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Combined vitamin B6-magnesium treatment in autism spectrum disorder (Review)

Nye C, Brice A

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Combined vitamin B6-magnesium treatment in autism spectrum disorder.
Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003497.
DOI: 10.1002/14651858.CD003497.pub2.

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[Intervention Review]

Combined vitamin B6-magnesium treatment in autism spectrum disorder

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Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003497. DOI: 10.1002/14651858.CD003497.pub2.

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ABSTRACT

Background

The use of mega-vitamin intervention began in the 1950s with the treatment of schizophrenic patients. Pyroxidine (vitamin B6) was first used with children diagnosed with "autism syndrome" when speech and language improvement was observed in some children as a result of large doses of B6. A number of studies attempted to assess the effects of vitamin B6-Magnesium (Mg) was found to reduce undesirable side effects from B6) on characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism.

Objectives

To determine the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication, and behavioural responses of children and adults with autism.

Search methods

We searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 1, 2005), MEDLINE (1966 to April 2005), EMBASE (1980 to April 2005), PsycINFO (1887 to April 2005), Dissertation Abstracts International (1861 to April 2005). The search engine FirstSearch was also used (April 2005). Reference lists for all the obtained studies and other review articles were examined for additional studies.

Selection criteria

All studies in which the participants had been diagnosed with autistic spectrum disorder were randomly allocated prior to intervention and in which outcomes were compared to either a placebo or non-treated group were included.

Data collection and analysis

Two reviewers independently evaluated and extracted data from all potential studies identified for inclusion.

Main results

The 2005 update includes a new trial (Kuriyama 2002) to bring the total of included studies to three (total n=33). One study, which used a cross-over design (Tolbert 1993) provided insufficient data to conduct an analysis. Another crossover study (Findling 1997) yielded no significant differences between treatment and placebo group performances following the B6 intervention on measures of social interaction, communication, compulsivity, impulsivity, or hyperactivity. The latest study (Kuriyama 2002) was motivated by evidence from epilepsy research and was focussed on a subgroup of children with pervasive developmental disorders (PDDs) who exhibited clinical

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features similar to those with pyroxidine-dependent epilepsy. This small study (n=8) only measured IQ and 'Social Quotient' and found a statistically significant benefit for IQ (5.2, 95% CI = [0.2 to 10.3]) when in the treated group, by using change scores.

Authors' conclusions

Due to the small number of studies, the methodological quality of studies, and small sample sizes, no recommendation can be advanced regarding the use of B6-Mg as a treatment for autism.

PLAIN LANGUAGE SUMMARY

Vitamin B6 and magnesium in combination for children with autism spectrum disorder

Studies investigating the effect of vitamin B6 in improving the behaviour of children with autism spectrum disorder have been reported for over three decades. The purpose of this review was to summarize those studies and analyse the effectiveness of vitamin B6 as an intervention. Only three studies met the inclusion criteria of this review and of these only one study reported adequate data for analysis. Results were inconclusive and sample sizes were small. Therefore the use of vitamin B6 for improving the behaviour of individuals with autism cannot currently be supported. Further research using larger, well-designed trials is needed.

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BACKGROUND

Description of the condition

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), autism is defined by significant deficits in social interaction, communication, and stereotypical behaviour patterns (APA 1994). The impairments in social interactions may result in such behaviours as isolation from others, withdrawal from socialising activities, and/or lack of development of play skills. Communication deficits centre on the inability to use expressive language appropriately, understand the rules of communicative exchange, and/or a lack of comprehension of the meaning of non-verbal language. Stereotypical behaviour patterns are seen in repetitive motor activity, engagement in ritualistic behaviours, and/or an exaggerated focus on parts of objects. A review and update of epidemiological studies published between 1966 and 2003 show reports of the estimated prevalence for autism has varied between 0.7 and 40 children per 10,000 (Fombonne 1999, Fombonne 2003).

Description of the intervention

The use of mega-vitamin intervention began in the early 1950s with the treatment of schizophrenic patients (Rimland 1964). Pyridoxine (vitamin B6) was first reported to improve speech and language in some children diagnosed with "autism syndrome" when Bönisch observed that some participants showed improvement in speech and language (Bönisch 1968). Other researchers (Ananth 1973; Bucci 1973; Greenberg 1970) also reported improved behavioural or biochemical functioning with schizophrenic participants given large doses of vitamin B6. These studies, along with individual anecdotal observations of parents and professionals, led Rimland and colleagues (Rimland 1978) to assess the effectiveness of this orthomolecular treatment. Rimland had recognised that large doses of vitamin B6 produced several undesirable side effects (including irritability, hypersensitivity to sound and enuresis, which could be countered with doses of magnesium [Mg]). Over the next 19 years, a number of investigators published studies in which attempts had been made to assess the effects of vitamin B6-Mg on a variety of characteristics such as verbal communication, non-verbal communication, interpersonal skills, and physiological function, in individuals with autism.

Why it is important to do this review

The published research included five double-blind crossover trials (Barthelemy 1980; Barthelemy 1981; Jonas 1984; Martineau 1985; Rimland 1978), eight non-randomized trials (Barthelemy 1985; Bönisch 1968; Lelord 1978; Martineau 1981; Martineau 1982; Martineau 1988; Martineau 1989; Menage 1992), two trials using open and double blind arms in their investigations (Lelord 1981; Lelord 1982), and three randomized double-blind placebo controlled trials (Tolbert 1993; Findling 1997, Kuriyama 2002). Non-randomized studies Rimland, Callaway and Dreyfus (Rimland 1978) reported a double-blind non-randomized study in which 16 "autistic type" children were treated with large doses of B6-Mg for varying periods of time and then withdrawn. The analysis of the data suggested that the behavioural changes were significant. However, Rimland et al failed to make a strong statement of advocacy for the B6-Mg regimen as a therapeutic intervention. This early study is noteworthy for the lack of methodological and statistical rigor for even the most generous of interpretations of the data.

Others (Barthelemy 1980; Barthelemy 1981; Jonas 1984; Martineau 1985) conducted double-blind crossover trials assessing behavioural, physiological, electrophysiological, and/or communicative functioning. Conclusions from these studies offer varying statements of support for the study and use of B6-Mg using terms such as 'promising', 'significant', 'tendency toward normal', and often call for additional study. Lelord and colleagues (Lelord 1981; Lelord 1982) utilised a combined open and double-blind crossover trial to measure the effects of B6-Mg therapy with autistic children in assessing behavioural, biochemical, and electrophysiological parameters. The methodological design of these studies required that the initial sample of participants was administered a B6-Mg procedure with dependent measures taken. After "several months", a subset of participants called 'responders' and 'non-responders' was investigated further in a new non-randomized double-blind crossover study. The results of the double-blind crossover trial indicated significant improvements in the treated participants as evidenced by their regression to pre-treatment levels when the intervention was removed.

