



## Magnesium for treatment-resistant depression: A review and hypothesis

George A. Eby III\*, Karen L. Eby

George Eby Research Institute, 14909-C Fitzhugh Road, Austin, Texas 78736, USA

### ARTICLE INFO

#### Article history:

Received 26 October 2009

Accepted 31 October 2009

### SUMMARY

Sixty percent of cases of clinical depression are considered to be treatment-resistant depression (TRD). Magnesium-deficiency causes *N*-methyl-D-aspartate (NMDA) coupled calcium channels to be biased towards opening, causing neuronal injury and neurological dysfunction, which may appear to humans as major depression. Oral administration of magnesium to animals led to anti-depressant-like effects that were comparable to those of strong anti-depressant drugs. Cerebral spinal fluid (CSF) magnesium has been found low in treatment-resistant suicidal depression and in patients that have attempted suicide. Brain magnesium has been found low in TRD using phosphorous nuclear magnetic resonance spectroscopy, an accurate means for measuring brain magnesium. Blood and CSF magnesium do not appear well correlated with major depression. Although the first report of magnesium treatment for agitated depression was published in 1921 showing success in 220 out of 250 cases, and there are modern case reports showing rapid terminating of TRD, only a few modern clinical trials were found. A 2008 randomized clinical trial showed that magnesium was as effective as the tricyclic anti-depressant imipramine in treating depression in diabetics and without any of the side effects of imipramine. Intravenous and oral magnesium in specific protocols have been reported to rapidly terminate TRD safely and without side effects. Magnesium has been largely removed from processed foods, potentially harming the brain. Calcium, glutamate and aspartate are common food additives that may worsen affective disorders. We hypothesize that – when taken together – there is more than sufficient evidence to implicate inadequate dietary magnesium as the main cause of TRD, and that physicians should prescribe magnesium for TRD. Since inadequate brain magnesium appears to reduce serotonin levels, and since anti-depressants have been shown to have the action of raising brain magnesium, we further hypothesize that magnesium treatment will be found beneficial for nearly all depressives, not only TRD.

© 2009 Elsevier Ltd. All rights reserved.

### Introduction

Neuropsychiatric disorders account for 36% of all non-communicable conditions, are the leading cause of all disability (more than twice that of cardiovascular diseases and malignant neoplasms) in the United States and Canada, with depressive disorders causing 40% of all neuropsychiatric disorders [1]. Major depression is expected to affect up to 25% of the American population at some point in their lives. Patients suffer in many areas of their lives, including sleep, eating, relationships, school, work, and self-image.

#### Increasing incidence of depression

Americans are developing major depression at higher rates and younger ages than ever before [2]. People born around 1900 rarely had childhood or early adult depression and only about 1% ever developed depression. People born between 1935 and 1944 had a

1% incidence of depression by age 15, a 2% rate of depression by age 25 and 9% incidence by age 45. People born in 1955, had a 1% incidence of depression by age 15, a 6% incidence by age 25, and a lifetime incidence of 25%. The onset of depression has greatly increased in incidence, and it is affecting people much earlier in their lives during the late 20th century and early 21st century than before the 20th century [2].

#### Classical depression treatments

Among those who seek professional help for clinical depression, some patients find relief for their condition using selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic anti-depressants, herbal 5-HTP, omega-3 EFAs and various medical and psychiatric treatments. The clinical efficacy of current anti-depressant drug therapies is unsatisfactory; anti-depressants induce a variety of unwanted side effects, and, moreover, their therapeutic mechanisms are not clearly understood. Thus, a search for better and safer agents is continuously in progress [3].

\* Corresponding author. Tel./fax: +1 512 263 0805.

E-mail address: [george.eby@george-eby-research.com](mailto:george.eby@george-eby-research.com) (G.A. Eby III).

### Treatment-resistant depression

A large proportion of the burden caused by depression is attributable to treatment-resistant depression (TRD). TRD itself is common, as high as 60% if TRD is defined – as it probably should be – as absence of remission from psychiatric medical and drug treatment. Duration and severity of illness are higher in TRD. In the short term, TRD is highly recurrent with as many as 80% of those requiring multiple treatments relapsing within a year of achieving remission. For those with a more protracted illness, the probability of recovery within 10 years is about 40%. Patients with TRD are more likely to suffer from comorbid physical and mental disorders, to experience marked and protracted functional impairment, and to incur higher medical and mental healthcare costs. Thus, in order to reduce the substantial burden caused by depression, TRD is one of the central focuses of medical research [4].

### Hypothesis

We hypothesize that there is a different cause for TRD relative to treatable depression, a cause perhaps resulting from changes in the diet, and that magnesium-deficiency is involved as the main factor. For a long time it was not accepted that food could have any influence on brain structure and its function including cognitive, mood and intellectual development. However, it is now very certain that magnesium plays important roles in all the major metabolisms in oxidation–reduction and in ionic regulation, among other roles in the brain [5]. Experience taught us the value of bioavailable oral magnesium in effectively and rapidly treating depression [6] and we hypothesized that magnesium treatment would be broadly effective, be of wide clinical benefit in TRD and reports of its efficacy would be readily and widely found in the literature. We searched for reviews and found that there were none that were comprehensive and all inclusive, and that such review was needed.

### Methods

To prepare this review, which we purport to be a comprehensive and all inclusive English-language review, we conducted a PubMed/Medline search for the terms magnesium and depression (1309 articles – only 76 related to mental health), magnesium and: “affective disorders” (40 articles), “treatment-resistant depression” (0 articles), “clinical depression” (0 articles), “major depressive disorder” (13 articles), and “major depression” (15 articles). The neurobiochemistry of magnesium and depression was reviewed mainly using neuroscience textbooks and a few of the 1232 related journal articles found on PubMed/Medline in a search for magnesium and NMDA. This review includes all related PubMed/Medline literature found prior to October 26, 2009, and is believed to not exclude any article for any reason. There was some overlap in the above searches.

### Results

Against the wide-spread belief that Western countries are the best fed people on planet Earth, we found evidence that intake of magnesium is inadequate in many Western countries and especially in the diets of depressives [7] perhaps explaining the cause of TRD.

### Food and magnesium

We found that magnesium intake has steadily declined over the preceding century, due to the practice of refining grain to make processed foods, making dietary choices low in magnesium-rich

foods, strong chemical sequestration of metals during food processing and complete removal of minerals from drinking water processed by distillation and reverse osmosis. Only 16% of the original magnesium and 24% of the zinc found in whole wheat remains in refined wheat processed foods [8]. These circumstances reduced the average bioavailable magnesium consumption from 450 mg in the 19th century and before to 250 mg per day or less in the 20th and early 21st centuries, resulting in significant and unhealthy magnesium-deficiency in the majority of the population [9]. Approximately 68% of US adults consume less than the American recommended daily allowance (RDA) of magnesium (420 mg/day for men, 320 mg/day for women), with 19% consuming less than half of the RDA [7].

### Food and excitotoxins

Conversely, extensive marketing and resultant consumption of excitotoxic glutamates and aspartates have greatly increased over the same period, even though there is a strong connection between dietary and endogenous excitotoxin excess and neurological dysfunction and mental illness [10,11].

### Neurobiochemistry of magnesium

An examination of the role of magnesium in the neuron provides some insight into the cause and possible treatment of TRD. Weston in 1921 reported that Meltzer and Auer first showed in 1905 that the primary effect of magnesium treatment upon nerve cells was that of paralysis without any preceding excitation, and the effect seemed to be exclusively of an inhibitory character [12].

### Magnesium and energy

Magnesium participates in numerous enzymatic reactions including all reactions that involve the formation and utilization of adenosine-5'-triphosphate (ATP) in energy metabolism [13]. Whenever neurons cannot generate sufficient ATP to keep their ion pumps working properly, membranes depolarize and excessive  $\text{Ca}^{2+}$  leaks into cells, triggering the synaptic release of glutamate, which further depolarizes neurons, further raising intracellular  $\text{Ca}^{2+}$  which causes even more glutamate to be released repeating in endless cycles [14] resulting in neuronal dysfunction and depression.

### Magnesium dynamics

Intracellular concentrations of  $\text{Mg}^{2+}$  are about four times extracellular and are regulated by several systems including ion pumps and intracellular binding sites [15]. The blood–brain barrier and choroid plexus regulate CSF and brain  $\text{Mg}^{2+}$  against acute changes in  $\text{Mg}^{2+}$  concentrations, however during extended periods of  $\text{Mg}^{2+}$  deficiency brain levels of  $\text{Mg}^{2+}$  decrease [15]. Inadequate central nervous system (CNS) concentration of  $\text{Mg}^{2+}$  has a critical level below which neurological dysfunction occurs [15,16]. The interchange of  $\text{Mg}^{2+}$  between the cerebrospinal fluid, extracellular fluid, and bone is more rapid and dynamic than has been previously believed [16], although the brain does not share in this interchange. This effect is magnified by hypertrophied parathyroid gland being associated with significant skeletal depletion of magnesium. Magnesium, much like calcium, has a large presence in bone, and it has a negative feedback relationship with the parathyroid gland. A critical decline in CNS magnesium may occur when the skeletal buffer system – orchestrated largely by the parathyroid glands – is activated by an increase in serum calcium in the presence of long-term magnesium-deficiency [17], moving  $\text{Mg}^{2+}$  ions from the CSF into the blood and eventually into the bone with

symptomatology being related to the degree of ion transfer [16,17]. The source of both excess calcium and magnesium-deficiency in the CNS appears to be dietary.

