Guide to Using Psychotropic Medication to Manage Behaviour Problems among Adults with Intellectual Disability

Technical Document

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Guide to Using Psychotropic Medication to Manage Behaviour Problems among Adults with a Learning Disability

Technical Document Section 3.8: Systematic Reviews: Vitamins and Others

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Vitamins and Others

Identification of primary trials on the use of vitamins and other supplements in the management of behaviour problems in adults with a learning disability.

Databases used

	Search 1	Search 2	Search 3
PsycInfo	1990 to week 2 Oct 2005	1872 to 1990	1990 to week 4 June 2005
Medline	1990 to week 1 Oct 2005	1966 to 1990	1990 to week 4June 2005
Embase	1990 to 43rd week of 2005	1980 to 1990	1990 to 27th week of 2005
Cinahl	1990 to week 2 Oct 2005	1982 to 1990	1990 to week 4 June 2005

Search terms

The databases were searched using the 84 phrases mentioned earlier, with the addition of the following search terms adapted specifically for the vitamins and other supplements review:

85. (Gluten free diet$ or Casein free diet$ or Phenylalanine free diet$).tw.
86. exp Gluten Free Diet/
87. exp Casein/
88. exp Phenylalanine/
89. (Vitamin$ B or riboflavin or thiamine or pabrinex or pyridoxine or nicotinamide or vitamin$ E or alpha tocopheryl or omega 3 or omacor or maxepa or zinc or solvazinc or iron or ferrous or feospan or ferrograd or slow-fe or fersaday or fersamal or galfer or plesmet or niferex or sytron).tw.
90. exp Vitamin B Group/
91. exp Alpha Tocopherol/
92. exp Omega 3 Fatty Acid/
93. exp ZINC/
94. exp IRON/
95. Paraldehyde.tw.
96. exp PARALDEHYDE/
97. (Thyroxine or levothyroxine).tw.
98. exp THYROXINE/
99. exp LEVOTHYROXINE/
100. (Cyproterone or androcur or Goserelin or zoladex or Medroxyprogesterone or provera or Estrogen$ or oestrogen$).tw.
101. exp GOSERELIN/
102. exp MEDROXYPROGESTERONE ACETATE/ or exp MEDROXYPROGESTERONE/
103. exp ESTROGEN/
104. exp CYPROTERONE ACETATE/ or exp CYPROTERONE/
105. (Donezepil or aricept or galantamine or reminyl or memantine or ebixa or rivastigmine or exelon).tw.
106. exp Galantamine/ or exp Donepezil/ or exp Rivastigmine/
107. exp MEMANTINE/
108. exp GLUTEN/
109. exp vitamin b complex/ or vitamin b 6/
110. or/85-109
111. exp NICOTINE/
112. 110 not 111
113. exp dietary restraint/
114. exp proteins/
115. exp Estrogens/
116. exp antiandrogens/
117. exp vitamins/
118. exp fatty acids/

119. exp GALANTHAMINE/
120. 110 or 113 or 114 or 115 or 116 or 117 or 118 or 119
121. 120 not 111
122. 82 and 121
123. limit 122 to (human and "300 adulthood <age 18 yrs and older>" and human and yr=1990-2005)

For search 2:
In order to perform this search, the limits of search 1 were reset so that all articles available in the databases, dated before 1990, could be retrieved. No new search terms were added to the original search.

For search 3:
In order to perform this search, the limits of search 1 were reset so that all articles related to children/ adolescents (under the age of 18 years) could be retrieved. No new search terms were added to the original search.

Results

Each of the databases retrieved the following number of citations for the different searches:

Database	Search 1	Search 2	Search 3
PsycInfo	81	18	41
Medline	135	5	83
Embase	216	17	193
Cinahl	507	8	166

Selection process

Search 1:
This search produced 939 citations overall. It was identified however, that the majority of the citations were clearly not relevant to the clinical question and so in all 905 were excluded based on duplication, title and abstract. This stage left 34 citations to which the inclusion/ exclusion criteria was applied and a further 22 exclusions were made. 9 citations were kept aside in a box due to relevance but small sample size and the full texts for the other 3 were required.