The eight open non-randomized trials (Barthelemy 1985; Bönisch 1968; Lelord 1978; Martineau 1981; Martineau 1982; Martineau 1988; Martineau 1989; Menage 1992) used a variety of methodologies including completely open trials, normal comparison participants, non-treated autistic participants or pre-treatment and post-treatment of a single, experimental group. As with the other non-randomized trials, the data from these investigations generally supported the use and/or further investigation of the use of B6-Mg in the treatment of autistic children.

It was not until Tolbert (Tolbert 1993) and Findling (Findling 1997) conducted randomized double-blind placebo-controlled studies that contrary results emerged. Using different rating scales to measure the behavioural outcomes of the B6-Mg intervention, both of these studies suggested that there was no statistically significant effect from the use of B6-Mg for improved behavioural outcomes in children with autism. However, Tolbert (Tolbert 1993) used lower doses of vitamin B6-Mg and concluded that they did not necessarily contradict earlier studies (Lelord 1982; Lelord 1982; Martineau 1981; Martineau 1985; Martineau 1988). Pfeiffer, Norton, Nelson, and Schott (Pfeiffer 1996) provided a narrative summary of the vitamin B6 research with autism that included 12 studies published up to 1989. Though Pfeiffer et al identified issues such as design, participant selection, treatment parameters and measurement differences, it was concluded that "B6-Mg treatment may be a promising adjunct in the treatment of autism" (p.491). Following previous research in children with pervasive developmental disorders (PDDs) who experienced epileptic seizures and for whom pyroxidine appeared to prevent seizures and raise intelligent quotient (IQ) scores, investigators in a recent trial (Kuriyama 2002) hypothesised that another subgroup (children diagnosed with PDDs who also exhibited clinical features similar to those with pyroxidine-dependent epilepsy, but did not have seizures) might benefit. The study recruited children who were higher-functioning than was typical in other groups, and only measured IQ and 'Social Quotient'.

The purpose of this systematic review was to assess the efficacy of B6-Mg treatment of individuals with autism spectrum disorders

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(ASD) for social interaction, communication, and stereotypical behavioural performance. Positive effects of B6-Mg intervention would result in improved verbal skills, non-verbal skills, social interaction skills, and reactions to environmental stimuli and changes.

OBJECTIVES

To determine the efficacy of vitamin B6 and magnesium (B6-Mg) for treating social, communication, and behavioural responses of children and adults with autism spectrum disorder.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized trials in which individuals with autism were administered vitamin B6-Mg were included in the review. The control groups included groups of individuals with a diagnosis of autism who received either placebo or no treatment.

Types of participants

Adults or children with ASD. ASD included pervasive developmental disorders (as described in DSM-IV [APA 1994] and ICD10 [WHO 1993] or diagnosed using a standard diagnostic instrument, eg the Childhood Autism Rating Scale (CARS) (Schopler 1980).

Types of interventions

The treatment studied was combined vitamin B6 with Mg, taken in tablet or powder form for a minimum of one week and a maximum of 52 weeks.

Types of outcome measures

The major outcome measures included measures of:
1. Verbal Behaviour: e.g. increased language usage;
2. Non-verbal Behaviour: e.g. improved response to environmental stimuli;
3. Social interaction: e.g. increased response to people.
Where possible, outcomes were examined with respect to the length of treatment i.e. short term (2 weeks) medium term (6 to 12 weeks) and long term (13 weeks and more). We also examined outcomes for any follow-up periods included in studies.

Search methods for identification of studies

Search strategy for identification of studies

The following databases were searched: the Cochrane Controlled Trials Register CENTRAL (The Cochrane Library, Issue 2, 2002, updated search run on 2005 Issue 2), MEDLINE (1966 to January 2002, updated search run to April week 3 2005), EMBASE (1980 to January 2002, updated search run to 2005 week 18), PsycINFO (1887 to January 2002, updated search run to April week 3 2005), Dissertation Abstracts International, (1861 to January 2002, updated search run to April 2005). The search engine FirstSearch was also used (January 2002). All issues of the *Journal of Autism and Developmental Disabilities* were also handsearched. In addition, the reference lists for all of the obtained studies and other review articles were examined for additional studies. Full-text copies of all potentially appropriate citations were obtained.

The following search strategy was used to search the Cochrane Controlled Trials Register and amended where appropriate for the other databases:

1) CHILD-DEVELOPMENT-DISORDERS-PERVASIVE*:ME
2) SPEECH-DISORDERS*:ME
3) AUTIS*
4) (PERVASIVE and (DEVELOPMENTAL and DISORDER*))
5) PDD
6) (LANGUAGE next DELAY*)
7) ((COMMUNICAT* or SPEECH) next DISORDER*)
8) (CHILDHOOD next SCHIZOPHRENIA)
9) KANNER*
10) ASPERG*
11) (((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10)
12) B6
13) PYRIDOXINE
14) MAGNESIUM
15) VITAMIN-B-COMPLEX*:ME
16) MAGNESIUM*:ME
17) VITAMIN-B6
18) VITAMIN-B
19) (((((#12 or #13) or #14) or #15) or #16) or #17)
20) (#11 and #19)

No language restrictions were applied. A filter to capture randomized controlled trials was used when appropriate.

Data collection and analysis

Selection of studies

All potential studies identified were independently evaluated for inclusion by two primary reviewers (Chad Nye [CN]) and Alejandro Brice [AB]). When questions arose as to the possible inclusion/exclusion of any individual study, a final consensus decision was reached by discussion between CN and AB. Provision was made for a third reviewer if consensus was unattainable, however, there were no studies requiring participation of the additional reviewer. The primary reviewers were not blind to author(s), institution(s), or publication source at any time during the selection process.

Data extraction and management

Each reviewer independently extracted the data for each study meeting the inclusion criteria identified above. In the event that insufficient data were available, the first author was contacted to provide data and clarification. If the requested data were made available and determined to be appropriate to the review, they were extracted and included. If the data were unavailable or otherwise inadequate, the study was reported but not included in the final data analysis. All studies meeting the inclusion criteria are summarized in the 'Included Studies' table. Comments on design, participants, interventions, and outcomes are included.

Assessment of risk of bias in included studies

Assessment of methodological quality

The categorization of methodological quality included consideration of the allocation concealment. Each study was assigned to one of three categories of methodological quality described in the Cochrane Reviewers' Handbook by both CN and AB (Alderson 2004).

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These categories are:
A - adequate concealment, B - unclear concealment and C - inadequate concealment. Adequate concealment included any form of random assignment in which the individual participant's group assignment was unknown prior to the actual assignment and an acceptable randomization procedure such as computer-generated allocation was used for group assignment. If the author(s) of the study indicated that participant assignment to the experimental and control conditions was accomplished using a randomized process but gave no specific information regarding the details of the randomizing process, that study would at best be classified as using an unclear concealment procedure. Only studies reporting adequate or unclear concealment were assigned to the included studies group. Studies reporting no randomizing procedure were automatically categorized as reflecting an inadequate concealment procedure and were not included for the review or analysis. As indicated in the protocol, it was decided that no study reporting more than 20% attrition would be assigned to the included studies group.

