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TITLE: **THE EFFECTS OF MAGNESIUM SUPPLEMENTATION ON SUBJECTIVE ANXIETY**

RUNNING HEAD: **Magnesium and Anxiety**

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Abstract

Experimental studies of anxiety in animal models, and evidence of efficacious outcomes of magnesium (Mg) supplementation in the treatment of acute clinical affective disorders, has increased interest in Mg as a potential novel treatment for symptoms of mild/moderate subjective anxiety. This short review examines the existing evidence for the effects of Mg supplementation on subjective anxiety in humans. Additionally, evidence from three unpublished studies that examined Mg and vitamin B_6 intake on subjective anxiety is summarised to supplement the existing literature. Conclusions: The efficacy of Mg in the treatment of anxiety in the mildly anxious and those reporting premenstrual syndrome-related anxiety is suggestive of a beneficial effect of Mg intake. Further randomised controlled trials are warranted to further establish the efficacy of Mg as a novel treatment for subjective anxiety.

Introduction

Dietary intake of Mg is insufficient in Western populations [1-3] and a Mg-poor diet is associated with poor health outcomes including hypertension, cardiovascular diseases and type II diabetes [4]. Magnesium may also play an important part in the etiology of affective mood disorders. Mood stabilizing effects of Mg supplementation have been demonstrated in clinical samples, including the improvement of clinical signs of mania [5], rapid cycling bipolar disorder [6], affective symptoms of chronic fatigue syndrome [7].

A relationship between Mg and depression has been demonstrated [8]. Hypomagnesemia increases depression behaviour in rodents, which is reversed by

antidepressant pharmaceuticals [9]. Diets low in Mg are associated with depression in humans [10] and Mg supplementation may provide an effective adjunctive therapy for treating major depression [11].

Depression is often comorbid with anxiety [12]. Anxiety related conditions are the most common affective disorders present in the general population with a lifetime prevalence of over 15% [13]. Hypomagnesemia elevates anxiety states in mouse models [9, 14-16]. Supplementing Mg levels in mice reduces the expression of anxiety-related behaviour [17, 18]. In humans, a modest relationship has been demonstrated between dietary Mg intake and anxiety symptomology [10].

Evidence of the association between Mg and anxiety has increased interest in the potential efficacy of Mg intake as a potential novel treatment to attenuate anxiety symptoms. This review summarises the existing evidence for the efficacy of Mg in the treatment of anxiety. Additionally, three unpublished studies that assessed the effects of Mg combined with vitamin B_6 on subjective anxiety are summarised to further supplement the existing literature.

Published evidence for the efficacy of Mg supplementation

The efficacy of Mg supplementation in the treatment of anxiety symptomology has been assessed in samples reporting pre-existing anxiety ‘vulnerabilities’; primarily individuals reporting existing symptoms of anxiety and women with premenstrual syndrome (PMS) complaints.

Hanus et al. [19] recruited individuals reporting mild anxiety (Hamilton Anxiety Scale; HAM-A [20]) or symptoms of general anxiety disorder (GAD; DSM-R-II). A 12 weeks intake of 75 mg Mg combined with Hawthorn (75 mg) and California poppy (20 mg) extracts significantly reduced subjective ratings on three subjective anxiety measures (HAM-A, visual analogue scales and physician global impression) vs. a placebo. A significant improvement in anxiety ratings was evident in the placebo condition. However, the reduction of anxiety symptoms was significantly greater in the Mg treatment group.

Two studies compared the effects of a 6 week intake of Mg lactate (300 mg) + vitamin B_6 (750 mg) to a pharmaceutical anxiolytic demonstrated to be effective in the treatment of anxiety (Lorazepam [3 mg]) in mildly anxious (HAM-A) samples [21, 22]. Whilst significant reductions in anxiety ratings were demonstrated in all conditions, there were no significant differences between the treatments. Comparable efficacy with pharmaceutical anxiolytics may be considered supportive of a positive effect of Mg on subjective anxiety. However, the lack of placebo control in these studies limits interpretation of the reported effects.