A breakdown of the selection process for this search is shown in figure 25.

Search 2:
All 48 citations produced by the searches for this review were examined to ensure that any relevant controlled trials would not be missed. However, with the exception of 1, all citations were excluded on the basis of duplication, title and abstract. The full texts for the 1 remaining citation plus 1 more discovered through hand searching were necessary for closer scrutiny. These latter 2 studies also failed to satisfy the inclusion criteria and were therefore excluded; the reasons for these are given in table 17.

A breakdown of the selection process for this search is shown in figure 26.

Search 3:
In total, 483 citations were produced altogether comprising of controlled trials to case series. All citations were scanned to ensure that no controlled trials would be overlooked. Nonetheless, most of the citations were eliminated based on duplication, title and abstract. As 5 citations could not be excluded at this stage, the full texts for these were obtained. Full text examination however, revealed that these studies did not meet the inclusion criteria either. The reasons for study exclusions based on their full texts are also given in table 17.

A breakdown of the selection process for this search is shown in figure 27.

Results: Included studies

Search 1:
From the full texts that were examined, it was feasible to exclude 2 for which the reasons are given in table 17. Data extraction and quality assessment was carried out on the remaining 1 study that was included in this review.

The only study included in this review was a clinical trial related to the impact of zinc supplementation in adults with pica-associated behaviour (Lofts *et al*, 1990). The characteristics of this study are provided in table 18. An update of this search in the 2nd week of October 2005 revealed one relevant case study (Kushner *et al*, 2005), which has been added to the relevant reference list and the full text boxed.

Search 2 and 3 yielded no additional studies.

An overall summary of the findings for these 3 searches is provided in figure 28.

