

Evidence based case report: Pyridoxine supplementation in children with pervasive developmental disorders

Sekarpramita Darmaputri¹, Tjhin Wiguna²

Pervasive developmental disorders (PDD) is defined as a neurodevelopmental disorder, characterized by social withdrawal, communication deficits, and repetitive behaviors. PDD include autistic disorder, Rett's syndrome, childhood disintegrative disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified or atypical autism.¹ Update of epidemiological studies published between 1966 and 2006 show reports of estimated prevalence for autism has varied between 3.31 and 86 children per 10,000,² and predominantly occurs in males than females (male:female ratio = 4:1).³

There is a hypothesis that behavioral problems in children with pervasive developmental disorder are highly associated with the neurotransmitter imbalances. Therefore, psychotropic medications (eg. atypical antipsychotics, selective serotonin reuptake inhibitors, and psychostimulants), which work on dopamine and serotonin receptors, are the FDA-approved medications for PDD.⁴ On the other hands, the use of novel, unconventional, and/or off-label treatments associated with the neurotransmitters pathway for children with PDD is increasing and more common.

Pyridoxine (vitamin B6) as a complementary therapy was first reported to improve speech and language in some children diagnosed with "autism syndrome" when Bonish (1968) observed that some

participants showed improvement in speech and language.⁴ Since then, the study of vitamin B6 use for PDD treatments has been extensively conducted and some clinicians administered it empirically, but none has been able to produce a conclusive result.

It was found that in autistic children the enzyme pyridoxal kinase, which works to phosphorylate vitamin B6 into the active form pyridoxal-5-phosphate or PLP, was impaired. Impaired conversion by pyridoxal kinase results in high plasma levels of total vitamin B6 and low levels of PLP.⁵ Pyridoxal-5-phosphate is a co-factor for 113 enzyme, including neurotransmitters serotonin, dopamine, gamma aminobutyric acid (GABA), and the catecholamines.⁶ Therefore, low levels of PLP could have wide-ranging effects on human metabolism, including those on mental function. However, supplementation of PLP as a therapy is implausible as the phosphate group is removed during digestion, so PLP would likely have no additional benefit.⁶ Ames et al then postulated that high doses (100-600 mg/day)⁷ of vitamin B6

From the International Class¹ and Division of Child and Adolescent Psychiatry², Department of Psychiatry, University of Indonesia Medical School, Jakarta, Indonesia.

Reprint requests to: Sekarpramita Darmaputri, University of Indonesia Medical School, Jalan Salemba Raya 4, Jakarta 10440, Indonesia. Tel +62-815-10383518. E-mail : d.sekarpramita@yahoo.com.