Assessment of heterogeneity

No meta-analysis is possible for the current version of this review, due to lack of reported data (Findling 1997) and differences in both clinical populations and outcome measures between Kuriyama 2002 and Tolbert 1993. Should sufficient data be available at future updates, consistency of results will be assessed visually and by examining I^2, a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error (Higgins 2002). This will be supplemented with a test of homogeneity to determine the strength of evidence that the heterogeneity is genuine.

Data synthesis

No meta-analysis was possible in the original or updated version of this review. Should sufficient data be obtained at future updates of this review, data analysis will be conducted using RevMan 4.2. For dichotomous data, such as number of children with improved behaviour, an odds ratio and a 95% confidence interval will be the statistic calculated. For continuous data, such as improvement of language test scores, a weighted mean difference will be used when the outcomes are measured in a standard way across different studies. When continuous data are from different but conceptually similar measures, such as different tests of language performance, a standardized mean difference statistic will be employed.

Sensitivity analysis

Neither sensitivity analyses nor subgroup analysis were viable options to assess the impact of study quality, clinical differences in the intervention, or clinically relevant differences between subject groups, such as age or clinical subgroupings, in the current version of this review.

RESULTS

Description of studies

A total of 58 abstracts were identified via the electronic and hand search strategy in original searches conducted in 2002. Of these, 41 were found to be ineligible for inclusion due to inappropriate topic, duplicate citations, or non-data based papers (e.g. reviews, topic discussions), and 15 were found to be ineligible for inclusion due to the use of a non-randomized controlled trial design. The two remaining studies met inclusion criteria (Tolbert 1993; Findling 1997). At the 2005 update, a total of 27 abstracts were identified via the electronic search strategy. Of these, one study met inclusion criteria (Kuriyama 2002).

General features of included studies

Included studies were published between 1993 and 2002. Two studies were conducted in the USA (Tolbert 1993; Findling 1997) and one in Japan (Kuriyama 2002). Twenty-three boys and ten girls took part. Diagnostic methods varied from DSM-III-R (Tolbert 1993) to the CARS (Schopler 1980) (Findling 1997) to DSM-IV criteria for PDDs (Kuriyama 2002). Administration of the intervention varied from 4 to 20 weeks. Dosage varied from 100mg B6 rising to 200mg per day after two weeks (Kuriyama 2002) (no magnesium use reported) to 200mg/70kg of B6 plus 100mg/70kg of magnesium (Tolbert 1993); to the higher dose of 30mg/kg body weight (maximum of 1 gram/day) and 10mg/kg body weight (maximum 350mg/day) (Findling 1997). Outcomes measured included behavioural ones (Tolbert 1993, Findling 1997), social functioning (Findling 1997, Kuriyama 2002) and IQ (Kuriyama 2002).

Tolbert 1993

Tolbert 1993 used a double-blind placebo-controlled asymmetric crossover with random assignment design where Experimental Group 1's order of treatment was TTP (treatment-treatment-placebo) while Experimental Group 2's order of treatment was TPT (treatment-placebo-treatment). In addition, Tolbert used a control group that received neither the placebo nor the B6 and magnesium. No participant attrition was reported. Following a five-week no-treatment baseline run-in period, half of the participants received active treatment for 20 consecutive weeks followed by 10 weeks of placebo. The other half of the participants received active treatment in 2 blocks of 10 weeks with a 10-week block of placebo treatment in between the active treatment blocks. A control group received no treatment at all during the treatment period. The dosage levels were 200mg/70kg of vitamin B6 and 100mg/70kg of magnesium. Tolbert reported a total participant sample of 15 males and 5 females with chronological ages ranging from 6 to 18 years, mental ages ranging from 2.0 to 6.7 years and IQ scores from less than 20 to 65. All participants met the diagnostic standards of DSM-III-R as measured by child psychiatrists. Five of the male subjects served as non-treated controls and were recruited from families that had opted not to participate in the pharmacological aspect of the trial but did agree to participate in the behavioural rating component of the trial. All participants were living in residential settings at the time of the study.

The outcome measures reported by Tolbert were taken from the Ritvo-Freeman Real Life Rating Scale for Autism (R-F) (Freeman 1986). This measure was used to assess the behavioural changes as observed in a classroom situation. The R-F measures behaviours in: (1) sensory motor, (2) social, (3) affective, (4) sensory responses, and (5) language. The measure of change is obtained by summing subscale scores. Higher scores indicated a greater presence ofsymptoms during intervention. Data for all outcomes were continuous. Average inter-rater reliability 94.2% (range 70 to100%) was achieved for the R-F scale observational scoring.

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Findling 1997

Findling et al administered a two-week single-blind placebo prior to initiating the randomized eight-week double-blind placebo-controlled crossover component of the study (Findling 1997). A total of 12 participants (11 males, 1 female; mean age=77 mo, range=36 to 155 mo) were enrolled in the study. At the conclusion of the two-week placebo baseline, two subjects were dropped from the study due to their inability to swallow the encapsulated medications leaving 10 participants (9 males, 1 female; mean age=73 mo, range= 36 to155 mo) for the treatment portion of the study. Beginning with week three of the study, the 10 remaining participants were randomly assigned to either the experimental condition receiving the B6-Mg or to the control condition receiving a placebo. Beginning with week seven, the participant groups were switched with each receiving the other intervention (B6-Mg versus placebo). No washout time elapsed between the end of the first four-week condition and the beginning of the second four-week condition. The dosage level for B6 and Mg was 30mg/kg body weight (maximum of 1 gram/day) and 10mg/kg body weight (maximum 350mg/day), respectively. Participants for this study met the diagnostic standards of DSM-III-R as measured by a certified child psychiatrist and child neurologist.

A pre-treatment measure reported by Findling for this study, the Childhood Autism Rating Scale (CARS) (Schopler 1980; DiLalla 1994), was used to verify participants' diagnostic classification of autism. Prior to the initiation of treatment, and weekly thereafter during the study, the following measures were administered to each participant: (1) The Clinical Global Impression Scale (CGI) (NIMH 1985), (2) Children's Psychiatric Rating Scale (CPRS) (Campbell 1985; Overall 1988), (3) Global Obsessive Compulsive Scale (OCS) (Insel 1983), (4) Conners Parent Rating Scale (PRS) (Goyette 1978), and (5) Conners Teacher Rating Scale (TRS) (Goyette 1978). The CARS is a 15-item scale designed to distinguish between mild to moderate and severe behavioural expressions, the CGI, CPRS, and OCS are all measures reflecting the degree of psychopathology. The PRS and TRS are measures of parent and teacher observations.