Figure 25: Search 1 – Vitamins and Others

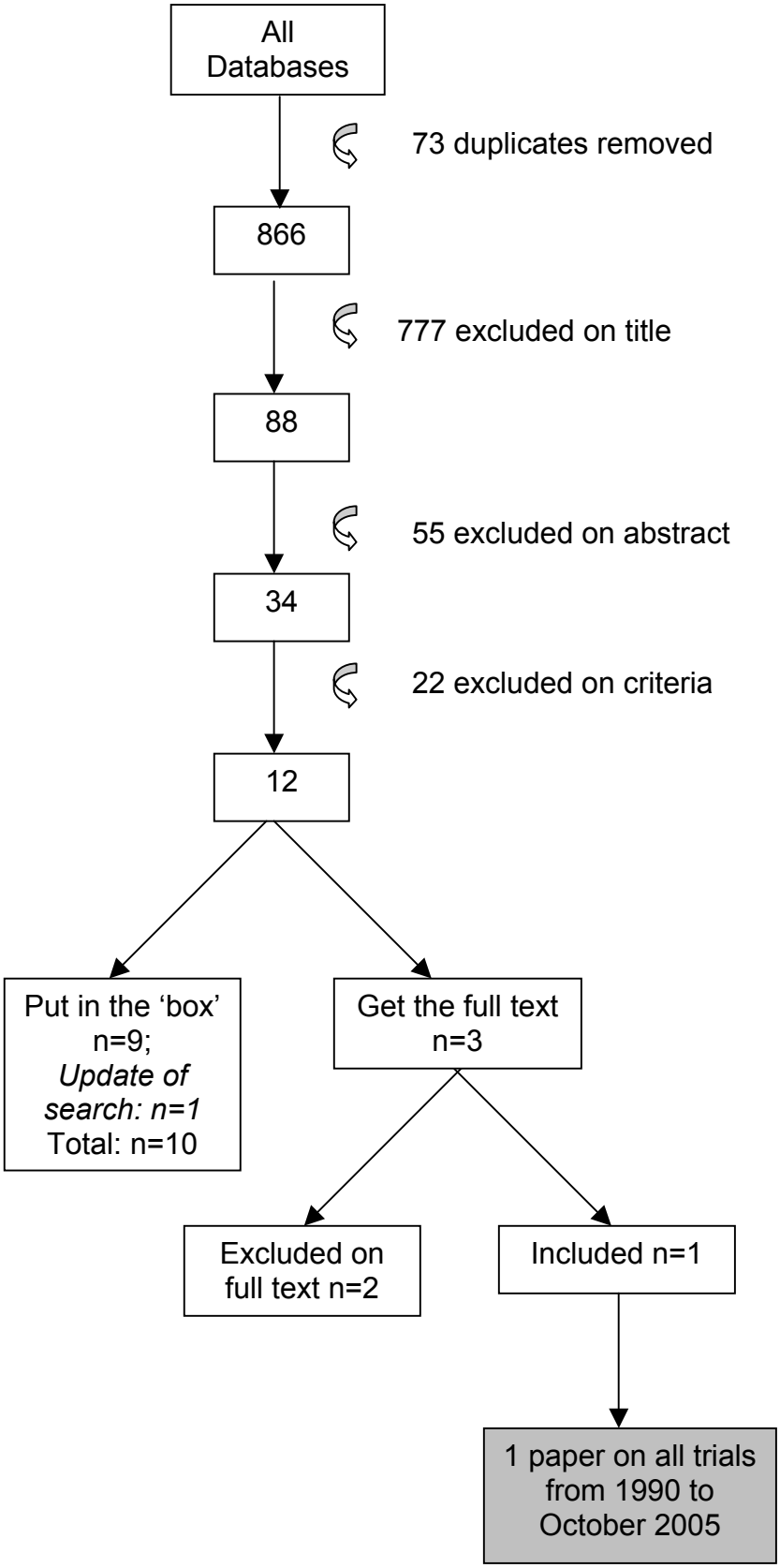


Figure 26: Search 2 - Vitamins and others