#### *NMDA receptors and magnesium*

Most of the brain's regular functions operate quickly and involve the excitatory amino acids glutamate and aspartate in the NMDA receptors. They are involved in NMDA nerve cell electrical conduction activity across brain cell synapses, a region hypothesized to function in a quantum mechanics manner [18]. Learning (long-term potentiation), memory and depression have their foundation in NMDA receptors. Magnesium-depletion is specifically deleterious to neurons by causing NMDA-coupled calcium channels to be biased towards opening [19], because magnesium is nature's calcium channel blocker [20]. The targets for glutamate binding to NMDA receptors are calcium and magnesium ion channels and to a lesser extent calcium and zinc channels [21]. At normal neuronal resting membrane potentials, pores of the glutamate-gated ion channel are blocked by  $Mg^{2+}$  ions [14,21–23]. The ion channel of the NMDA-receptor complex is subject to voltage-dependent regulation by magnesium ions [21,24,25].

Normally operating NMDA receptors admit into neurons only the amount of  $Ca^{2+}$  that is vital to their function, but abnormally functioning NMDA receptors increase influx of cellular  $Ca^{2+}$  beyond manageable levels leading to the generation of toxic reactive oxygen species and of toxic amounts of nitric oxide (NO) radicals [10,21,26]. Imbalances in  $Na^+$  and  $Cl^-$  gradients as well as  $Ca^{2+}$  overloading are also implicated in neuronal swelling and cell death [27], while depolarization of membranes relieves the  $Mg^{2+}$  block and allows  $Na^+$  and  $Ca^{2+}$  to enter [14]. Certain drugs can act in place of magnesium including memantine [21] and ketamine [28] with each producing benefits in depression.

#### *Other aspects of neuronal magnesium-deficiency*

Over 325 enzymes are magnesium dependent with many being brain enzymes. Magnesium-deficit modifies the turnover of various types of neurotransmitters including amino acids, nitric oxide, neuropeptides, and cytokines [29]. Intracellular effects of  $Mg^{2+}$  ions are mainly opposite to those of  $Ca^{2+}$  ions, possibly owing to competition at sites where  $Ca^{2+}$  ions activate  $K^+$  ion channels [30]. Magnesium-deficiency produces epileptiform activity in the CNS which can be blocked by NMDA-receptor antagonists. Other mechanisms, including alterations in  $Na^+/K^{(+)}$ -ATPase activity, cAMP/cGMP concentrations and calcium currents in pre- and postsynaptic membranes, may also be at least partially responsible for the neuronal injury associated with low brain magnesium and depression [31].

#### *Therapeutic potential of magnesium*

Magnesium ions appear to have therapeutic potential in clinical depression [32]. Examinations of the sleep-electroencephalogram (EEG) and of endocrine systems pointed to the involvement of the limbic-hypothalamus-pituitary-adrenocortical [HPA] axis as  $Mg^{2+}$  affect all elements of this system. Magnesium has the property to suppress hippocampal kindling, to reduce the release of adrenocorticotrophic hormone (ACTH) and to affect adrenocortical sensitivity to ACTH. The role of  $Mg^{2+}$  in the CNS could be mediated via the NMDA-antagonistic, gamma-aminobutyric acid-agonistic or the angiotensin II-antagonistic property of magnesium. A direct impact of  $Mg^{2+}$  on the function of the transport protein *p*-glycoprotein at the level of the blood-brain barrier has also been demonstrated, possibly influencing access of corticosteroids to the brain [32]. Furthermore,  $Mg^{2+}$  dampens the  $Ca^{2+}$ -protein kinase C related

neurotransmission and stimulates Na-K-ATPase. All these systems have been reported to be involved in the pathophysiology of depression [32]. Low ATP appears to respond to  $Mg^{2+}$  treatment. Magnesium treatment partially reverses sleep EEG and nocturnal neuroendocrine changes occurring during aging by increasing aldosterone and renin and lowering cortisol [33]. The similarities of the effect of  $Mg^{2+}$  and that of the related electrolyte  $Li^+$  furthermore supports the possible efficacy of  $Mg^{2+}$  as a mood stabilizer [33]. Magnesium appears to have GABA(A)-agonistic or NMDA-antagonistic effects on sleep and nocturnal hormonal secretion and hence may be useful in controlling depressive symptoms and seizures [34]. Magnesium is necessary for serotonin receptor binding [35]. The anti-depressant-like effect of magnesium is dependent on its interaction with the serotonergic, noradrenergic and dopaminergic receptors [36].

#### *Glutamate toxicity*

L-glutamate is the predominant excitatory neurotransmitter in the brain, but it can be cytotoxic under certain conditions [27]. Interaction between neurons may be either excitatory or inhibitory. Major excitatory amino acid neurotransmitters are glutamate and aspartate, while GABA ( $\gamma$ -aminobutyric acid), glycine (aminoacetic acid), and taurine are inhibitory [21]. Some of the earliest indicators that glutamate and many synthetic glutamate receptor agonists are toxic in excess were obtained in the 1970's [37–40]. Glutamate, although it is vital for neuronal transactions, when present in the slightest excess appears more toxic to neurons than cyanide [21]. Even endogenous glutamate may cause neurotoxicity via a process of depolarization-induced excitotoxicity [2]. Processes that increase the sensitivity of glutamate receptors or affect glutamate homeostasis often induce cell death, and they are usually connected with calcium overload. Over-stimulation of both non-NMDA and NMDA receptors with glutamate results in a large influx of calcium into the cell interior, particularly into neuronal mitochondria. Normal levels of both are necessary for correct cellular processes [27]. If the intra-neuronal mitochondrial concentration of  $Ca^{2+}$  is excessive, such can result in the activation of a series of calcium-dependent enzymes that are normally suppressed. When these enzymes, like lipid peroxidase, nitric oxide synthetase, and xanthine oxidase, are activated they cause the production of free radicals and nitric oxide, cytoskeletal breakdown, failure to generate ATP, lipid peroxidation, and nucleic acid fragmentation, each of which leads to neuronal death [21]. Experimentally, excess of glutamate produces neurofibrillary tangles and is toxic to neurons. A deficiency of  $Mg^{2+}$  – which blocks the action of glutamate by blocking NMDA receptors – would exacerbate the effects of glutamate and thereby increase the potential for neurodegenerative diseases [15]. Traumatic brain injury often resulted in excessive release of glutamate and neural degeneration [41], which appeared reversible with magnesium treatment [42].

#### *Animal models of magnesium in depression*

Animal models have provided insight into the role of stress on magnesium status, effects of magnesium-deficiency and effects of magnesium treatment in depression.

#### *Magnesium malnutrition in animals*

Malnutrition by magnesium-depletion altered behavior in established animal models of depression and anxiety. Compared to control mice fed a normal diet, mice receiving low magnesium diet (10% of daily requirement) for several weeks displayed increased immobility time in the forced swim test, indicating enhanced depression-like behavior. The forced swim test measures

the duration of time they are immobile during simulated drowning [43]. In addition, the partial magnesium-depletion feed increased anxiety-related behavior in the light/dark and open field test, while locomotor activity or motor coordination was not influenced. Magnesium-depletion led to depression- and anxiety-related behavior in mice, which was further validated by the reversibility of the behavioral changes by anti-depressant and anxiolytic substances, with a relation between magnesium status and mood disorders being suggested [43]. Magnesium-deficiency in rats was associated with significantly depleted erythrocyte and plasma  $Mg^{2+}$  levels compared to control rats, and it resulted in depression-like and anxiety-related behavior in rats. Magnesium salts alone and in combination with vitamin B6 increased the  $Mg^{2+}$  level in plasma and erythrocytes and provided an anti-depressant- and anxiolytic-like activity [44].

#### *Magnesium treatment in stressed animals*

Immobility-induced stress caused depression-like behavior in the forced swim test (FST) in mice and rats, and magnesium treatment provided strong anti-depressant activity [45–48]. The FST increased the magnesium concentration in serum; and decreased it in the brain compared to naive animals, showing that there is a stress-induced translocation of magnesium from the brain into the serum. Involvement of NMDA/glutamate pathways in the anti-depressant-like activity of magnesium was shown in mouse FST suggesting anti-depressant properties of magnesium. Brain magnesium levels declined after traumatic brain injury (TBI) in rats, a decline believed associated with ensuing neuronal cell death and subsequent functional impairment, and magnesium sulfate reduced the incidence of post-traumatic depression/anxiety in the rat model of diffuse TBI from 61% to less than 30% [41].

#### *Magnesium treatment in normal animals*

From the similarity in action between  $Mg^{2+}$  and the D-alpha-amino acid group of NMDA antagonists, it was suggested that the central depressant action of low concentrations of  $Mg^{2+}$  involves predominantly a post-synaptically mediated interference with the action of an excitatory amino acid transmitter [49]. Under conditions of magnesium-deficiency, CSF concentrations decline, although this decline lags behind and is less pronounced than the changes observed in plasma magnesium concentrations. Decreases in CSF magnesium concentrations correlate with the alterations observed in extracellular brain magnesium concentrations in animals following the dietary deprivation of magnesium. CSF magnesium concentrations can readily be restored following magnesium supplementation, although high dose magnesium therapy, such as that used in the treatment of convulsions in eclampsia, increase CSF magnesium concentrations to a limited degree (approximately 11–18%) above physiological concentrations [31]. Magnesium and copper are important modulators of NMDA-receptor activity. Recent data indicate that disturbances of glutamatergic transmission (especially via NMDA-receptor) are involved in pathogenesis of mood disorders. Magnesium-deficiency, the same as disturbances in turn over of copper, are related to a variety of psychological symptoms especially depression [50].

Aspects of zinc and magnesium in depression were described by Szewczyk et al. in 2008 [3]. Their work showed that these minerals exhibited anti-depressant-like activity in a variety of tests and models in laboratory animals, and they enhanced the activity of conventional anti-depressants (e.g., imipramine and citalopram). Zinc demonstrated activity in stress models in rats, while magnesium was active in stress-induced depression-like behavior in mice. The anti-depressant mechanisms of zinc and magnesium

were discussed in the context of glutamate, brain-derived neurotrophic factor and glycogen synthase kinase-3 hypotheses.

