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Complementary Medicine Products Used in Autism - Evidence for Efficacy and Safety

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1. Introduction

In Chapter 3 the rationale for a range of CAM products that are used in the management of autism was presented with the view to inform researchers and health care professionals about the theoretical or proven basis for a range of CAM products in autism.

This Chapter is the second part of the two-part review and examines the evidence for efficacy and safety of a range of CAM products in autism. Each CAM product for which randomised controlled trials have been conducted has been assigned to a category of the Natural Standard Research Collaboration grading rationale for efficacy (Natural Standard Research Collaboration 2010). To determine safety of the range of CAM products investigated, all types of trials where specific a CAM product has been investigated in autism were examined.

2. Aim

To systematically review the literature to determine the efficacy and safety of a range of CAM products used in autism. Specifically, the following interventions were investigated: vitamins A, B, C and E, dimethylglycine (DMG), calcium, iron, magnesium, selenium, zinc, probiotics, digestive enzymes, colostrum, secretin, olive leaf extract, polyunsaturated fatty acids (PUFAs), melatonin, chelating agents (dimercaptosuccinic acid, DMSA & thiamine tetrahydrofuryl disulphide, TTFD), glutathione and glutamine.

3. Method

The method used to retrieve articles for the purposes of the review of efficacy and safety of CAM products used in autism was as described in Chapter 3.

Randomised controlled trials or randomised cross-over trials that were retrieved via the method described in Chapter 3, were used to assess effectiveness of specific CAM products in individuals with autism spectrum disorder (ASD). The grading system used by the Natural Standard Research Collaboration (Natural Standard Research Collaboration 2010) was used to assign a rating (A to F) signifying the level of evidence that exists for the use of

each complementary medicine in treating autism. A rating A is assigned to strong positive evidence and a rating of F indicates strong negative evidence.

Relevant articles were read in full by two independent reviewers and data extracted using a pre-defined protocol including study design, number and characteristics of subjects, interventions and comparisons, length of follow-up, outcome measures, and results. Randomised controlled trials, used to examine evidence for efficacy, were assessed for study quality and given a rating from 0 to 5 on the Jadad scale (Jadad et al. 1996). This scale awards points for description of randomisation, blinding and drop-outs with a score of 5 indicating the highest study quality. Any discrepancies between reviewers were resolved by discussion. Studies published only in abstract form were excluded from the analysis of efficacy. Adverse effects reported in all relevant studies were summarised and assessed. Clinical trials of all designs were used to examine reported adverse effects of the CAMs products in the autism population.

4. Results

4.1 Efficacy

Overall there is a distinct lack of good quality clinical evidence to support the efficacy of the wide variety of CAM products that are used in autism. There were no published studies of any kind conducted specifically examining efficacy for the following CAM products in autism: vitamin A or E, selenium, calcium, zinc, olive leaf extract, colostrum, Metallothionein promoter or glutamine. For the remainder of the CAM products investigated, various types of trials were retrieved. Evidence for efficacy was assessed based on findings from randomised controlled trials. For those CAM products where randomised controlled trials have been published, evidence for efficacy in autism was rated as being either unclear or conflicting for the majority of agents i.e. a Natural Standard Research Collaboration Efficacy Rating C as shown in Table 1.

4.1.1 High dose pyridoxine and magnesium (HDPM)

A total of 15 studies describing the administration of vitamin B6 and/or magnesium to children with autism were identified through the literature search (Lelord et al. 1978; Rimland et al. 1978; Barthelemy et al. 1980; Martineau et al. 1981; Lelord et al. 1982; Barthelemy et al. 1983; Jonas et al. 1984; Martineau et al. 1985; Martineau et al. 1986; Martineau et al. 1988; Martineau et al. 1989; Ménage et al. 1992; Tolbert et al. 1993; Findling et al. 1997; Kuriyama et al. 2002;). As shown in Table 2, there were three randomised controlled trials that examined the effects of pyridoxine and magnesium in autism that had a Jadad score of 3 or above and therefore were of sufficient quality to use to determine evidence for efficacy. A study by Kuriyama et al. (2002) comparing pyridoxine versus placebo found that verbal IQ improved in the treatment group while two other studies by Findling et al (1997) and Tolbert et al. (1993) found no significant differences in response between HDPM and placebo. The sample sizes of all studies were small i.e. n = 8, 10 & 15 respectively. Notably, a study by Mousain-Bosc et al. (2006) found children with PDD had significantly lower magnesium prior to supplementation with HDPM which normalised following treatment with an improvement in PDD symptoms. According to the Natural Standard Research Collaboration grading rationale (Natural Standard Research Collaboration 2010), vitamin B6 plus or minus magnesium for the treatment of autism as shown in Table 1 would be assigned to category C. This corresponds to unclear or conflicting scientific evidence

Complementary Medicine	Natural Standard Research Collaboration Rating	Trials used to determine the Natural Standard Research Collaboration Rating
Vitamin B6 + magnesium	C	Kuriyama et al. 2002; Findling et al. 1997; Tolbert et al. 1993
Vitamin B12	C	Bertoglio et al. 2010
Multivitamins/minerals (Spectrum Support)	C	Adams&Holloway 2004
Dimethylglycine (DMG)	C	Bolman &Richmond 1999; Kern et al. 2001
Vitamin C	C	Dolske et al. 1993
Probiotics	C	Parracho et al. 2010
Digestive enzymes	D	Munasinghe et al. 2010
Secretin	F	Williams et al. 2009 (Cochrane review that examined 14 randomised controlled trials)
Polyunsaturated fatty acids (PUFAs)	C	Amminger et al. 2007; Bent et al. 2010
Melatonin	B	Garstang&Wallis 2006; Wright et al. 2011
All others	Lack of scientific evidence	

Level of Evidence Grade A: Strong Scientific Evidence; B: Good Scientific Evidence; C: Unclear or conflicting scientific evidence; D: Fair Negative Scientific Evidence; F: Strong Negative Scientific Evidence.

Table 1. Evidence for the efficacy of selected complementary medicines in treating autism

on the basis that there is no apparent majority of the properly-conducted trials indicating evidence of benefit or ineffectiveness. In conclusion, the long-term administration of high-dose vitamin B6 to autistic children should not be recommended, pending further research. There is a need for randomised, controlled clinical trials with adequate power to be performed in this population before efficacy can be confirmed.

4.1.2 Vitamin B12, folinic acid and betaine

A small case control study by James et al (2004) showed that the metabolic profile within the folate/methionine pathway was normalised in children with autistic disorder (AD) when they received supplementation with folinic acid and betaine for three months (n=8), particularly the ratio of S-adenosyl-methionine: S-adenosylhomocysteine (SAM:SAH), comparable to the profile in individuals without autism. The addition of vitamin B12 to this regimen for a further one month acted mainly on the trans-sulphuration pathway, increasing the ratio of reduced glutathione: oxidised glutathione (GSH:GSSG), although it also led to further normalisation of methionine metabolites. Clinical improvements in both speech and cognition were observed but these were not quantitatively measured. The same researchers conducted a larger intervention in 40 children with AD and reduced methylation capacity or GSH:GSSG in which they were supplemented with folinic acid and

methylcobalamin for 3 months (James et al. 2009). The new regimen, which used half the dose of folinic acid than their earlier study (James et al. 2004), improved the mean metabolite concentrations significantly after intervention, although they remained below those in unaffected control children. In the earlier 2004 study, objective behavioural measures were not reported. As these studies were not randomised controlled trials and behavioural measures were not quantitatively measured and reported, vitamin B12 and folinic acid plus or minus betaine for the management of autism would be assigned to the 'lack of evidence' category of the Natural Standard Research Collaboration grading rationale.