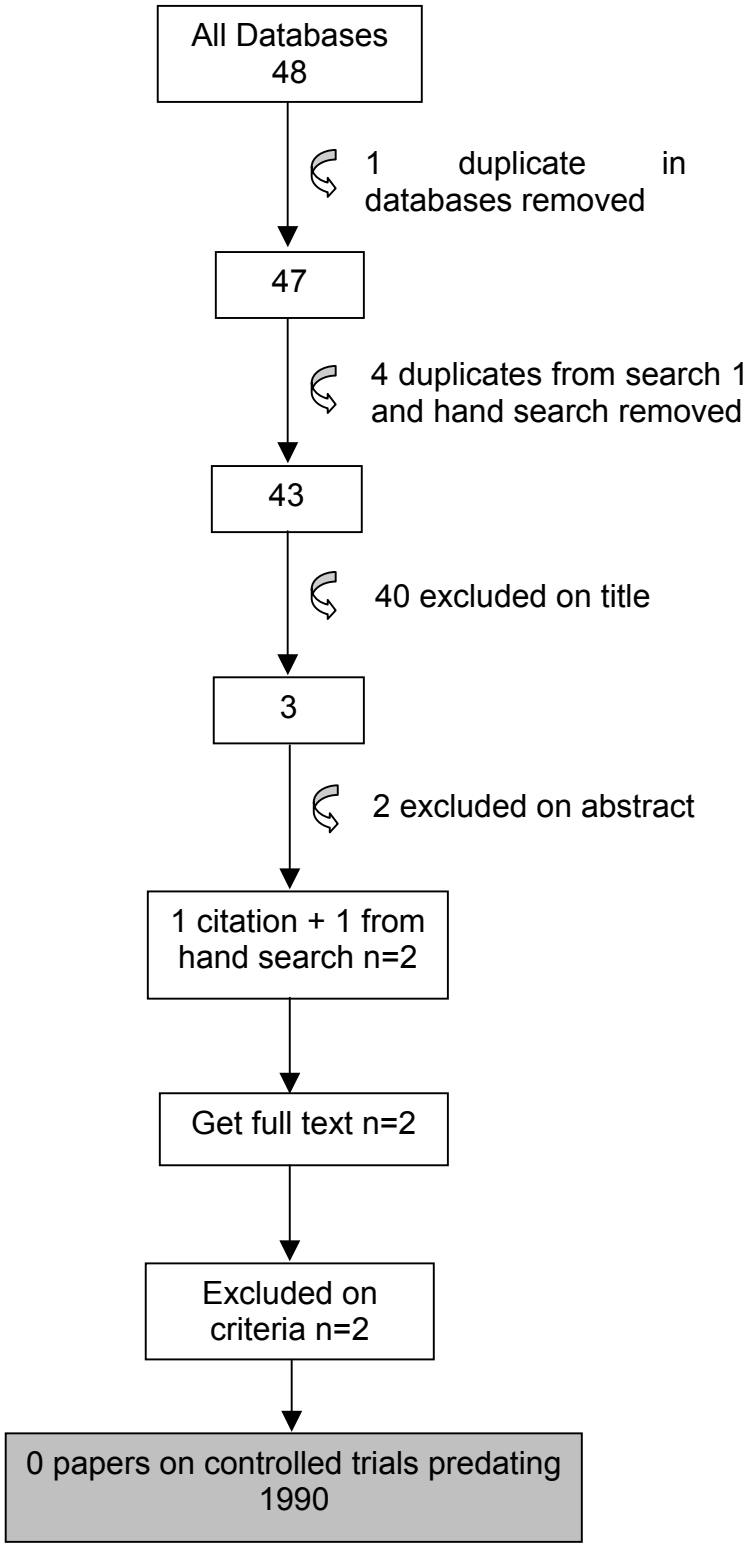


Figure 27: Search 3 - Vitamins and others

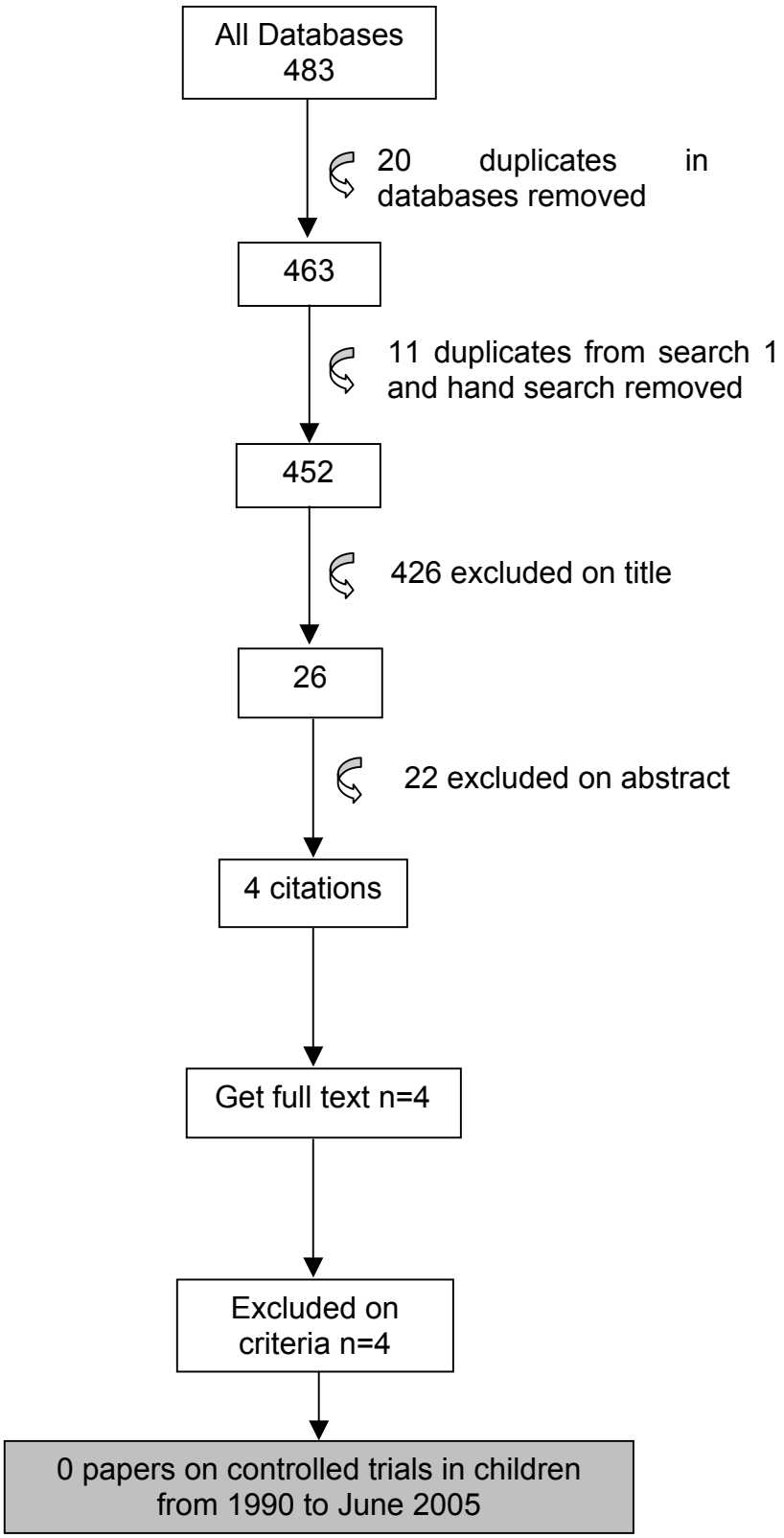
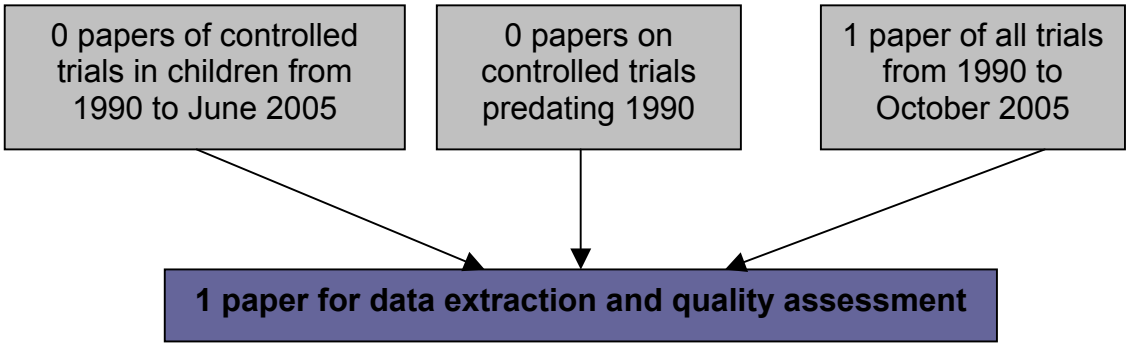