They suggested that all the available data indicated the importance of zinc and magnesium homeostasis in the psychopathology and therapy of affective disorders.

#### *Magnesium and human depression*

Findings from our experiences, the neurobiochemistry of magnesium and the observations of efficacy in animal models of depression suggested that magnesium would be generally efficacious in the treatment of human TRD [6]. Over the preceding 100 years there has been progress in determining and understanding the implications of magnesium malnutrition in human depression. Observations have been difficult and reliance on blood and serum-magnesium concentrations appears to have produced misleading results, while CSF  $Mg^{2+}$  levels have produced more consistently reliable measures of low neuronal magnesium. More recently human brain magnesium measurements by phosphorus nuclear magnetic resonance spectroscopy (NMR) have been performed [51,52]. This method may provide a sufficient way to determine Mg-concentrations in specific anatomical areas in the living brain.

#### *Magnesium treatment of depression in history*

The earliest substance (1921) to be reported effective in the treatment of agitated depression was magnesium [12]. Although magnesium was not considered in a 1963 review of electrolytes and depressive illness [53], plasma magnesium and calcium were noted as being altered (either elevated or lowered) in clinical depression as early as 1967 by several researchers, and some suggested that magnesium-deficiency was the cause of major depression [54–62].

#### *Magnesium-deficiency in diseases overview*

Magnesium-deficiency was found to cause numerous neurological and neuromuscular symptoms including hyperexcitability, depression, behavior disturbances, tetany, headaches, generalized tonic-clonic as well as focal seizures, ataxia, anxiety, vertigo, muscular weakness, tremors, irritability, and psychotic behavior, each of which were reversible by magnesium repletion [63–65]. Hypomagnesemia was also seen in patients with various diseases such as cancer, hepatic cirrhosis, cardiovascular, cerebrovascular disease, and generally poor condition. The most common clinical findings of hypomagnesemia were personality changes and major depression showing that differentiation of brain hypomagnesemia from psychiatric disease is important [66]. Deficits of magnesium result due to inadequate intake or malabsorption and due to the renal loss of magnesium that occurs in certain disease states (alcoholism, diabetes) and with drug therapy (antidiuretics, aminoglycosides, fluoroquinolones, cisplatin, digoxin, cyclosporin, amphotericin B) [31].

#### *Magnesium-deficiency in psychiatric disorders*

Magnesium has been consistently described as an important modulator of NMDA-receptor activity in humans. Disturbances of glutamatergic transmission (especially via NMDA-receptor) are known to be involved in pathogenesis of mood disorders [50]. Psychiatric symptoms of magnesium-deficiency were shown to be non-specific, ranging from apathy and depression to psychosis, and were often attributed to other disease processes associated with poor intake, defective absorption, or excretion of magnesium [67]. Marginal magnesium malnutrition were found to occur in patients with anxiety, irritability, depression and psychological

complaints, showing the necessity for further consideration of the possibility that chronic magnesium-deficit may contribute to depression, tetany and weakness [68].

The main mechanisms of the chronopathological forms of magnesium-depletion (differentiated from deficiency) associated with low magnesium intake are various dysregulating biorhythms, such as those with hyperfunction of the biological clock resulting in over production of melatonin (MT) resulting in nervous hypoexcitability: depression; cephalalgias nocturnal without photophobia (i.e. cluster headaches); advanced sleep phase syndrome; asthenia and myalgias (i.e. fibromyalgia, chronic fatigue syndrome) with the main comorbidity found in depressive states; or alternately, with hypofunction of the biological clock (marker: decrease in MT) resulting in various signs of nervous hyperexcitability: anxiety (from generalized anxiety to panic attacks); cephalalgias diurnal with photophobia (mainly migraine); dyssomnia (delayed sleep phase syndrome) particularly, jet lag, night work disorders, age related insomnia, sometimes with inappropriate behavior; photogenic epilepsy, generalized or focal; some clinical forms of chronic fatigue syndrome and fibromyalgia with the main comorbidity being found in migraine and/or epilepsy [69].

Anxiety due to magnesium-deficiency was suggested to be caused by increased production of epinephrine, and that magnesium and taurine were antidotes [70]. Taurine appears to counteract intra-neuronal toxicities through its membrane-stabilizing,  $\text{Ca}^{2+}$ -binding and cGMP level-lowering effects. Taurine through non-specific functions, and perhaps also through a specific action as an “ $\text{Mg}^{2+}$ -sparing agent”, appears to be an important factor in the regulation of  $\text{Mg}^{2+}$  homeostasis [71]. CNS symptoms of magnesium-deficiency were described as consisting of anxiety, hyperemotionality, depression, fatigue, panic, headaches, migraines, insomnia, light-headedness, dizziness, nervous fits, faintness, sensation of lump in the throat and blocked breathing [71].

#### *Magnesium in the diets of depressives*

Examination of the association between magnesium intake and depression and anxiety in 5708 individuals who participated in the Hordaland Health Study in Western Norway showed an inverse association between standardized energy-adjusted magnesium intake and standardized depression scores that was not confounded by age, gender, body build or blood pressure. The association was attenuated after adjustment for socioeconomic and lifestyle variables, but remained statistically significant [7].

#### *Magnesium in the blood of depressives*

Magnesium can be high, normal or low in blood tests of depressives, but may not be representative of brain magnesium. Elevated serum-magnesium normalized with resolution of clinical depression. Both elevated erythrocyte and plasma magnesium and cortisol were associated with the intensity of the depression reflecting the findings that 99% of the body's magnesium is found intracellularly. Highly depressed, drug-free patients had the highest erythrocyte magnesium values, showing that there has been a shift of intracellular magnesium to extracellular compartments [72–74]. Enhanced  $\text{Na}/\text{Mg}$  exchange  $V_{\max}$  appeared to contribute to normalization of red blood cell magnesium content, which correlated with mood improvement [74]. Hypermagnesemia appeared to be associated with psychomotor retardation in depressed patients [74]. Magnesium-deficiency was related to a variety of psychological symptoms, especially depression [50]. Hypomagnesemia was independently associated with depressive symptoms in older people with diabetes [75]. Serum-magnesium was often normal or elevated while erythrocyte and white blood cell magnesium was often low [76].

No significant correlation between total plasma  $\text{Mg}^{2+}$  levels, severity of depression, and anxiety were observed [77]. Significant differences between groups were found for serum  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ . Elevations of serum  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , plasma  $\text{Mg}^{2+}$  but not plasma  $\text{Ca}^{2+}$  were noted in the lithium-treated patients. Depressive symptoms were negatively correlated to plasma Ca in the acute state and positively to Mg in remission and long-standing depression. Differences between plasma and serum in relation to symptoms could reflect a change in a calcium binding factor present in plasma but not in serum, connected with biological factors of affective disease [78]. In 71 in-patients and out-patients with mood disorders and in 30 healthy controls, serum Mg levels were found to be significantly higher in patients with mood disorders than in controls. Serum  $\text{Mg}^{2+}$  levels showed no significant correlation with patient sex, age, diagnosed subtype and disease phase in the mood disorder group. Serum  $\text{Mg}^{2+}$  levels in patients with major depressive disorder who were taking psychotropic drugs were not significantly different from levels seen in patients with major depressive disorders who were not taking psychotropic drugs. These results suggest that the high serum  $\text{Mg}^{2+}$  levels noted in patients with mood disorder are related to the underlying disorder itself and are not influenced by clinical background factors [79]. Some reports showed significant differences (up or down) in  $\text{Mg}^{2+}$  serum levels while others reported no change in eight trials reviewed from 1964–1972 [80]. Patients having TRD with chronic pain were found to be consistently magnesium deficient and taurine was low or absent – among a number of other biochemical abnormalities – in 100% of patients with depression and chronic pain [81]. Erythrocyte magnesium was decreased in patients with severe major depression vs. control subjects, and an increase of erythrocyte magnesium resulted from use of some psychotropic drugs (sertraline, amitriptyline, haloperidol, risperidone, carbamazepine and sodium valproate) [76,82] and an increase of intracellular magnesium may be part of the mechanism of action of anti-depressants [82].

#### *Magnesium in cerebral spinal fluids of depressives*

In affective disorder, cerebral spinal fluid (CSF) magnesium levels varied significantly according to gender (with lower concentrations in women) but not with respect to age, diagnosis, mood state, or treatment with carbamazepine or lithium. Abnormalities of magnesium in affective disorders, if they existed, were not readily detectable in CSF [83]. Patients who had made suicide attempts had significantly lower mean CSF  $\text{Mg}^{2+}$  level irrespective of the diagnosis. Low CSF  $\text{Mg}^{2+}$  correlated significantly with low CSF 5-hydroxyindoleacetic acid (5-HIAA). Both variables seemed to be primarily related to recorded suicide attempts, but decreased  $\text{Mg}^{2+}$  was not limited to violent cases. Cerebrospinal  $\text{Ca}/\text{Mg}$  ratios were also found to be elevated in depressed patients compared with controls. Inadequate  $\text{Mg}^{2+}$  appeared to have reduced serotonin levels suggesting that  $\text{Mg}^{2+}$  repletion might be effective in the treatment of depressive disorders [84–87]. Acute schizophrenics with depression had statistically significant lower levels of CSF  $\text{Mg}^{2+}$  than schizophrenics in remission. Severe depression was also marked by elevated calcium to magnesium ratios in the CSF of patients [88,89]. A significantly higher CSF glutamine/glutamate concentrations associated with the NMDA-receptor systems was found in patients with depression [90]. Erythrocyte and plasma Mg were shown to be associated with the intensity of depression.

