

The role for vitamin B-6 as treatment for depression: a systematic review

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Background. Major depression is the leading cause of disability worldwide, and among the 10 most frequent indications for using alternative medicine therapies, especially dietary supplements.

Objective. To assess the evidence evaluating vitamin B-6 supplementation as treatment for depression.

Methods. Medline, Psychinfo, AMED, and Cochrane Controlled Trials Register were searched from database inception through September 2001. All randomized controlled trials, controlled clinical trials, intervention studies, case-control studies, reviews, and case reports examining the evidence behind vitamin B-6 in depression among humans were selected. No limits were placed for demographics or co-morbidities. Only English language papers were abstracted and assessed for trial quality. Two abstractors independently evaluated each study, then reconciled findings. As data were available, between group treatment effect size was noted or, as needed, calculated. When studies reported outcome effects using multiple measures, data were abstracted to permit the greatest possible comparisons among papers.

Results. Ten articles met inclusion criteria; three reviews, one case report, five RCTs, and one intervention study. There was no common outcome measure among all studies, eliminating opportunity for direct comparison of effect sizes. As an alternate means of comparison, effects were plotted as they related to the null hypothesis.

Conclusion. Viewed as a whole, meaningful treatment effect of vitamin B-6 for depression in general was not apparent. However, examination of papers addressing depression in premenopausal women only, reveals a consistent message about the value of using vitamin B-6 supplementation. Further study of vitamin B-6 as independent and adjuvant therapy for hormone related depression in women is indicated.

Keywords. Alternative medicine, complementary therapies, depression, dietary supplement, vitamin B-6.

Introduction

Major depression is ranked as the leading cause of disability throughout the world, and the fourth most important cause of premature mortality.¹ Prevalence is estimated at 2–4%, and there exists about a 20% risk of developing major depression or dysthymic disorder over the lifespan.² Lifetime rate is 1.7–2.7 times greater

for women than for men.³ The overall economic burden was estimated at \$43 billion/year in 1990;⁴ 30% of that cost is direct medical care, and 70% is due to loss of productive years and workplace efficiency.²

Current conventional treatment of depression is largely pharmacologic, with or without psychotherapy. Selective serotonin re-uptake inhibitors have become available over the past 20 years, improving the side effect profile, simplifying dosing and increasing patient adherence over the older tricyclic antidepressants and monoamine oxidase inhibitors.² Efficacy of antidepressant medication is estimated at 50%, a figure that has not changed significantly since the 1950s.⁵ Psychotherapy has a similar efficacy profile, and it is unknown whether the combination of pharmacotherapy and psychotherapy has a cumulative effect.²

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Complementary and alternative medicine (CAM) encompasses those interventions that are beyond the scope of conventional clinical care.⁶ Over 42 million Americans use CAM,⁷ including such diverse therapeutic modalities as nutraceuticals, meditation, massage, homeopathy, Ayurveda, acupuncture, Reiki, and chiropractic.⁶ CAM therapies are used more than conventional therapies by people with self-defined anxiety and severe depression.⁸ Depression is among the 10 most frequent indications for using CAM therapies.⁸ CAM treatment of depression is as broad in terms of the number of modalities used as it is varied with respect to scientific validation of efficacy. Responsible summation of the topic is beyond the purview of this article; more complete overviews may be found elsewhere.⁹ Among the most popular CAM interventions for depression are dietary interventions and vitamin supplementation, especially the B vitamins.

Traditionally, the role of B vitamins in mental health was limited to recognition of the manifestations of psychiatric symptoms in thiamine, folate, B-12, and B-6 deficiencies, and appropriate replacement. A number of studies have examined the correlation between folate levels and psychiatric disorders;¹⁰ prominent among these is the treatment of depression.¹¹ From the B vitamin replenishment literature grew scientific inquiry into the role of B-6 as treatment, both adjuvant and primary, for depression. Reported here is the result of a systematic review examining the therapeutic efficacy of vitamin B-6 for depression.

Methods

In 2000, the Yale Prevention Research Center was funded by the Centers for Disease Control and Prevention to conduct a 'systematic review' of the evidence underlying CAM. The investigative team, working in collaboration with a multi-disciplinary group of NIH-funded researchers and CAM practitioners representing diverse modalities, developed a systematic and replicable 9-step process termed *evidence mapping*.¹² Using strict criteria, published previously,¹² more than 200 medical conditions were paired with CAM interventions, and then prioritized by public health significance for systematic review (when evidence existed) or for pilot study development (when evidence did not exist). Initially, vitamins and depression was prioritized as the number one pair identified for full systematic review. Upon review of articles researching a myriad of mechanisms of action for different vitamins and their effect on different types of depression, the original pair was reduced to vitamin B-6 and depression.