Kuriyama 2002

Kuriyama 2002 recruited 15 children diagnosed with PDDs to participate in the study of pyridoxine (vitamin B6) versus a placebo. Two participants were excluded because of current use of B6, two had a history of epilepsy, and three were unable to be tested for baseline IQ. The remaining eight children (8 to 12 years of age) were randomly assigned to either an experimental or placebo condition and administered both the pretest and posttest measures. In each group one child was diagnosed with Asperger Syndrome and three children were diagnosed with Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS). The treatment program consisted of B6 administered in 100mg dose once each day for two weeks followed by two weeks of twice daily doses. Outcomes for this study included a measure of intelligence (Wechsler Intelligence Scale for Children-III) and social intelligence (Social Maturity Scale).

Risk of bias in included studies

Three studies (Findling 1997; Kuriyama 2002; Tolbert 1993) were identified as meeting the inclusion criteria. All studies reported randomly assigning participants to the experimental and control conditions. No study provided a clear description of the method of participant assignment. All senior authors were contacted for additional information regarding the randomization procedure. Tolbert (Tolbert 1993) could not provide additional information on the randomization procedure while Findling (Findling 1997) reported that all subjects were randomly assigned at the conclusion of a two-week baseline period but could not provide specific details of the randomization procedure; information is awaited from Kuriyama et al (Kuriyama 2002).

Tolbert et al reported a single-blind condition in which parents/guardians were given a two-week supply of placebo. Following the baseline, subjects were randomized into the double-blind portion of the study (Tolbert 1993). Findling et al reported a double-blind assignment to treatment and control conditions (Findling 1997). Neither study reported any participant attrition. Kuriyama et al (Kuriyama 2002) had no 'run-up' period and reported blinding of participants, investigators, outcome assessors and statisticians. There was no loss to follow-up reported for this study.

Effects of interventions

No meta-analysis is possible in the current version of this review. One study (Tolbert 1993) presented data in a form unsuitable for meta-analysis. Diversity of participants and clinical populations and inconsistent use of outcome measures across remaining studies, mean that no synthesis of data is suitable for meta-analysis.

Tolbert 1993

Tolbert et al reported only an omnibus F-test and p value as a summary of the data for his study (Tolbert 1993). A Treatment x Phase analysis yielded a significant reduction across the four treatment phases ($F(3,51)=6.17$, $p=.001$). Non-significant differences were reported for both treatment effects ($F(2,17)=1.3$, $p>.2$) and interaction ($F(6,61)=0.25$, $p>2$ (i.e. placebo and treatment phases all showed an improvement but no difference in improvement was seen for treatment when compared to placebo). Standard deviations and means (such as are necessary to use in meta-analysis performed in RevMan) were not provided in the published paper. When contacted to provide additional appropriate data to include in the analysis, Dr Tolbert was unable to locate the data; therefore this study was not included in the analysis of data for this review.

Findling 1997

Findling et al (Findling 1997) provided appropriate group means and standard deviations for data for analysis of five measures of behavioural performance during the treatment program, none of which showed a significant difference. Behaviours associated with individuals with autism CPRS was used as an assessment of behaviour in children with autism including social interactions, communication skills, and level of physical activity. At two weeks post-treatment onset, no significant differences between the experimental and control groups emerged (2.70, 95% CI= -6.29, 11.69). An analysis of the data as printed in the published paper for this outcome at four weeks post-treatment onset yields a significant difference in favour of the treated group (-28.00, 95% CI= -37.25, -18.75); however, these data (which include a score of 3.2 when values at all other points are closer to 32) are in conflict with the triallists' own analysis, which did not report a significant change. Triallists have been contacted but any further information or data are reported to be unavailable.

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Compulsive Behaviour (Findling 1997)
The CGI was used to assess degrees of compulsive behaviour in children. At two weeks post-treatment the CGI performance revealed a non-significant difference between the treatment and control groups (.20, 95%CI= -.92, 1.32). At four weeks post-treatment onset a non-significant difference emerged in favour of the treated group (.10, 95% CI= -1.08,1.28).

Obsessive-Compulsive Behaviour (Findling 1997)
The OCS was used to assess children's compulsive behaviours. Findling et al reported no significant difference between the treated and control groups at either the two week (.30, 95%CI= -5.41, 4.81) or four week interval of measurement post-treatment (2.30, 95% CI= -6.52,1.92).

Teacher rating of hyperactivity (Findling 1997)
The TRS is an observational teacher rating scale of child behaviour. For this study, Findling 1997 used only the seven items assessing the hyperactivity factor. Results of the rating by teachers revealed a non-significant difference between the experimental and control conditions at two and four weeks post-treatment (.60, 95% CI= -6.82,8.02 and .60, 95% CI= -6.25,7.45), respectively. However, it should be pointed out that 25% of the TRS questionnaires were not completed and the authors did not indicate at which time or for which child (baseline or placebo lead-in) the questionnaire was not completed.

Parent rating of impulsivity-hyperactivity (Findling 1997)
The PRS is a parent observational rating scale of children's impulsivity-hyperactivity behaviour. Results of these observations revealed no significant difference between the experimental and control groups at either two or four weeks post-treatment onset (-.30, 95% CI= -3.04,3.64 and .30, 95% CI= -3.88, 3.28), respectively. As with the TRS observations, 16.7% of the PRS questionnaires were not completed. No follow-up measurements were reported subsequent to the treatment period. These analyses were compared to analyses performed in the trial report and all effects were likewise found to be non-significant.

Kuriyama 2002
Three components of the WISC-III performance were reported including Verbal IQ, Performance IQ and Total IQ (Kuriyama 2002). An analysis of the group performances for these (see Analysis 2.1, Analysis 3.1, and Analysis 1.1) revealed no significant effects for any of the measures reported (see also Table 1, calculated using individual patient data supplied by authors). This is in contrast to the authors' stated findings, a discrepancy which can be accounted for by differences between groups at baseline, and investigators' use of change scores in compensation. The authors of Kuriyama 2002 reported 'net gains in IQ or SQ scores', calculated as follows: "net gain in IQ or SQ scores=(the postintervention IQ or SQ scores of the pyridoxine group minus the baseline IQ or SQ scores of the pyridoxine group) minus (the postintervention scores of the placebo group minus the baseline IQ or SQ scores of the placebo group). Student's t-tests were used to compare the net gain in IQ or SQ scores between the pyridoxine and placebo groups. Analysis of covariance (ANCOVA) was used to add adjustment for potential confounders.' Net gain in verbal IQ scores in the pyridoxine group as relative to the placebo group showed a significant difference (5.2, 95% confidence interval 0.2 to 10.3). Kuriyama concluded that this study 'demonstrated that pyridoxine was associated with improvement in the verbal IQ scores. This result suggests that the subgroup of PDDs might have a similar pathophysiological mechanism to pyridoxine-dependent epilepsy' but the authors themselves warned that their results should be 'interpreted with caution because [of] the small sample size... and because it was 'a short-term study for four weeks. A long-term study of the beneficial and adverse effects of pyridoxine is necessary' (Kuriyama 2002).