#### *Brain magnesium in TRD*

Intracellular magnesium levels were found lower in the brains of TRD patients than in healthy volunteers using phosphorus NMR spectroscopy, a methodology which can be used frequently

in patients without risk [51], while the same method has been used effectively in animal traumatic brain injury research since before 1990 [91]. Assessing the free cytosolic magnesium in the human brain using phosphorus NMR allows study of the involvement of magnesium in different neurological pathologies and particularly in those where defective mitochondrial energy production represents the primary causative factor in the pathogenesis [52].

#### *Gender differences*

Sex differences in mean serum-magnesium levels in depression have been known for some time [60]. Pregnancy and chronic use of birth control pills are known to result in low magnesium, while menopause restores it [92]. Low magnesium resulting from use of birth control pills is hypothesized to cause the significant gender-differences in depression and suicide attempts, especially in the 12% suicide rate of female American psychiatrists. Post partum depression (PPD) may result in populations that have inadequate magnesium in the prenatal diet since the fetus requires very large amounts of magnesium and has priority. PPD appeared preventable with magnesium treatment in a few case reports [6]. A relationship between severity of depressive symptoms and decreased serum zinc (but not serum-magnesium) concentration was found in a very specific type of affective disorder, the postpartum depression [93], reflecting the observations that zinc is primarily an extracellular cation, while magnesium is primarily an intracellular cation. Magnesium was not considered in a complementary and alternative medicine review of perinatal depression [94]. Many prenatal vitamin and mineral supplements do not contain magnesium, or they contain ineffective dosages or biologically non-available magnesium oxide [95–97].

#### *Effect of hypothyroidism on magnesium levels*

In 135 un-medicated patients with mild to moderate primary major depressive disorder a significant correlation between mean serum  $Mg^{2+}$  levels and mean circulating T4 thyroid levels was observed. There was no significant correlation between any of the other thyroid indices and either serum  $Mg^{2+}$  or  $Ca^{2+}$ . The thyroid axis is known to regulate magnesium metabolism possibly by regulation of the transport of  $Mg^{2+}$  from extracellular to intracellular fluid compartments. For T4, and to a lesser extent serum  $Mg^{2+}$ , the most consistent changes were observed with response to anti-depressant treatment [98].

#### *Effect of stress on brain biochemistry*

In major depression there is a selective and persistent loss of hippocampal volume. Overt hippocampal neuron death could cause this loss. The subtypes of depression associated with hippocampal atrophy typically involve significant hypersecretion of glucocorticoids, the adrenal steroids secreted during stress. Steroids have a variety of adverse affects, direct and indirect, in the hippocampus. Thus, excessive glucocorticoids, either natural or iatrogenic, contribute to neuron death. Glucocorticoids cause or exacerbate cellular changes associated with hippocampal neuron loss [99].

#### *Effect of stress on magnesium*

Chronic stress intensifies release of catecholamines (adrenaline, noradrenaline and dopamine) and corticosteroids, driving down intracellular  $Mg^{2+}$  ions. Where magnesium-deficiency existed, stress increased risk of cardiovascular damage and depression. Dietary imbalances such as high intakes of fat and calcium intensified magnesium inadequacy, especially under conditions of stress.

Adrenergic stimulation of lipolysis intensify magnesium-deficiency by complexing it with liberated fatty acids [100]. A high Ca/Mg ratio increased release of catecholamines, which further lowered tissue magnesium levels and also favored excess release or formation of factors that are vasoconstrictive and platelet aggregating. Auto-oxidation of catecholamines yielded free radicals, which explained the enhancement of the protective effect of magnesium by anti-oxidant nutrients against damage caused by catecholamines [100]. Chronic stress decreased both free and total plasma ionized magnesium and simultaneously increased oxidative stress in humans. These findings supported the necessity for magnesium supplementation with anti-oxidant vitamins for patients living in conditions of chronic stress [101]. Accordingly, chronic stress whether physical (i.e. exertion, heat, cold, critical illness, trauma – accidental or surgical, noise, burns), or emotional (i.e. pain, anxiety, excitement or depression) increases need for magnesium [100]. Post-traumatic stress disorder (PTSD) in humans may respond to long-term magnesium treatment, however only animal noise-research so far supports that possibility [42].

#### *Effect of stress on magnesium, IQ, memory and attention*

Depression-inducing severe loss of IQ, memory and attention in children from loss of neuronal  $Mg^{2+}$  occurred while living in conditions of exceptional stress (orphanage living) compared with home living. Stress worsened mental health by  $Mg^{2+}$  depletion, and stress was to be minimized for the most effective treatment with magnesium [102]. Memory loss, IQ loss and attention deficits associated with onset of severe depression appeared completely reversible upon magnesium treatment in a case report [6]. In familial depression with low IQ, poor memory and poor concentration, low brain serotonin was suggested to result from inadequate vitamin B6, magnesium, zinc and manganese needed to convert tryptophan to serotonin, with their deficiencies being common in diets of families of depressives [103]. Test anxiety in students resulted in increased losses of magnesium in the urine [104].

Little is known by medical students and physicians about magnesium and stress, resulting in approximately 50% of students experiencing burnout, depression and 10% experience suicidal ideation during medical school [105].

#### *Effects of magnesium treatment in depressive disorders*

In 220 out of 250 doses of magnesium sulfate (one or two cc of a 25% or 50% solution) given hypodermically to 50 patients having agitated depression in 1921 caused patients to relax and sleep from 4 to 6 h resulting in a 90% success rate for magnesium [12]. The sedative side effects from giving too much magnesium were quickly and easily reversed by giving small amounts of intravenous calcium chloride.

Magnesium was beneficial in the treatment of rapid cycling bipolar disorder in ten patients [106].

In tests of magnesium lactate and vitamin B6 (pyridoxine) in the treatment of 25 patients with anxiety–depression and epilepsy, the combination exerted positive non-specific influences on patient's mental state, especially with regard to affective disorders. The positive effects of magnesium treatment emerged on the 14th day of treatment and achieved a statistically significant level by the 28th day. Treatment was well tolerated and did not cause any side effects [107].

A 69-year-old woman with hypokalemia, which had been treated by oral potassium for more than ten years without benefit, responded immediately to magnesium treatment. The woman had complained of headache, knee joint pain, sleeplessness and paresthesia and, most prominently, major depression. Laboratory data suggested Gitelman's syndrome. Intravenous supplement of

magnesium sulfate (20 mEq/day dissolved in 100 ml normal saline given over 2 h each day for 3 days) immediately terminated both the depression and the paresthesia, suggesting that hypomagnesemia played a role in the clinical manifestations of depression [108]. Oral magnesium oxide treatment was ineffective and promoted diarrhea.

Oral magnesium treatment was described as being effective in treating major depression. Magnesium ion neuronal deficits were described to be inducible by stress hormones, excessive dietary calcium, glutamate and aspartate as well as by dietary deficiencies of magnesium. In homeopathy mental health indications for magnesium treatment included depression, anxiety, intellectual difficulties, delusions, hallucinations, irritability, moodiness, fear and nervousness. Case histories were presented showing rapid recovery (less than 7 days) from major depression using 125–300 mg of magnesium (magnesium glycinate) with each meal and at bedtime, while restricting calcium, glutamates and aspartates. Magnesium-deficiency was suggested as causing most major depression episodes, unexplained and sudden IQ losses, and drug and alcohol addiction; and that restoration of magnesium balance was enormously important to mental health. Fortifying refined grain and drinking water with biologically available magnesium to pre-20th century levels to improve mental health and prevent depression was recommended [6].

Magnesium chloride ( $\text{MgCl}_2$ ) was evaluated in the treatment of newly diagnosed depression in the elderly with type-2 diabetes and hypomagnesemia. Twenty-three elderly patients with type-2 diabetes and hypomagnesemia were enrolled and randomly allocated to receive orally either 50 mL of  $\text{MgCl}_2$  5% solution (equivalent to 450 mg of elemental magnesium) or 50 mg imipramine daily during 12 weeks. Widowhood or divorce in the last six months, alcoholism, degenerative illnesses of the nervous central system, recent diagnosis of diabetes, previous or current treatment with anti-depressants, chronic diarrhea, use of diuretics, and reduced renal function were exclusion criteria. At baseline, there were no differences by age, duration of diabetes, serum-magnesium levels, and depression scores in the groups with  $\text{MgCl}_2$  and imipramine, respectively. At end of the treatment period, the depression scores were identical between the groups in the study; whereas serum-magnesium levels were significantly higher in the group with  $\text{MgCl}_2$  than in the subjects with imipramine,  $p = 0.0005$ . Magnesium chloride was as effective in the treatment of depressed elderly type-2 diabetics with hypomagnesemia as imipramine 50 mg daily [110]. To the best of our knowledge, this is the first randomized clinical trial that presents totally unambiguous evidence concerning the efficacy and safety of magnesium in the treatment of depression.