4.1.3 Folinic acid

Studies have reported the effect of treatment with folinic acid on low cerebrospinal fluid (CSF) levels of 5-methyltetrahydrofolate (5-MTHF) in a subgroup of children with autism and at least one symptom of cerebral folate deficiency (CFD) (Moretti et al. 2005; Ramaekers et al. 2007; Moretti et al. 2008). One of these studies showed that treatment with folinic acid resulted in improved autistic, motor and other neurological symptoms in young children (<3.5 years) and improvements in motor and neurological symptoms in older children, although there was no change in autistic symptoms in the older age group (Ramaekers et al. 2007). It remains to be determined whether gains can be achieved with folinic acid supplementation in children with AD without CFD. As these studies were not randomised controlled trials, folinic acid for the management of autism would be assigned to the 'lack of evidence' category of the Natural Standard Research Collaboration grading rationale.

4.1.4 Vitamin B12

As summarised in Table 2, a double-blinded randomised placebo-controlled trial was recently published where participants (n=30) were administered either methyl-cobalamin or placebo for 6 weeks and then switched without washout for a further 6 weeks (Bertoglio et al. 2010). Overall, there was no significant change in GSH, GSH:GSSH or behaviour, however, 30% of participants showed a significant improvement against objective behavioural measures which correlated with improved plasma GSH and GSH:GSSH. Therefore, given there was no overall benefit but a benefit shown in a subgroup of children with autism, vitamin B12 for the treatment of autism would be assigned to category C of the Natural Standard Research Collaboration grading rationale as shown in Table 1. Further studies in the subgroup which show improvements in plasma GSH and GSH:GSSH with B12 treatment are warranted.

4.1.5 Multivitamin/mineral supplement

Multivitamins are widely implemented by caregivers of children with autism and one physician survey found 49% of respondents recommended their use in children with autism (Golnik&Ireland 2009). Adams & Hollloway (2004) conducted a 3-month pilot randomised controlled trial of a moderate dose multivitamin/mineral supplement (Spectrum Support II transitioning to III) in children with autism (n=20). Mothers completed a Global Impressions survey and results showed statistically significant improvements in sleep and gastrointestinal (GI) symptoms in those children taking the supplement versus placebo. Therefore this study shows Spectrum Support multivitamin/mineral supplement holds promise for the treatment of sleep and GI disturbance in autism. However, due to the small sample size it would be assigned to category C of the Natural Standard Research Collaboration grading rationale as shown in Table 1 and indicates a larger study is warranted.

4.1.6 Dimethylglycine (DMG)

Although there are numerous anecdotal reports that DMG reduces autistic behaviours and improves speech, as summarised in Table 2, administration of low dose DMG demonstrated no statistically significant effect on autistic behaviours in two double-blind, placebo-controlled trials ($n = 8$ & 37) (Bolman & Richmond 1999; Kern et al. 2001). Therefore, DMG for the treatment of autism would be assigned to category C of the Natural Standard Research Collaboration grading rationale, i.e. unclear or conflicting scientific evidence as shown in Table 1. This is on the basis that although there is an indication that DMG is ineffective in two randomised controlled trials, the sample sizes are too small to provide conclusive evidence.

4.1.7 Vitamin C

One small randomised double-blind, crossover study ($n=18$) reported decreased stereotypic behaviours in children who received ascorbic acid (Dolske et al. 1993). This study had a number of methodological flaws including a small sample size, heterogeneity of subjects, lack of ascorbate-free baseline and a lack of different, multiple dependent variables. In addition this study has not been replicated (Levy & Hyman 2003). As the study was of poor quality (i.e. a Jadad rating of 2) vitamin C as a treatment for autism is assigned to category C of the Natural Standard Research Collaboration grading rationale i.e. unclear or conflicting scientific evidence on the basis that there is no apparent majority of the properly-conducted trials indicating evidence of benefit or ineffectiveness. It is important to note that the use of vitamin C to prevent/treat deficiency (scurvy) in any individual would gain a Natural Standard Research Collaboration rating of A (strong scientific evidence), however the focus of this study is to examine the efficacy of vitamin C as a treatment for the disorder of autism.

4.1.8 Iron

An open-label uncontrolled study was undertaken as a pilot study to examine the effects of iron supplementation in children with autism ($n=33$, 2-10 years of age) (Dosman et al. 2007). The study examined effects on ferritin levels and sleep. An oral iron supplement at a dose of 6 mg elemental iron/kg/day was administered for 8 weeks. Parents completed two sleep questionnaires, a three-day food record, and a Clinical Global Impression Scale questionnaire at baseline and after 8 weeks of iron supplementation. Blood samples were taken at baseline and post-treatment to determine serum ferritin and transferrin receptor and other blood chemistry. There was a significant increase ($p < 0.001$) in blood ferritin levels from 15.72 microgram/L at baseline to 28.8 microgram/L post-treatment. The Restless Sleep score improved significantly post-treatment ($p < 0.04$), however no statistically significant relationship was found between Restless Sleep score and ferritin concentration. One study has shown that iron levels may be problematic in children with ASD (Latif et al. 2002), and clearly there are obvious benefits in treating iron deficiency. However, in terms of actually improving sleep and behaviour, the study conducted by Dosman et al. (2007) provides insufficient evidence for efficacy and is assigned to the 'lack of evidence' category of the Natural Standard Research Collaboration grading rationale.

4.1.9 Probiotics

Probiotics are widely used in autism, with one survey reporting 19% of medical practitioners recommend probiotics as a treatment in autism (Golnik & Ireland 2009).

Probiotics are live bacteria that, when administered, can provide health benefits to the host. As summarised in Table 2, a randomised double-blind, placebo-controlled, crossover-designed probiotic feeding study was undertaken in children diagnosed with ASD. Children (n=17, 4-16 years of age) received either *Lactobacillus plantarum* WCFS1 for 3 weeks with a 3 week wash out period. The overall indicator of behavioural/emotional disturbances was not significantly different between the two feeding periods. The observed benefit of the probiotic was a higher percentage of 'formed' stool samples compared to the placebo feeding, whilst the percentage of 'hard' stool samples was lower during probiotic feeding. No significant differences were observed between probiotic and placebo for GI disturbance (Parracho et al. 2010). Although probiotics hold promise as a treatment in autism they are currently assigned to category C of the Natural Standard Research Collaboration grading rationale as shown in Table 1. Notably Parracho et al.'s study (2010) only examined one type of probiotic feeding i.e. with *Lactobacillus plantarum* WCFS1 and thus even the benefits on stool consistency are not be generalisable to all probiotic interventions.

4.1.10 Digestive enzymes

One randomised double-blind, placebo-controlled, crossover-designed study (Munasinghe et al. 2010) examined the efficacy of 3 months treatment (with a 1 week washout) with a digestive enzyme (Peptizyde™) in autism (n=27, mean age 69.4 months). As summarised in Table 2, this study found treatment with enzyme compared with placebo was not associated with clinically significant improvement in behaviour, food variety, GI symptoms, sleep quality, engagement with therapist, or the Language Development Survey Vocabulary or Sentence Complexity Scores (Munasinghe et al. 2010). As this study was of high quality (i.e. Jadad score of 5) and showed no benefit on a range of outcome measures it is assigned to category D of the Natural Standard Research Collaboration grading rationale. Notably, only one type of enzyme product was tested and results may not be generalisable to other digestive enzyme products that are used for this purpose.

Although only randomised controlled trials were used to assess efficacy in this study, it is noteworthy that Brudnak et al. (2002) reported a case series with post-test outcomes following supplementation with a formulated combination of enzymes in children with ASD. Twenty-nine of the 46 subjects completed the trial, with personal issues, lack of palatability, and behavioural or medical side effects given as reasons for withdrawal from the study. The results of this study are limited due to its open, uncontrolled design, however Brudnak et al. (2002) reported a significant positive trend for each of the 13 parameters measured on the Symptom Outcome Survey.

