoulos et al., 2015; Raison et al., 2006; Raison et al., 2013; Wium-Andersen et al., 2013). Meta-analyses point to several cytokines—interleukin 1 beta (IL-1ß), interleukin 6 (IL-6), tumor necrosis factor (TNF), and Creactive protein (CRP), as strong indicators of antidepressant treatment response (Gimeno et al., 2009; Goldsmith et al., 2016; Haapakoski et al., 2015; Howren et al., 2009; Khandaker et al., 2014; Metcalf et al., 2017; Miller et al., 2009; Osimo et al., 2019).

Elevating systemic cytokines through activation or deliberate administration to nondepressed subjects evokes sickness behaviour—a condition whose symptomatic repertoire is indiscernible from depression and can be reversed with antidepressants (Capuron et al., 2002; Dantzer, 2009; Raison & Miller, 2013). In other words, infections can be mistaken for depression, depression can be mistaken for infection, and these inflamed events can provide insight into the treatment resistance seen in TRD (Ratcliffe, 2013). Further, the depressive symptoms associated with other illnesses such as psoriasis, obesity, and rheumatoid arthritis are significantly reduced upon anti-cytokine therapy (Kappelmann et al., 2018; Menter et al., 2010; Soczynska et al., 2011; Tyring et al., 2006). While adaptive and innate immune systems appear to play instrumental roles in TRD, perspective into other non-drug interventions, predispositions, and factors affecting these immunological pathways is needed for progress and understanding.

MAGNESIUM, CYTOKINES, AND DEPRESSION

Micronutrient deficiencies, common in modernized cultures, are associated with poorer health outcomes such as cognitive decline, cancer, obesity, immune dysfunction, and depression (Wang et al., 2018). Magnesium (Mg) is an essential cofactor and mineral cation found primarily within cells. Due to its highly involved importance, it is kept within tight homeostatic control through dietary absorption, urinary output, and bone stores. There are numerous

channels that can lead to changes in Mg absorption or excretion including consumption of alcohol or dietary compounds such as phytic acid or oxalates, malnutrition, medications, aging, smoking, diabetes, hypernatremia, hypercalcemia, disorders affecting the gastrointestinal system, and chronic stress—to name a few (Barbagallo et al., 2009; Dickerman & Liu, 2011; Eby and Eby, 2006; Kieboom et al., 2015; Pochwat et al., 2014; Tarleton, 2018; Topf & Murray, 2003; Volpe, 2013).

Low dietary Mg has been correlated with depression in young adults, adding a 50% increased risk for depression in those found at the lowest intake quintile (Tarleton & Littenberg, 2014). Mg deficiency has also been associated with elevations in IL-1ß, IL-6, TNF, and CRP (Dibaba et al., 2014; Nielsen, 2018; Sugimoto et al., 2012). Meta-analyses and other studies have revealed an inverse relationship between dietary Mg intake and serum CRP levels (Dibaba et al., 2014; King et al., 2005; Simental-Mendia et al., 2017).

Mechanism

Mg is a calcium antagonist and calcium channel blocker. Low or deficient Mg stimulates the opening of L-type calcium channels allowing an influx of calcium, a rise in intracellular calcium, and calcium release from the sarcoplasmic reticulum (Dacey, 2001; Gums, 2004; Lin et al., 2010). Increased intracellular calcium promotes the release of IL-1ß, IL-6, TNF or CRP, stimulating phagocytic cells and the production of reactive oxygen species (Libako, et al., 2010). Repletion of Mg has been found to effectuate a reversal of these calcium-inducing effects, consequently attenuating cytokine production (Lin et al., 2010; Sugimoto et al., 2012).

Animals depleted of Mg were also found to activate the N-methyl-D-aspartic acid (NMDA) receptor leading to an influx of intracellular calcium, production of substance P in C fibers, increased cytokines, and oxidative stress (Blache et al., 2006; Reynolds, 1998; Weglicki, 2012; Zarate et al., 2013). In the chronic mild stress (CMS) model of depression, particular glutamatergic subunits of NMDA receptors—GluN1, GluN2A, GluN2B and PSD-95, within the hippocampus, amygdala, and PFC—areas associated with depression, were found to be upregulated or downregulated upon administration of Mg under stressed conditions (Pochwat, 2014). The effects that Mg repletion impart on cytokine regulation appear to result from its antagonistic actions on calcium, calcium channel and NMDA receptor inhibition, and modulation of NMDA receptor expression (Lin et al., 2010; Lodge & Johnson, 1990).