Figure 28: Summary of the vitamins and other supplements search



Vitamins and Others Review: Summaries of included studies

Prospective study

Adults

Lofts et al. (1990)

Participants
128 adults of which informed consent was obtained for 83, median age for the treatment (n=69) and control (n=14) groups were 46 and 41 years respectively (57% male overall). The control group was matched for level of LD but did not display pica behaviour. The two groups did not differ on other problem behaviour measures. All participants had a LD ranging from mild to profound and resided in a residential facility. Pica behaviour was determined as the ingestion of a non-food item.

Intervention
Zinc supplementation mean dose 100mg per day for a period of 2 weeks.

Method
An open, clinical trial. Although there were 2 groups of patients: LD and pica and LD and no pica, those with serum zinc level of 0.85 ug/dl or below at baseline were treated and results for all treated participants were presented overall.

Follow-up
Participants were assessed during the 2-week baseline and the 2-week treatment period.

Outcomes
1. Standard methods already used in facility of recording pica behaviour by direct care staff in medical records, thus records of pica recorded behaviour in case notes over the study period were analysed.
2. Blood tests were also carried out to record serum zinc levels during baseline for both groups and during supplementation for the pica group.

Results
An average of 23 incidents of pica were recorded per individual over the 2-week baseline, whereas an average of 4.3 incidents of pica were recorded during the 2-week treatment period. Serum zinc levels changed from 0.7ug/dl at baseline to 1.3ug/dl under treatment. 3 of the treated participants showed no reduction of pica.

Comments

Zinc had a significant impact on pica behaviour for most participants. The authors have stated that the quality of the data collected from patient records may well have been inconsistent affecting the overall results. This study scored 5/9 on quality assessment.