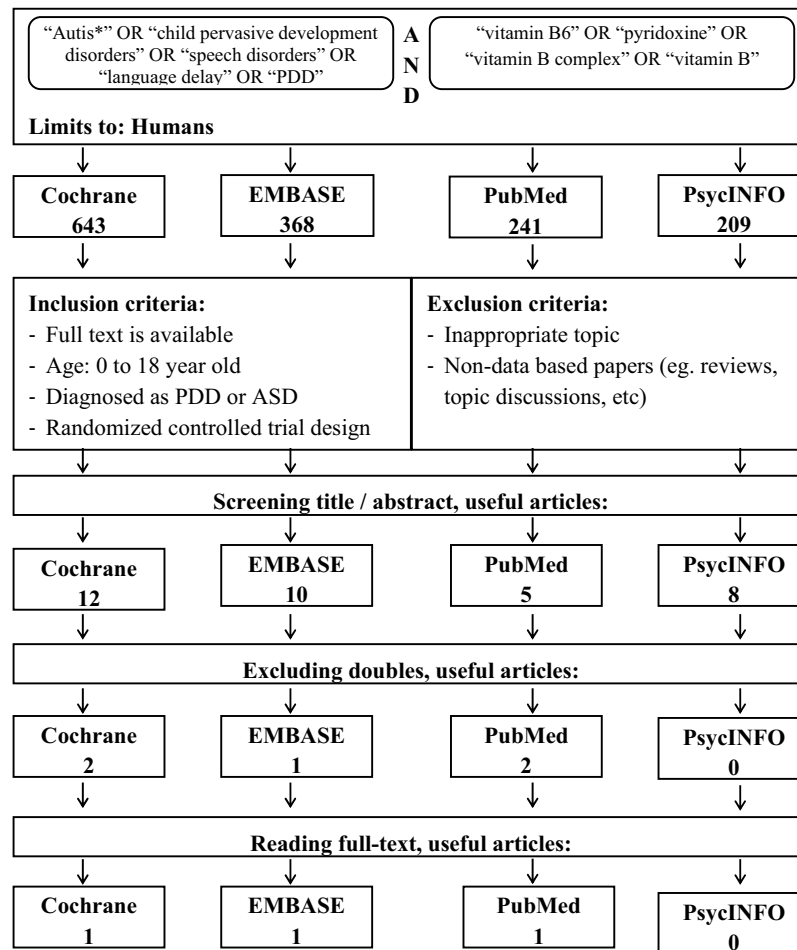


Figure 1. Flowchart of the searching and selection strategy

increased intracellular substrate concentrations and thus activated the defective enzymes to phosphorylate into PLP⁸

In our center, vitamin B6 is often empirically prescribed in low-dose (not in accordance with standard operational procedure), although no prior assessment to its efficacy ever studied before. Hence this review is conducted to increase the awareness of and to investigate whether pyridoxine supplementation is superior to placebo as a therapeutic management in children with PDD.

Case illustration

A 7-year old boy with autistic spectrum disorder accompanied by her mother came for a routine control

at the Child and Adolescent Psychiatry Polyclinic. Two years ago, his mother realized that he could not behave calmly, frequently got temper tantrum, and easily got upset and uneasy. He also could not communicate verbally or non-verbally. There was no significant eye contact, and he did not follow simple instructions. He repeatedly talked “ti-ti” or “bi-bi” without any meanings. However, there was not any self-destructive behavior nor any attempt to harm other people. He was taken to hospital to have speech and occupational therapy.

Two months ago, a therapist told his mother that the patient is diagnosed as autistic spectrum disorder and could not be helped only with the speech and occupational therapy only. He also needed a medication for reducing his autistic behavior.

Currently, he cannot express his communication

verbally and is quite difficult in expressing his needs by using a non-verbal behavior. Although he is getting better at maintaining his eye contact, but he is still reported to have few friends at his school, have no social reciprocity and lack of social judgment. Additionally, he also shows a stereotyped, repetitive, or idiosyncratic language. He did not show any response when another child asked him to play together. During examination, he kept on interested in the washing bin, walked around the examination room, and even climbed up the chair. According to his mother, he likes to flap his fingers every time he feels extremely happy or extremely upset. He was given Risperidone 2x0.5 mg and pyridoxine 2x5 mg.

Methods

The *The Cochrane*, *EMBASE*, *PubMed*, *PsycINFO* database were searched, using keywords (“Autis*” OR “child pervasive development disorders” OR “speech disorders” OR “language delay” OR “PDD”) AND (“vitamin B6” OR “pyridoxine” OR “vitamin B complex” OR “vitamin B”) on 9-17 April 2012. All journal articles related with the comparison of vitamin B6 and placebo in improving social, communication, and behavioral responses for children with PDD were collected.

Searches were limited to randomized controlled trials (RCTs), systematic review, or meta-analysis as their designs. RCTs are excluded if they have been reviewed in a systematic review and/or meta-analysis. Other inclusion criteria include children (0-18 years), diagnosed with PDD, and full-text availability. Exclusion criteria included irrelevant topics and study is not written in English or Indonesian language. The flowchart of searching and selection strategy can be seen in **Figure 1**.