4.1.11 Secretin

A systematic review of intravenous secretin for ASD was undertaken through the Cochrane Collaboration and published in 2005. An editorial update to this review in 2009 made no changes to the conclusions of the review (Williams et al. 2009). The objectives of the review were to examine whether intravenous secretin: a) improved the core features of autism; b) improved the non-core aspects of behaviour or function ; c) improved the quality of life of individuals with ASD and their carers; d) had a short term and long term effects on outcomes; e) caused harm. The review included literature covered by major health and biomedical databases and unpublished studies that could be located from 1998 to March 2005. Studies were included if they were randomised controlled trials of intravenous

secretin comparing it with a placebo treatment in children or adults diagnosed with ASD, where at least one standardised outcome measure (such as a standardised checklist) was reported. Studies under consideration were evaluated for methodological quality and relevance by two independent reviewers using standardised Cochrane methods for assessing study quality.

Fourteen studies met the inclusion criteria for the review. These studies represented data for 618 children aged under 18 years. Nine studies used a cross-over design and five were a parallel design. The analysis of cross-over trials in the review was limited to the first phase to prevent biased underestimation of treatment effectiveness due to potentially inadequate wash-out periods. Different types of secretin were used in different studies including porcine, synthetic porcine and synthetic human secretin. Some studies used single doses of secretin while others used two or three doses of secretin 4 – 6 weeks apart.

It was found that 25 established standardised outcome measures were reported in the included studies with no more than four studies reporting the same outcome measure. Outcomes were reported at between three and six weeks with no outcomes beyond six weeks post-intervention reported in the included studies. It was only possible to perform a meta-analysis on the outcome measure of the Childhood Autism Rating Scale (CARS).

Ten studies presented information about core features of autism as an outcome measure. Analyses of outcome measures including subscales of the Autism Behavior Checklist (ABC), the Autism Diagnostic Observation Scale (ADOS), the Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale: Autism Quotient and Autism Behavior Checklist found no significant differences between secretin and placebo. Overall it was concluded that the “RCTs of efficacy of secretin in autism have not shown improvements for core features of autism”. Overall, analysis of individual areas such as communication, behaviour, affect, visio-spatial skills and quality of life found no conclusive evidence in favour of secretin.

The authors concluded that there was no evidence that secretin was effective in ASD and should not be recommended as a treatment. While no conclusions could be drawn about the effectiveness of secretin for certain subgroups of people with autism, it was suggested that further explorations of effectiveness in such subgroups should only be undertaken if there is a biologically plausible explanation for effectiveness in these groups. Secretin is therefore assigned to category F of the Natural Standard Research Collaboration grading rationale i.e. strong negative evidence for efficacy as shown in Table 1.

4.1.12 Polyunsaturated fatty acids (PUFAs)

PUFAs (also called omega -3 and -6 fatty acids), are recognised as vital building blocks for developing neurological systems. These essential fatty acids (EFAs) are present in fish oils, evening primrose oil and linseed (flaxseed) oil (Bell et al. 2004). A study by Green et al. (2006) revealed that 27.8% of caregivers of children with autism implemented PUFAs in their affected child. One survey reported PUFAs are recommended by 25% of medical practitioners for the management of autism (Golnik&Ireland 2009).

As summarised in Table 2, one small randomised controlled trial (n = 13) investigating the efficacy of PUFAs (1.5g/day) in autism noted non-significant improvements in hyperactivity and stereotypy after 6 weeks treatment (Amminger et al. 2007). Another randomised controlled trial by Bent et al. (2010) examined PUFAs (1.3 g/day) for the treatment of hyperactivity in 27 children with ASD. They also found there were non-significant improvements after 12 weeks in hyperactivity, as measured by the ABC. The

remaining five studies, four uncontrolled trials in children and one case report were small ($n = 30, 22, 19, 9,$ and 1) with four (Johnson&Hollander 2003; Bell et al. 2004; Patrick&Salik 2006; Meguid et al. 2008) reporting improvements in a wide range of outcomes including language and learning skills, parental observations of general health and behaviour, a clinician administered symptom scale, and clinical observations of anxiety. In contrast one uncontrolled trial in young adults with severe autism did not show a benefit (Politi et al. 2008).

In summary, the small sample size for both PUFA randomised controlled trials limits the conclusions that can be drawn. Although both studies were of high quality, and showed a lack of significant effect overall (but with a trend towards improvements in hyperactivity), the sample sizes are too small to give a conclusion of negative evidence. Therefore, the evidence for the efficacy of PUFAs in autism is currently inconclusive and PUFAs are assigned to category C of the Natural Standard Research Collaboration grading rationale.

4.1.13 Melatonin

Melatonin is another complementary medicine that is currently receiving attention in the management of sleep problems in autism. One survey found 25% of medical practitioners reported they recommend melatonin as a treatment in autism (Golnik&Ireland 2009). As summarised in Table 2, two randomised controlled trials ($n=7$ & 17) have been performed in autism that suggest melatonin is effective at reducing sleep latency, or time taken for initiation of sleep, and total sleep time in children with sleep problems and autism (Garstang&Wallis 2006; Wright et al. 2011). Further, one of the trials also showed melatonin improved the number of wakings per night (Garstang&Wallis 2006) and the other showed it improved daytime behaviour (Wright et al. 2011). Therefore on the basis of the findings in the two randomised controlled trials, melatonin is assigned to category B of the Natural Standard Research Collaboration grading rationale as shown in Table 1.

Other types of trials also support the benefits of melatonin in the treatment of sleep disturbance in autism. There have also been two open trials conducted in a population of subjects with ASD (Paavonen et al. 2003; Giannotti et al. 2006). Paavonen et al. (2003) found a statistically significant reduction in sleep latency with melatonin administration to 15 children with Asperger's Syndrome (AS) and Giannotti et al. (2006) found sleep patterns of all children with autism ($n=20$) improved during treatment. There were significant reductions in bedtime resistance and number and duration of night awakenings, and a significant increase in sleep duration. Andersen et al. (2008) and Galli-Carminati et al. (2009) have conducted observational retrospective trials in autistic populations ($n= 107$ children & 6 adults respectively). Andersen et al.'s (2008) melatonin study found parents of 27/107 (25%) children no longer reported sleep concerns after initiation of melatonin. Parents of 64/107 (60%) of children reported improved sleep but with ongoing concerns. Parents of 14 children (13%) continued to report sleep problems as an ongoing concern with only 1 child (1%) having worse sleep after starting melatonin, and 1 child having undetermined response (1%). Melatonin resulted in improvements in adults including length of sleep, time to fall asleep, nocturnal awakenings and early morning awakenings (Galli-Carminati et al. 2006).

4.1.14 Chelating agents

Approved uses for chelation therapy include heavy metal poisoning and digitalis toxicity, although it used in an off-label manner in autism. Practitioners are using a variety of

chelating agents and routes of administration for children with ASD, with oral dimercaptosuccinic acid (DMSA), also known as succimer, probably the most common. Several of the agents are not approved for use or are given through unlicensed routes of administration such as rectally or transdermally. A 5-year old child with autism died after being administered intravenous edetate disodium (Atwood&Woeckner 2009). The survey conducted by Golnik and Ireland (Golnik&Ireland 2009) reported that 61% of medical practitioners surveyed discouraged caregivers' use of chelation in the management of autism.