Table 17: Studies excluded on full text

Study	Summary	Reason for exclusion
Carlton, 2000	This was a RCT in 20 children with a LD. Minerals and vitamin B nutrient supplements were administered to investigate their efficacy on academic performance. Improvements were seen in 19/20 who completed the study in terms of higher grades and placements. Withdrawal led to a decline in performance.	The intervention was given to improve academic performance rather than to manage a behaviour problem.
Ellis, 1983	This was a double blind, placebo controlled trial of vitamin/ mineral supplements in adults with a LD whom were identified as requiring improvements in their cognitive abilities and self-help skills. However, the interventions showed no effect.	The intervention was given to improve self-help skills such as eating, toilet use and cleanliness, rather than to manage a behaviour problem.
Ghaziuddin, 1993	In this paper, 24 women with a LD who presented with premenstrual symptoms in the form of aggressivity, screaming and self-injurious behaviour were monitored on vitamin B and non-steroidal anti-inflammatory agents. At 6 months, only 5/24 showed sustained improvement, the others deteriorated or showed no change.	The age range of the participants was 14-52 years, with no separate data for those aged 18 and over.
Griffiths, 1997	This was a triple-blind, crossover study in children whom presented with classical, continuously treated phenylketonuria and were exposed to differing conditions of high versus low phenylalanine supplements. The dietary manipulation did not have any effect on the behaviour ratings of these children.	The participants had classical phenylketonuria but not a LD.
Mason, (Ongoing trial)	This was an ongoing clinical trial whereby the results for the completed first 3 months were presented. Supplements of fish oil and evening primrose oil were given to children with learning difficulties such as dyspraxia, dyslexia and autism, in an attempt to improve their reading skills and the ability to concentrate. So far some of the children have shown improvement in these areas.	The intervention was not given to manage a behaviour problem and this was not a controlled trial in children.
Primrose, 1979	This was a double blind, crossover trial in individuals with a LD who presented with self-injurious behaviour. Participants who had previously improved with Baclofen were chosen for the trial. Many of the participants showed significant improvement in their behaviour following the trial.	This is effectively a withdrawal study as participants were withdrawn from their previous dosage and then randomised to the experimental conditions.

Table 17: Studies excluded on full text (continued)

Study	Summary	Reason for exclusion
Richardson, 2002	This was a RCT in which highly unsaturated fatty acid supplements were given to manage ADHD-related symptoms (including behavioural and learning problems) in 41 children. The supplement was found to be significantly more effective than placebo in reducing a wide range of symptoms.	The children in this study were dyslexics associated with ADHD and their mean IQ was too high to merit inclusion in search 3 with an average IQ of 101.2.
Rossi, 1999	This was an open trial of Niaprazine in 25 participants with autistic disorder associated with severe mood disorders and aggressiveness. The intervention was more efficacious in those with a mild/ moderate learning disability.	The age of the participants was 12 years or over, with no separate data for those aged 18 and over.

Table 18: Studies included in the vitamins and other supplements review: Adults

Author/ **Evidence category (EC)**	**Medication/ Average daily dose**	**Target behaviour**	**Type of study**	**N**	**Outcome measures**	**Results**
Lofts, 1990 EC III	Zinc supplementation 100mg	Pica-related behaviour	Prospective, Open trial	83	Standard documentation of pica behaviour in medical records, blood tests for serum levels	Only 3 participants showed no improvement in pica behaviour. Serum zinc levels changed from 0.7ug/dl at baseline to 1.3ug/dl under treatment.

Evidence Categories III: other non-experimental studies such as case series

References for search 1

Vitamins and other supplements Review

Included studies (N≥10)

1. Lofts RH, Schroeder SR & Maier RH. Effects of serum zinc supplementation on pica behavior of persons with mental retardation. *American Journal on Mental Retardation* 1990; 95 (1): 103-109.