#### *Adverse effect of calcium in depression*

Decreases in CSF calcium accompanied mood elevation and motor activation in depressed patients. Similarly, decreases in CSF calcium occurred during acute psychotic agitation or mania. Periodic recurrences of such agitated states were accompanied at their onset by transient increases in serum calcium and phosphorus. Several observations suggested that such serum ion shifts triggered the more enduring and opposite shifts in CSF calcium and, in turn, the manic behavior. Progressive restriction of dietary calcium was earlier reported to mitigate and finally abolish both rhythmic rises in serum calcium and periodic agitated episodes. Conversely, a modest oral calcium lactate supplement (approximately one additional recommended daily allowance of dietary calcium) intensified agitation and worsened depression. In patients, manic symptomatology grew significantly and substantially worse during 2–6 weeks of oral vitamin D administration. On the other hand, in 12 patients, subcutaneous injections of synthetic salmon calcitonin

decreased serum calcium and phosphorus, increased cerebrospinal fluid calcium, and augmented depressive symptomatology. Salmon calcitonin, which lowers blood calcium levels, also decreased quantified motor activity, frequency and severity of periodic agitated episodes, serum creatine phosphokinase and prolactin, and nocturnal sleep, while vitamin D or calcium lactate raised them [110]. A dietary supplement of 500 mg calcium immediately and severely worsened depression, which was extinguisable within one hour by orally treating with 400 mg capsules of magnesium as magnesium glycinate [6]. In a study of electrolytes in CSF from depressives, a positive correlation was found between calcium concentration and symptom severity in hospitalized depressed patients. CSF calcium levels tended to decrease as patients improved. In rapidly cycling patients, CSF calcium was higher during depression than during mania [111]. Major depression was found to be accompanied by hyperactivity of subcellular calcium signaling, and any means of reducing pathological neuronal calcium ion flow to reduce resulting pathological nitric oxide neuronal output would have anti-depressant effects [112]. Hypercalcemia from excessive vitamin D intake, hyperparathyroidism or other causes was emphatically stressed to lead to clinical depression by lowering brain magnesium [113].

#### **Discussion**

Our hypothesis that the benefits of magnesium in treating human depression, and especially TRD, would be found to be well known in the medical literature was not well supported. However, we found substantial information that – when taken together – shows a significant rationale for treatment of TRD with magnesium, continued research and more randomized, double-blind, placebo-controlled clinical trials of magnesium for TRD.

#### *Laboratory tests*

Although we found considerable interest in understanding the role of magnesium in brain chemistry and explanation of its role there, we found little consensus as to the value of magnesium measurements in blood (serum, plasma or cellular) as a diagnostic tool useful in treating depression. CSF concentrations of magnesium in depression were also conflicted, although there appeared agreement that CSF  $\text{Mg}^{2+}$  values were low only in severe depression associated with suicide attempts, supporting the notion that magnesium would be useful specifically for TRD, which is often much more severe than treatable depression.

Since 99% of magnesium is intracellular, serum-magnesium testing of the remaining 1% in serum produces misleading results [114]. Although serum values less than 0.9 mmol/Mg demonstrate magnesium-deficiency in non-depressives [115], it is often normal or elevated in depression and serum tests are of negative utility, and blood cell tests may also be of questionable value. Although various tests for brain magnesium-deficiency and calcium excess appear desirable; the response to magnesium treatment and calcium reduction is always the deciding criteria, especially when supported by phosphorus NMR spectroscopy testing.

Brain compartments of magnesium are isolated from blood and bone compartments requiring different analytical means. Measuring brain magnesium – the apparent best predictor of magnesium efficacy in the treatment of TRD – can be safely accomplished in humans using phosphorus NMR spectroscopy [51,52], and these tests need to be validated by repeated trials as a reliable means to determine low brain magnesium in the diagnosis of low brain magnesium as cause of human TRD.

### *Animal studies*

We found evidence that magnesium was useful in treating animal models of depression, which further suggested that magnesium would be useful in TRD. As one writer commented, “All the available data indicate the importance of zinc and magnesium homeostasis in the psychopathology and therapy of affective disorders” [3].

### *Human studies*

We found a number of case reports of medical use of magnesium to treat affective disorders successfully, but only one article specifically relating an experience of testing magnesium in TRD. All reports of treating affective disorders (agitated depression; severe, therapy-resistant manic agitation; rapid cycling bipolar disorder; anxiety–depression and epilepsy; major depression; and depression in the elderly with diabetes) with magnesium were successful, but we have no knowledge of unpublished failures – if any. The report having the most data (220 successes out of 250 efforts) showing value of magnesium in treating agitated depression in hospital practice was written in 1921 by Weston [12], and it is hardly representative of TRD in today’s stress-filled and magnesium-depleted population. The 2008 article by Barragán-Rodríguez et al. [109] was the main article found to show statistical significance in 23 patients in treatment of human depression in diabetics (a known hypomagnesia condition) with magnesium, showing equivalence in effect to the strong, tricyclic anti-depressant, imipramine. Magnesium was both safe and effective and produced substantially fewer side effects than imipramine. Safety in psychiatric medicine has been a long-standing but difficult to achieve goal of psychiatry.

### *Human malnutrition*

Concerning our hypothesis that magnesium malnutrition causes TRD, we found only one clinical research report of evidence to support such hypothesis. Magnesium dietary intake was found to be low in depression and anxiety compared with controls [7] and such appears to be the main source of neuronal magnesium-deficiency required to induce depression and other mental disorders. Due to the difficulty in obtaining valid clinical results, magnesium-deficiency is probably the most under-diagnosed nutrient deficiency in current medical practice. Compared to the other cations, very little emphasis is placed on the importance of magnesium, and its effects are usually forgotten – or never learned – by practicing physicians [116].

### *Contributing factors*

There are many causes of clinical depression that must be considered in the differential diagnosis of depression that are outside this review. It is assumed that a comprehensive differential diagnosis leaves TRD untreated, and it is those cases (approximately 60% of all depression) that we are suggesting to be caused mainly by low brain magnesium. Low ATP and high stress (with each possibly being magnesium-deficiency induced) also contribute to TRD, especially in severe depression, suicidal ideation, and where suicide attempts have occurred. Excitatory calcium, glutamate and aspartate are common food additives found in ever increasing supply, and their excess can create an imbalance worsening depression. Perhaps magnesium-deficiency and excesses of these additives underlie the great majority or all of the neurobiochemical abnormalities found in TRD. A poor sex life can also contribute to depression, and low seminal plasma magnesium is associated with

premature ejaculation [117] due to hyperexcitability of the CNS, the correction of which improves mood.

In addition to other causes of depression, certain coexisting diseases and conditions that suppress brain magnesium need correction to allow proper magnesium homeostasis and recovery from TRD. These include (without prioritization) excessive stress and catecholamines (natural or iatrogenic) [9], heavy metal toxicity, hypercalcemia [9], hyperparathyroidism [118], irritable bowel disease, diarrhea, malabsorption [9], alcoholism [9], hypothyroidism [9], diabetes [9], kidney disease [9], excessive glutamate [119], aspartate and vitamin D intake, and insufficient acid-resistant probiotics. Excessive glutamate as food flavoring also damages the hypothalamic regulation of appetite, and thereby greatly increases voracity and obesity, and in children, it causes short stature [119].

We are also concerned about the elevated suicide rate of physicians and especially psychiatrists [120] and suggest that magnesium supplementation (500–800 mg/day) would prevent physician TRD-induced suicide.

Dietary fibers affect intestinal absorption of magnesium. Inulin, a prebiotic that supports bifidobacteria and lactobacilli, has been confirmed to be important in absorption of magnesium in the large intestines [121,122] nearly doubling magnesium absorption and reducing tendency to diarrhea while taking magnesium. Large doses of psyllium seed husks appeared to reduce greatly absorption [123] and gum arabic significantly increased both the intestinal and renal excretion of magnesium [124].

### *Magnesium bioavailability*

Useful magnesium compounds are those that have a sufficiently low first stability constant to be bioavailable and include: magnesium acetate, chloride, citrate, gluconate, glycinate, lactate, malate, oxalate, succinate, sulfate and tartarate [125].

### *Harmful magnesium compounds*

We have observed that magnesium glutamate and magnesium aspartate severely worsened depression [6], apparently due to neurotoxic ligands. Magnesium compounds that are not biologically available, not soluble and not ionizable are useless in TRD, and they are reported to include magnesium oxide [95–97,108] and magnesium hydroxide. Magnesium taurate, attractive due to the taurine moiety, may be bound chemically too tightly and may not be useful in all patients.

### *Future clinical research*

We are concerned that there were only a few clinical trials of magnesium and depression found, and suggest that future trials be of larger populations in formal, double-blind, placebo-controlled, clinical trials, or comparative trials against a proven anti-depressant such as imipramine 50 mg daily. Only when the evidence has become overwhelming are psychiatrists likely to adopt magnesium for TRD. From the reports reviewed herein, we suggest that in future TRD clinical research, the initial treatment of TRD utilize IV drip magnesium sulfate in the manner of Enya et al. 2004 [108], (20 mEq/day dissolved in 100 ml normal saline given over 2 h each day for 3 days) to provide an expected rapid (<3 days) initial induction of remission followed by oral bioavailable magnesium (125–300 mg 4 t/d) maintenance treatment in the manner of Eby and Eby 2006 [6] or Barragán-Rodríguez 2008 [109] using bioavailable magnesium compounds with emphasis on magnesium glycinate.



## Safety

We are not concerned about the safety of these specific protocols considering that Heiden et al. [126] gave nearly 4.5 g of magnesium daily as an intravenous infusion for up to 23 days in the effective treatment of severe mania. Although some patients developed bradycardia, it was effectively treated by stopping magnesium treatment.

## Impediments to success and precautions

We are concerned that there are many impediments to absorption of magnesium in large therapeutic doses by the oral route, with intestinal issues, especially inflammatory bowel disease [127] and diarrhea being primary concerns. Magnesium without calcium may exponentially increase *Candida albicans* intestinal growth [128], causing or worsening diarrhea and impairing absorption of magnesium, while adding calcium may greatly worsen depression.

One hundred milligram magnesium throat lozenges (100 mM) provide rapid rescue in allergy-induced asthma but greatly worsen common colds (since it can increase rhinovirus release 8–310-fold), worsens *Candida albicans*-induced chronic rhinosinusitis [129] and, hypothetically, might cause severe sequela and fatalities in rhinovirus-induced asthma especially in children [130].

Intestinal support aids to protect from magnesium-induced *Candida albicans*, such as biotin, inulin, acid-resistant probiotics (*Bacillus coagulans*) and antifungals are suggested.