Magnesium and TRD

While the relationship with depression and Mg to inflammation is convincing, the relation between Mg and depression remains unclear. Some studies have been unable to establish a link between Mg status and depressive outcome (Dickerman & Liu, 2011; Phelan et al., 2018; Wang et al., 2018), while other studies have determined a distinct inverse correlation between Mg and depression. In animal models, the behavioural despair endophenotype of depression was reproduced in mice using the forced swim test (FST), demonstrating that Mg depletion increases immobility whereas Mg repletion reduces immobility when compared to placebo (Poleszak et al., 2004; Singewald et al., 2004). In human models, the prevalence (cross-sectional) and incidence (longitudinal) of depression and Mg intake in self-reporting groups reveal a strong inverse relationship—Mg depletion exacerbates depressive symptoms and symptom improvement occurs upon Mg repletion (Eby & Eby, 2006; Jacka et al., 2009; Tarleton & Littenberg, 2015; Tarleton et al., 2017; Yary et al., 2016). Moreover, interesting results measured by phosphorus nuclear magnetic resonance (NMR) spectroscopy reveal that TRD subjects have significantly lower levels of intracellular Mg in the brain compared to non-TRD subjects (Eby III & Eby, 2010; Iosifescu et al., 2008).

Co-administration of Mg and antidepressants such as imipramine or citalopram, were reported to augment antidepressant efficacy (Poleszak et al., 2005; Szewczyk et al., 2008). The antidepressant-like effects promoted by Mg have been traced to its binding interactions with the serotonergic, noradrenergic, and dopaminergic systems (Cardoso et al., 2009; Eby III & Eby, 2010; Kantak, 1988). As low levels of brain Mg seem to decrease serotonin, and antidepressants appear to improve intracellular concentrations of brain Mg (Eby III & Eby, 2010), confidence surrounding this particular cofactor builds as a potential therapy for TRD.

The mechanism of action of Mg appears to be widespread, circuitous, and intricate, along with regulatory effects on the hypothalamic-pituitary adrenal (HPA) axis and adrenocorticotrophic hormone (ACTH)—other points of Mg control in depression that have been aptly described in previous work (Eby III & Eby, 2010; Murck, 2002; Sartori et al., 2012). In the Mg-depletion model of depression, inadequate Mg levels lead to NMDA overactivity, cytokine production, and increased symptoms of depression. Administering NMDA receptor antagonists like ketamine and Mg have been found to support: synaptogenesis, reversal of stress-in-

duced atrophy, and symptomatic improvement in TRD (Berman et al., 2000; Zarate et al., 2013).

DISCUSSION

The data suggests that Mg repletion is a necessary or plausible treatment approach in TRD or depression in general, respectively. The current review sought to reconcile the shared mechanisms between magnesium and TRD while acknowledging the nutritional neglect often encumbering the depressed individual. Modern food practices over the last century have contributed to lacking dietary Mg density and intake estimated in Westernized populations (Gums, 2004). Low Mg food sources further predispose depressed subjects to nutrient deficiencies, as the disorder often directs poor dietary choices. The ubiquitary nature of stress and inflammation highlights a growing impact on gene expression and the call to identify sites of origin and maintenance. Mutual crossover points relating to cytokine production, Mg, and TRD suggest an increased likelihood that Mg supplementation would be a beneficial treatment option for TRD and depressed persons that are or are not medicated, excluding the elderly unless newly diagnosed with depression associated with type 2 diabetes (Blanchflower & Oswald, 2008; Eby III & Eby, 2010; Tarleton & Littenberg, 2015). The strong relationship between Mg and immune response emerging from the extant literature prompts continued investigation (Tam et al., 2003).