Vitamins and other supplements Review

Relevant studies (N<10)

1. Dion E, Prevost MJ, Carriere S, Babin C & Goisneau J. Phenylalanine restricted diet treatment of the aggressive behaviours of a person with mental retardation. *British Journal of Developmental Disabilities* 2001; 47 (1): 21-29.
2. Fitzgerald B, Morgan J, Keene N, Rollinson R, Hodgson A & Dalrymple-Smith J. An investigation into diet treatment for adults with previously untreated phenylketonuria and severe intellectual disability. *Journal of Intellectual Disability Research* 2000; 44 (1): 53-59.
3. Harvey EL & Kirk SF. The use of a low phenylalanine diet in response to the challenging behaviour of a man with untreated phenylketonuria and profound learning disabilities. *Journal of Intellectual Disability Research* 1995; 39 (6): 520-526.
4. Hier DB, Ahluwalie S, Melyn M & Hoganson GE, Jr. Estrogens control aggressive behavior in some patients with Sanfilippo syndrome. *Neurological Research* 1999; 21 (6): 611-612.
5. Hoskin RG, Sasitharan T & Howard R. The use of a low phenylalanine diet with amino acid supplement in the treatment of behavioural problems in a severely mentally retarded adult female with phenylketonuria. *Journal of Intellectual Disability Research* 1992; 36 (2): 183-191.
6. Kushner SA & Guze BH. Treatment of psychomotor agitation and self-injurious behaviour with estrogen and progesterone in a patient with Sanfilippo syndrome. *General Hospital Psychiatry* 2005; 27 (4):
7. Merrick J, Aspler S & Schwarz G. Phenylalanine-restricted diet should be life long. A case report on long term follow-up of an adolescent with untreated phenylketonuria. *International Journal of Adolescent Medicine & Health* 2003; 15 (2): 165-168.
8. Myers BA. Treatment of sexual offenses by persons with developmental disabilities. *American Journal on Mental Retardation* 1991; 95 (5): 563-569.
9. Thompson SBN. Observed behavior of a woman with a childhood diagnosis of phenylketonuria and a profound learning disability. *British Journal of Developmental Disabilities* 1995; 41 (81, Pt 2): 133-141.
10. Williams K. Benefits of normalizing plasma phenylalanine: impact on behaviour and health. A case report. *Journal of Inherited Metabolic Disease* 1998; 21 (8): 785-90.

Vitamins and other supplements Review

Excluded studies

1. Aarsland D, Hutchinson M & Larsen JP. Cognitive, psychiatric and motor response to galantamine in Parkinson's desease with dementia. *International Journal of Geriatric Psychiatry* 2003; 18 (10): 937-941.
2. Anonymous. Minerva. *British Medical Journal* 1996; 313 (7057).
3. Aoki K, Washimi Y, Fujimori N, Maruyama K & Yanagisawa N. Familial idiopathic vitamin E deficiency associated with cerebellar atrophy. *Rinsho Shinkeigaku [Clinical Neurology]* 1990; 30 (9): 966-71.
4. Burd L, Stenehjem A, Franceschini LA & Kerbeshian J. A 15-year follow-up of a boy with pyridoxine (vitamin B6)-dependent seizures with autism, breath holding, and severe mental retardation. *Journal of Child Neurology* 2000; 15 (11): 763-5.
5. Coleman E, Siributr P, Leelamanit V & Tapanya S. The treatment of fetishism and socially inappropriate sexual behavior in a young male with dull normal intelligence. *Journal of the Medical Association of Thailand* 1993; 76 (9): 531-4.
6. Crowley C, Koch R, Fishler K, Wenz E & Ireland J. Clinical trial of 'off diet' older phenylketonurics with a new phenylalanine-free product. *Journal of Mental Deficiency Research* 1990; 34 (4): 361-369.
7. Fenton WS, Dickerson F, Boronow J, Hibbeln JR & Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *American Journal of Psychiatry* 2001; 158 (12): 2071-2074.
8. Fisch RO, Matalon R, Weisberg S & Michals K. Phenylketonuria: Current dietary treatment practices in the United States and Canada. *Journal of the American College of Nutrition* 1997; 16 (2): 147-151.
9. Gassio R, Campistol J, Vilaseca MA, Lambruschini N, Cambra FJ & Fuste E. Do adult patients with phenylketonuria improve their quality of life after introduction/resumption of a phenylalanine-restricted diet? *Acta Paediatrica* 2003; 92 (12): 1474-8.
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11. Hemingway-Eltomey JM & Lerner AJ. Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. *American Journal of Psychiatry* 1999; 156 (9): 1470.
12. Kenny AM, Fabregas G, Song C, Biskup B & Bellantonio S. Effects of Testosterone on Behavior, Depression, and Cognitive Function in Older Men with Mild Cognitive Loss. *Journals of Gerontology Series A: Biological Sciences & Medical Sciences 59* 2004; (1): 75-78.
13. Kishnani PS, Sullivan JA, Spiridigliozzi GA, Heller JH & Crissman BG. Donepexil use in Down syndrome. *Archives of Neurology* 2004; 61 (4): 605-606.
14. Pietz J, Fatkenheuer B, Burgard P, Armbruster M, Esser G & Schmidt H. Psychiatric disorders in adult patients with early-treated phenylketonuria. *Pediatrics* 1997; 99 (3): 345-350.