Since oral magnesium can be problematic, we emphasize the importance of investigating non-oral means of increasing brain magnesium in TRD, such as use of IV drips, injections, intracranial, intrathecal, rectal and transdermal administration, especially when kidney or other health issues further complicate the clinical picture. For example, we effectively used topical magnesium chloride (33% aqueous solution) to treat prednisone-induced irritability and depression in a woman with Crohn's disease.

## Testing

Concerning the diagnosis of magnesium-deficiency as the cause of TRD, we suggest that the notion of magnesium treatment being the most reliable indicator of efficacy be modified, with support by phosphorus NMR spectroscopy verification of initial low brain magnesium that it has been restored to normal by treatment. Since brain magnesium has a completely separate compartment from exterior compartments, which have unlimited access to bone and muscle magnesium, whereas the brain does not (personal communication, Robert Vink, University of Adelaide, 2009), we suggest that phosphorus NMR spectroscopy be used in human magnesium and TRD research as has been used by Iosifescu et al. [51] and Iotti and Malucelli in humans [52] and by McIntosh et al. as used in research animals [91]. We suggest that since there is little relationship between brain magnesium and circulatory magnesium, that blood and CSF tests be either avoided, or given little or no significance in diagnoses of low brain magnesium and resulting treatment response.

## Some other comments

Since taurine and glycine, inhibitory neurotransmitters, are also found to be low in TRD especially when accompanied by chronic pain [81] and anxiety [6] and because they are each important in regulating magnesium homeostasis [70], they are also suggested to be supplemented in doses up to 20 g (in split doses) per day. Since zinc performs a role similar to magnesium, supplements of

zinc (30–60 mg/day) may also be helpful. Rebalancing sodium and potassium and adding GABA may also be helpful.

Magnesium intake in depression is starting to receive attention [131] and much more work is needed in all aspects of magnesium and TRD. Changes in serum Mg level and serum Ca/Mg ratio may be involved in the mechanism for the progression of depressive mood or stress perception in women [132].

## Conclusions

Due to its safety and efficacy, physicians should prescribe magnesium for TRD without further delay, even though much more clinical research is needed to confirm and extend this important line of research.

## Brain magnesium

Neurons require adequate magnesium to prevent excessive intra-neuronal excitation by calcium, which if unchecked can result in depression and anxiety-like behavior. Since magnesium is required for many brain enzymes, there is no doubt that it is vital for proper mental health. Reduction in incidence of TRD should result by increasing magnesium in the diet, reducing stress, reducing excessive dietary calcium, glutamates and aspartates, and terminating iatrogenic and natural causes of low magnesium. Benefits of IV magnesium treatment of TRD have been found to be extremely rapid and unequivocally strong and are suggested for treatment initiation. Magnesium oral maintenance treatment is expected to treat TRD effectively, to prevent reoccurrence of TRD, and to increase happiness, particularly when calcium, glutamate and aspartate are restricted.

We conclude that excessive  $\text{Ca}^{2+}$  and glutamate and prolonged insufficient  $\text{Mg}^{2+}$ , particularly in the hippocampus, play a vital role in brain cell synaptic dysfunction leading to increased nitric oxide production, which appears to humans as depression and anxiety, hyperexcitability, convulsions, memory loss, and various other symptoms ranging from apathy to psychosis.

Without sufficient  $\text{Mg}^{2+}$  neurons operate without adequate control, moving excessive  $\text{Ca}^{2+}$  through the synapses causing harm to neurons, which has the potential for severe disruptions in thinking, mood, memory and behavior.

## Student stress management

The stress and test-anxiety depletion of magnesium findings (resulting in lowered IQ, attention and memory) in students and the elevated burnout rate, depression and suicidal ideation of students, especially medical students, appear to have immediate implications to the education of students in increasingly stress- and anxiety-filled classrooms, as they are counterproductive to learning without restoration and maintenance of brain magnesium (and taurine) balance. Students should be advised to increase their magnesium intake to prevent stress-induced mental illnesses such as depression.

## Serotonin question

Since inadequate brain magnesium appears to reduce serotonin levels, and since anti-depressants have been shown to have the action of raising brain magnesium, we further hypothesize that magnesium treatment will be found beneficial for nearly all depressives, not only TRD. Severe depression and especially TRD have many attributes of magnesium-deficiency or depletion, and the brain is more subject to magnesium-depletion than other

tissues. Magnesium intake should be increased to support serotonin to prevent other types of depression.

### Brain magnesium testing

Diagnosis of low brain magnesium is likely to be best and most accurately performed using phosphorus NMR spectroscopy since brain pools of magnesium are not believed related to exterior, circulatory magnesium. Blood and CSF tests may be misleading and should not be relied upon for proper diagnosis of low brain magnesium. Lack of accurate brain magnesium diagnostic equipment has most likely been the cause of failure to previously accept that inadequate brain magnesium causes mental illnesses. Phosphorus NMR spectroscopy should be used to test for low brain magnesium as cause of mental illnesses.

### Our hypothesis

With respect for our hypothesis of expectation to find great utility of magnesium in treating depression in the literature, had there been stronger clinical support, such would be greatly preferred. Lack of numerous, definitive, large-scale, double-blind, placebo-controlled clinical trials is the main limiting factor in making strong, unequivocal magnesium for TRD treatment recommendations. Countering that point of view is the superior safety of magnesium compared to side-effect prone anti-depressant and anti-anxiety medications, some of which promote suicide, commonly in use. From the evidence reviewed here, the relationship between inadequate dietary magnesium and TRD appears to have immense public health and treatment implications.

### Conflicts of interest statement

None declared.

### Acknowledgements

We thank the George and Patsy Eby Foundation for financial support.

### References

- [1] World Health Report. Changing history annex table 3: burden of disease in DALYs by cause, sex and mortality stratum in WHO regions estimates for 2002. Geneva: The World Health Organization; 2004.
- [2] Meyer JS, Quenzer LF. Psychopharmacology: drugs the brain and behavior. Sunderland, MA: Sinauer Associates Inc.; 2005. p. 163–82, 386.
- [3] Szweczyk B, Poleszak E, Sowa-Kucma M, et al. Antidepressant activity of zinc and magnesium in view of the current hypotheses of antidepressant action. *Pharmacol Rep* 2008;60:588–9.
- [4] Fekadu A, Wooderson SC, Markopoulou K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J Affect Disord* 2009;116(1–2):4–11.
- [5] Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain part 1: micronutrients. *J Nutr Health Aging* 2006;10:377–85.
- [6] Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. *Med Hypotheses* 2006;67:362–70.
- [7] Jacka FN, Overland S, Stewart R, Tell GS, Bjelland I, Mykletun A. Association between magnesium intake and depression and anxiety in community-dwelling adults: the Hordaland Health Study. *Aust N Z J Psychiatry* 2009;43:45–52.
- [8] Heart gains from whole grains. *Harv Heart Lett* 2002;13:2–4.
- [9] Seelig MS, Rosanoff A. The magnesium factor. New York, NY: Avery Publishing Group; 2003. p. 5.
- [10] Blaylock RL. Food additive excitotoxins and degenerative brain disorders. *Med Sentinel* 1999;4:212–5.
- [11] Walton RG, Hudak R, Green-Waite RJ. Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. *Biol Psychiatry* 1993;34:13–7.
- [12] Weston PG. Magnesium as a sedative. *Am J Psychiatry* 1921–22;1:637–8.
- [13] Connolly E, Worthley LI. Intravenous magnesium. *Crit Care Resusc* 1999;1:162–72.
- [14] Bear MF, Connors BW, Paradiso MA. Neurotransmitter systems. In: Neuroscience exploring the brain. Baltimore, MD: Lippincott Williams and Wilkins; 2001. p. 131–62.
- [15] Yasui M, Ota K, Murphy VA. Magnesium-related neurological disorders. In: Yasui M, Strong MJ, Ota K, Verity MA, editors. Mineral and metal neurotoxicology. Boca Raton, FL: CRC Press LLC; 1997. p. 219–26 [chapter 22].
- [16] Langley WF, Mann D. Central nervous system magnesium deficiency. *Arch Intern Med* 1991;151:593–6.
- [17] Langley WF, Mann D. Skeletal buffer function and symptomatic magnesium deficiency. *Med Hypotheses* 1991;34:62–5.
- [18] Macgregor RJ. Quantum mechanics and brain uncertainty. *J Integr Neurosci* 2006;5:373–80.
- [19] Sapolsky RM. Stress the aging brain and the mechanisms of neuron death. Cambridge, MA: A Bradford Book, The MIT Press; 1992. p. 192.
- [20] Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J* 1984;108:188–93.
- [21] Mark LP, Prost RW, Ulmer JL, et al. Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. *AJNR Am J Neuroradiol* 2001;22:1813–24.
- [22] Kandel ER, Schwartz JH, Jessell TM. Synaptic integration. In: Essentials of neural science and behavior. Stamford, CT: Appleton and Lange; 1995. p. 219–41.
- [23] McMenimen KA, Dougherty DA, Lester HA, Petersson EJ. Probing the Mg<sup>2+</sup> blockade site of an N-methyl-D-aspartate (NMDA) receptor with unnatural amino acid mutagenesis. *ACS Chem Biol* 2006;1:227–34.
- [24] Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular biology of the cell. 4th ed. New York, NY: Garland Science; 2002. p. 615–58.
- [25] Decollogne S, Tomas A, Lecerc F, Adamowicz E, Seman M. NMDA receptor complex blockade by oral administration of magnesium: comparison with MK-801. *Pharmacol Biochem Behav* 1997;58:261–8.
- [26] Carafoli E. Calcium – a universal carrier of biological signals. *FEBS J* 2005;272:1073–89.
- [27] Gillissen T, Budd SL, Lipton SA. Excitatory amino acid neurotoxicity. In: Alzheimer C, editor. Molecular and cellular biology of neuroprotection in the CNS series: advances in experimental medicine and biology, vol. 513. New York, NY: Kluwer Academic/Plenum Publishers, Georgetown, TX: Landes Bioscience; 2002. p. 3–40.
- [28] Hollmann MW, Liu HT, Hoeneemann CW, Liu WH, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium part II: interactions with volatile anesthetics. *Anesth Analg* 2001;92:1182–91.
- [29] Durlach J, Bac P. Mechanisms of action on the nervous system in magnesium deficiency and dementia. In: Yasui M, Strong MJ, Ota K, Verity MA, editors. Mineral and metal neurotoxicology. Boca Raton, New York: CRC Press; 1997. p. 201–9.
- [30] Krnjevic K, Lamour Y, MacDonald JF, Nistri A, Pail E, Werman R. Intracellular divalent cations and neuronal excitability. *Can J Physiol Pharmacol* 1979;57:957–72.
- [31] Morris ME. Brain and CSF magnesium concentrations during magnesium deficit in animals and humans: neurological symptoms. *Magnes Res* 1992;5:303–13.
- [32] Murck H. Magnesium and affective disorders. *Nutr Neurosci* 2002;5:375–89.
- [33] Held K, Antonijevic IA, Künzel H, et al. Oral Mg<sup>(2+)</sup> supplementation reverses age-related neuroendocrine and sleep EEG changes in humans. *Pharmacopsychiatry* 2002;35:135–43.
- [34] Murck H, Steiger A. Mg<sup>2+</sup> reduces ACTH secretion and enhances spindle power without changing delta power during sleep in men – possible therapeutic implications. *Psychopharmacology (Berl)* 1998;137:247–52.
- [35] Kantak KM. Magnesium deficiency alters aggressive behavior and catecholamine function. *Behav Neurosci* 1988;102:304–11.
- [36] Cardoso CC, Lobato KR, Binfaré RW, et al. Evidence for the involvement of the monoaminergic system in the antidepressant-like effect of magnesium. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:235–42.
- [37] Olney JW, Ho OL. Brain damage in infant mice following oral intake of glutamate aspartate or cysteine. *Nature* 1970;227:609–11.
- [38] Olney JW, Ho OL, Rhee V, DeGubareff T. Letter: neurotoxic effects of glutamate. *N Engl J Med* 1973;289:1374–5.
- [39] Olney JW, Ho OL, Rhee V. Brain-damaging potential of protein hydrolysates. *N Engl J Med* 1973;289:391–5.
- [40] Olney JW, Rhee V, Ho OL. Kainic acid: a powerful neurotoxic analogue of glutamate. *Brain Res* 1974;77:507–12.
- [41] Stein DG, Glasier MM. An overview of developments in research on recovery from brain injury. In: Rose FD, Johnson DA, editors. Recovery from brain damage reflections and directions. New York, NY: Plenum Press; 1992. p. 1–22.
- [42] Fromm L, Heath DL, Vink R, Nimmo AJ. Magnesium attenuates post-traumatic depression/anxiety following diffuse traumatic brain injury in rats. *J Am Coll Nutr* 2004;23:529S–33S.
- [43] Singewald N, Sinner C, Hetzenauer A, Sartori SB, Murck H. Magnesium-deficient diet alters depression- and anxiety-related behavior in mice – influence of desipramine and *Hypericum perforatum* extract. *Neuropharmacology* 2004;47:1189–97.
- [44] Spasov AA, Iezhitsa IN, Kharitonova MV, Kravchenko MS. Depression-like and anxiety-related behaviour of rats fed with magnesium-deficient diet. *Zh Vyssh Nerv Deiat Im I P Pavlova* 2008;58:476–85 [Article in Russian].