Searching

Electronic searches were completed using Medline, Psychinfo, AMED (Allied and Complementary Medicine), and Cochrane Controlled Trials Register.

The use of electronic search engines was limited to those in wide use among diverse practitioners, and more or less universally accessible to assure that results would be pertinent to the broadest possible readership. The searches, conducted from December 2000 to September 2001, investigated each database from the earliest date available to the present (Medline 1966; Psychinfo 1987; AMED 1983; Cochrane Controlled Trials Register 1995) and included articles in all languages. Each condition-intervention pair was searched with the following study design terms: randomized controlled trial (RCT), meta-analysis, review article, case-control study, controlled clinical trial (CCT), intervention study, case report, and pilot study.

Selection/inclusion and exclusion criteria/study characteristics

All RCTs, CCTs, intervention studies, case-control studies, reviews, case reports and pilot projects that examined the evidence behind vitamin B-6 in depression among human subjects were selected. No limits were placed on study populations for demographics or co-morbidities. Although papers in all languages were culled, only those in English were abstracted and assessed for trial quality.

Data abstraction

The investigative team developed an on-line data abstraction form based on methods applied by the Centers for Disease Control and Prevention (CDC) to the *Guide to Community Preventive Services* (CDC), and incorporating criteria from The Cochrane Reviewers' Handbook 4.0.¹³ After intensive training and testing by the Principal Investigator, two masters educated research associates abstracted the accepted articles, using a standardized process. The two abstractors independently evaluated each study, and then reconciled their findings.

Validity assessment

As means of quality assessment, studies were 'accepted', 'rejected', or 'audited' relative to explicit criteria for identifying threats to internal and external validity. Articles were 'rejected' if at least one major flaw in reporting was identified that compromised validity. This included: failure to report on comparability of the units of analysis prior to exposure to the intervention, neglecting to specify the sampling frame for the study population, omitting a description of the intervention, failing to correct for controllable variables, or neglecting to institute procedures to limit bias. Articles were 'audited' if minor flaws in reporting were identified, such as omission of study power analysis, description of the study population, or screening criteria for study eligibility; or deficiencies such as not conducting statistical testing, not reporting which statistical test were used, or not conducting intention to treat analysis.

The project coordinator and members of the investigative team reviewed the audited papers and determined if they should be accepted or rejected. 'Accepted' papers were those that did not have any flaws identified during abstraction, or were deemed acceptable after audit.

Quantitative data synthesis/determination of effect sizes

All studies that involved an intervention and that met criteria for either 'accept' or 'audit' were further analysed to facilitate comparison. Whenever possible, plots were generated of outcome effect based on a common measure. As data were available, a between group treatment effect size was noted or, if need be, calculated by determining the difference between groups of the change from baseline to final outcome. When outcome effects were measured by heterogeneous means, the studies were plotted together using a simple indication of favorable versus unfavorable outcome effects relative to a null line. Whenever possible, point estimates were surrounded by 95% confidence intervals but when sufficient data to generate confidence bounds were lacking in the original papers, a point estimate alone was plotted. In such cases where confidence intervals were lacking, *P*-values reported in the papers were used to indicate on plots whether or not the results observed were statistically significant. Within group effects were plotted separately from between-group effects whenever appropriate. When sufficient data were available to allow for a quantitative pooled effect measure of the studies, this was generated as a point estimate and included on the plot. Once such information was made available with regard to a specific measure of outcome effect, an attempt was made to derive favorable and unfavorable effects with regard to intensity on an ordinal scale ranging from modest to great. When studies reported outcome effects using multiple measures, appropriate data were abstracted to permit the greatest possible array of comparisons among subgroups of papers. This at times results in papers being shown on several plots in comparison to other studies using comparable outcome measures or addressing similar populations. When a single intervention study reported distinct outcome effects within several different populations, these effects were plotted separately as appropriate. The calculation of pooled effect, whenever appropriate, represents a weighted measure adjusted for the sample size of the various papers under consideration.

Results

Study characteristics

Ten articles were found that assessed vitamin B-6 as an intervention for depression. Three of the articles are

reviews,^{14–16} one is a case report,¹⁷ five are RCTs,^{18–22} and one is an intervention study²³ (Table 1).

Quality assessment

After the data abstraction and reconciliation phases, two of the studies were rejected (one RCT²² and the intervention study²³) because of major design flaws that compromised internal validity²² and external validity.²³ The remaining RCTs and the case report all had at least 2 'audits', indicating minor flaws in reporting; they were ultimately accepted (Table 1).