A study conducted by Adams et al. (2009a; 2009b) examined the effects of oral DMSA as a chelating agent in children with a diagnosis of ASD. While the study was designed as a randomised double-blind study, the complex study design and carry-over effects from the first round of DMSA administered to all participants in the first phase of the study meant that the study lacked a true placebo control group. Essentially the study compared the effects of one round of DMSA therapy (and 6 rounds of placebo) with 7 rounds of DMSA. A round of DMSA therapy consisted of oral DMSA 10mg/kg administered three times a day for three days. This was followed by 11 days of no DMSA. Patients randomised to receive a topical reduced glutathione lotion (180 mg reduced l-glutathione/day) in the initial phase of the study received the DMSA therapy (up to 7 rounds in total) in the second study phase, while those receiving a placebo lotion received placebo in the second phase. A total of 82 children were enrolled with 65 completing phase one and 41 completing phase two. Effects on urinary excretion of toxic metals and blood chemistry were examined, with a single round of DMSA found to cause a significant increase urinary excretion of lead, tin and bismuth and normalisation of red blood cell glutathione levels. Effects on behaviour were also assessed using a variety of measures including the Autism Diagnostic Observation Schedule (ADOS); Severity of Autism Scale (SAS); Pervasive Developmental Disorders – Behaviour Inventory (PDD-BI), Autism Treatment Evaluation Checklist (ATEC), and Parental Global Impressions questionnaire. Both the groups receiving one round and seven rounds of DMSA therapy were found to have significant improvements compared to baseline using most of these measures. However the differences in improvement between the groups were not significant.

Another uncontrolled study assessed a combination of DMSA (administered orally at 10mg/kg three times a day) with the anti-androgen leuprolide acetate (administered intramuscularly and subcutaneously) in 11 children with ASD (Geier and Geier, 2006). DMSA was to be administered transdermally if oral dosing caused severe GI disturbance. However, the number of participants, if any, experiencing GI disturbances was not reported. It was reported that the treatment had no adverse effect on kidney, thyroid or liver function tests. Children in the study received vitamin and mineral supplementation during the study and no effects on serum potassium, calcium, iron, magnesium, copper or zinc were observed.

On the basis that these chelation trials were not properly conducted randomised controlled trials chelation for the management of autism would be assigned to the 'lack of evidence' category of the Natural Standard Research Collaboration grading rationale.

4.1.15 Others

No studies of any description investigating use in children with autism were located for the remainder of the interventions under investigation i.e. calcium, selenium, colostrum, glutamine, magnesium, metallotheionein, olive leaf extract, vitamin A or vitamin E. Hence,

the remaining interventions are assigned to the ‘lack of evidence’ category of the Natural Standard Research Collaboration grading rationale with respect to their use in the management of autism. It is important to remember that, as with vitamin C, supplementation with vitamin A, vitamin E, calcium and magnesium to treat or prevent deficiency in any individual would gain a Natural Standard Research Collaboration rating of A (strong scientific evidence). The focus of this study, however, was to examine their efficacy when used to specifically reducing the symptoms of autism, where they all lacked evidence for use.

Reference	No. of Subjects	Patient Characteristics	Intervention	Comparison	Length of Follow-up	Outcome Measure(s)	Results	Funding Source	Comments
Trials of pyridoxine/magnesium									
Findling et al. (1997)	12 patients enrolled, 10 completed the study (2 patients withdrew during two week lead-in period due to refusal to take study medicine).	Aged 3-17, met Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for autistic disorder, all living at home with a parent/ guardian. Exclusion criteria: Significant past or current medical or neurological disorder, use of a psychotropic agent within 3 months prior to start of study.	Pyridoxine 30mg/kg/day (max. 1g) + Mg. oxide 10mg/kg/day (max. 350mg) Doses given twice daily at 8am and 12pm. All subjects received placebo for the first two weeks (baseline period), after which they were randomised and received either treatment or placebo for four weeks, and then the opposite for the next four weeks.	Placebo (identical appearance, efforts made to match taste) At baseline, all subjects received placebo for 2 weeks in a single-blind fashion before randomisation.	Subjects were evaluated every other week for a 10-week period.	Childhood Autism Rating Scale (CARS), Clinical Global Impression scale (CGI scale), Children's Psychiatric Rating Scale(CPRS), Obsessive Compulsive Scale (OCS).	ANOVA revealed no statistically significant effects of vit.B6 + Mg. on any of the outcome measures. 50% of patients had a ≥ 30% reduction in CPRS score during the placebo lead-in phase of the study.	Not specified	Jadad score = 4
Kuriyama et al. (2002)	15 patients were recruited, but four met the exclusion criteria. 11 completed the baseline study, 3 were then excluded based on immeasurable IQs. Therefore 8 patients were randomised (4 in treatment group, 4 in placebo).	Met DSM-IV criteria for PDDs, had expressive verbal disorders, developmental motor coordination disorders and hypersensitivity to sound, aged 6-17. Exclusion criteria: History of epilepsy or an epileptiform EEG, use of a psychotropic agent within 3 mths of starting the study, inability to measure IQ, brain image abnormalities on MRI, history of homocystinuria or fragile-x syndrome. In both groups, one child had AS and three PDD-NOS.	Pyridoxine 100mg in powder form once daily for the first 2 weeks, 100mg twice daily for the second 2 weeks (after breakfast and after dinner).	Placebo (powder form, identical in appearance and taste).	Subjects were evaluated at baseline and after 4 weeks of treatment.	Changes in IQ scores (both verbal IQ and performance IQ) using the Wechsler Intelligence Scale for Children-III (WISC-III), social quotient (SQ) scores measured with the Social Maturity Scale (SM) test assessed by the subjects' parents.	There was a statistically significant increase in verbal IQ in the vit.B6 group relative to the placebo group, although verbal IQ did increase in both groups (by 11.2 in the treatment group and by 6.0 in the placebo group). The difference was still significant after controlling for sex, age, body weight, interval between tests and baseline verbal IQ using ANOVA. No significant difference in performance IQ and SQ scores was found.	Not specified	Jadad score = 5 Limited by small sample size and short-term nature Mg was not given
Tolbert et al. (1993)	15 patients were randomised. A further 5 subjects not receiving any treatment served as controls.	Ages 6-18, all diagnosed with autism according to the DSM-III-R criteria, all residential students and receiving a standardised diet. No subjects had lactose intolerance, no pyridoxine deficiencies were	Pyridoxine 200mg/70kg/day in 50mg tablets in divided doses. Magnesium 100mg/70kg/day in 27mg tablets in divided doses.	Placebo (matching tablets) and control. Group 1: treatment for 20 weeks then placebo for 10 weeks Group 2: treatment for 10 weeks, placebo for 10 weeks,	Subjects were evaluated after baseline and after each of three 10-week blocks (i.e. 30 weeks)	Ritvo-Freeman Real Life Rating Scale for Autism (R-F) - quantitates 47 specific behaviours grouped into 5 subscales: sensory-motor, social, affective, sensory responses language.	No significant differences among the three groups at any of the time points. There was a statistically significant reduction in scores across the time period for each group, possible due to other non-pharmacological therapy that patients	Not specified	Jadad score = 3 This study specifically used much lower doses of pyridoxine than previous studies in an attempt to reduce the risk of