- [45] Poleszak E, Szewczyk B, Kedzierska E, Wlaz P, Pil A, Nowak G. Antidepressant and anxiolytic-like activity of magnesium in mice. *Pharmacol Biochem Behav* 2004;78:7–12.
- [46] Poleszak E, Wlaz P, Kedzierska E, et al. Effects of acute and chronic treatment with magnesium in the forced swim test in rats. *Pharmacol Rep* 2005;57:654–8.
- [47] Poleszak E, Wlaz P, Kedzierska E, et al. Immobility stress induces depression-like behavior in the forced swim test in mice. Effect of magnesium and imipramine. *Pharmacol Rep* 2006;58:746–52.
- [48] Poleszak E, Wlaz P, Kedzierska E, et al. NMDA/glutamate mechanism of antidepressant-like action of magnesium in forced swim test in mice. *Pharmacol Biochem Behav* 2007;88:158–64.
- [49] Ault B, Evans RH, Francis AA, Oakes DJ, Watkins JC. Selective depression of excitatory amino acid induced depolarizations by magnesium ions in isolated spinal cord preparations. *J Physiol* 1980;307:413–28.
- [50] Siwek M, Wrobel A, Dudek D, Nowak G, Zieba A. The role of copper and magnesium in the pathogenesis and treatment of affective disorders. *Psychiatr Pol* 2005;39:911–20.
- [51] Iosifescu DV, Bolo NR, Nierenberg AA, Jensen JE, Fava M, Renshaw PF. Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biol Psychiatry* 2008;63:1127–34.
- [52] Iotti S, Malucelli E. In vivo assessment of  $Mg^{2+}$  in human brain and skeletal muscle by  $^{31}P$ -MRS. *Magnes Res* 2008;21:157–62.
- [53] Gibbons JL. Electrolytes and depressive illness. *Postgrad Med J* 1963;39:19–25.
- [54] Boursier B. Nervous depression due to magnesium deficiency, crenotherapy by sulfur, calcium and magnesium water. *Presse Therm Clim* 1967;104:174–8.
- [55] Coppen A. The biochemistry of affective disorders. *Br J Psychiatry* 1967;113:1237–64.
- [56] Coppen A. Electrolytes and mental illness – review. *Proc Annu Meet Am Psychopathol Assoc* 1969;58:397–409.
- [57] Fischbach R. Changes in calcium and magnesium metabolism in depression and delirium tremens. *Wien Med Wochenschr* 1971;121:292–4.
- [58] Frazer A, Ramsey TA, Swann A, Bowden C, Brunswick D, Garver D, et al. Plasma and erythrocyte electrolytes in affective disorders. *J Affect Disord* 1983;5:103–13.
- [59] Frizel D, Coppen A, Marks V. Plasma magnesium and calcium in depression. *Br J Psychiatry* 1969;115:1375–7.
- [60] Herzberg L, Bold AM. Sex difference in mean serum-magnesium levels in depression. *Lancet* 1972;1(7760):1128–9.
- [61] Herzberg L, Herzberg B. Mood change and magnesium. A possible interaction between magnesium and lithium? *J Nerv Ment Dis* 1977;165:423–6.
- [62] Pavlinac D, Langer R, Lenhard L, Deftos L. Magnesium in affective disorders. *Biol Psychiatry* 1979;14:657–61.
- [63] Wacker WEC, Parisi AF. Magnesium metabolism. *N Engl J Med* 1968;278:772–6 [Review].
- [64] Wacker WEC, Parisi AF. Magnesium metabolism. *N Engl J Med* 1968;278:712–7 [Review].
- [65] Wacker WEC, Parisi AF. Magnesium metabolism. *N Engl J Med* 1968;278:658–63 [Review].
- [66] Hashizume N, Mori M. An analysis of hypermagnesemia and hypomagnesemia. *Jpn J Med* 1990;29:368–72.
- [67] Rasmussen HH, Mortensen PB, Jensen IW. Depression and magnesium deficiency. *Int J Psychiatry Med* 1989;19:57–63.
- [68] Seelig MS, Berger AR, Spielholz N. Latent tetany and anxiety marginal magnesium deficit and normocalcemia. *Dis Nerv Syst* 1975;36:461–5.
- [69] Durlach J, Pagès N, Bac P, Bara M, Guiet-Bara A, Agrapart C. Chronopathological forms of magnesium depletion with hypofunction or with hyperfunction of the biological clock. *Magnes Res* 2002;15:263–8.
- [70] Durlach J, Durlach V. Speculations on hormonal controls of magnesium homeostasis: a hypothesis. *Magnesium* 1984;3:109–31.
- [71] Durlach J, Durlach V, Bara M, Guiet-Bara A. Diverse applications of magnesium therapy. In: Berthou G, editor. *Handbook of metal-ligand interactions in biologic fluids – bioinorganic medicine*. New York, NY: Marcel Dekker; 1995.
- [72] Widmer J, Bovier P, Karege F, et al. Evolution of blood magnesium sodium and potassium in depressed patients followed for three months. *Neuropsychobiology* 1992;26:173–9.
- [73] Widmer J, Stella N, Raffin Y, et al. Blood magnesium potassium sodium calcium and cortisol in drug-free depressed patients. *Magnes Res* 1993;6:33–41.
- [74] Widmer J, Henrotte JG, Raffin Y, Bovier P, Hilleret H, Gaillard JM. Relationship between erythrocyte magnesium plasma electrolytes and cortisol and intensity of symptoms in major depressed patients. *J Affect Disord* 1995;34:201–9.
- [75] Barragan-Rodríguez L, Rodríguez-Morán M, Guerrero-Romero F. Depressive symptoms and hypomagnesemia in older diabetic subjects. *Arch Med Res* 2007;38:752–6.
- [76] Nechifor M. Interactions between magnesium and psychotropic drugs. *Magnes Res* 2008;21:97–100.
- [77] Barra A, Camardese G, Tonioni F, et al. Plasma magnesium level and psychomotor retardation in major depressed patients. *Magnes Res* 2007;20:245–9.
- [78] Linder J, Brismar K, Beck-Friis J, Saaf J, Wetterberg L. Calcium and magnesium concentrations in affective disorder: difference between plasma and serum in relation to symptoms. *Acta Psychiatr Scand* 1989;80:527–37.
- [79] Imada Y, Yoshioka S, Ueda T, Katayama S, Kuno Y, Kawahara R. Relationships between serum magnesium levels and clinical background factors in patients with mood disorders. *Psychiatry Clin Neurosci* 2002;56:509–14.
- [80] Cundall RL, Moir AT, Martin MJ. Plasma and erythrocyte magnesium levels in affective disorders. *Lancet* 1972;2(7771):281.
- [81] Shealy CN. The neurochemistry of depression. *Am J Pain Manag* 1992;2:13–6.
- [82] Nechifor M. Magnesium in major depression. *Magnes Res* 2009;22:163S–6S.
- [83] George MS, Rosenstein D, Rubinow DR, Kling MA, Post RM. CSF magnesium in affective disorder: lack of correlation with clinical course of treatment. *Psychiatry Res* 1994;51:139–46.
- [84] Banki CM, Vojnik M, Papp Z, Balla KZ, Arato M. Cerebrospinal fluid magnesium and calcium related to amine metabolites, diagnosis, and suicide attempts. *Biol Psychiatry* 1985;20:163–71.
- [85] Banki CM, Arato M, Kilts CD. Aminergic studies and cerebrospinal fluid cations in suicide. *Ann N Y Acad Sci* 1986;487:221–30.
- [86] Hakim AH, Bomb BS, Pandey SK, Singh SV. A study of cerebrospinal fluid calcium and magnesium in depression. *J Assoc Physicians India* 1975;23:311–5.
- [87] Pliszka SR, Rogness GA. Calcium and magnesium in children with schizophrenia and major depression. *Biol Psychiatry* 1984;19:871–6.
- [88] Levine J, Rapoport A, Mashiah M, Dolev E. Serum and cerebrospinal levels of calcium and magnesium in acute versus remitted schizophrenic patients. *Neuropsychobiology* 1996;33:169–72.
- [89] Levine J, Stein D, Rapoport A, Kurtzman L. High serum and cerebrospinal fluid Ca/Mg ratio in recently hospitalized acutely depressed patients. *Neuropsychobiology* 1999;39:63–70.
- [90] Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. Increased cerebrospinal fluid glutamine levels in depressed patients. *Biol Psychiatry* 2000;47:586–93.
- [91] Heath DL, Vink R. Neuroprotective effects of  $MgSO_4$  and  $MgCl_2$  in closed head injury: a comparative phosphorus NMR study. *J Neurotrauma* 1998;15:183–9.
- [92] Stanton MF, Lowenstein FW. Serum magnesium in women during pregnancy while taking contraceptives and after menopause. *J Am Coll Nutr* 1987;6:313–9.
- [93] Wójcik J, Dudek D, Schlegel-Zawadzka M, et al. Antepartum/postpartum depressive symptoms and serum zinc and magnesium levels. *Pharmacol Rep* 2006;58:571–6.
- [94] Freeman MP. Complementary and alternative medicine for perinatal depression. *J Affect Disord* 2009;112:1–10.
- [95] Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. *Magnes Res* 2001;14:257–62.
- [96] Lindberg JS, Zobitz MM, Poindexter JR, Pak CY. Magnesium bioavailability from magnesium citrate and magnesium oxide. *J Am Coll Nutr* 1990;9:48–55.
- [97] Walker AF, Marakis G, Christie S, Byng M. Mg citrate found more bioavailable than other Mg preparations in a randomised double-blind study. *Magnes Res* 2003;16:183–91.
- [98] Joffe RT, Levitt AJ, Young LT. The thyroid, magnesium and calcium in major depression. *Biol Psychiatry* 1996;40:428–9.
- [99] Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disord* 2002;4:117–28.
- [100] Seelig MS. Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review). *J Am Coll Nutr* 1994;13:429–46.
- [101] Cernak I, Savić V, Kotur J, et al. Alterations in magnesium and oxidative status during chronic emotional stress. *Magnes Res* 2000;13:29–36.
- [102] Papadopoulou V, Tuchendria E, Palamaru I. Magnesium and some psychological features in two groups of pupils (magnesium and psychic features). *Magnes Res* 2001;14:27–32.
- [103] Reading CM. Family tree connection: how your past can shape your future health a lesson in orthomolecular medicine. *J Orthomol Med* 1988;3:123–34.
- [104] Grases G, Pérez-Castelló JA, Sanchis P, et al. Anxiety and stress among science students. Study of calcium and magnesium alterations. *Magnes Res* 2006;19:102–6.
- [105] Dyrbye LN, Thomas MR, Massie FS, et al. Burnout and suicidal ideation among US medical students. *Ann Intern Med* 2008;149:334–41.
- [106] Chouinard G, Beauclair L, Geiser R, Etienne P. A pilot study of magnesium aspartate hydrochloride (Magnesiocard) as a mood stabilizer for rapid cycling bipolar affective disorder patients. *Prog Neuropsychopharmacol Biol Psychiatry* 1990;14:171–80.
- [107] Kalinin VV, Zheleznova EV, Rogacheva TA, et al. A use of magnesium and vitamin B6 in the treatment of anxiety-depressive states in patients with epilepsy. *Zh Nevrol Psikhiatr Im S S Korsakova* 2004;104:51–5.
- [108] Enya M, Kanoh Y, Mune T, et al. Depressive state and paresthesia dramatically improved by intravenous  $MgSO_4$  in Gitelman's syndrome. *Intern Med* 2004;43:410–4.
- [109] Barragan-Rodríguez L, Rodríguez-Morán M, Guerrero-Romero F. 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* 2008;21:218–23.
- [110] Carman JS, Wyatt RJ. Calcium: bivalent cations in the bivalent psychoses. *Biol Psychiatry* 1979;14:295–336.
- [111] Jimerson DC, Post RM, Carman JS, et al. CSF calcium: clinical correlates in affective illness and schizophrenia. *Biol Psychiatry* 1979;14:37–51.
- [112] Paul IA. Antidepressant activity and calcium signaling cascades. *Hum Psychopharmacol* 2001;16:71–80.