Results

A total of 35 studies were retrieved after screening for possible relevant titles/abstract and evaluated for potential inclusion, of which 7 studies remained after excluding irrelevant topic and doubles related to same title extracted from different databases. After reading full-text and excluded some RCTs have been reviewed

in a systematic review, only 3 studies included into this review.⁹⁻¹¹ No meta-analysis is identified.

Nye & Brice (2009) in *Cochrane Review* reported only 3 out of 85 studies met the inclusion criteria are relevant to the study.¹²⁻¹⁴ Nye & Brice stated it is impossible to produce a meta-analysis due to lack of necessary data for analysis (Tolbert, 1993)¹⁴ and differences in both clinical populations and outcome measures between another two remaining studies (Findling, 1997¹² and Kuriyama, 2002¹³). Nevertheless, the review by Nye & Brice is able to produce a systematic review which concluded a finding that current studies are unable to provide sufficient data to warrant the effectiveness and efficacy of vitamin B6 as a therapy for PDD.¹⁰ This conclusion is supported by Rossignol et al (2009)¹¹ who also reviewed the exact same studies as Nye & Brice (2009).

An updated systematic review is conducted by Murza et al (2010),⁹ who reviewed one study by Adams & Holloway (2004).⁵ However, Adams & Holloway did not exclusively administer vitamin B6/Mg as their therapy, but instead a moderate dose of multivitamin and mineral supplement. Hence, result of the study might be erroneously interpreted. Considering the shortcomings of the study, Murza et al concluded they supported Nye & Brice's review.

Critical appraisal of Tolbert et al.¹⁰

We assessed the Tolbert *et al.* study as valid. They described and randomized their treatment assignments (control group, group 1, and group 2) clearly. However, no details of the randomizing process were given in their report. Characteristics of participants in the groups were not significantly different. Participants were followed up for a sufficient duration and completely (35 weeks), analyzed in the groups to which they belonged, and were treated similarly, except for the experimental treatment. Participants and clinicians were blinded to treatment.¹⁰

Nonetheless, the importance of this journal article could not be assessed, as the data was insufficient for analysis of relative risk (RR), adjusted relative risk (ARR), relative risk reduction (RRR), and number needed to treat (NNT).⁸ Nor did the authors use pooled SD and effect size.⁹ Applicability analysis of this article revealed that it could not be applied to

Table 1. Description of the eligible RCTs reviewed by Nye & Brice (2009)¹⁰ and Rossignol (2009)¹¹

	Tolbert et al. (1993) ¹⁰	Findling et al. (1997) ¹¹	Kuriyama et al. (2002) ¹²
Research questions of the study	To assess the safety and efficacy of low-dose vitamin B6/Mg	To assess the short-term safety and efficacy of vitamin B6/Mg	To assess the effectiveness of vitamin B6 in improving IQ and social quotient (SQ) scores in children with PDD
Study design	Randomized, double-blind, controlled, asymmetric cross-over trial	Randomized, double-blind, controlled, cross-over trial	Randomized, double-blind, controlled, cross-over trial; outcome assessor and statistician also blinded
Participants	20 participants; aged 6–18 years	12 participants; aged 3–12.9 years - 10 completed the program	8 PDD participants; aged 6–17 years
Interventions	B6 (20 wks) → placebo (10 wks) B6 (10 wks) → placebo (10 wks) → B6/Mg (10 wks) Control → received nothing.	B6 (4 wks) → placebo (4 wks) Placebo (4 wks) → B6/Mg (4 wks)	B6 1x100 mg (2 wks) → B6 2x100 mg (2 wks) Placebo 1x1 (2 wks) → placebo 2x1 (2 wks) Parent's diary
Vitamin B6 dose	200 mg/70 kg/day	30 mg/kg/day (max: 1 gram/day)	1x100 mg/day followed with 2x100 mg/day
Magnesium dose	100 mg/70 kg/day	10 mg/kg/day (max: 350 mg/day)	-----
Outcome measurements	Scores on Rivot-Freeman Real-Life Rating Scale for Autism	Performance on CARS, CGI, CPRS, OCS, Conners teacher, and Conners parent scale	IQ (Wechsler Intelligence Scales for Children-III) test 9 SQ scores (Social Maturity Scale test)
Results	Low dose vitamin B6/Mg was ineffective for PDD; safety unclear	Vitamin B6/Mg was ineffective for autism disorder treatment; safe for short-term.	No significant increase of total IQ, verbal IQ, performance IQ and SQ scores.
Length of follow up	35 weeks	10 weeks	4 weeks
Lost to follow up	None	16.67% did not complete the program	None
Risk of bias: Allocation concealment	Unclear; reported data not in useable form for analysis; control group not randomly assigned.	Unclear	Unclear