The majority of studies conducted on Mg included males and females across all ages and body types, improving the generalizability of the findings; however, gender-specific biases in Mg levels may not have been accounted for, e.g. contraceptive use (Stanton & Lowenstein, 1987). Studies that found positive correlations between depression and negative serum or cerebrospinal fluid (CSF) Mg levels were excluded due to methodological concerns regarding the use of serum or CSF Mg as an indicator of intracellular or total body Mg levels, as either can be within normal limits while the other is not (Arsenian, 1993; Elin, 1994; Purvis, 1992). For instance, in TRD, serum Mg can be high, normal, or low and unrelated to levels of brain Mg (Eby III & Eby, 2010), while depressed patients not on medication can have high erythrocyte Mg scores (Widmer et al., 1992; Widmer et al., 1995; Widmer et al., 1993). In other words, intracellular and extracellular Mg concentrations vary across tissue types and between individual temperament, physiological demand, and other health-related contexts. Further, the biological half-life of Mg is nearly six months (Elin, 1994), while repletion of Mg body stores through oral supplementation can take weeks or months (Gums-Dorup et al., 1993; Whang et al., 1994). It is possible that the symptomatic reduction and positive effects seen with acute Mg repletion in these studies would require repeat high doses of Mg over an extended period to maintain the observed effects until adequate intracellular brain levels were achieved, after which a lower dosage or proper dietary routine could suffice. Mg homeostasis is complex, therefore delayed clinical presentation of Mg deficiency within certain tissues is expected and comparable to the lagging clinical appearance of calcium deficiency in postmenopausal women (Gums, 2004). Such uncertain mechanics could explain the dissonant results found across studies using serum or CSF Mg levels prior to a clear understanding around how Mg levels shift within different tissues and physiological states.

FUTURE DIRECTIONS

Environmental stressors are known to influence gene expression, biological process, neural function, cognition, behaviour, and well-being. Over the past two decades, an integrated approach to understanding depression has led to several multilevel paradigms including the Social Signal Transduction Theory of Depression. This theory describes the proportional immune response, specifically increases in IL-6, that follows psychosocial stress, impairs executive function, and advances or worsens the development of depression (Quinn et al., 2020; Slavich & Irwin, 2014). The incidence of stress and depression has become a common social reality. For TRD sufferers, conventional medications are not an option; for others, philosophical or lifestyle choices drive the alternative wish to avoid the use of pharmaceutical drugs. For all those concerned, research around orthomolecular medicines that encourage recovery or stress-induced inflammatory resistance would benefit those hoping for improved outcomes. As well, focus on hygiene theory, gut microbiota, and the developing immune system of young children might lead to gentler, cost-effective, and preventative measures for TRD and general depression.

CONCLUSION

The immune system is a complex security and surveillance network regulating all matters of functional breach, averse to nutritional deficiencies that create openings for pathogenic insult. Low Mg is associated with various chronic conditions including major depression, postpartum depression, hypothyroidism, Alzheimer's, stroke, hypertension, cardiovascular disease, migraine headaches, and type 2 diabetes mellitus (Eby & Eby, 2006; Kawano et al., 1998; Volpe, 2013). While inflammation plays a role in the aforementioned dysfunctions, the potential harm of pharmaceutical anti-inflammatory or anti-cytokine therapy in patients with or without inflammation must be acknowl-

edged. The potential use of Mg as a therapeutic agent in TRD is tenable, safe, and practical for daily use to promote health and prevent disease in those predisposed to Mg depletion, stress, TRD, and depression (Eby III & Eby, 2010; Gums, 2004; Tam et al., 2003; Volpe, 2013); hypermagnesemia—a rare concern, with caution typically reserved for those inclined to renal failure. Prospective work confirming the efficacy of Mg in TRD must be pursued to authenticate its restorative value.

REFERENCES

Arsenian, MA (1993) Magnesium and cardiovascular disease. *Progress in Cardiovascular Diseases*. 35(4): 271-310.

Aschbacher K, Epel E, Wolkowitz OM, Prather AA, Puterman E & Dhabhar FS (2012) Maintenance of a positive outlook during acute stress protects against proinflammatory reactivity and future depressive symptoms. *Brain, Behavior, and Immunity*. 26(2): 346-352.

Barbagallo M, Belvedere M & Dominguez LJ (2009) Magnesium homeostasis and aging. *Magnesium Research* 22(4): 235-246.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS & Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry* 47(4): 351-354.