		identified.		treatment for 10 weeks. (after 5-week baseline period)		Raters observed subjects involved in classroom activities from a room equipped with one-way mirrors and sound amplification.	were receiving throughout the trial.		peripheral neuropathies .
Trials of dimethylglycine (DMG)									
Bolman and Richmond (1999)	10 were recruited, 8 completed full testing.	Ages 4-30, diagnosed according to DSM-III-R criteria, not taking other medication within one month prior to the study.	DMG tablets, doses varied with weight (from 125mg/day for under 70lbs to 375mg/day for over 120lbs)	Look-alike placebos 2-week baseline period, 4 weeks of either DMG or placebo, 2-week washout period, 4 weeks of placebo or DMG, 2-week baseline period.	14 weeks (3 ½ months)	Campbell-NIMH 14-point Autism Rating Scale (ARS)(patients were videotaped weekly following a semi-structured set of guidelines in a playroom) An experimental 10-item checklist developed by Rimland Individualised scales developed with help of parents (3 scales)	Videotaping (ARS): no significant changes in behaviour observed. Experimental checklist: no significant differences between any of the study periods Individualised scales: From a group total of 55 scale items, 5 showed improvement with DMG vs. placebo, 14 worsened and 36 showed no difference.	Not specified	Jadad score = 3 Only 3 out of 8 parents could correctly guess during which period their child had taken DMG or placebo (less than chance).
Kern et al. (2001)	39 began the study, 37 completed it	Ages 3-11, diagnosis of autism or pervasive developmental disorder (DSM-IV) 7 children were on psychoactive medications (held constant throughout the study).	Foil-wrapped 125mg DMG tablets (no. of tablets taken varied with weight, from 125mg/day for under 40lbs to 625mg/day for over 130lbs).	Identical placebo tablets (mannitol 125mg)	4 weeks	Behavioural Assessments (Vineland Maladaptive Behaviour Domain, Aberrant Behaviour Checklist) Neurologic assessments	Combined analysis of behavioural assessments revealed a significant improvement over the 4 weeks across all subjects (both placebo and treatment). There was no difference in improvement between the DMG group and the placebo group. No effect of DMG on any of the behavioural measures was observed. DMG treatment did not affect the neurological status.	Not specified	Jadad score = 4 Parents reported improvement t in 58% of the DMG group and 53% of the placebo group. Parents reported worsening in 16% of the DMG group and 32% of the placebo group
Trials of ascorbic acid									
Dolske et al. (1993)	18 (13 male and 5 female).	Inclusion: subjects diagnosed under the DMS-III-R criteria by two independent child psychiatrists, no lactose intolerance and plasma ascorbate levels >30µg/ml i.e. within normal range. Prior to the initiation of the study, subjects ascorbic acid supplementation ranged from 0-4g/70kg/day. Participants were aged between 6 and 19 years (mental age ranged from 2.0-6.7, IQs ranged from <20-65). Subjects received a standardised diet throughout the duration of the study	Ascorbic acid was administered at 8g/70kg/day in 500mg tablets, divided into two or three separate doses. Phase 1: Initially all subjects received ascorbic acid for a ten-week block. Phase 2: After the first ten-week block, half the subjects were randomly assigned to continue to receive the ascorbic acid (Group 1) and the other half to receive a placebo (Group 2) for an additional ten weeks. Phase 3: For the final ten weeks the treatments were reversed.	Matching placebo tablet (film coated and identical in appearance).	Each treatment phase lasted 10 weeks and behaviours were rated weekly using the R-F scale. The weekly R-F scores (total and each subscale) in each 10-week block were averaged for each subject. 30-week trial overall.	R-F was used as an instrument to determine drug treatment evaluation. Raters observed subjects participating in routine classroom activities from an observation room equipped with one-way mirrors and sound amplification.	Comparison of total scores revealed a significant interaction when comparing Phase 2 and Phase 3 (p=0.02). Behaviour worsened in group 1 when going from ascorbate (Phase 2) to placebo (Phase 3), where as behaviour improved in group 2 when going from placebo (Phase 2) to ascorbate (Phase 3). On the sensory motor scale (subscale 1), a significant interaction was found (group x phase 2 and 3) p=0.01. No other subscales revealed significant findings for main effects of group and phase interaction.	Not stated	Jaded score= 2 Article did not report any adverse effects. Small sample size, heterogeneous population, lack of ascorbate-free baseline, confounding neuroleptic variable, lack of different multiple dependent measures.

		Nine of the children were on neuroleptics concurrent with the study. Prior to the study, the neuroleptic doses had been stabilised and were maintained throughout the study.					There were no significant differences ($p>0.05$) between R-F total scores and subscales of children receiving vs not receiving neuroleptic medication during the initial 10-week phase of the trial. Therefore this medication variable was not included in the subsequent analyses.		
Trials of vitamin B12									
Bertoglio et al. 2010	30 cases	Children aged 3-8 diagnosed with autism with DSM-IV-TR and Autism Diagnostic Observation Schedule (ADOS) plus non-verbal IQ ≥ 49 measured by Wechsler Preschool and Primary Scale of Intelligence, Mullen Scales of Early learning or Wechsler Intelligence Scale for Children.	Methyl-cobalamin 64.5 $\mu\text{g/kg}$ sc for 6 wks followed by cross-over for 6 wks (no washout period).	Placebo	12 week trial was followed by 6 month open label for 22 cases	Plasma GSH and GSH:GSSH linked to Global Clinical Impressions Score and other objective behavioural measures	Overall, no significant difference in GSH, GSH: GSSH or behavioural outcomes. No serious adverse events were reported, only hyperactivity and increased mouthing of objects.	Institute of the University of California, Davis Medical Centre	Jadad score = 4 Increased GSH, & GSH:GSSH and improved behavioural outcomes in 9/30 children which were identified as a “responder group”.
Trials of multivitamin supplements									
Adams et al. (2004)	25 subjects were enrolled, 5 dropped out for varying reasons (20 completed - 9 in placebo group, 11 in supplement group)	Ages 3-8 yrs, diagnosis of ASD by a psychiatrist, no changes in any treatment therapies within 2 months prior to the start of the study, no prior use of a multivitamin/mineral supplement other than a standard children’s multivitamin/mineral.	Spectrum Support II -dosage was increased to maximum over 24 days and then held constant until day 34. Gradual transition during days 35-50 to Spectrum Support III which was continued until day 90. Full dosage: 1ml/5lbs bodyweight three times daily with food.	Placebo, matched to colour and consistency.	3 months	Global Impressions survey filled out by mothers	Mothers reported statistically significant improvements in sleep and GI symptoms in those children taking the supplement versus placebo.	Not specified	Jadad score = 4 Spectrum support is a liquid multi-vitamin preparation with a moderate level of vit.B6 and no copper
Trials of probiotics									
Parracho et al. (2010)	39 subjects, Group I (n=19), Group II (n=20) commenced the study. 17 participants withdrew before end of first arm, 8 from group I and 9 from group II. 3 subjects withdrew due to adverse effects, 1 with rash, 1 with diarrhoea and 1 with weight loss in feeding period. A further 2 subjects withdrew after first feeding arm and 3 after first	Children with ASD aged 4-16y	Lactobacillus plantarum WCFS1 (4.5×10^{10} colony-forming units per capsule). Probiotic feeding for 3 wks followed by cross-over for 3 wks (3 week washout period).	Placebo	12 weeks	DBC administered immediately prior to commencing the feeding period i.e. baseline (B1), at the end of each feeding (F1 & F2) and washout period (W1 & W2). Two faecal samples were taken in the week prior to the study (commencing B1 & B2) and at F1, F2, W1 and W2 and bacterial populations examined. Bowel function and GI symptoms were also determined.	The overall indicator of behavioural/emotional disturbances i.e. Total Behaviour Problem Score (TBPS) was not significantly different between the two feeding periods. Probiotic feeding resulted in a higher percentage of ‘formed’ stool samples (73.3 %) compared to the placebo feeding (64.8 %), whilst the percentage of ‘hard’ stool samples was lower during probiotic feeding. No significant differences were observed between probiotic and	Not stated	Jadad score = 5 Encapsulation of both placebo and probiotic, and blind coding of the capsules, was performed by Orafiti (Belgium). Adverse effects monitored for. <i>Lactobacillus plantarum</i> WCFS1 and the placebo were supplied by Nizo Food Research, The Netherlands. High drop-out rate from study affected statistical power