Adverse events
It has been reported that a long-term administration of pyridoxine may induce adverse effects such as a sensory peripheral neuropathy (Schaumberg 1983), but no such effects were reported in these (relatively short-term) studies. Findling 1997 reported some side effects, but only during the placebo phases of the study (there were a few reports of upper respiratory infection and one each of headache, increase in bedwetting, and decrease in appetite).

DISCUSSION

This review is limited to three studies representing a total of 28 participants with autism spectrum disorder.

Sample size is problematic in this review. Since all three included studies had small numbers of participants, the results obtained may in part be due to a lack of power to detect group differences. Future research should be conducted using appropriately large sample sizes in order to assess any changes in measured performances in a reliable way. This may be particularly important if the outcome measures do not have appropriately robust psychometric properties.

Analysis could be accomplished for only one of the three included studies (Findling 1997). Of the ten measures post-treatment, only one (the CPRS score at four weeks, as reported in the data table) showed a significant difference between the treated and control group performances. The discrepancy between the apparently significant data reported for the CPRS measure of behaviour at four weeks and the authors' conclusion that the intervention produced no significant differences calls into question the accuracy of the data reported in the tables. While such a finding, if accurate, may suggest that a longer treatment period might produce more positive effects for the CPRS measure, it must be remembered that all other measures revealed no significant differences. Findling et al did present a summary of the effect of time on the five measures. It was concluded that there were no significant differences across the 10 weeks of treatment (Findling 1997). In addition, the two measures of compulsive behaviour yielded similar results. No significant differences emerged between the treatment and control conditions at either two or four weeks post-treatment. The teacher and parent ratings are even more difficult to interpret due to the lack of specificity regarding the completion of the questionnaires, as reported above. All of the missing questionnaires may have come from the treatment period and the values presented may reflect the two participants who were dropped from the treatment arm of the study, while the values representing the treatment periods were based on less than the total sample (10 participants). Correspondence with the author did not yield clarification on this issue.

Analysis of Kuriyama is difficult due to small sample size (n=8) (substantially underpowered) and in the case of the VIQ and TIQ scores, even positive effects may be misleading (Kuriyama 2002). Also, the diagnostic classification of the participants is markedly different from Findling 1997 in that the children in Kuriyama's study

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are typically considered to be higher functioning than children diagnosed with autism. Both Asperger Syndrome (AS) and PDDNOS have different developmental histories and differential diagnosis characteristics. The label of AS and PDDNOS do place children so diagnosed under the umbrella of 'autism spectrum disorder', but they are functionally less severe and often qualitatively different in their deficit abilities; moreover, the investigators themselves emphasised the use of their work as hypothesis-generating for those interested in the pathophysiological mechanisms in PDDs.

Several important issues were not addressed in the studies reviewed that might fall into the category of confounding factors, and future research should certainly attempt to address many of these. For example, the age range for these studies may not have been sensitive to response variations in accounting for treatment effects. The age range for studies was quite large (Tolbert's inclusion criteria went from 6 to 18 years while Findling's participants were between 3 and 13 years of age and Kuriyama's 8 to 12) (Tolbert 1993, Findling 1997, Kuriyama 2002). In Findling's study, two of the five participants of the treatment arm of the study were six or more years older than the eldest of the remaining participants. Excluding these two older participants reduces the mean age of the participants by more than 20 months. Such a period of time is not inconsequential in the development of young children and might lead to a different level of response.

Considering the severity of the condition, some individuals with autism may need longer treatment periods in order to benefit from treatment, and future research should address this issue. While Findling 1997 measured outcomes at two and four week intervals, no rationale was given as to why the total treatment period of four weeks was established. It could be that longer treatment would provide a greater response variation for some individuals. Furthermore, this response variation may be an interactive factor with other variables such as age, severity, or outcome. Lastly, the nature of the outcomes measured should be considered. Tolbert et al did provide for a measure of quality of life using the R-F Scale and concluded that no significant differences were observed between treatment and placebo conditions (Tolbert 1993). However, Findling et al assessed outcomes that sought to measure improvement in core features of autism, such as behaviour rating, hyperactivity, and compulsiveness (Findling 1997). Future research should take into account measurement of other meaningful outcomes such as quality of life, educational readiness, independence and daily living skills.

AUTHORS' CONCLUSIONS

Implications for practice

No changes in conclusions resulted with the updated version of this review (2005). Due to the small number of studies, the methodological quality of studies, and small sample sizes, no recommendation can be advanced based on this review regarding the use of B6-Mg as a treatment for autism. There is simply not sufficient evidence to demonstrate treatment efficacy.

Implications for research

This review was able to identify a total of 19 studies that have attempted to address the efficacy of vitamin B6 interventions. As only three studies were constructed in such a manner as to reflect the standards of high quality research design, the most pressing need is to develop well-controlled studies to adequately assess the effectiveness of B6-Mg as an intervention for treating individuals with autism. The major problem facing any research program in this area is the low incidence of autistic participants. Even though large sample studies may not be feasible, multiple smaller sample studies as multi-centre trials are feasible. Such a research model would allow for the aggregation of data across studies to increase the power of the analysis and findings.

ACKNOWLEDGEMENTS

We would like to thank Martine Vanryckeghem and Charles Delalonde of the University of Central Florida, who served as translators of French and German
language articles.

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REFERENCES

References to studies included in this review

Findling 1997 *{published data only}*

Findling RL, Maxwel K, Scotese-Wojtila L, Husang J, Yamashita T, Wiznitzer M. High-dose pyridoxine and magnesium administration in children with autistic disorder: An absence of salutary effects in a double-blind, placebo-controlled study. *Journal of Autism and Developmental Disabilities* 1997;**27**(4):467-478.

Kuriyama 2002 *{published and unpublished data}*

Kuriyama S, Kamiyama M, Watanabe M, Tamahashi S, Muraguchi I, Watanabe T, et al. Pyridoxine treatment in a subgroup of children with pervasive developmental disorders. *Developmental Medicine & Child Neurology* 2002;**44**:283-286.