Quantitative data synthesis

No common outcome measure was found among all the studies (Table 1), eliminating the opportunity for direct comparison of precise effect sizes. An alternate means of comparison was established by plotting the effects as they related to the null hypothesis: favorable, unfavorable, or null (Tables 1 and 2). The four RCTs^{18–21} all had comparably small sample sizes, and assessed between-group differences; three of the studies^{18–20} used a placebo control, one²¹ used a non-intervention control. A favorable and significant between-group effect was seen in two studies looking exclusively at women.^{18,20} One other study showed favorable, though non-significant outcome effects.¹⁹ The one study that exclusively studied men,²¹ demonstrated no effect between subjects administered vitamin B-6 supplementation and those who were not.

Two of the articles^{20,21} used the Beck Depression Index (BDI) as a measure of outcome, thus allowing a direct comparison of common outcome effect. One of the studies, examining women on oral contraceptive pills with moderate to severe depression as assessed by the BDI,²⁰ showed a significant, favorable effect when comparing subjects given supplemental vitamin B-6 to those receiving placebo. The second study, looking only at male submariners²¹ showed no difference between groups.

Among the 8 articles, 3 had exclusively female study populations,^{17,18,20} without a common metric. The 2 RCTs of women^{18,20} indicate significant and favorable differences between women exposed to vitamin B-6 and those receiving placebo. Both female study populations were pre-menopausal; one with moderate to severe depression on OCPs, the other with premenstrual syndrome (PMS) with depressive symptoms. Neither RCT used intention to treat analysis; both sustained considerable attrition [49% (Doll), 31% (Adams)] among their study populations. The third study is a case report of one woman with premenstrual depression treated with vitamin B-6;¹⁷ a favorable outcome was reported.

Discussion

When viewing the literature as a whole, there does not appear to be suggestion of a meaningful treatment effect

TABLE 1 Summary of vitamin B-6 and depression literature

| Author/ Year | Population (<i>n</i>) | Study type | Outcome measure | Duration of study | Dose of B-6 | Effect size | Quality assessment |
|----------------------|--|-----------------------|--|----------------------|---|---------------------------------------|-----------------------|
| Adams PW 1973 | Depressed women on OCPs (22) | RCT | Beck Depression Index | 2 months | 40 mg/d (po) | 11 point increase (favorable) | Accept |
| Bell IR 1992 | Adults with major depression (14) | RCT | Montgomery Asberg Depression Rating | 1 month | 10 mg/d (po) | 5 point increase (favorable) | Accept |
| Doll H 1989 | Women with PMS depression (32) | RCT | Symptom Diary | 7 months | 50 mg/d (po) | 2.97 point increase (favorable) | Accept |
| Reynolds RD 1988 | Male submariners (23) | RCT | Beck Depression Index | 3 months | 0.5 mg/d (po) | Not reported | Accept |
| Mattes JA 1982 | Woman with premenstrual depression (1) | Case report | Reported symptoms | 6 months | 50 mg/d (po) | Not reported | Accept |
| DeSouza MC 2000 | Women with PMS depression (37) | RCT | Menstrual Health Questionnaire | 5 months | 50 mg/d (po) | N/A | Reject ^a |
| Holsboen F 1985 | Women with major depression | Intervention study | Hamilton Depression Scale | 1 month | 120 mg/d (administration route not reported) | N/A | Reject ^b |
| Wyatt KM 1999 | PMS | Review | N/A | N/A | N/A | N/A | N/A |
| Bernstein AL 1990 | Clinical Neurology | Review | N/A | N/A | N/A | N/A | N/A |
| Bender DA 1999 | Non-nutritional uses of B-6 | Review | N/A | N/A | N/A | N/A | N/A |

N/A = non-applicable.

^aThis paper was rejected because the intervention was inadequately described, and the independent variables were not reliable.

^bThis paper was rejected because the study population was inadequately described, no screening criteria was specified, and the sampling frame for the study population was not provided.

of vitamin B-6 for depression in general. However, when examining only papers that address depression in pre-menopausal women, there appears to be a consistent message about the value of using vitamin B-6 supplementation. While there were many limitations in the studies to obscure confident interpretation of the results, there is a hint of benefit for the women studied who had PMS or OCP related depression, suggesting a relationship between female sex steroids and depressive symptoms.