CARS: Childhood Autism Rating Scale, CGI: Clinical Global Impression, CPRS: Children's Psychiatric Rating Scale, OCS: Obsessive-Compulsive Symptoms, RCT: Randomized Controlled Trial, IQ: Intelligent Quotient, SQ: Social Quotient

our patient, despite the similarity of the study sample characteristics to our patient's condition and the clinical question asked. Additionally, Tolbert *et al.* reported no benefit and no harm from administering low doses of pyridoxine/Mg therapy.¹⁰ Values and preferences of the patient were not assessed. Hence, applicability to our patient remains questionable.

Critical appraisal of Findling *et al.*¹¹

Findling *et al.* (1997) described and randomized their treatment assignment (control group and vitamin B6/Mg). However, they did not report the details of their randomization process. Characteristics of participants were not significantly different between groups. Two participants withdrew from the study.

Participants were followed up for a sufficient duration and completely (10 weeks), analyzed in the groups to which they belonged, and were treated similarly, except for the experimental treatment. Participants and clinicians were blinded to treatment.¹¹

The importance of this journal article was assessed using the Critical Appraisal Worksheet from Dartmouth College: Therapy study with continuous outcome calculations.⁹ An intervention review by Nye *et al.* (2009) provided the necessary mean difference and 95%CI of the study.⁷ Pyridoxine showed no significantly beneficial effect for improving behavioral deficits in autistic spectrum disorder in children. A disadvantage of the Findling *et al.* study was that 25% of Conners teacher and 16.7% of Conners parent questionnaires were not completed.¹¹

Applicability analysis of this article revealed that it could be applied to our patient, however, no beneficial effect was shown in the study. The study sample characteristics were similar to that of our patient and they asked similar clinical questions. However, the study reported no beneficial effect based on the performance scales assessed as well as mild adverse effects of treatment. As such, there was no clear indication for us to start treating our patient with the combination. Additionally, patient's value and preferences had not yet been assessed.

Critical appraisal of Kuriyama et al.¹²

Kuriyama et al. (2002) described and randomized their treatment assignment (control and pyridoxine groups). However, they did not report the details of their randomization process. Characteristics of participants were not significantly different between groups. Participants were followed up in the short term (4 weeks), analyzed in the groups to which they belonged, and were treated similarly, except for the experimental treatment. Participants and clinicians were blinded to treatment.¹²

The importance of this journal article was assessed using the Critical Appraisal Worksheet from Dartmouth College: Therapy study with continuous outcome calculations.⁹ Kuriyama et al. (2002) did not report the details on their research,¹² however, an intervention review by Nye et al.⁷ (2009) provided the study data from Kuriyama et al. The study showed no significant results for total IQ, verbal IQ, performance IQ, or social quotient scores. Hence, pyridoxine showed no significant beneficial effect on IQ or SQ compared to placebo.

Applicability analysis of this article revealed that it could not be applied to our patient as it did not match his characteristics, was not feasible, and the values and preferences of the patient had not yet been assessed.