Blache D, Devaux S, Joubert O, Loreau N, Schneider M, Durand P… Berthelot A (2006) Long-term moderate magnesium-deficient diet shows relationships between blood pressure, inflammation and oxidant stress defense in aging rats. *Free Radical Biology and Medicine*. 41(2): 277-284.

Blanchflower DG & Oswald AJ (2008) Is well-being U-shaped over the life cycle? *Social Science & Medicine* 66:1733–1749.

Cabaj JL, McDonald SW & Tough SC (2014) Early childhood risk and resilience factors for behavioural and emotional problems in middle childhood. *BMC Pediatrics*. 14(1): 166.

Capuron L, Gumnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB & Miller AH (2002) Neurobehavioral effects of interferon-α in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology*. 26(5): 643-652.

Cardoso CC, Lobato KR, Binfaré RW, Ferreira PK, Rosa AO, Santos ARS & Rodrigues ALS (2009) Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium. *Progress in Neuro psychopharmacology and Biological Psychiatry*. 33(2): 235-242.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H… Poulton R (2003) Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*. 301(5631): 386-389.

Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DN, Drevets WC… Bullmore ET (2019) Treatment resistant depression and peripheral C-reactive protein. *The British Journal of Psychiatry*. 214(1): 11-19.

Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y… Egger M (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *Focus*. 16(4): 420-429.

Csoka A, Bahrick A & Mehtonen OP (2008) Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors. *The Journal of Sexual Medicine*. 5(1): 227-233.

Dacey MJ (2001) Hypomagnesemic disorders. *Critical Care Clinics*. 17(1): 155-173.

Dantzer R (2009) Cytokine, sickness behavior, and depression. *Immunology and Allergy Clinics*. 29(2): 247-264.

Dantzer R, O'Connor JC, Freund GG, Johnson RW & Kelley KW (2008) From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*. 9(1): 46-56.

Davies J & Read J (2019) A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive Behaviors*. 97: 111-121.

Dibaba DT, Xun P & He K (2014) Dietary magnesium intake is inversely associated with serum C-reactive protein levels: Meta-analysis and systematic review. *European Journal of Clinical Nutrition*. 68(4): 510-516.

Dickerman B & Liu J (2011) Do the micronutrients zinc and magnesium play a role in adult depression? *Topics in Clinical Nutrition*. 26(3): 257.

Eby GA & Eby KL (2006) Rapid recovery from major depression using magnesium treatment. *Medical Hypotheses*. 67(2): 362-370.

Eby III GA & Eby KL (2010) Magnesium for treatment-resistant depression: A review and hypothesis. *Medical Hypotheses*. 74(4): 649-660.

Elin RJ (1994) Magnesium: The fifth but forgotten electrolyte. *American Journal of Clinical Pathology*, 102(5): 616-622.

Fava M (2003) Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*. 53(8): 649-659.

Fumagalli M, Sironi M, Pozzoli U, Ferrer-Admetlla A, Pattini L & Nielsen R (2011) Correction: Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *PLoS Genetics*. 7(11).

Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J… Coker-Schwimmer E (2019). Defining treatment-resistant depression. *Depression and Anxiety*. 37(2).

Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A… Ferrie JE (2009) Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological Medicine*. 39(3): 413-423.

Goldsmith DR, Rapaport MH & Miller BJ (2016) A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Molecular Psychiatry*, 21(12): 1696-1709.

Gums JG (2004) Magnesium in cardiovascular and other disorders. *American Journal of Health-System Pharmacy*. 61(15): 1569-1576.

Gurven M & Kaplan H (2007) Longevity among hunter-gatherers: a cross-cultural examination. *Population and Development Review*. 33(2): 321-365.

Haapakoski R, Mathieu J, Ebmeier KP, Alenius H & Kivimäki M (2015) Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain, Behavior, and Immunity*. 49: 206-215.

Howren MB, Lamkin DM & Suls J (2009) Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*. 71(2): 171-186.

Iosifescu DV, Bolo NR, Nierenberg AA, Jensen JE, Fava M & Renshaw PF (2008). Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biological Psychiatry*. 63(12): 1127-1134.

Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I & Mykletun A (2009) Association between magnesium intake and depression and anxiety in community dwelling adults: The Hordaland Health Study. *Australian and New Zealand Journal of Psychiatry*. 43(1): 45-52.

Kantak KM (1988) Magnesium deficiency alters aggressive behavior and catecholamine function. *Behavioral Neuroscience*. 102(2): 304.

Kappelmann N, Lewis G, Dantzer R, Jones PB & Khandaker GM (2018) Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Molecular Psychiatry*. 23(2): 335-343.

Kawano Y, Matsuoka H, Takishita S & Omae T (1998) Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension*. 32(2): 260-265.

Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM… Benjet C (2010) Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry*. 197(5): 378-385.

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R & Jones PB (2015) Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. *The Lancet Psychiatry*. 2(3): 258-270.

Khandaker GM, Pearson RM, Zammit S, Lewis G & Jones PB (2014) Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: A population-based longitudinal study. *JAMA Psychiatry* 71(10): 1121-1128.

Kieboom BC, Kiefte–de Jong JC, Eijgelsheim M, Franco OH, Kuipers EJ, Hofman A… Hoorn EJ (2015) Proton pump inhibitors and hypomagnesemia in the general population: A population-based cohort study. *American Journal of Kidney Diseases*. 66(5): 775-782.

Kim JM, Stewart R, Kim S., Kang HJ, Jang JE, Kim SW… Kim YH (2013) A one year longitudinal study of cytokine genes and depression in breast cancer. *Journal of Affective Disorders*. 148(1): 57-65.

Kim-Cohen J, Moffitt TE, Taylor A, Pawlby SJ & Caspi A (2005) Maternal depression and children's antisocial behavior: Nature and nurture effects. *Archives of General Psychiatry*. 62(2): 173-181.

King DE, Mainous III AG, Geesey ME & Woolson RF (2005) Dietary magnesium and C-reactive protein levels. *Journal of the American College of Nutrition*. 24(3): 166-171.

Koo JW, Russo SJ, Ferguson D, Nestler EJ & Duman RS (2010) Nuclear factor-κB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proceedings of the National Academy of Sciences*. 107(6): 2669-2674.

Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P… Juhasz G (2016) Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. *Journal of Neural Transmission*. 123(5): 541-548.

Lacasse JR & Leo J (2005) Serotonin and depression: a disconnect between the advertisements and the scientific literature. *PLoS Medicine*. 2(12).

Libako P, Nowacki W, Rock E, Rayssiguier Y & Mazur A (2010) Phagocyte priming by low magnesium status: Input to the enhanced inflammatory and oxidative stress responses. *Magnesium Research*. 23(1): 1-4.

Lin CY, Tsai PS, Hung YC & Huang CJ (2010) L-type calcium channels are involved in mediating the anti-inflammatory effects of magnesium sulphate. *British Journal of Anaesthesia*. 104(1): 44-51.

Liu RT & Alloy LB (2010) Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. *Clinical Psychology Review*. 30(5): 582-593.

Lodge D & Johnson KM (1990) Noncompetitive excitatory amino acid receptor antagonists. *Trends in Pharmacological Sciences*. 11(2): 81-86.

Menter A, Augustin M, Signorovitch J, Andrew PY, Wu EQ, Gupta SR… Mulani P (2010) The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: A randomized clinical trial. *Journal of the American Academy of Dermatology*. 62(5): 812-818.

Metcalf SA, Jones PB, Nordstrom T, Timonen M, Mäki P, Miettunen J… Veijola, J (2017) Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study. *Brain, Behavior, and Immunity*. 59: 253-259.

Michopoulos V, Rothbaum AO, Jovanovic T, Almli LM, Bradley B, Rothbaum BO… Ressler KJ (2015) Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *American Journal of Psychiatry*. 172(4): 353-362.

Miller AH, Maletic V & Raison CL (2009) Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*. 65(9): 732-741.

Miller AH & Raison CL (2016) The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*. 16(1): 22.

Murck H (2002) Magnesium and affective disorders. *Nutritional Neuroscience*. 5(6): 375-389.

Nielsen FH (2018) Magnesium deficiency and increased inflammation: current perspectives. *Journal of Inflammation Research*. 11: 25.