Anxiety forms one of the primary symptoms of PMS [23]. A number of studies have examined the efficacy of Mg intake as a novel treatment to reduce PMS symptomology. For example, De Souza et al. [24] reported a significant reduction of anxiety-related PMS symptoms (nervous tension, mood swings, irritability, and anxiety) vs. baseline and placebo after 200 mg Mg oxide + vitamin B_6. Fathizadeh et al. [25] demonstrated positive effects of Mg (250 mg) + vitamin B_6 (40 mg) on

subjective PMS symptomology. Significant reductions in symptoms were evident in all treatments ([i] Mg; [ii] Mg + vitamin B_6 [iii] placebo). However, the combination of Mg + vitamin B_6 resulted in the greatest improvement ($p < .05$). A significant reduction in total PMS symptom score (including nervous tension and anxiety subscales; Moos MDQ [26]), and score on an anxiety subscale of a PMS symptom diary has also been demonstrated after intake of 250 mg of Mg [27]. However, these effects were relative to screening visit and baseline scores. This study failed to administer any form of control or placebo.

Evidence of the efficacy of Mg intake on anxiety-related PMS symptoms is inconsistent. For example, Walker et al. [28] found no effects of 2 months administration of 200 mg Mg oxide. A further study by this group reported that a placebo (1305 mg sorbitol) significantly reduced anxiety-related PMS symptoms compared to multiple doses of Mg [29]. The available evidence from studies assessing the efficacy of Mg intake on anxiety-related PMS symptoms therefore suggest the effects of Mg combined with vitamin B_6 may be more consistent than Mg administered alone.

Unpublished evidence for the efficacy of Mg supplementation

Table 1 summarises three clinical trials that examined the efficacy of Mg + vitamin B_6 supplementation on subjective anxiety symptomology in mildly anxious samples. The studies are unpublished in their full form. A conference abstract summary of the Rouillon et al. (1993) trial was published in 1995 [30]. Two studies by Caillard (1992; 1995) have not been published in any form. Full data from these studies were kindly

provided by Sanofi, France. The reviewed studies summarise the effects of Mg + vitamin B_6 supplementation on a total of 295 mixed sex adults reporting mild/moderate subjective anxiety. The samples were comparable in age (average age across 3 RCTs $\bar{x}$= 38.57 years) and administered the same Mg + vitamin B_6 dose (Mg lactate 192 mg + 20 mg vitamin B_6) for 6 weeks. All studies employed the HAM-A to recruit anxiety vulnerable samples and as a primary outcome variable. However, the methods of characterising the samples were not equivalent across studies. Caillard (1992, unpublished) and Rouillon et al. (1993) employed different variants of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for GAD (DSM-III and DSM-IIIR respectively). Caillard (1995, unpublished) screened and assessed subjective somatic anxiety symptoms. Two studies employed a placebo condition (Caillard, 1992; 1995, unpublished). Rouillon et al. (1993) administered a pharmaceutical positive verum (Buspirone).

<INSERT TABLE 1 HERE>

Caillard (1992, unpublished) demonstrated a significant reduction in total HAM-A score (primary outcome; $p < .03$) and the HAM-A Physic anxiety subscale ($p < .03$) following 192 mg of Mg lactate + 20 mg vitamin B_6 vs. placebo. This effect was temporally specific to 21 days of treatment and was not sustained after 42 days of intake. Despite the superior efficacy of Mg supplementation, a sizeable placebo effect was evident, highlighting the potential placebo sensitivity of mildly anxious samples.

Rouillon et al. (1993) demonstrated a significant reduction in total HAM-A score after treatment with both 192 mg of Mg lactate + 20 mg vitamin B_6 and Buspirone 40 mg. However, no significant difference between the treatments was evident after 21 or 42 days. This study did not administer a placebo condition alongside the positive verum. However, an initial 7 day placebo washout period was employed prior to full study participation to remove participants that exhibited sizeable placebo effects (≥ 50% improvement in total HAM-A score during placebo washout period). The clinical efficacy of Buspirone in the treatment of mild anxiety and GAD has been positively established, both compared to placebo and other anxiolytic preparations [31-33]. Therefore, the comparable efficacy of Mg to Buspirone may be interpreted as an impressive outcome. The inclusion of a placebo in future studies would give further insight into the relative efficacy of Mg intake.

Caillard (1995, unpublished) recruited participants based upon reports on existing somatic anxiety complaints (HAM-A criteria) and examined the capacity for Mg +

vitamin B_6 to alleviate the symptoms of functional impairment associated with anxiety. Somatic score on the HAM-A reflects the physical symptoms of anxiety; namely, muscular, sensory, cardiovascular, respiratory, autonomic, behavioural, genitourinary, and gastrointestinal symptoms [20]. A 7 day placebo washout period to exclude placebo responders prior to full study participation was employed (≥ 20% improvement in somatic HAM-A score during placebo washout period). Magnesium + vitamin B_6 significantly reduced somatic anxiety complaints vs. placebo treatment after 21 (p= .004) and 42 days (p= .02) of supplementation (controlling for baseline somatic ratings). Findings are suggestive of a specific capacity for Mg + vitamin B_6 supplementation to alleviate somatic symptoms of anxiety.