Tolbert 1993 *{published data only}*

Tolbert L, Haigler T, Waits MM, Dennis T. Brief report: Lack of response in an autistic population to a low dose clinical trial of pyridoxine plus magnesium. *Journal of Autism and Developmental Disabilities* 1993;**23**(1):193-199. [MEDLINE: 93216596]

References to studies excluded from this review

Barthelemy 1980 *{published data only}*

Barthelemy C, Garreau B, Leddet I, Sauvage D, Domenech J, Muh JP, Lelord G. Biological and clinical effects of oral magnesium and associated magnesium-vitamin B6 administration on certain disorders observed in infantile autism (author's transl). *Therapie* 1980;**35**(5):627-632. [MEDLINE: 81153850]

Barthelemy 1981 *{published data only}*

Barthelemey C, Garbeau B. Leddet I, Ernouf D, Muh JP, Lelord G. Behavioral and biological effects of oral magnesium, vitamin B6, and combined magnesium-B6 administration in autistic children. *Magnesium Bulletin* 1981;**2**:150-153.

Barthelemy 1983 *{published data only}*

Barthelemy C, Garreau B, Leddet I, Sauvage D, Muh JP, Lelord G, Callaway E. Value of behavior scales and urinary homovanillic acid determinations in monitoring the combined treatment with vitamim B6 and magnesium of children displaying autistic behavior [Interet des echelles de comportement et des dosages de l'acide homovanilique urinaire pour le controle des effets d'un traitement associant vitamine B6 et magnesium chez des enfants ayant un comportement autistique]. *Neuropsychiatrie de l Enfance et de l'Adolescence* 1983;**31**(5-6):289-201.

Barthelemy 1985 *{published data only}*

Barthelemy C, Martineau J, Bruneau N, Garreau B, Barthelelemy, Muh JP, Lelord, G. Marqueurs cliniques (items d'echelles de comportement), electrophysiologiques (potentials evoques conditionnes) et biochimiques (acide homovanillique urinaire) dans l'autisme de l'enfant [Clinical (behavioral scale items), electrophysiological (evoked potentials) and biochemical (urinary HVA) markers in autistic children.]. *L'Encephale* 1985;**11**:101-106.

Bönisch 1968 *{published data only}*

Bonish E. Experiences with pyrithioxin in brain-damaged children with autistic syndrome [Erfahrungen mit Pyrithioxin bei hirngeschadigten Kindern mit autistischem Syndrom]. *Praxis der Kinderpsychologie und Kinderpsychiatrie.* 1968;**17**(8):308-310.

Jonas 1984 *{published data only}*

Jonas C, Etienne T, Barthelemy C, Jouve J, Mariotte N. Clinical and biochemical value of Magnesium + vitamin B6 combination in the treatment of residual autism in adults [Interet clinique et biochimique de l'association vitamine B6 + magnesium dans le traitement de l'autisme residuel a l'age adulte]. *Therapie* 1984;**39**(6):661-669. [MEDLINE: 85168896]

Lelord 1978 *{published data only}*

Lelord G, Callaway E, Muh JP, Arlot JC, Sauvage, D, Garreau B, Domenech J. L'acide homovanilique urinaire et ses modifications par ingestion de vitamine B6: Exploration fonctionnelle dans l'autisme de l'enfant? Rev. Neurol (Paris) 1978;134(12):797-801.Lelord G, Muh JP, Barthelemy C, Martineau J, Garreau J. Effects of pyridoxine and magnesium on autistic symptoms-initial observations [Modifications in urinary homovanillic acid after ingestion of vitamin B6; functional study in autistic children (author's transl)]. *Rev. Neurol (Paris)* 1978;**134**(12):797-801. [MEDLINE: 79248361]

Lelord 1981 *{published data only}*

Lelord G, Muh JP, Barthelemy C, Martineau J, Garreau J. Effects of pyridoxine and magnesium on autistic symptoms-initial observations. *Journal of Autism and Developmental Disabilities* 1981;**11**(2):219-230.

Lelord 1982 *{published data only}*

Lelord G, Callaway E, Muh JP. Clinical and biological effects of high doses of vitamin B6 and Magnesium on autistic children. *Acta Vitaminologica et Enzymologica* 1982;**4**(1-2):27-44.

Martineau 1981 *{published data only}*

Martineau J, Garreau B, Barthelemy C. Effects of vitamin B6 on averaged evoked potentials in infantile autism. *Biological Psychiatry* 1981;**16**(7):627-641.

Martineau 1982 *{published data only}*

Martineau J, Garreau B, Barthelemy C, Callaway E, Lelord G. Comparative effects of oral B6 Mg and Mg administration on evoked potentials conditioning in autistic children. In: Rothenberger editor(s). Event-related potentials in children. New York: Elsevier Biomedical Press, 1982:411-416.

Martineau 1985 *{published data only}*

Martineau J, Barthelemy C, Garreau B, Lelord G. Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. *Biological Psychiatry* 1985;**20**(5):467-478.

Martineau 1988 *{published data only}*

Martineau J, Barthelemy C, Cheliakine C, Lelord G. Brief Report: An open middle-term study of combined vitamin B6-Magnesium in a subgroup of autistic children selected on their sensitivity to

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this treatment. *Journal of Autism and Developmental Disorders* 1988;**18**(3):435-447. [MEDLINE: 89008019]

Martineau 1989 *{published data only}*

Martineau J, Barthelemy C, Roux S, Garreau B, Lelord G. Electrophysiological effects of fenfluramine or combined vitamin B6 and magnesium on children with autistic behaviour. *Developmental Medicine & Child Neurology* 1989;**31**(6):721-727. [MEDLINE: 90092791]

Menage 1992 *{published data only}*

Menage P, Thibault G, Barthelemy C, Lelord G, Bardos P. CD4+ CD45RA+ T lymphocyte deficiency in autistic children: effect of a pyridoxine-magnesium treatment. *Brain Dysfunction* 1992;**5**(5-6):326-333.

Rimland 1978 *{published data only}*

Rimland B, Callaway E, Dreyfus P. The effect of high doses of Vitamin B6 on autistic children: a double-blind crossover study. *American Journal of Psychiatry* 1978;**135**(4):472-475. [MEDLINE: 78142345]

Additional references

Alderson 2004

Alderson P, Green S, Higgins JPT. Cochrane Reviewers' Handbook 4.2.2 (updated December 2003). In: The Cochrane Library, Issue 1, 2004. Chichester UK: John Wiley & Sons Ltd, 2004.

Ananth 1973

Ananth JV, Ban TA, Lehmann HE. Potentiation of therapeutic effects of nicotinic acid by pyridoxine in chronic schizophrenics. *Canadian Psychiatric Association Journal* 1973;**18**(5):377-83.

APA 1994

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Fourth. Washington, DC: American Psychiatric Association, 1994.

Bucci 1973

Bucci L. Pyridoxine and schizophrenia. *British Journal of Psychiatry* 1973;**122**(567):240.

Campbell 1985

Campbell M, Palij M. Behavioral and cognitive measures used in psychopharamocologic studies of infantile autism. *Psychopharamacology Bulletin* 1985;**21**:1047-1053.

DiLalla 1994

DiLalla D, Rogers SJ. Domains of the Childhood Autism Rating Scale; Relevance for diagnosis and treatment. *Journal of Autism and Developmental Disorders* 1994;**24**:115-128.