Discussion

Autism may be due to defects in a PLP-requiring enzyme or enzymes involved in the metabolism of serotonin and dopamine, although a genetic link to a vitamin B6-requiring enzyme has not been

established yet.⁸ Most commonly clinical sign of autism is an elevation of whole-blood serotonin (5-hydroxytryptamine), which is found in >30% of the patients.¹⁵ Increased concentrations of homovanillic acid, a breakdown product of dopamine, have also been found in several autistic patients.¹⁶

Pyridoxine therapy has been reported to be successful in autism,⁷ raising the possibility a PLP-requiring enzyme might be defective in those patients responsive to vitamin B6. The only PLP-requiring enzyme directly involved with the synthesis or degradation of dopamine and serotonin is AADC (dihydroxyphenylalanine decarboxylase)⁸ However, elevated homovanillic acid, which is at least partially reversible with pyridoxine therapy in some vitamin B6-responsive patients, does not suggest a defect in this enzyme.⁸ Additionally, cases of AADC deficiency have been reported in the literature and result only in a very severe inborn metabolic disorder involving deficient concentrations of dopamine and serotonin.⁸

It remains to be a question whether other enzymes in the metabolic pathways of these neurotransmitters may be responsible for the various forms of autism that involve altered neurotransmitter metabolism. In addition to PLP, the coenzymes FAD, NAD, S-adenosylmethionine, tetrahydrobiopterin, and ascorbate are also used by enzymes in serotonin and dopamine metabolism.⁸ Therefore, it is hypothesized if different autistic patients harbor mutations in different metabolic enzymes, it may be possible to reverse the effects of autism by targeting a treatment to each individual patient. However, what should be taken into consideration is autism is diagnosed by clinical, not biochemical indexes. Furthermore, so little is known about the biochemical basis of this condition, hence it is difficult to associate a treatment response with a particular biochemical or physiologic pathway.⁸

The conclusion that pyridoxine is an effective treatment of autism remains as a challenge due to methodological shortcomings inherent in the studies.⁷ Moreover, newer systematic reviews by Nye & Brice (2009)¹⁰ and Murza et al (2010)⁹ consistently stated that vitamin B6 may not be effective in improving clinical manifestations of autism in comparison with placebo. Although vitamin B6 is relatively safe to administer due to its water-solubility characteristic,

however possible adverse effects as a result of high-dose vitamin B6 and magnesium should be taken into account when prescribing vitamin B6 in patients with PDD. It has been documented that high dose of vitamin B6 is associated with dorsal root ganglia impairment, painful and neurological problems, peripheral neuropathy (eg. numbness or tingling, weakness, feelings of burning, tickling, or pricking in the distal extremities), uncoordinated movements, breathing difficulties, fatigue, and vomiting.^{17, 18} Another adverse effects, which are commonly reported are enuresis, irritability, and sensitivity to sound.¹⁹ Combining pyridoxine with magnesium lessened some of the adverse effects when only pyridoxine is given.^{17, 19}

Rossignol *et al* (2009)¹¹ graded pyridoxine/magnesium as grade C treatment in their review. They also describe the recommended adjunctive treatment for autism spectrum disorders as follows:

- Grade A: melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy;
- Grade B: carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, oxytocin, and vision therapy; and
- Grade C: carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, pyridoxine/Mg, elimination diets, chelation, cyroheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

Considering the efficacy and safety of pyridoxine, systematic review conducted by Rossignol *et al* (2009)¹¹, and availability, feasibility, and cost-effectiveness of the supplementations reviewed, vitamin C may be a better adjunctive treatment for PDD children compared to pyridoxine/Mg supplementation. Dolske *et al* (1993) carried out a randomized double-blinded placebo-controlled crossover study of vitamin C (8 g/70 kg body weight/day) in 500 mg tablets, divided into 2-3 separate doses in 18 children with ASD. The study reported significant improvements in stereotypical behaviors, including rocking, pacing, and whirling without any adverse effect were noted.²⁰ No study is found regarding the drug interaction between vitamin B6 and vitamin C with risperidone, as the FDA-approved medication

for PDD.