	washout. 17 subjects completed study (9 from group I and 8 from group II).						placebo for GI symptoms (abdominal pain, intestinal bloating and flatulence)		
Trials of digestive enzymes									
Munasingh et al. (2010)	43 subjects, 27 completed intervention. 3 were lost to follow up; 2 from Sequence 1 (S1) & 1 from Sequence (S2). 1 subject withdrew due to family issues (S1), 4 because of perceived behaviour deterioration (3 from S1 & 1 from S2), 5 due to difficulties with capsule administration (4 from S1 & 1 from S2) and 3 gave no reason (S2).	Children diagnosed with AD or PDD-NOS with the DSM-IV. Mean age was 69.4 months.	Digestive Enzyme S1 received Peptizyde™ for 3 months, then crossed over and received placebo. S2 received placebo for 3 months, then crossed over and received Peptizyde™ for 3 months. (1 week washout period between treatment sequences)	Placebo	6 months and 1 week	Global Behaviour Rating Scale (GBRS), Additional Rating scale (ARS), Language Development Survey (LDS)	No significant difference on the GBRS, ARS and LDS questionnaires. A small statistically significant improvement on enzyme therapy was seen for the food variety scores that was not deemed clinically significant.	Not stated	Jadad score = 5 Enzyme and placebo provided by Houston Nutraceuticals
Trials of polyunsaturated fatty acids (PUFAs)									
Amminger et al. (2007)	13 subjects, PUFA (n =7) or placebo (n =6). One individual from the placebo group withdrew from the trial after 2 weeks because of GI complaints and lack of symptom improvement.	Children with average age 10.4, (5-17y) diagnosed with autism with DSM-IV-TR and ADOS	7X 1g capsules of Menhaden fish oil containing 840 mg eicosa-pentaenoic acid (EPA), 700 mg docosa-hexaenoic acid (DHA) & 7 mg Vitamin E (i.e. 1.54g of PUFA/day) for 6 weeks	Placebo i.e. coconut oil with 1 mg fish oil and 1 mg vitamin E	6 weeks	Aberrant Behavior Checklist (ABC)	Non-significant trends towards improvement. Mild adverse events reported included fever in the experimental group and headache and insomnia in the placebo group.	Not stated	Jadad score = 4 Small sample size Trends for improvement in hyperactivity, but not statistically significant. Omega Protein Co-operation, provided medication
Bent et a. (2010)	25 subjects included in analysis, PUFA (n=13) or placebo (n=12). PUFA group, lost to follow-up (n=1, disliked taste), discontinued intervention (n=4, 2 disliked taste, 1 rash, 1 GI symptoms). Placebo group, lost to follow-up (n=1, blood draw anxiety), discontinued intervention (n=2, 1 disliked taste, 1 increased self-stimulatory behaviour)	Children ages 3-8 diagnosed with ASD (with the ADOS, social communication questionnaire (SCQ) & DSM-IV-TR) and hyperactivity (with the ABC)	PUFAs were provided as orange-flavoured pudding packets (Coromega, Vista, CA) containing 650 mg of omega-3 fatty acids, including 350 mg of EPA and 230 mg of DHA, given twice daily for a daily dose of 1.3 g of PUFAs (and 1.1 g of DHA/EPA) for 12 weeks.	Placebo packets had the same orange-flavoured pudding with an identical appearance and taste, but included safflower oil instead of the PUFAs.	12 weeks	ABC (hyperactivity was primary outcome measure) Peabody Picture Vocabulary Test Expressive Vocabulary Test Social Responsiveness Scale Behavioral Assessment System for Children Clinical Global Impression-Improvement (CGI-I) scale.	Overall there were no statistically significant changes in any of the outcome measures. Hyperactivity as measured on the ABC improved 2.7 (+/-4.8) points in the PUFA group compared to 0.3 (+/-7.2) points in the placebo group (p = 0.40; effect size = 0.38) but was not statistically significant.	Autism Speaks, the Higgins Family Foundation, The Emch Foundation, The Taube Foundation, NIH/NCR R UCSF-CTSI Grant Number UL1 RR024131 (Dr. Bent) and the MIND Institute.	Jadad score = 5 Small sample size (pilot study) Correlations were found between decreases in five fatty acid levels and decreases in hyperactivity. Treatment was well tolerated.
Trials of melatonin									
Garstang & Wallis (2006)	7 children completed the study.	Children with a diagnosis of ASD (by a	Melatonin 5mg, given at bedtime for 4 weeks	Placebo	No follow-up	Parents kept daily sleep logs from which the	Mean and 95% confidence interval (CI) reported. There	Coventry primary care trust	Jadad score = 4 Possible

	11 children were initially enrolled (2 discontinued the study after the trial was suspended as placebo capsules were empty, 1 dropped out because of a house move and 1 dropped out because she was involved in a child protection enquiry.	paediatrician or psychiatrist) aged 4-16, with significant difficulties sleeping at night				primary outcome measures were sleep latency, total hours of sleep, and number of night awakenings.	was a decrease in mean sleep latency, wakings per night and increased total sleep time with melatonin compared to baseline & placebo Sleep latency : Baseline 2.60 h [95% CI 2.28-2.93]; Placebo 1.91 h [1.78-2.03]; melatonin 1.06h [0.98-1.13] Wakings per night: Baseline 0.35 [0.18-0.53]; Placebo 0.26 [0.20-0.34]; melatonin 0.08 [0.04-0.12] Total sleep : Baseline 8.05 h [7.65 - 8.44]; Placebo 8.75 h [8.56-8.98]; melatonin 9.84 h [9.68-9.99]	The melatonin and placebo were supplied free of charge by Penn Pharmaceuticals Ltd.	unblinding due to problems with placebo capsules. Statistical methods were not clearly described Adverse effects not described Small sample size
Wright et al. (2011)	20 subjects were enrolled, 17 included in analysis.	Children diagnosed with ASD based on ICD-10 and confirmed by Autism Diagnostic Interview – Revised (ADI) or ADOS if necessary. Included 14 with autism, 4 atypical autism and 2 with AS. Children had all been referred for serious sleep problems. Children were aged 4-16 years and not taking psychotropic medication.	2 mg and titrated up to 10mg standard release melatonin, 1 hour prior to bedtime for 3 months	Placebo		Parents completed sleep diaries daily which were collected monthly for 9 months. Primary outcome measures were sleep latency, total sleep time, and number of awakenings Sleep Difficulties Questionnaire, Developmental Behaviour Checklist (DBC) and General Health Questionnaire collected at the start and end of each 3-month period of medication/ placebo and on completion. A Side Effects Questionnaire was completed at start, end and at end of each 3-month period of medication/ placebo	Melatonin significantly improved sleep latency (by an average of 47 minutes, p=0.004) and total sleep (by an average of 52 minutes, p = 0.002) compared to placebo, but not number of night awakenings p = 0.209. There was a statistically significant difference in the total score of the DBC of 6.0 between melatonin and placebo (p=0.05). There was a significant difference in favour of melatonin for the dysomnias subscale of the Sleep Difficulties questionnaire p=0.041) but not other subscales. Adverse effect profile low and similar between arms.	York Innovations Fund and the London law Trust	Jadad score = 5 Placebo was manufactured to be identical in appearance and constitution as the active form.

Table 2. Published randomised, double-blind, controlled trials of CAM products for the treatment of autism.

4.2 Safety

Most interventions were associated with only mild adverse effects, although there is a lack of long-term safety data available (Table 3).