Egger 1997

Egger M, Davey Smith G, Schneider, M, & Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Fombonne 1999

Fombonne E. The epidemiology of autism: a review. *Psychological Medicine* 1999;**29**:769-786.

Fombonne 2003

Fombonne E. The prevalence of autism. *JAMA* 2003;**289**:87-89.

Freeman 1986

Freeman BJ, Ritvo ER, Yokota A, Ritvo A. A scale for rating symptoms of patients with the syndrome of autism in real life settings. *Journal of the American Academy of Child Psychiatry* 1986;**25**(1):130-136.

Goyette 1978

Goyette CH, Conners, CK, Ulrich RF. Normative data on revised Conners parent and teacher rating scales. *Journal of Abnormal Child Psychology* 1978;**6**:221-236.

Greenberg 1970

Greenberg GH. An evaluation of niacinamide in the treatment of childhood schizophrenia. *American Journal of Psychiatry* 1970;**127**(1):89-96. [MEDLINE: 70227238]

Insel 1983

Insel TR, Murphy, DL, Cohen, RM, Alterman I, Kilts C, Linnoila M (. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. *Archives of General Psychiatry* 1983;**40**:605-612.

NIMH 1985

National Institutes of Mental Health. Clinical Global Impression Scale. *Psychopharamacology Bulletin* 1985;**21**:839-843.

Overall 1988

Overall JE, Campbell M. Behavioral assessment of psychopathology in children: Infantile autism. *Journal of Clinical Psychology* 1988;**44**:708-716.

Pfeiffer 1996

Pfeiffer SL, Norton J, Nelson L, Schott S. Efficacy of vitamin B6 and magnesium in the treatment of autism: A methodology review and summary of outcomes. *Journal of Autism and Developmental Disorders* 1996;**25**(5):481-493.

Rimland 1964

Rimland B. Infantile autism: The syndrome and its implications for neural theory of behavior. New York: Appleton Century Crofts, 1964.

Rimland 1973

Rimland B. High-doseage levels of certain vitamins in the treatment of children with mental disorders. In: Hawkins D, Pauling L editor(s). Orthomolecular psychiatry: treatment of schizophrenia. San Francisco, CA: W. H. Freeman, 1973.

Schaumberg 1983

Schaumberg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. Sensory neuropathy from pyridoxine abuse. *New England Journal of Medicine* 1983;**309**:445-8.

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Schopler 1980

Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood autism rating scale (CARS). *Journal of Autism and Developmental Disabilities* 1980;**1**:91-103.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Findling 1997

Methods	Randomized, double blind placebo-controlled, crossover trial. Following a 2 week pre-randomization placebo lead-in period
Participants	12 participants enrolled, 10 (9 boys, 1 girl) completed program; mean age 6yrs 3 mo, range 3 yrs old to 12.9 years old
Interventions	1. B6+Mg (4 weeks) then Placebo (4 weeks)2.Placebo (4 weeks) then B6+Mg (4 weeks)Dosage: B6: 30mg/kg/day (max =1gram);Mg:10mg/kg/day (max =350mg/day)
Outcomes	Performance on CARS, CGI, CPRS, OCS scales
Notes	B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kuriyama 2002

Methods	Randomised double blinded placebo controlled trial. Outcome assessors and statistician also blinded.
Participants	15 children with PDD recruited initially. All had been diagnosed with PDD (two with Asperger syndrome) and also demonstrated features of a 'subgroup of children with PDDs who exhibit clinical features similar to those of pyroxidine dependent epilepsy but do not have a history of seizures'. Then, 2 were excluded because of history of epilepsy; 2 because they were already using B-complex vitamins, 3 because their IQs were not measurable. 8 (4 males, 4 females) children remained. Mean age 10 years 6 months (SD = 1 year 8 months). Placebo group of 2 males, 2 females. Mean age 10 years 10 months (SD = 1 year). For both groups, mean body weight was 44.5 (SD = 16.3) and 44.5 (SD = 18.3) kg, mean verbal IQ scores 74.3 (SD = 22) and 77.5 (SD = 15), mean performance IQ scores 78.8 (SD = 30.8) and 68.8 (SD = 5.2) and mean Social Quotient (SQ) scores 73.5 (SD = 14.6) and 81 (SD = 11.9), respectively.
Interventions	1. B6 100 mg daily for 2 weeks, then twice a day 100 mg each time, for two weeks 2. Placebo in identical powder form. Note compliance was measured by parent report and by blood measurements after the trial 3 Parents were asked to complete a diary, recording any change in their child's clinical signs or behaviour
Outcomes	IQ and social quotient SQ scores IQ scores measured using Wechsler Intelligence Scales for Children -III (WISC-III) test 9. This test assigns both verbal IQ scores and performance IQ scores. All IQ tests were conducted on each patient by the clinical psychologist both at baseline and at end of fourth week of medication. The standard score of each IQ has a mean of 100 and a standard deviation of 15. SQ scores were measured with the Social Maturity Scale (SM) test. 10 SQ scores were calculated as social age divided by calendar age. All SM tests were assessed by patients' parents.

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Kuriyama 2002 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tolbert 1993

Methods	Randomized double-blind placebo controlled, asymmetric cross-over trial; 10 week treatment blocks
Participants	Treated participants:10 males & 5 females diagnosed using DSM-III-R criteria (age range, 6 to 18)
Interventions	1.B6+Mg (20 weeks) then Placebo 10 (weeks) 2.B6+Mg (10 weeks) then Placebo (10 weeks)then B6+Mg (10 weeks) Dosage: B6: 200mg/70kg weight Mg: 100mg/70kg weight
Outcomes	Sensory-motor; social behaviour; affective behaviour; sensory responses; language
Notes	Reported data not in useable form for analysis; Control group not randomly assigned

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barthelemy 1980	lack of random group assignment to conditions
Barthelemy 1981	non-random group assignment
Barthelemy 1983	non-random group assignment
Barthelemy 1985	non-random group assignment
Bönisch 1968	varied diagnosis for participants; no control condition
Jonas 1984	non-random group assignment
Lelord 1978	non-random group assignment; didn't measure behaviour change
Lelord 1981	open trial; non-random group assignment