Conclusions:

The effects of Mg on clinical affective disorders and experimental studies of anxiety in animal models provide a clear rationale to propose that Mg supplementation will have a beneficial effect on mild/moderate anxiety. The current evidence of the efficacy of Mg supplementation on parameters of subjective anxiety is suggestive of a potential positive effect of Mg intake. Magnesium has been demonstrated to alleviate subjective symptoms of anxiety in the mildly anxious and those reporting PMS symptomology. Combining Mg with additional ingredients, such as vitamin B_6, may increase treatment efficacy. Comparable efficacy with established pharmaceutical anxiolytics has been reported but the absence of a concurrent placebo comparator undermines the strength of these findings; especially since sizeable placebo effects are often reported in the reviewed studies. Further well controlled studies that appropriately employ a placebo comparator are recommended.

Whilst there is positive evidence for the potential for Mg supplementation to alleviate subjective anxiety, the current available evidence is not entirely consistent and, combined with the mixed quality of studies, is insufficient to offer a conclusive opinion of the efficacy of Mg supplementation at the present time. However, the evidence is sufficient to warrant further examination of the anxiety-reducing potential of Mg.

Finally, Mg modulates activity of the hypothalamic pituitary adrenal axis (HPAA; [34, 35]) which is a central substrate of the stress response system. Activation of the HPAA instigates adaptive responses to cope with the demands of the stressor; including increasing anxiety. Exposure to stress also moderates serum [noise stress; 36] and intracellular [exam stress; 37] Mg levels. Therefore, Mg may further influence anxiety states via the moderation of the stress response. The effects of Mg intake on parameters of stress is a promising area of future research.

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Table 1. Summary of unpublished studies reporting the effects of Mg + B_6 on subjective anxiety in mild to moderately anxious individuals

Author	Study Design	Condition	Sample (N)	Sex	Age (y)	Treatment(s)	Control	Duration	Anxiety Outcome Measure	Results
Caillard, 1992 (Unpublished)*	RCT	**Mild anxiety/general anxiety disorder** (Hamilton Anxiety Scale score 15 - 30 & general anxiety disorder [DSM III criteria])	N = 93	25M:68F	x = 41 (SD = 12; 18 - 65)	Mg lactate 192 mg + vitamin B_6 20 mg	Placebo	6 weeks	Hamilton Anxiety Scale	Significant change from baseline (Total score) between groups at Day 21 (Mg + vitamin B_6: x = 12.1 [SD = 6.0]; placebo: x = 15.5 [SD = 5.8]) vs. Day 0 (Mg + vitamin B_6: x = 21.0 [SD = 4.5]; placebo: x = 22.6 [SD = 4.4]; p < .03). No significant differences between Day 0 and Day 42.
Rouillon et al., (1993)*	RCT	**Mild anxiety/general anxiety disorder** (Hamilton Anxiety Scale score 15 - 30 & general anxiety disorder [DSM III-R criteria])	N = 99 (Mg n = 51; Buspirone n = 48)	38M:61F	x = 37.7 (SD = 10.7; 19 - 65)	Mg lactate 192 mg + vitamin B_6 20 mg	Buspirone 40 mg (positive verum)	6 weeks	Hamilton Anxiety Scale	Decrease in anxiety scores in both treatment groups across intake. No significant difference between the efficacy of Mg + vitamin B_6 and Buspirone.
Caillard, 1995 (Unpublished)*	RCT	**Symptoms of functional impairment associated with anxiety or a somatic disorder** (Hamilton Anxiety Scale[1]; Raskin depression scale < 7; COVI anxiety scale = 7)	N = 103	26M:77F	x = 37 (18 - 65)	Mg lactate 192 mg + vitamin B_6 20 mg	Placebo	6 weeks	Hamilton Anxiety Scale (somatic score)	Significantly lower somatic anxiety rating after treatment at Day 21 (x = 8.4 [SD= 3.8]; p = .004) and Day 42 (x = 6.5 [SD = 3.0]; p = .02) vs. placebo (Day 21: x = 9.9 [SD= 2.9]; Day 42: x = 7.8 [SD = 3.6]).

Mg - Magnesium; mg - milligrams; + positive treatment effect; - negative treatment effect; x no treatment effect; RCT - randomised controlled trial

*Data provided by Sanofi, France, [1]Total Score > 20, with sum of 2 first items < 5 & score for item 6 (depressed mood) < 2.