In conclusion, there is insufficient evidence to warrant the advocacy of vitamin B6 whether in monotherapy or in combination with magnesium as therapeutic approach to improve individuals with PDD main domains (social, communication, and behavioral responses) when compared to placebo. Furthermore, administration of high-dose vitamin B6 may lead to several adverse effects.

References

1. Currenti S. Understanding and determining the etiology of autism. *Cell Mol Neurobiol.* 2010;30:161-71.
2. Hughes J. Update on autism: A review of 1300 reports published in 2008. *Epilepsy & Behavior.* 2009;16:569-89.
3. Levy S, Mandell D, Schultz R. Autism. *Lancet.* 2009;374:1627-38.
4. Bonish V. Experiences with vitamin B6 with brain-damaged children with autistic syndrome. *Proxis der Kinderpsychologie.* 1968;309:445-7.
5. Adams J, Holloway C. Pilot Study of a Moderate Dose Multivitamin/Mineral Supplement for Children with Autistic Spectrum Disorder. *The Journal of Alternative and Complementary Medicine.* 2004;10(6):1033-9.
6. Adams J, George F, Audhya T. Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. *J Altern Complement Med.* 2006;12(1):59-63.
7. Pfeiffer S, Norton J, Nelson L, Shott S. Efficacy of Vitamin B6 and Magnesium in the Treatment of Autism: A Methodology Review and Summary of Outcomes. *J Autism Dev Disord.* 1995;25:481-93.
8. Ames B, Elson-Schwab I, Silver E. High-dose vitamin therapy stimulates variant enzymes with decreased coenzymes binding affinity (increased Km): Relevance to genetic disease and polymorphisms. *Am J Clin Nutr.* 2002;75:616-58.
9. Murza K, Pavelko S, Malani M, Nye C. Vitamin B6-magnesium treatment for autism: the current status of the research. *Magnesium Research.* 2010;23(2):115-7.
10. Nye C, Brice A. Combined vitamin B6-magnesium treatment in autism spectrum disorder. *The Cochane Collaboration.* 2005:1-19.
11. Rossignol D. Novel and emerging treatment for autism spectrum disorders: a systematic review. *Annals of Clinical Psychiatry.* 2009;21:213-36.
12. Findling R, Maxwell 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. *J Autism Dev Disord.*

- 1997;27:467-78.
13. 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;44:283-6.
 14. Tolbert L, Haigler T, Waits M, Dennis T. Brief report: Lack of response in an autistic population to a low dose clinical trial of pyridoxine plus magnesium. *J Autism Dev Disord*. 1993;23:193-9.
 15. Buitelaar J, Willemsen-Swinkels S. Autism: current theories regarding its pathogenesis and implications for rational pharmacotherapy. *Paediatr Drugs*. 2000;2:67-81.
 16. Martineau J, Barthelemy C, Garreau B, Lelord G. Vitamin B6, Magnesium, and Combined B6-Mg: Therapeutic Effects in Childhood Autism. *Biol Psychiatry*. 1985;20:467-78.
 17. Schaumburg H, Kaplan J, Winderbank A, Vick N, Rasmus S, Pleasure D, *et al*. Sensory neuropathy from pyridoxine abuse. *N Engl J Med*. 1983;309:445-7.
 18. University of Virginia: Health System. Peripheral Neuropathy and Vitamin B6. Virginia: University of Virginia; [29 April 2012]; Available from: <http://uvahealth.com/services/cancer-center/images-and-docs/neuropathy.pdf>.
 19. Rimland B. An orthomolecular study of psychotic children. *Orthomolecular psychiatry*. 1974;3:371-7.
 20. Dolske M, Spollen J, McKay S, Lancashire E, Tolbert L. A preliminary trial of ascorbic acid supplemental therapy for autism. *Prog Neuropsychopharmacol & Biol Psychiatry*. 1993;17:765-74.