Several physiological mechanisms have been associated with depression, including, but not limited to, various neurotransmitters as well as hormonal dysfunction. Neurotransmitters implicated in depression are serotonin, norepinephrine, cholinergic system, dopamine, and GABA. The serotonin deficiency hypothesis proposes a functional deficiency of serotonin in the brain as a cause of depression. Specifically, research supports the existence of disturbances in the transportation of L-tryptophan into the blood-brain barrier and its

conversion to serotonin, as well as decreased density in serotonin uptake sites.²⁴ The noradrenergic hypothesis posits various abnormalities in the synthesis, release, and metabolism of norepinephrine as playing causal roles in depression.²⁵ Empirical support for this hypothesis has been equivocal.²⁴ The cholinergic supersensitivity hypothesis asserts hyperactivity of the cholinergic system manifests in depression.²⁶ In fact, cholinergic drugs have been associated with increased depressive symptoms, such as depressed mood, fatigue, emotional withdrawal, and sleep disturbances.²⁴ The dopamine-deficiency and GABA deficiency hypotheses propose low levels of dopamine or dopamine metabolites and GABA, respectively, as causal factors in depression. Research has demonstrated both lower and higher levels of the dopamine metabolite HVA, as well as lower levels of GABA concentrations, associated with depression.²⁴

Hormonal dysfunction, specifically the effects of hypothalamic, pituitary, thyroid, adrenal, and gonadal hormones, have been associated with depression. Mood

TABLE 2 Between-group effect of B-6 for depression, studies with no common outcome measure

| Author/year | Study population and setting | Study design | Primary outcome measures | SD | P-value | Main findings |
|-------------------------|--|--|--|-----|------------------------------|---|
| Studies of Women only: | | | | | | |
| Adams P 1973 | Women with OCP induced depression, age 20–29, registered at out-patient clinic. 32 enrolled; 22 completed. | Randomized cross-over trial; individuals randomized to receive B-6 or placebo for 2 months, than cross-over. | Beck Depression Index; hematologic and urinary assessments of B vitamin levels. | 12 | $P < 0.05$ between groups | Women with B-6 deficiency ($n = 11$) responded favorably to B-6 supplementation; those without documented deficiency did not respond to B-6. |
| Doll 1989 | Women with moderate to severe PMS, age 18–49, registered at out-patient clinic. 63 enrolled; 32 completed. | Randomized cross-over trial; randomized to receive B-6 or placebo for 3 months, than cross-over. | Diary assessing: emotional, somatic, menstrual symptoms. | NR | $P < 0.05$ between groups | Participants had considerable cycle variability in symptoms reported. Overall NS effect; however statistically significant benefit of B-6 on emotional symptoms. |
| Study of Men and Women: | | | | | | |
| Bell IR 1992 | 3 men and 11 women with major depression; all inpatients on tricyclics; mean age 75y. | RCT; individuals randomized to receive adjuvant B-6 ($n = 8$) or placebo ($n = 6$). | Montgomery Asberg Depression Rating; hematologic assessment of B vitamin levels. | 6.2 | $P = 0.10$ NS between groups | Demonstrated NS trends suggesting B-6 may augment tricyclic therapy in the geriatric population. |
| Study of Men only: | | | | | | |
| Reynolds 1988 | 23 males on submarine duty, age 18–35. | RCT; individuals randomized to receive B-6 ($n = 12$) or no intervention ($n = 11$). | Beck Depression Index; hematologic and urinary assessments of B vitamin levels. | NR | NS between groups | Despite progressive increase in B-6 deficiency while at sea, there was NS difference in plasma, urinary, or BDI scores between those receiving supplementation and those not. Note: B-6 dose was only 0.5 mg/day. |

NR = not reported; NS = non-significant.

changes and increased depressive symptoms in premenopausal women have been associated with low levels of serum estrogen, as well as changes in other gonadal hormones, especially during the luteal phase of the menstrual cycle.²⁷ Although the exact mechanism by which low levels of estrogen produce symptoms of depression is unclear, it appears to be related to its dopamine and serotonin blocking properties, as well as its involvement in the release of several other neurotransmitters.²⁴ Despite this ambiguity, research on the effects of various surgical and medical treatments seems to indicate a positive connection. For example, PMS symptoms have been attenuated via hysterectomy and oophorectomy²⁸

and estrogen replacement therapy.²⁹ As such, research seems to support the existence of a specific type of depression, related to hormonal dysfunction.

Vitamin B-6, comprised of pyridoxal, pyridoxamine, and pyridoxine, is one alternative treatment that may be a mitigating factor in hormone related depression, via its role in the proper metabolism of various neurotransmitters considered relevant in the manifestation of depression.¹⁵ Deficiencies in B-6 have been reported in women with hormone related depression (i.e. premenstrual syndrome, PMS and premenstrual dysphoric disorder, PMDD) and linked to symptoms of discomfort.²⁷ It has been hypothesized that B-6 may be successful

in treating hormone related depression based on an association between B-6 deficiencies and concurrent symptoms of depression and based on its role in metabolism of carbohydrates and gonadal steroids.³⁰

Further study of vitamin B-6 as independent and adjuvant therapy for hormone related depression in women is indicated.

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Declaration

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Ethical approval: this project was approved by the Institutional Review Board at Griffin Hospital.

Conflicts of interest: none.

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