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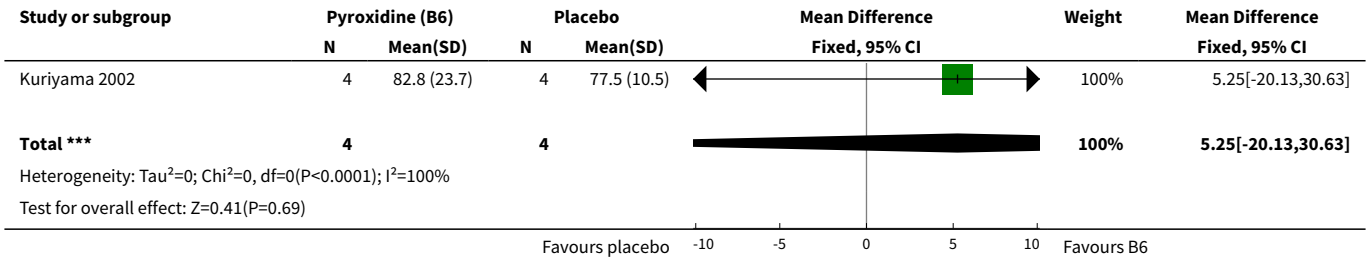
Study	Reason for exclusion
Lelord 1982	open trial; non-random group assignment
Martineau 1981	non-random group assignment; non-comparable group comparison
Martineau 1982	non-random group assignment; didn't measure behavioral change
Martineau 1985	non-random group assignment; didn't measure behavioural change
Martineau 1988	open trial; non-random group assignment
Martineau 1989	open trial; non-random group assignment
Menage 1992	open trial; non-random group assignment
Rimland 1978	open study: non-random group assignment of participants

DATA AND ANALYSES

Comparison 1. Intelligence quotient (IQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 B6 versus placebo	1	8	Mean Difference (IV, Fixed, 95% CI)	5.25 [-20.13, 30.63]

Analysis 1.1. Comparison 1 Intelligence quotient (IQ), Outcome 1 B6 versus placebo.



Comparison 2. Verbal intelligence quotient

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 B6 versus placebo	1	8	Mean Difference (IV, Fixed, 95% CI)	2.0 [-18.22, 22.22]

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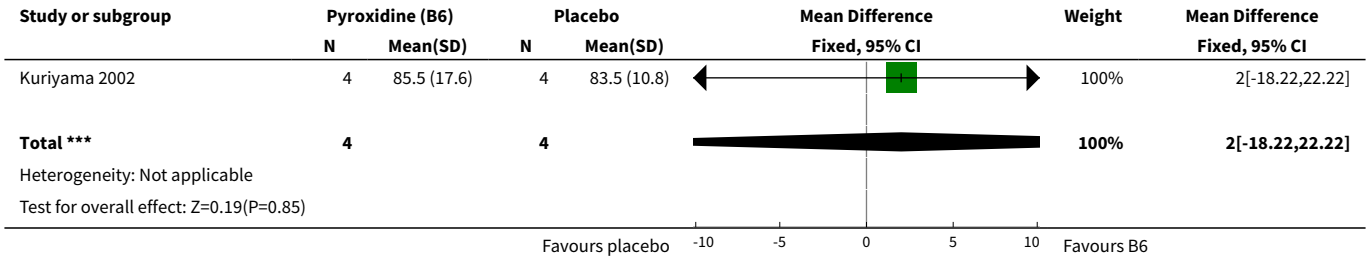
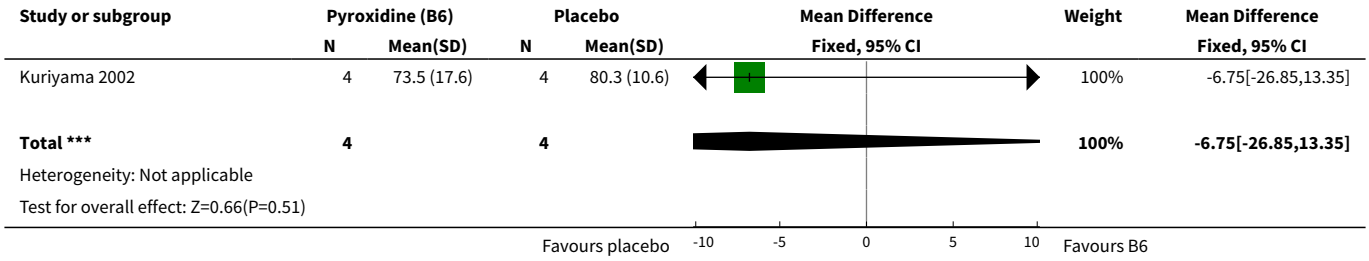
Analysis 2.1. Comparison 2 Verbal intelligence quotient, Outcome 1 B6 versus placebo.



Comparison 3. Perfomance IQ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 B6 versus placebo	1	8	Mean Difference (IV, Fixed, 95% CI)	-6.75 [-26.85, 13.35]

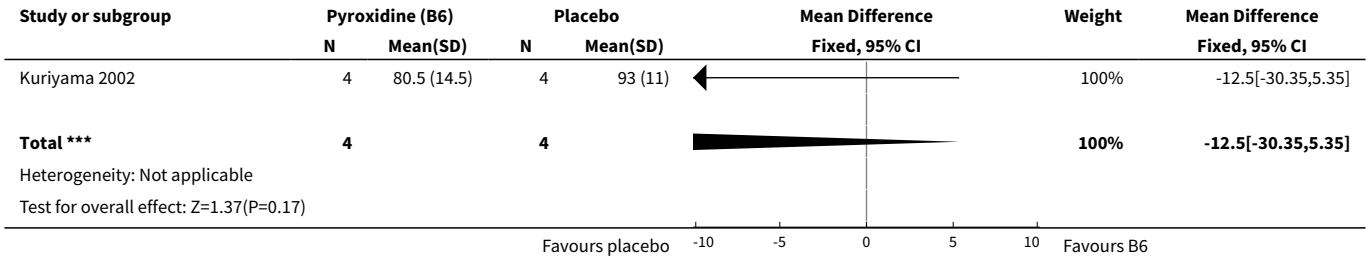
Analysis 3.1. Comparison 3 Perfomance IQ, Outcome 1 B6 versus placebo.



Comparison 4. Social quotient (SQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 B6 versus placebo	1	8	Mean Difference (IV, Fixed, 95% CI)	-12.5 [-30.35, 5.35]

Analysis 4.1. Comparison 4 Social quotient (SQ), Outcome 1 B6 versus placebo.



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WHAT'S NEW

Date	Event	Description
7 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 1, 2003

Date	Event	Description
9 August 2005	New citation required and conclusions have changed	Substantive amendment
8 August 2005	Amended	Conclusions changed: 9 August 2005
30 June 2005	Amended	New studies found and included or excluded: 1 July 2005

CONTRIBUTIONS OF AUTHORS

The searching of databases was conducted by first author Chad Nye and Jo Abbott (Trial Search Coordinator) and data entry was conducted by Chad Nye. Both Chad Nye and Alejandro Brice contributed to the selection of papers for inclusion and exclusion, the extraction and analysis of data, and the writing of the text of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Autistic Disorder [*drug therapy]; Drug Therapy, Combination; Magnesium [*therapeutic use]; Randomized Controlled Trials as Topic; Vitamin B 6 [*therapeutic use]; Vitamin B Complex [*therapeutic use]

MeSH check words

Adult; Child; Humans

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