15. Prasher VP, Huxley A & Haque MS. Down syndrome Ageing Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease--pilot study. *International Journal of Geriatric Psychiatry* 2002; 17 (3): 270-8.
16. Quint EH, Elkins TE, Sorg CA & Kope S. The treatment of cyclical behavioral changes in women with mental disabilities. *Journal of Pediatric & Adolescent Gynecology* 1999; 12 (3): 139-142.
17. Razagui IB, Barlow PJ, Izmeth MGA & Taylor KDA. Iron status in a group of long-stay mentally handicapped menstruating women: Some dietary considerations. *European Journal of Clinical Nutrition* 1991; 45 (7): 331-340.
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19. Rossi PG, Posar A, Parmeggiani A, Pipitone E & D'Agata M. Niaprazine in the treatment of autistic disorder. *Journal of Child Neurology* 1999; 14 (8): 547-550.
20. Serratrice J, Disdier P, Kaladjian A, Granel B, Azorin JM, Laugier R, Berenguer M & Weiller PJ. Psychosis revealing a silent coeliac disease in a young woman exhibiting Down's syndrome. *Presse Medicale* 2002; 31 (33): 1551-1553.
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22. Swift I, Paquette D, Davison K & Saeed H. Pica and trace metal deficiencies in adults with developmental disabilities. *British Journal of Developmental Disabilities* 1999; 45 (89, Pt 2): 111-117.
23. Yap S, Rushe H, Howard PM & Naughten ER. The intellectual abilities of early-treated individuals with pyridoxine-nonresponsive homocystinuria due to cystathionine beta-synthase deficiency. *Journal of Inherited Metabolic Disease* 2001; 24 (4): 437-447.
24. Zeman J, Pijackova A, Behulova J, Urge O, Saligova D & Hyanek J. Intellectual and school performance in adolescents with phenylketonuria according to their dietary compliance: The Czech-Slovak collaborative study. *European Journal of Pediatrics, Supplement* 1996; 155 (1): 56-58.

References for search 2

Vitamins and other supplements Review

Final Excluded List

1. Ellis NR & Tomporowski PD. Vitamin/mineral supplements and intelligence of institutionalised mentally retarded adults. *American Journal of Mental Deficiency* 1983; 88(2): 211-214.
2. Primrose DA. Treatment of self-injurious behaviour with A GABA analogue. *Journal of Mental Deficiency Research* 1979; 23: 163-173.

References for search 3

Vitamins and other Supplements Review

Excluded studies

1. Carlton RM, Ente G, Blum L, Heyman N, Davis W & Ambrosino S. Rational dosages of nutrients have a prolonged effect on learning disabilities. *Alternative Therapies* 2000; 6 (3): 85-91.
2. Griffiths P, Smith C & Harvie A. Transitory hyperphenylalanaemia in children with continuously treated phenylketonuria. *American Journal of Mental Retardation* 1997; 102(1): 27-36.
3. Mason P. Could food supplements help children with common learning difficulties? *Pharmaceutical Journal* 2002; 268 (7199): 713-714.
4. Richardson AJ & Puri BK. A randomised double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2002; 26(2): 233-239.