- [113] Keddie KM. Severe depressive illness in the context of hypervitaminosis D. *Br J Psychiatry* 1987;150:394–6.
- [114] Mann J, Truswell AS. *Essentials of human nutrition*. 2nd ed. New York, NY: Oxford University Press; 2002. p. 141.
- [115] Liebscher DH, Liebscher DE. About the misdiagnosis of magnesium deficiency. *J Am Coll Nutr* 2004;23:730S–1S.
- [116] Gambling DR, Birmingham CL, Jenkins LC. Magnesium and the anesthetist. *Can J Anaesth* 1988;35:644–54.
- [117] Aloosh M, Hassani M, Nikoobakht M. Seminal plasma magnesium and premature ejaculation: a case–control study. *BJU Int* 2006;98:402–4.
- [118] Gatewood JW, Organ Jr CH, Mead BT. Mental changes associated with hyperparathyroidism. *Am J Psychiatry* 1975;132:129–32.
- [119] Hermanussen M, García AP, Sunder M, Voigt M, Salazar V, Tresguerres JA. Obesity, voracity, and short stature: the impact of glutamate on the regulation of appetite. *Eur J Clin Nutr* 2006;60:25–31.
- [120] Schernhammer E. Taking their own lives – the high rate of physician suicide. *N Engl J Med* 2005;352:2473–6.
- [121] Scholz-Ahrens KE, Schrenzenmeir J. Inulin and oligofructose and mineral metabolism: the evidence from animal trials. *J Nutr* 2007;137(Suppl. 11):2513S–23S.
- [122] Rondón LJ, Rayssiguier Y, Mazur A. Dietary inulin in mice stimulates Mg<sup>2+</sup> absorption and modulates TRPM6 and TRPM7 expression in large intestine and kidney. *Magnes Res* 2008;21:224–31.
- [123] Asvarujanon P, Ishizuka S, Hara H. Inhibitory effects of psyllium on rat mineral absorption were abolished by reduction of viscosity with partial hydrolysis. *Biosci Biotechnol Biochem* 2004;68:1737–42.
- [124] Nasir O, Artunc F, Saeed A, et al. Effects of gum arabic (*Acacia senegal*) on water and electrolyte balance in healthy mice. *J Ren Nutr* 2008;18:230–8.
- [125] Furia TE. Sequestrants in foods. In: Furia TA, editor. *Handbook of food additives*. Cleveland, OH: The Chemical Rubber Co.; 1968. p. 289–312 [chapter 7].
- [126] Heiden A, Frey R, Presslich O, Blasbichler T, Smetana R, Kasper S. Treatment of severe mania with intravenous magnesium sulphate as a supplementary therapy. *Psychiatry Res* 1999;89:239–46.
- [127] Galland L. Magnesium and inflammatory bowel disease. *Magnesium* 1988;7:78–83.
- [128] Holmes AR, Cannon RD, Shepherd MG. Effect of calcium ion uptake on *Candida albicans* morphology. *FEMS Microbiol Lett* 1991;61:187–93.
- [129] Eby GA. Rescue treatment and prevention of asthma using magnesium throat lozenges: hypothesis for a mouth–lung biologically closed electric circuit. *Med Hypotheses* 2006;67:1136–41.
- [130] Eby GA. Hypothesis for risk of death or serious sequela from pediatric asthmatic use of magnesium throat lozenges due to 8 to 310-fold rhinovirus release increase by concentrated magnesium. *Med Hypotheses* 2009;74:206–7.
- [131] Wilson K, Brakoulias V. Magnesium intake and depression. *Aust N Z J Psychiatry* 2009;43:580.
- [132] Jung KI, Ock SM, Chung JH, Song CH. Serum Mg level and serum Ca/Mg ratio may be involved in the mechanism for the progression of depressive mood or stress perception in relatively healthy, adult women. *Biol Trace Elem Res* 2009; June 19.