Osimo EF, Baxter LJ, Lewis G, Jones PB & Khandaker GM (2019) Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychological Medicine*. 49(12): 1958-1970.

Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH & Heim CM (2006) Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry*. 163(9): 1630-1633.

Phelan D, Molero P, Martínez-González MA & Molendijk M (2018) Magnesium and mood disorders: systematic review and meta-analysis. *BJPsych Open*. 4(4): 167-179.

Pittenger C & Duman RS (2008) Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*. 33(1): 88-109.

Pochwat B, Szewczyk B, Sowa-Kucma M, Siwek A, Doboszewska U, Piekoszewski W… Nowak G (2014) Antidepressant-like activity of magnesium in the chronic mild stress model in rats: alterations in the NMDA receptor subunits. *International Journal of Neuropsychopharmacology*. 17(3): 393-405.

Poleszak E, Szewczyk B, Kędzierska E, Wlaź P, Pilc A & Nowak G (2004) Antidepressant-and anxiolytic-like activity of magnesium in mice. *Pharmacology Biochemistry and Behavior*. 78(1): 7-12.

Poleszak E, Wlaź P, Szewczyk B, Kędzierska E, Wyska E, Librowski T… Nowak G (2005) Enhancement of antidepressant-like activity by joint administration of imipramine and magnesium in the forced swim test: Behavioral and pharmacokinetic studies in mice. *Pharmacology Biochemistry and Behavior*. 81(3): 524-529.

Purvis JR & Movahed A (1992) Magnesium disorders and cardiovascular diseases. *Clinical Cardiology*. 15(8): 556-568.

Quinn ME, Stanton CH, Slavich GM & Joormann J (2020) Executive control, cytokine reactivity to social stress, and depressive symptoms: Testing the social signal transduction theory of depression. *Stress*. 23(1): 60-68.

Raison CL, Capuron L & Miller AH (2006) Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*. 27(1): 24-31.

Raison CL, Lowry CA & Rook GA (2010) Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Archives of General Psychiatry*. 67(12): 1211-1224.

Raison CL & Miller AH (2013) The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Molecular Psychiatry*. 18(1): 15-37.

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF… Miller AH (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 70(1): 31-41.

Ratcliffe M (2013) A bad case of the flu? The comparative phenomenology of depression and somatic illness. *Journal of Consciousness Studies* 20(7-8): 198-218.

Reynolds IJ (1998) Intracellular calcium and magnesium: critical determinants of excitotoxicity? *Progress in Brain Research*. 116: 225-243.

Sachs-Ericsson N, Kendall-Tackett K & Hernandez A (2007) Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. *Child Abuse & Neglect*. 31(5): 531-547.

Sartori SB, Whittle N, Hetzenauer A & Singewald N (2012) Magnesium deficiency induces anxiety and HPA axis dysregulation: Modulation by therapeutic drug treatment. *Neuropharmacology*. 62(1): 304-312.

Sayyah M, Eslami K, AlaiShehni S & Kouti L (2016) Cognitive function before and during treatment with selective serotonin reuptake inhibitors in patients with depression or obsessive-compulsive disorder. *Psychiatry Journal*. 2016.

Simental-Mendia LE, Sahebkar A, Rodriguez-Moran M, Zambrano-Galvan G & Guerrero-Romero F (2017) Effect of magnesium supplementation on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. *Current Pharmaceutical Design*. 23(31): 4678-4686.

Singewald N, Sinner C, Hetzenauer A, Sartori SB & Murck H (2004) Magnesiumdeficient diet alters depression-and anxiety-related behavior in mice—influence of desipramine and Hypericum perforatum extract. *Neuropharmacology*. 47(8): 1189-1197.

Slavich GM & Irwin MR (2014) From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, 140(3): 774.

Soczynska JK, Kennedy SH, Woldeyohannes HO, Liauw SS, Alsuwaidan M, Yim CY & McIntyre RS (2011) Mood disorders and obesity: Understanding inflammation as a pathophysiological nexus. *Neuromolecular medicine*, 13(2), 93-116.

Stanton MF & Lowenstein FW (1987) Serum magnesium in women during pregnancy, while taking contraceptives, and after menopause. *Journal of the American College of Nutrition*, 6(4): 313-319.

Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Kitchen CMR, Funderburg N… Bernstein HB (2012) Magnesium decreases inflammatory cytokine production: A novel innate immunomodulatory mechanism. *The Journal of Immunology*. 188(12): 6338-6346.

Szewczyk B, Poleszak E, Sowa-Kucma M, Siwek M, Dudek D, Ryszewska-Pokrasniewicz B… Nowak G (2008) -Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. *Pharmacological Reports*. 60(5): 588.

Tam M, Gomez S, Gonzalez-Gross M & Marcos A (2003) Possible roles of magnesium on the immune system. *European Journal of Clinical Nutrition*. 57(10): 1193-1197.

Tarleton EK (2018) Factors influencing magnesium consumption among adults in the United States. *Nutrition Reviews*. 76(7): 526-538.

Tarleton EK & Littenberg B (2015) Magnesium intake and depression in adults. *The Journal of the American Board of Family Medicine*. 28(2): 249-256.

Tarleton EK, Littenberg B, MacLean CD, Kennedy AG & Daley C (2017) Role of magnesium supplementation in the treatment of depression: A randomized clinical trial. *PLoS One*. 12(6): e0180067.

Tartter M, Hammen C, Bower JE, Brennan PA & Cole S (2015) Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1β in youth. *Brain, Behavior, and Immunity*. 46: 104-111.

Topf JM & Murray PT (2003) Hypomagnesemia and hypermagnesemia. *Reviews in Endocrine and Metabolic Disorders*, 4(2), 195-206.

Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A… Cella D (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. *The Lancet*. 367(9504): 29-35.

Volpe SL (2013) Magnesium in disease prevention and overall health. *Advances in Nutrition*. 4(3): 378S-383S.

Wang J, Um P, Dickerman BA & Liu J (2018) Zinc, magnesium, selenium and depression: A review of the evidence, potential mechanisms and implications. *Nutrients*. 10(5): 584.

Weglicki WB (2012) Hypomagnesemia and inflammation: Clinical and basic aspects. *Annual Review of Nutrition*, 32: 55-71.

Widmer J, Bovier P, Karege F, Raffin Y, Hilleret H, Gaillard JM & Tissot R (1992) Evolution of blood magnesium, sodium and potassium in depressed patients followed for three months. *Neuropsychobiology*. 26(4): 173-179.

Widmer J, Henrotte JG, Raffin Y, Bovier P, Hilleret H & Gaillard JM (1995) Relationship between erythrocyte magnesium, plasma electrolytes and cortisol, and intensity of symptoms in major depressed patients. *Journal of Affective Disorders*. 34(3): 201-209.

Widmer J, Stella N, Raffin Y, Bovier P, Gaillard JM, Hilleret H & Tissot R (1993) Blood magnesium, potassium, sodium, calcium and cortisol in drug-free depressed patients. *Magnesium Research*. 6(1): 33-41.

Williams LM, Goldstein-Piekarski AN, Chowdhry N, Grisanzio KA, Haug NA, Samara Z… Yesavage J (2016) Developing a clinical translational neuroscience taxonomy for anxiety and mood disorder: Protocol for the baseline-follow up Research domain criteria Anxiety and Depression ("RAD") project. *BMC Psychiatry*. 16(1): 68.

Wium-Andersen MK, Ørsted DD, Nielsen SF & Nordestgaard BG (2013) Elevated C-reactive protein levels, psychological distress, and depression in 73,131 individuals. *JAMA Psychiatry*. 70(2): 176-184.

Wohleb E, Gerhard D, Thomas A & Duman RS (2017) Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. *Current Neuropharmacology*. 15(1): 11-20.

Yary T, Lehto SM, Tolmunen T, Tuomainen TP, Kauhanen J, Voutilainen S & Ruusunen, A (2016) Dietary magnesium intake and the incidence of depression: A 20-year follow-up study. *Journal of Affective Disorders*. 193: 94-98.

Zarate C, Duman RS, Liu G, Sartori S, Quiroz J & Murck H (2013) New paradigms for treatment-resistant depression. *Annals of the New York Academy of Sciences*. 1292, 21