4.2.1 High dose pyridoxine and magnesium (HDPM)

Each of the 15 original studies that investigated the effects of pyridoxine plus or minus magnesium was analysed in order to determine adverse effects seen with administration of vitamin B6 and/or magnesium to an autistic population. In two studies (Martineau et al. 1988; Kuriyama et al. 2002), no subjects reported adverse effects. Loose stools and symptoms

Complementary medicine	Most prevalent adverse effects
Vitamin B6 + magnesium	Loose stools, URTI symptoms, nausea, excitability
Vitamin B12	Hyperactivity and increased mouthing of objects
Dimethylglycine (DMG)	Agitation, hyperactivity
Vitamin C	None mentioned
Iron	GI irritation, stained teeth
Probiotics	Rash, diarrhoea, weight loss
Digestive enzymes	Hyperactivity, aggression, diarrhoea, increased self-stimulatory behaviours, loose stools, provocation or red ears and cheeks, increased hunger and cessation of eating.
Secretin	Rash, hyperactivity, fever, tachycardia, vomiting, photosensitivity, increased irritability and generalised flushing.
Polyunsaturated fatty acids	GI irritation, hyperactivity, behavioural worsening, increase the risk of bleeding
Melatonin	Tiredness, headache, dizziness, diarrhoea, agitation
Thiamine tetrahydrofuryl disulphide (TTFD)	Unpleasant odour
DMSA	Sleep problems, increased tantrums

Table 3. Major adverse effects observed during trials of selected CAM products in people with autism

of an upper respiratory tract infection (URTI) were each experienced by five subjects in the study by Findling et al. (1997), with emesis and fatigue experienced by a single subject. The authors hypothesised that the loose stools could have been caused by the cathartic effect of magnesium oxide. Lelord et al. (1981) reported nausea in 3 subjects, increased excitability in 3 subjects and an increase in autistic symptoms in 4 subjects. No other studies mentioned monitoring for adverse effects, which does not necessarily indicate that they did not occur. Safety reviews of pyridoxine based on data from human and animal studies in wider populations were conducted in the 1980s and 1990s (Cohen&Bendich 1986; Bendich&Cohen 1990). It was found that pyridoxine doses of less than 500mg/day appeared to be safe in adults, based on durations of administration ranging from 6 months to 6 years, but that daily doses of greater than 500mg for extended periods can cause sensory neuropathy. Since April 2006, the Therapeutic Goods Administration in Australia (Therapeutic Goods Administration 2006) has required products containing pyridoxine, pyridoxal or pyridoxamine to carry a label stating ‘this medicine may be dangerous when used in large amounts or for a large period of time’, indicating that these findings are still relevant.

4.2.2 Vitamin B12

In the B12 randomised controlled trial by Bertoglio et al. (2010) reported side effects were increased hyperactivity and increased mouthing of objects. No serious adverse events were reported. The authors concluded that the mild nature, and limited number of side-effects

observed, supports that subcutaneous administration of methyl B12 appears safe to use in autism.

4.2.3 Dimethylglycine (DMG)

In the DMG study by Kern et al. (2001), a greater number of adverse effects occurred in the placebo group than in the group receiving DMG. In the DMG group, 1 subject experienced difficulty sleeping, another experienced increased aggressiveness and 2 were reported to have hyperactivity. These same effects were observed in the placebo group, but in greater numbers. Bolman and Richmond (1999) reported that 1 subject became more 'edgy' during their DMG trial. The average scores on Rimland's checklist were lower with DMG than placebo for the areas of speech, cooperation, understanding, attention, bizarre behaviour, tantrums, and activity level, indicating an overall worsening of behaviour with DMG.

4.2.4 Vitamin C

The single publication located examining the use of high dose vitamin C in children with autism did not mention adverse effects (Dolske et al. 1993). The Natural Medicines Comprehensive Database (Natural Medicines Comprehensive Database 2011) and the Mayo Clinic (Mayo Clinic 2011) state that Vitamin C supplements are generally regarded as safe if used within recommended doses in the general population. Adverse effects are rarely reported and are dose-related. Such adverse effects can include nausea, vomiting, heartburn, abdominal cramps and headaches. Doses of vitamin C greater than the tolerable upper limit of intake have been associated with significant adverse effects such as kidney stones, severe diarrhoea, nausea and gastritis. In addition, large doses may precipitate haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (Mayo Clinic 2011). Rare reports of flushing, dizziness, faintness and fatigue have also been noted. There are also rare reports of scurvy due to tolerance or resistance following cessation after long-term use of vitamin C (Mayo Clinic 2011; Natural Medicines Comprehensive Database 2011).

4.2.5 Iron

In the iron study conducted by Dosman et al (2007), nine of the 33 (27%) children who completed the study experienced GI effects including constipation, loose stools abdominal pain and decreased appetite. However, there was a high rate of baseline GI symptoms in 76% (25/33) of participants. While it was reported that there was exacerbation of GI symptoms in some of the children (possibly related to the high dose of elemental iron administered) it was stated this was not a common reason for withdrawal from the study. Stained teeth were reported for two children (6%).

4.2.6 Probiotics

In the probiotic study conducted by Parracho et al. (2010), three subjects withdrew from the study because of adverse events. One experienced a skin rash three days after starting the first feeding period (probiotic) and withdrew from the study. Two further subjects withdrew from the study after the first washout period, one experienced diarrhoea during the probiotic feeding period and the other lost 1.2 kg during the probiotic feeding period.

The Mayo Clinic (Mayo Clinic 2011) and The Natural Medicines Comprehensive Database (Natural Medicines Comprehensive Database 2011) agree that the common probiotics *Lactobacillus acidophilus*, *Bifidobacteria* and *Saccharomyces boulardii* (taken orally) are well

tolerated in the general population and few side effects are reported when used at recommended doses. Orally, probiotics can cause GI upset including: abdominal discomfort and flatulence. It is reported that this effect is usually transient and mild and subsides with continued use (Mayo Clinic 2011; Natural Medicines Comprehensive Database 2011). In addition, *Bifidobacteria* can cause diarrhoea in children (Natural Medicines Comprehensive Database 2011).

Since probiotic preparations contain live and active microorganisms there is concern that they might cause pathological infection in some patients. There have been rare reports of septicaemia (*Lactobacillus acidophilus* and *Bifidobacteria*) and fungaemia (*Saccharomyces boulardii*) in severely ill and/or immunocompromised patients. This effect would not be expected to occur from taking oral probiotics in most healthy patients (Mayo Clinic 2011; Natural Medicines Comprehensive Database 2011).

4.2.7 Digestive enzymes

An open and uncontrolled trial that investigated the efficacy of a dietary enzyme supplement (ENZYMAID) in autism also investigated adverse effects (Brudnak et al. 2002). Six of the children (13%) enrolled in the study experienced adverse effects including: hyperactivity, increased aggression, increased self-stimulatory behaviours, diarrhoea, loose stools, provocation or red ears and cheeks, increased hunger and cessation of eating. In addition behavioural or medical side effects were listed as reasons for leaving the study.

In the randomised controlled trial investigating the efficacy of Peptizyde™, no serious adverse effects were noted during the study period (Munasinghe et al. 2010). Two children were observed by their parents to have transient behavioural deterioration which they initially attributed to commencement on capsules. The behaviours described included increased irritability and aggression and inattentiveness. Both families opted to discontinue the study, however, follow-up in subsequent weeks showed that the behavioural difficulties persisted despite cessation. A further two children were observed by their parents to have negative changes in behaviour again initially attributed to capsule use. The behaviours included irritability, and difficulties engaging in the classroom. Both opted to withdraw from the study, however, on follow-up felt that changing family and school environmental factors were probably the significant precipitants.

4.2.8 Secretin

No serious adverse events, such as anaphylaxis, were reported in the 14 trials included in the systematic review of intravenous secretin use in autism (Williams et al. 2009). Some adverse effects possibly attributable to secretin were reported in some studies including rash, hyperactivity, fever, tachycardia, vomiting, photosensitivity, increased irritability and generalised flushing.

4.2.9 Polyunsaturated fatty acids (PUFAs)

GI side effects are reported in the general population following treatment with PUFAs and include: nausea, diarrhoea, increased belching, acid/reflux/heartburn/ indigestion, abdominal bloating, and abdominal pain. Fishy after-taste is commonly experienced and rare reports of skin rash have occurred (Mayo Clinic 2011).

In the PUFA randomised controlled trial conducted by Amminger et al. (2007) where children with autism received a 6 week course of PUFAs or placebo, 1/13 children withdrew due to GI complaints and lack of perceived benefit. In another randomised controlled trial conducted by

Bent et al. (2010), no serious adverse events were reported during the study in the 27 participants, and there was no difference in the number of reported non-serious adverse events in the two treatment groups. 5/14 patients reported adverse events in the PUFA group (2 rashes, 1 upper respiratory infection, 1 nose bleed, 1 increased GI symptoms); 4/13 patients reported adverse events in the placebo group (3 increased hyperactivity, 1 increased self-stimulatory behaviour). In an uncontrolled study by Patrick and Salik (Patrick&Salik 2006), 2/22 children withdrew due to reports of increased physical activity, but no other adverse effects were noted. In another uncontrolled study, a “few parents” reported “increased hyperactivity and behavioral problems” (Bell et al. 2004). Two uncontrolled studies (Meguid et al. 2008; Politi et al. 2008) and a case report (Johnson&Hollander 2003) did not discuss whether adverse events were assessed. Meiri et al. (2009) conducted an open study where 9 children with autism received a 12 week course of PUFAs and no adverse effects were reported. A systematic review by Bent et al. (2009) that examined safety and efficacy of PUFAs in autism highlighted that most studies indicate that omega-3 fatty acids are relatively safe, although there are some concerns that it may increase the risk of bleeding (and therefore should be avoided in persons at increased risk for bleeding).

4.2.10 Melatonin

In the randomised controlled trial of melatonin conducted by Garstang and Wallis (2006), adverse effects were not described. In the randomised controlled trial in 17 children with autism by Wright et al. (2011) adverse effects were low and similar between the two arms. The side effects that occurred more frequently in the melatonin arm were as follows: daytime drowsiness, reduced appetite, reduced alertness and diarrhoea however, differences in the frequency of these adverse effects were not statistically significant. The observational retrospective study in 107 children with autism conducted by Andersen et al. (2008) reported 3 children experienced mild adverse effects including increased enuresis, morning sleepiness and "fogginess". In Paavonen et al.'s study (2003) in a cohort of 15 children with AS one subject reported extreme tiredness, diarrhoea, headache and dizziness; one reported mild tiredness and headache on days 1 and 2 of the study and another reported prolonged wakeful periods at the beginning of the treatment. In the open prospective study in 20 young children with autism conducted by Gianotti et al. (2006) and the observational retrospective study in six adults with autism by Galli-Carminati (2009) no adverse effects were reported but were monitored for. A recent case series reported melatonin induced agitation in three patients with intellectual disability (Richings&Feroz-Nainar 2010).

In a recent review of the safety and efficacy of exogenous melatonin used for secondary sleep disorder in a more generalised population (Buscemi et al. 2006), it was reported that the most frequently-occurring adverse effects were headache, dizziness, nausea and drowsiness. However, the incidence of these effects was found to be similar during both the placebo and melatonin phases of trials. The safety review encompassed a total of 17 studies, both controlled and uncontrolled, with 651 participants overall. No mention of an increase in seizure frequency being caused by melatonin administration was made.

4.2.11 Chelating therapies

Lonsdale et al. (2002) examined the efficacy of the chelating agent TTFD in autism in an open pilot study in children with autism aged 3 to 8 (n=10) The only adverse effect documented by Lonsdale et al. (2002) was parental reports of a ‘skunk-like odour’ in 9/10 subjects. There was

also a worsening of autistic symptoms in 1 subject. According to the Mayo Clinic, long-term doses of thiamine up to 200mg daily are considered non-toxic, although doses greater than 100mg may result in drowsiness or muscle relaxation (Mayo Clinic 2011).

Adverse effects were monitored for in the study by Adams et al (2009a; 2009b) examining the chelating agent DMSA in autism. In phase one of the study: one “mild adverse reaction” (lethargy and decreased appetite) was reported. In Phase two, four participants dropped out due to adverse effects including sleep problems (one on DMSA); behaviour and some skills worsened (one on DMSA); worsened behaviour (two on placebo). Additionally, two participants on DMSA who ended the study early had moderate sleep problems (both children) and increased tantrums (one child) that resolved on stopping treatment.

Despite the availability of the studies of the chelating agent DMSA in autism that showed some benefits, and acceptable levels of tolerability in a limited number of children, there are significant concerns about the safety of chelation therapy in the management of autism. It is notable that a randomised controlled trial designed to examine the safety and efficacy of DMSA for mercury chelation in autism was halted by the US National Institute for Mental Health after an assessment that the study treatment presented more than minimal risk (Mitka 2008). This was partly due to a study in rats designed to assess the effects of chelation with DMSA following lead exposure. This study had the unexpected finding that a single 3-week course of succimer treatment in rats not exposed to lead during their early development produced lasting cognitive dysfunction when assessed over a 7-month period (Stangle et al. 2007).

Furthermore the US Food and Drug Administration (FDA) issued a warning in 2010 to manufacturers of a number of different chelation products available without prescription and readily obtained over the internet (FDA, 2011). The FDA has indicated that the companies have not provided evidence to substantiate their claims that their products are safe and effective in treating conditions such as ASD. The FDA has threatened legal action if companies continue to make unsubstantiated claims.

4.2.12 Others

No studies of any description involving children with autism were located for the remainder of the interventions under investigation. Hence, safety of the remaining CAM products in autism could not be elucidated. The authors refer the reader to the monographs available through the Mayo Clinic website (Mayo Clinic 2011) and the Natural Medicines Comprehensive Database (Natural Medicines Comprehensive Database 2011) that both report side effects associated with taking a range of supplements in the general population.

5. Conclusion

Available evidence for efficacy and safety for a range of CAM products has been compiled that will equip health professionals with information so they can sensitively disclose and discuss CAM product usage with patients and their families. Therefore, health professionals can ethically and responsibly assist patients and caregivers with their decision making regarding CAM product usage. Pleasingly, when medical practitioners were surveyed regarding which CAMs they recommended to caregivers for their children with autism it was revealed it was the agents for which there is emerging evidence for benefit and reasonable safety profiles i.e. multivitamins (49%), PUFAs (25%), melatonin (25%) and probiotics (19%) (Golnik&Ireland 2009). On the other hand, 61% of medical practitioners

surveyed reported they discourage use of chelation therapy which does not have evidence of benefit in the management of autism and potential safety risks (Golnik&Ireland 2009). The information compiled can also be accessed by researchers. This study highlights there is an urgent need for more well-designed clinical trials to improve the evidence base on which people with autism, caregivers and health care professionals can make decisions about treatment options. Health care professionals and caregivers need to be informed that for many CAM products, the rationale for use is only theoretical and not biologically proven. Further, the use of CAM products in autism is not risk-free and often lacks sound clinical evidence for efficacy.

6. References

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Autism spectrum disorders are a major topic for research. The causes are now thought to be largely genetic although the genes involved are only slowly being traced. The effects of ASD are often devastating and families and schools have to adapt to provide the best for people with ASD to attain their potential. This book describes some of the interventions and modifications that can benefit people with ASD.

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